The use of Normal Human Immunoglobulin (NHIG) in the public health management of communicable diseases: effectiveness and efficiency

Dr Megan Young MBBS MPH FAFPHM

School of Medicine
Faculty of Health
Griffith University
Australia

Submitted in fulfilment of the requirements of the degree of Doctor of Philosophy.

September 2019
Abstract

Passive immunisation is an important means of preventing communicable diseases post-exposure, particularly for subpopulations most vulnerable to complications from infection. The blood product normal human immunoglobulin (NHIG) is used in Australia for post-exposure prophylaxis in certain non-immune populations to prevent measles and hepatitis A and is recommended in certain circumstances for non-immune pregnant women to prevent rubella and congenital rubella syndrome. Practices with respect to passive immunisation post-exposure for these conditions vary around the globe and importantly, vary among countries similar to Australia such as New Zealand, the United Kingdom and the United States. The series of studies presented here aimed to understand the possible reasons behind these differences in practice and, using this information, make recommendations for the most effective and efficient use of NHIG in public health practice in Australia.

An overview of passive immunisation, rubella, measles, and hepatitis A and the public health management of these conditions, current at the time of thesis commencement, is provided. This is followed by an exploration of why practices of passive immunisation post-exposure to measles, rubella and hepatitis A might vary among high-income countries, concluding that a lack of collated evidence of the effectiveness of passive immunisation for preventing measles and rubella, unanswered questions about the minimum effective doses of NHIG as post-exposure prophylaxis for each disease, and differences in disease-specific antibodies in available immunoglobulin products may be significant.

To redress these deficits, two systematic reviews collated existing evidence of the effectiveness of passive immunisation for preventing measles, and rubella and congenital rubella syndrome; disease-specific antibody concentrations were measured in samples of Australian blood products used for passive immunisation; and simulation modelling validated by the preliminary results of a clinical trial were used to estimate the minimum effective doses of NHIG required for post-exposure prophylaxis for each disease. A budgetary impact assessment was then conducted utilising the data from a study of NHIG usage in Australia to examine the financial implications of the recommended changes to passive immunisation practice in Australia made as a result of the newly available evidence.

The first systematic review collated and synthesised the evidence of the effectiveness of passive immunisation for preventing measles post-exposure concluding that passive
immunisation is effective for preventing measles up to seven days post-exposure and that a dose-response is likely. The second systematic review collated and synthesised the evidence of the effectiveness of passive immunisation for preventing rubella and congenital rubella syndrome post-exposure concluding that passive immunisation seems to be effective for preventing rubella up to five days post-exposure, but that insufficient evidence exists to directly examine effectiveness for preventing congenital rubella syndrome. Again, a dose-response seemed likely.

The concentrations of measles and rubella antibodies in Australian NHIG and intravenous immunoglobulin (IVIG) were quantified. Measles titres in Australian NHIG ranged from 51 to 76 IU/mL and those in IVIG ranged from 6 to 24 IU/mL as measured by the plaque-reduction neutralisation test. The minimum concentration of rubella antibodies measured in Australian NHIG was 2108 IU/mL, while in Australian IVIG it was 268 IU/mL as measured by a chemiluminescent assay. Australian NHIG is made to the European Pharmacopoeia standard of 100 IU/mL of hepatitis A antibodies, so these were not further quantified.

Pharmacokinetic modelling using a two-compartment model with first order absorption estimated the minimum effective doses of NHIG required to prevent measles, rubella and hepatitis A. The minimum effective dose of measles-specific antibodies was estimated as 25.5 IU/kg. The minimum effective dose of rubella-specific antibodies was estimated as less than 13 IU/kg. The minimum effective dose of hepatitis A-specific antibodies was estimated at 3.6 IU/kg. Model predictions of serum concentrations of hepatitis A antibodies seemed consistent with the preliminary results of the clinical trial of NHIG administration to healthy non-immune volunteers.

Comparing the estimated minimum effective doses alongside the evidence of effectiveness with current practice resulted in the following recommendations for alterations to post-exposure passive immunisation in Australia:

- For measles control: Increase the dose of NHIG recommended to 0.5 mL/kg without a volume limit. Where calculated doses are large, consider including the option of intravenous IG dosing and if this is adopted, limit the recommendations for post-exposure passive immunisation to those most vulnerable to measles complications.
- For rubella control: Decrease the dose of NHIG to 0.5 mL for non-immune pregnant women weighing up to 160 kg or 1 mL for those weighing greater than 160 kg. Offer post-exposure passive immunisation within five days of first
exposure followed by serial serology to enable identification of asymptomatic disease.

- For hepatitis A control: Individual clinical assessment may indicate an increased dose is warranted for contacts weighing more than 85 kg. In this case, the recommended dose is 0.036 mL/kg.

The use of NHIG in public health practice in Queensland and Australia over a decade was documented from routinely collected data, highlighting that NHIG was used variably for measles post-exposure prophylaxis, rarely for hepatitis A post-exposure prophylaxis and hadn’t been documented for rubella post-exposure prophylaxis. The potential budgetary impact at a national level of implementing the recommended changes to passive immunisation practice using the cost calculator method was found to be minimal, even in a ‘worst case’ scenario analysis where the maximal spend was for measles control and was less than AU$350 000 per year. When the scenario for analysis approximated historical estimates, implementing the recommended changes was either approximately equal in cost to current practice, or cost saving.

It was therefore concluded that public health practice with respect to passive immunisation post-exposure to measles, rubella and hepatitis A should change in Australia in line with the above recommendations.

Adoption of the recommendations of this program of research on the effectiveness and efficiency of passive immunisation for the public health management of measles, rubella and hepatitis A in Australia may improve the effectiveness of this intervention and either minimally impact on government health spending or be cost saving. A number of the studies contained herein provide valid benchmarks for future research or quality audits, including the first published concentrations of measles and rubella antibodies in Australian NHIG and IVIG, and the first published Australian usage of NHIG for post-exposure prophylaxis. At a global level, the systematic reviews of effectiveness of passive immunisation for preventing measles and rubella and congenital rubella post-exposure, and also the published pharmacokinetic model, have application for countries revising their own public health guidelines.
Statement of Originality

This work has not previously been submitted for a degree or diploma in any university. To the best of my knowledge and belief, the thesis contains no material previously published or written by another person except where due reference is made in the thesis itself.

(Signed)

Dr Megan Young
## Table of Contents

Abstract ii  
Statement of Originality v  
List of Tables and Figures ix  
Acknowledgements x  
Acknowledgement of published papers included in this thesis xiii  
List of Acronyms, Abbreviations and Units xv  
Glossary xvi  

### Chapter 1  Background and Scope 1  
1.1 Passive Immunisation 1  
1.2 Normal Human Immunoglobulin (NHIG) and Intravenous Immunoglobulin (IVIG) 2  
1.3 Measles 4  
1.4 Hepatitis A 5  
1.5 Rubella 7  
1.6 Current Public Health Management Circa 2013 9  
1.7 Possible reasons for differences in practice circa 2013 12  
1.8 Conclusions circa 2013 25  
1.9 Aims and Objectives 26  
1.10 Methodology 26  

### Chapter 2  The effectiveness of passive immunisation for preventing measles 28  

### Chapter 3  The effectiveness of passive immunisation for preventing rubella 89
Appendix 2 Conference presentations of thesis work 295

Appendix 3 Publications and conference presentations related to thesis work 296

Appendix 4 Publisher Permissions 297
List of Tables and Figures

Table 1. Expenditure on Health of Four Developed Countries, 2009 (95) .................. 13
Table 2. Overall Population Health of Four Developed Countries .......................... 13
Table 3. Comparison of four developed countries on disease-specific possible reasons for differences in passive immunisation practices ............................................. 16
Table 4. Geometric mean titre (GMT) of hepatitis A antibodies in the serum of trial participants ........................................................................................................ 241
Table 5. Serum hepatitis A antibody concentrations at day 50 and dose of disease-specific antibodies administered for each trial participant ................................. 242
Table 6. Eligible populations for passive immunisation under base case and comparison case budget impact analysis ............................................................................. 267
Table 7. Unit costs related to utilising passive immunisation for the control of measles, rubella and hepatitis A in Australia ................................................................. 269
Table 8. Treatment mixes for passive immunisation under base case and comparison case budget impact analysis .................................................................................. 270
Table 9. Annual cost estimates (2018 AU$) for comparison case compared to base case for historical, trough and peak year numbers of contacts ................................. 274

Figure 1. Average levels and standard deviations of anti-HAV IgG in Australian NHIG produced by CSL Ltd, 1994 to 2012 (graph courtesy of CSL Behring Australia Ltd.) ........................................................................................................................................... 23
Figure 2. Serum concentrations of hepatitis A antibodies at day 50 after administration of 200 IU at 75% bioavailability according to weight .............................................. 225
Figure 3. Consort flow diagram for the trial: Validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A ......................................... 239
Figure 4. Serum concentrations of hepatitis A antibodies for Test Dose group participants .................................................................................................................. 240
Figure 5. Serum concentrations of hepatitis A antibodies for Usual Care group participants .................................................................................................................. 241
Figure 6. Predicted pharmacokinetics compared to measured serum concentrations of Hepatitis A antibodies for participants in the test dose group (0.025 mL/kg NHIG) ................................................................................................................... 243
Figure 7. Predicted pharmacokinetics compared to measured serum concentrations of Hepatitis A antibodies for participants in the usual care group (2 mL NHIG) ...... 244
Acknowledgements

Thanks to the Acute Respiratory Infections Group at the Cochrane Collaboration for editorial assistance and support during the following systematic reviews: “Post-exposure passive immunisation for preventing measles” and “Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome”.

Thanks to CSL Australia Ltd., in particular, Dr Darryl Maher, Mr Joe Bertolini, and Ms Pushpa Kotharu for their collaboration, including assisting my understanding of blood product processing, and undertaking the quantitative antibody testing on NHIG and IVIG samples.

Thanks to my colleagues Associate Professor Shu-Kay Ng and Associate Professor Louise Gordon for their helpful comments on Chapters 5 and 7 respectively.

Thanks to my supervisors, Prof Allan Cripps and Prof Graeme Nimmo for their continual support, guidance, input and editorial assistance to the overall thesis.

Thanks to my co-authors for their input and editorial assistance on the following publications and poster presentations:


Young MK, Cripps AW. Passive immunisation for the public health control of communicable diseases: Current status in four high-income countries and where to next? *Human Vaccines & Immunotherapeutics* 2013; 9(9): 1885-1893.


Lastly, but by no means least, my love and thanks to my family for their enduring patience, voluminous support and unconditional love through the often very trying times of PhD candidature.
Acknowledgement of published papers included in this thesis

Section 9.1 of the Griffith University Code for the Responsible Conduct of Research ("Criteria for Authorship"), in accordance with Section 5 of the Australian Code for the Responsible Conduct of Research, states:

To be named as an author, a researcher must have made a substantial scholarly contribution to the creative or scholarly work that constitutes the research output, and be able to take public responsibility for at least that part of the work they contributed. Attribution of authorship depends to some extent on the discipline and publisher policies, but in all cases, authorship must be based on substantial contributions in a combination of one or more of:

- conception and design of the research project
- analysis and interpretation of research data
- drafting or making significant parts of the creative or scholarly work or critically revising it so as to contribute significantly to the final output.

Section 9.3 of the Griffith University Code ("Responsibilities of Researchers"), in accordance with Section 5 of the Australian Code, states:

Researchers are expected to:

- Offer authorship to all people, including research trainees, who meet the criteria for authorship listed above, but only those people.
- accept or decline offers of authorship promptly in writing.
- Include in the list of authors only those who have accepted authorship
- Appoint one author to be the executive author to record authorship and manage correspondence about the work with the publisher and other interested parties.
- Acknowledge all those who have contributed to the research, facilities or materials but who do not qualify as authors, such as research assistants, technical staff, and advisors on cultural or community knowledge. Obtain written consent to name individuals.

Included in this thesis are published papers in Chapters 2, 3, 4, 5 and 6 which are co-authored with other researchers. My contribution to each co-authored paper is outlined at the front of the relevant chapter. The bibliographic details for these papers including all authors are:

Chapter 2:

Chapter 3:

Chapter 4:


Chapter 5:

Chapter 6:

The copyright status and publisher permission for each paper is included in Appendix 4. Appropriate acknowledgements of those who contributed to the research but did not qualify as authors are included in each published paper.

(Signed)
Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
<table>
<thead>
<tr>
<th>Acronym</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELISA</td>
<td>enzyme-linked immunosorbent assay</td>
</tr>
<tr>
<td>FBC</td>
<td>full blood count</td>
</tr>
<tr>
<td>HAI</td>
<td>haemagglutination inhibition</td>
</tr>
<tr>
<td>IU/mL</td>
<td>international unit per millilitre</td>
</tr>
<tr>
<td>IVIG</td>
<td>intravenous immunoglobulin</td>
</tr>
<tr>
<td>MMR</td>
<td>measles, mumps, rubella vaccine</td>
</tr>
<tr>
<td>NHIG</td>
<td>Normal human immunoglobulin (intramuscular formulation)</td>
</tr>
<tr>
<td>NZ</td>
<td>New Zealand</td>
</tr>
<tr>
<td>SCIG</td>
<td>subcutaneous immunoglobulin</td>
</tr>
<tr>
<td>UK</td>
<td>United Kingdom</td>
</tr>
<tr>
<td>US</td>
<td>United States of America</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>------------------------------</td>
<td>---------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Active immunisation</td>
<td>Induction of immunity after exposure to an antigen</td>
</tr>
<tr>
<td>Anaphylaxis</td>
<td>A potentially life threatening severe allergic reaction involving multiple body systems.</td>
</tr>
<tr>
<td>Antibodies</td>
<td>Serum proteins that aid in the neutralisation and clearance of pathogens or antigens</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>Pain in a joint</td>
</tr>
<tr>
<td>Arthritis</td>
<td>Disorder of a joint involving an inflammatory process that causes the joint to be painful</td>
</tr>
<tr>
<td>Buffering</td>
<td>Neutralising small amounts of added acid or base to maintain a relatively stable pH</td>
</tr>
<tr>
<td>Convalescent</td>
<td>Someone recovering from an illness or medical treatment</td>
</tr>
<tr>
<td>Cytotoxicity</td>
<td>Resulting in cell death</td>
</tr>
<tr>
<td>Dyspnoea</td>
<td>Shortness of breath</td>
</tr>
<tr>
<td>Elute</td>
<td>Remove by washing with a solvent</td>
</tr>
<tr>
<td>Encephalitis</td>
<td>Inflammation of the brain</td>
</tr>
<tr>
<td>Generalised hypersensitivity reactions</td>
<td>Symptoms of an allergic reaction that are widespread over the body</td>
</tr>
<tr>
<td>Haemolytic anaemia</td>
<td>Low levels of the protein haemoglobin in the blood as the result of abnormal breakdown of red blood cells</td>
</tr>
<tr>
<td>Haemorrhage</td>
<td>Bleeding</td>
</tr>
<tr>
<td>Immunisation</td>
<td>The process of becoming immune to an infectious agent</td>
</tr>
<tr>
<td>Immunosuppressed</td>
<td>The state of having an immune system that is dampened or has lowered efficacy to fight infection</td>
</tr>
<tr>
<td>Infusion</td>
<td>A method of putting fluids including drugs directly into the bloodstream</td>
</tr>
<tr>
<td>Intravenous Immunoglobulin (IVIG)</td>
<td>A blood product made from pooled blood donations that is manufactured to be infused</td>
</tr>
<tr>
<td>Ionic attraction</td>
<td>The pull of atoms towards each other as a result of being oppositely charged</td>
</tr>
<tr>
<td>Lymphadenopathy</td>
<td>Swelling or enlargement of the lymph nodes</td>
</tr>
<tr>
<td>Malaise</td>
<td>A general feeling of discomfort or illness</td>
</tr>
<tr>
<td>Myalgia</td>
<td>Pain in a muscle or group of muscles</td>
</tr>
<tr>
<td>Nausea</td>
<td>A queasy sensation including an urge to vomit</td>
</tr>
<tr>
<td>Normal Human Immunoglobulin (NHIG)</td>
<td>A blood product made from pooled blood donations that is manufactured to be given by intramuscular injection</td>
</tr>
<tr>
<td>Opsonization</td>
<td>Enhancement of phagocytosis caused by antibody binding such that foreign material is identified to phagocytic cells</td>
</tr>
<tr>
<td>Term</td>
<td>Definition</td>
</tr>
<tr>
<td>----------------------</td>
<td>----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Osmolality</td>
<td>A measure of the number of particles dissolved in a kilogram of fluid</td>
</tr>
<tr>
<td>Palpitation</td>
<td>A noticeably rapid, strong or irregular heartbeat</td>
</tr>
<tr>
<td>Passive immunisation</td>
<td>The transfer of antibodies to a person</td>
</tr>
<tr>
<td>Phagocytosis</td>
<td>The process by which a cell ingests or engulfs other cells or particles</td>
</tr>
<tr>
<td>Pharmacokinetics</td>
<td>The movement of drugs inside the body</td>
</tr>
<tr>
<td>Plasma</td>
<td>The liquid part of blood including clotting factors</td>
</tr>
<tr>
<td>Precipitation</td>
<td>Creation of a solid from a solution</td>
</tr>
<tr>
<td>Prodrome</td>
<td>Early signs or symptoms that often indicate the onset of disease</td>
</tr>
<tr>
<td>Rigors</td>
<td>Shivering accompanied by feeling cold in the presence of a fever</td>
</tr>
<tr>
<td>RNA</td>
<td>Ribonucleic acid – a polymeric molecule with roles in coding, decoding, regulation and expression of genes</td>
</tr>
<tr>
<td>Serum</td>
<td>The liquid part of blood without the clotting factors</td>
</tr>
<tr>
<td>Supernatent</td>
<td>A liquid lying above a solid residue after crystallisation, precipitation or other process</td>
</tr>
<tr>
<td>Tachycardia</td>
<td>A raised heart rate</td>
</tr>
<tr>
<td>Urticaria</td>
<td>Hives – pink or red raised itchy rash</td>
</tr>
<tr>
<td>Vertigo</td>
<td>Dizziness</td>
</tr>
<tr>
<td>Viremia</td>
<td>The presence of viruses in the blood</td>
</tr>
<tr>
<td>Virolysis</td>
<td>The breakup of a virus</td>
</tr>
<tr>
<td>Virucidal</td>
<td>Something that deactivates or destroys viruses</td>
</tr>
</tbody>
</table>
Chapter 1 Background and Scope

1.1 Passive Immunisation

Passive immunisation refers to the transfer of antibodies from donor to recipient, and occurs naturally during pregnancy, with antibodies crossing the placenta from mother to foetus, predominantly in the last four weeks of a term pregnancy (1-3). Of the five antibody isotypes, IgG is the only class of antibody to cross the placenta (4). Maternal antibodies afford some protection against infectious disease to the infant whose immune system is otherwise largely naïve at birth (2). The protection, against the diseases to which the mother was immune, wanes as the antibodies decay over the first year of life (5). The half-life of IgG has been cited as 21-23 days (4), but may be influenced by factors such as age (6), nutrition, and co-infection (3), and disease-specificities (7) resulting in regional differences in the rate of decay of disease-specific levels of maternal IgG in infants (3, 6). The biochemical half-life of maternal measles antibodies, for example, varied between 40 and 53 days across Black’s samples of infants from four different populations (6). Total transferred maternal anti-measles antibody levels (dependent on maternal antibody levels, placental function and gestation) together with the other factors mentioned above that effect the rate of decay of the transferred antibodies are the main determinants of the longevity of infant protection (6), which may vary from 2 to 12 months for the particular disease (3).

As early as the late 1800s, the short-term protection against infectious diseases afforded by passive immunisation was being investigated (8, 9), with convalescent human serum first being utilised for the prevention of measles in 1907 (8). Over subsequent decades, convalescent serum, either from individuals or from a small number of donors pooled together, was documented to prevent or ameliorate disease when administered to exposed people (9). During the 1930s, the practice of post-exposure prophylaxis via passive immunisation was widespread in the medical community (9).

Current public health management of contacts of cases of measles and hepatitis A in Australia still includes, but is not limited to, passive immunisation (10, 11). In some cases passive immunisation is also recommended for non-immune pregnant contacts of rubella (12, 13). Rather than convalescing serum from an individual case or a small number of cases, modern passive immunisation involves administration of a blood
product constituted mainly of the concentrated antibodies from at least 1000 adult blood donations (14).

Once administered, the antibodies distribute throughout the recipient’s body in the extracellular spaces (4). The recipient is then protected from contracting the infectious disease via interaction between the antibodies, the invading microorganisms, and the cells and molecules of their own immune system (15). The exact mechanisms vary according to the structure and functionality of the particular antibodies as they encounter the particular microorganisms (15), and are not completely understood (16). For viruses in general, several mechanisms of action of antibodies in the extracellular space are thought to occur. Firstly, and most importantly, antibodies bind to the invading particles, directly preventing their entry into cells; a process called neutralization (4, 17). Secondly, antibodies may block cell surface receptors, preventing the virus from entering the cell (15). Thirdly, antibodies can activate the complement cascade resulting directly in virolysis (16). Fourthly, IgG coated antigens are recognised by the recipient’s own phagocytes (4). This process of assisting phagocytosis is known as opsonization (4) and leads to virolysis within the phagocyte (17). Finally, antibodies bind to infected cells facilitating antibody dependent cytotoxicity (16) or complement-dependent cytotoxicity (17). These general mechanisms of action do not differ, regardless of whether the recipient is passively immunised via injection or infusion.

1.2 Normal Human Immunoglobulin (NHIG) and Intravenous Immunoglobulin (IVIG)

NHIG is a blood product for intramuscular injection made by Cohn cold ethanol fractionation of pooled donated human plasma (18). Cold ethanol fractionation is a process that was developed by Dr Edwin Cohn in the 1940s (19). Ethanol is added to the pooled plasma, varying the concentration, pH, temperature, and ionic strength to enable precipitation of different proteins separately. The lower molecular weight gamma globulins (antibodies) (Fraction II) are initially precipitated together with other gamma globulins (Fraction III) such as prothrombin, before being purified by solubilizing and reprecipitating them at a lower ethanol concentration and lower osmolality (19). The precipitants are collected by filtration (20). These processes result in some aggregation of the antibodies, which can cause anaphylaxis if the product is injected intravenously (18).
Other reported adverse reactions associated with NHIG include: local redness, tenderness and stiffness at the injection site; malaise; drowsiness; sensation of fever; chills; urticaria; and rarely headache, dizziness, nausea, or generalised hypersensitivity reactions (18).

A product for intravenous administration is available in Australia (IVIG), manufactured, after separation from Cohn fraction I, by chromatographic fractionation (18). Here, the remaining proteins in the supernatant bind to a solid medium; the result of ionic attraction (21). The concentration of the buffering salt solution is then varied to elute protein molecules with similar strength of ionic charge (21). As the pH of the solution need not be varied, the process preserves immunoglobulin functioning, increasing the yield of the fractionation process (20). The process also removes the aggregates and therefore reduces the likelihood of anaphylaxis upon intravenous administration. (20)

However, both hypersensitivity and anaphylaxis have been reported to occur rarely in association with IVIG administration (18). Other reported adverse reactions associated with IVIG include: malaise; headache; migraine; nausea; vomiting; vertigo; fatigue; rigors; fever; myalgia; abdominal pain; hot flushes; urticaria; rash; anxiety; lumbar pain; wheezing; dyspnoea; palpitation; tachycardia; alterations in blood pressure; and chest tightness (8, 18). Lowering the infusion rate can stay many of these adverse reactions. Haemolytic anaemia has been found to occur in some people on high dose therapy with blood group A or AB, related to infused anti-A antibodies (18).

Both IVIG and NHIG may potentially transmit infectious diseases (18). However, there have been no reports of infectious disease transmission since the response to transmission of hepatitis C in the mid-1990s (8). Safeguards against disease transmission include interview screening potential donors and screening donated plasma for antigens of HIV, Hepatitis B and Hepatitis C (20). In addition, the production processes for both NHIG and IVIG are virucidal (18). These measures adhere to the World Health Organization guidelines for the production of plasma products (14, 22).

In addition to its recommended use for the post-exposure prevention of infectious diseases, NHIG has been used in the treatment of primary congenital immunodeficiency syndromes for several decades (23). More recently, IVIG has been preferred for these cases (8). IVIG is recommended as an alternative to intramuscular immunoglobulin for the prevention of measles in susceptible contacts in NZ who are immunosuppressed, have reduced muscle bulk, or for whom large doses are required,
and for susceptible immunosuppressed contacts in the UK (24, 25). It is also clinically indicated in the treatment of a number of immune deficiencies both inherited and acquired, a number of autoimmune diseases including juvenile rheumatoid arthritis, Kawasaki disease and acute immune thrombocytopenic purpura (ITP), and in some cases of infectious diseases (23, 26).

In Australia, IVIG is licenced for use in the treatment of primary immunodeficiency, severe secondary hypogammaglobulinaemia with recurrent infections, congenital acquired immune deficiency syndrome with recurrent infections, idiopathic thrombocytopenic purpura (ITP) in adults or children at high risk of bleeding or prior to surgery to correct platelet count, allogeneic bone marrow transplantation, Kawasaki disease, and Guillain-Barre Syndrome (GBS) (27). NHIG is licenced for use in the treatment of acquired and congenital forms of primary hypogammaglobulinaemia, and secondary hypogammaglobulinaemia and in the post-exposure prophylaxis of susceptible contacts of measles, hepatitis A, rubella, and poliomyelitis (27). (In practise, vaccination has replaced passive immunisation in the management of poliomyelitis in Australia (28, 29)).

1.3 Measles

Measles is a highly communicable viral illness (30). The measles virus is an enveloped, single-stranded RNA Morbillivirus of the family Paramyxoviridae (30, 31). The virus is shed from the respiratory tract of infected persons and transmitted by aerosolised droplets or by direct contact with respiratory secretions (31). Someone with measles is contagious from one day before the symptoms start until four days after the rash appears. For public health purposes, a contact is anyone who has spent time in the vicinity of the case while they were infectious, including people who have been in a room the case has left up to 30 minutes earlier (11). A contact is deemed to be susceptible to measles if they were born after 1965 and do not have either: documented evidence of receiving an appropriate regimen of 2 doses of a measles-containing vaccine, documented evidence of immunity, or documented laboratory evidence of prior measles infection (11). A susceptible person exposed to measles will usually develop symptoms after around 10 days but this may range from 7 to 18 days after exposure (30).

Symptoms of measles include: fever, conjunctivitis, runny nose, cough and a red blotchy rash (32). The illness is often more severe in infants and adults than in children.
Complications occur more frequently in cases in developing than industrialised countries (75% or more vs 10-15% of cases)(32). Middle ear infection and pneumonia are fairly common complications, occurring in 5-15%, and 5-10% of children with measles respectively (31). Encephalitis is a serious, but rarer, complication of measles, occurring in about 1 out of every 1000 cases (31). A slowly progressing neurological disease, subacute sclerosing panencephalitis (SSPE), very rarely (1 out of 100 000 cases) occurs several years after the original measles infection, most often in children infected with measles under the age of two years (30).

Australia offers free combined measles, mumps and rubella (MMR) vaccination at 12 months and measles, mumps, rubella and varicella (MMRV) vaccination at 18 months to its children (33, 34). A 2002 Australian national serosurvey found 94% of the population to be immune to measles (35). Indeed, reported coverage of Australian children at age five years with two doses of MMR was 90.5% at December 2011 (36). Correspondingly, the average annual notification rate is low at 0.33 per 100 000 population for 2006-2007 (37). However, outbreaks do still occur in Australia, and there remains the potential for relatively large outbreaks in subsections of the population with low vaccination rates (38).

Globally, there remains a considerable burden of disease related to measles, with cases exceeding 300 000 in 2010 (39), and deaths at around 164 000 in 2008 (40). Indeed, large outbreaks in some regions in 2010 resulted in an increase over previous incidence figures (41). Despite previous and ongoing elimination targets in most regions (42-45), there are concerns about the feasibility of true global measles eradication (46). Certainly, developed countries can expect to be managing outbreaks for some time to come (46).

1.4 Hepatitis A

Hepatitis A is a non-enveloped single-stranded RNA hepatovirus; a member of the Picornaviridae family (47). It is shed in the faeces of an infected person and transmitted via the faeco-oral route, usually by contaminated food or fluids (48). The virus is stable under varying conditions including freezing, and may persist in the environment for a prolonged period of time (49). A person with hepatitis A is infectious while they are shedding virus in their faeces. However, this period is ill-defined (30). For those who develop symptoms, it has been reported as: from a few days (50), one to two weeks (49) or several weeks (51) before the onset of symptoms, until one week
after the onset of jaundice (49, 50). However, much longer periods of excretion have been documented (52, 53). Hepatitis A does not result in a chronic carrier state (30).

For public health purposes, contacts of someone with hepatitis A are those people who have had the highest likelihood of exposure to the virus during the case’s presumed infectious period. This includes: people who live with the case; people who stayed at the case’s residence and shared primary household facilities; people who consumed food not subject to further cooking that was prepared by the case; people who shared intimate personal items or drug equipment with the case; if the case wears nappies, people who provided direct care to the case; and if the case attends childcare or preschool, other children and adults in the same classroom or care group or those who share the same toilet (10 p13). Contacts are susceptible to hepatitis A if they have not been previously infected with the hepatitis A virus (HAV), or have not been vaccinated against hepatitis A. Detection of anti-HAV IgG indicates immunity (10), and this persists for life (54). A susceptible contact exposed to hepatitis A virus is likely to develop symptoms of the disease (if any) at around 28 to 30 days after their exposure, although this may range from 15 to 50 days (10, 51).

Hepatitis A can vary from an asymptomatic infection to fulminant hepatitis, with the likelihood of severe disease increasing with age (47). Seventy percent of children under the age of six years have asymptomatic disease, whereas, 70% of older children and adults experience symptoms (49). Initial symptoms are typically malaise, anorexia, nausea, vomiting, abdominal discomfort and diarrhoea (47). Fever, headache, arthralgia and myalgia may also occur. This prodromic phase is followed within a few days by the onset of jaundice (10). Prolonged or relapsing illness occurs in an estimated 10-15% of cases (51, 54). Case fatality ranges from 0.1-0.3% (30), although it increases with age (55).

Hepatitis A vaccine is offered free to Aboriginal and Torres Strait Islander children living in areas at high risk of infection in Australia (33). This includes the following states: Queensland, Northern Territory, Western Australia and South Australia. Data from 2007 indicate coverage pertaining to the recommended two-dose schedule among Indigenous children in these states at 33 months of age is less than 29% (56). The vaccine is also recommended, but not funded, for individuals with chronic liver disease, individuals with developmental disabilities, travellers to areas of moderate to high endemnicity, and individuals whose occupation or lifestyle places them at increased risk of disease (34). The most recent published national hepatitis A serosurvey results
(from 1998) indicate 41% of the population were immune (57). Although more recent serosurveys of Victorian and blood donor subpopulations within Australia report higher seroprevalence at 55% and 51% respectively (58, 59). The annual notification rate is higher than for measles, at 1.1 per 100 000 in 2006-2007, but has declined since the 1990s (37). Some large outbreaks occurred in Australia in the 1990s, associated with high-risk populations (60, 61) and contaminated food (62). Continuing sporadic cases are often associated with travel to endemic countries (37). The potential for large outbreaks continues in view of the large proportion of the population who are not immune.

Other developed countries have similarly low or very low endemicity, and similar patterns of disease (54). However, globally, hepatitis A poses a significant burden of disease, with 212 million cases and 35 245 deaths in 2005 (48). There is evidence that the global burden has increased since the 1990s (48).

1.5 Rubella

Rubella virus is an enveloped, single-stranded RNA Rubivirus of the family Togaviridae (63). It is shed in the respiratory secretions of an infected person (64), and is transmitted via respiratory droplets (65) or direct contact with respiratory secretions (30). A person with rubella is generally considered infectious from one week before the onset of rash until four days afterwards (12, 13, 63, 65), but viral shedding, and therefore potential infectivity, may continue for up to two weeks post rash onset (63, 64, 66).

Close contact is usually required for transmission of rubella (66), but for public health purposes, a contact is anyone who is likely to have been exposed to the respiratory secretions of an infectious case (13), that is, anyone who has had direct contact with them (67). A contact is deemed to be susceptible to rubella if they were born after 1965 and do not have either laboratory evidence of immunity or written documentation of receiving an appropriate schedule of two doses of rubella-containing vaccine (13). Pregnant contacts require serological testing irrespective of these factors (13, 67). A person exposed to rubella virus is likely to develop symptoms (if any) after about 14 days, although this may vary from 12 to 23 days (66).

Up to 50% of cases of rubella are asymptomatic (64, 66). When symptoms do occur, rubella is usually a mild disease, typically manifesting with lymphadenopathy (most
often the suboccipital, postauricular and posterior cervical lymph nodes), mild fever, malaise and mild conjunctivitis (64). Headache, sore throat and cough may also occur (66). This prodrome is more likely to be experienced by adults than children (66). Five or more days after the prodrome onset, a maculopapular, erythematous rash begins on the face and neck and spreads down the body, lasting for up to a few days (64). Arthralgia or arthritis lasting up to a month is the most common complication, and occurs most frequently in adult women (66). Complications such as encephalitis, haemorrhage and Guillain-Barre syndrome rarely occur (one in several thousand or more cases) (37, 64).

However, rubella control and elimination is sought because of the potential for congenital rubella syndrome (CRS). Maternal infection with rubella during the first trimester of pregnancy results in CRS in about 80-85% of cases (66). CRS may include: cataracts, retinopathy, deafness, cardiac defects and neurological deficit (30). Nine confirmed cases of CRS were notified in Australia between 2003 and 2007 (37).

Australia does not offer a rubella-only vaccine, instead using the combined MMR and MMRV vaccines (34). The schedule for rubella vaccination, and vaccine coverage rates, are therefore the same as for measles, and, as with measles, rubella immunity in Australia is high. Between 1996 and 2003, a serosurvey of 15-34 year old women in Australia revealed that 97.3% were immune to rubella (68). However, only 84% of males of the same age group were immune. A serosurvey on samples collected between 1997 and 1998 revealed 94% of people aged 19-49 years were immune to rubella (69). Notifications of rubella are correspondingly low (0.23 per 100 000 per year for 2006-07), attributable to the high proportion of cases that are asymptomatic as well as population immunity (37). Also similar to measles, there are subgroups of the Australian population with low levels of immunity. Indigenous women in rural and remote areas of the Northern Territory were found to have low levels of immunity in a 1999 survey (70). Immigrants to Australia are also a vulnerable group (37, 71).

Globally, rubella and CRS continue to pose a significant burden of disease, particularly in developing countries. Many countries still do not have established rubella vaccination programs, and the populations of these countries account for the majority of pregnancies globally (72). More than 120 000 cases of rubella, and 165 cases of CRS were reported to the World Health Organisation in 2009, although significant under-reporting is likely (72). Elimination goals have been set in some regions (64).
and met in the Americas (73), but even this region identifies the ongoing public health importance of rubella in their countries (73).

1.6 Current Public Health Management Circa 2013

Even in 2019, Australian public health management of measles, and hepatitis A is inconsistent with practice in other developed countries such as New Zealand (NZ), the United States (US) and the United Kingdom (UK) (65, 67, 74-83); and the recommended management of non-immune pregnant women exposed to rubella is inconsistent from state to state within Australia (12, 13, 84). The following account of the practices of these comparable high-income countries in 2013, and examination of possible reasons for the differences in practice formed the rationale for this thesis which was commenced around this time.

*Measles*

Measles is given ‘urgent’ public health priority status in Australia, with a reported suspected case resulting in immediate public health action (85). Susceptible contacts are offered vaccine if less than 72 hours have elapsed since first contact with the case and they are older than 9 months, are not pregnant and not immunosuppressed. If any of these conditions is not met, then NHIG is offered to susceptible contacts as post-exposure prophylaxis up until 6 days after first contact exposure (85).

In the UK, recommendations offer NHIG only to susceptible individuals who are immunosuppressed, pregnant or under the age of 12 months and recommend administration as soon as possible after contact with measles and up until 6 days post-exposure (76). In NZ, the national immunisation handbook recommends the use of NHIG for susceptible contacts for whom vaccination is contraindicated as soon as possible and up to six days after measles exposure (80). Similar to Australian recommendations, this includes all susceptible individuals identified more than 72 hours after exposure. However, advice for health professionals in the Auckland region recommends NHIG only for susceptible individuals who are immunosuppressed, pregnant or under the age of six months (83). The US recommends NHIG within six days of exposure to susceptible household or close contacts in whom the vaccine is contraindicated, or who haven’t been vaccinated within 72 of exposure, and particularly for individuals at greatest risk of complications (less than 12 months old, pregnant, or immunocompromised) (49, 74, 86).
Both the UK and NZ recommendations vary from Australian recommendations with respect to the dosage of NHIG for post-exposure measles prophylaxis. For example, Australian guidelines recommend 0.2 mL/kg for susceptible infants under the age of 9 months, where UK and NZ guidelines both recommend 0.6 mL/kg (76, 80, 85). The UK guidelines base the recommended dosages on the publication by Endo et al that identified 10.9 IU/kg as providing effective post-exposure prophylaxis (75, 87). The NZ guidelines reference the UK guidelines (75, 80). US guidelines are similar to, but not the same as Australian guidelines with respect to NHIG dosage for post-exposure measles prophylaxis. The US recommends 0.5 mL/kg for immunocompromised individuals and 0.25 mL/kg for others, with a maximum of 15 mL (49). Australia also recommends 0.5 mL/kg for immunocompromised individuals, but 0.2 mL/kg for others (85).

**Hepatitis A**

Hepatitis A is of high public health importance in Australia, with reported cases resulting in public health action within one working day (50). Susceptible contacts are offered post-exposure prophylaxis within two weeks of their last exposure to the case. Unless contraindicated, contacts are offered vaccination if they are over the age of one year, not immunosuppressed, and do not have chronic liver disease. NHIG is offered to infants, individuals who are immunosuppressed or have chronic liver disease, or for whom the vaccine is contraindicated (50).

UK recommendations reserve NHIG only in conjunction with Hepatitis A vaccine, and only for contacts aged 50 years or over, or with chronic liver disease or immunosuppression (88). NZ and US recommendations are the same as Australian recommendations, with the exception that NHIG is offered over vaccine to adults over the age of 40 years (80, 81).

Recommended doses of NHIG for hepatitis A post-exposure prophylaxis are difficult to compare across countries. Australian guidelines give recommended volume by weight categories (0.5 mL for <25 kg; 1.0 mL for 25-50 kg; 2.0 mL for >50 kg) (50). This is roughly similar to the NZ and US guidelines that recommend 0.02 mL/kg although these guidelines don’t give a maximum dose (80, 81). The UK Immunoglobulin Handbook notes that hepatitis A antibody levels in NHIG are lower than the WHO standard of 100 IU/mL and therefore recommended doses have been increased (77). The Handbook recommends 500 mg for individuals aged <10 years, and 750 mg for
individuals aged 10 years or more. They indicate that 750 mg is approximately 5mL (77).

Rubella
Rubella is not the subject of Australian national public health unit guidelines. The National Immunisation Handbook sets national recommendations on vaccination against rubella and does cover passive immunisation for rubella contacts. It states "Post-exposure prophylaxis with normal human immunoglobulin (NHIG) does not prevent infection in non-immune contacts and is, therefore, of little value for protection of susceptible contacts exposed to rubella" (89). Yet, the Handbook also states that NHIG may prolong the incubation period, which may reduce risk to the foetus, and if it is given it "might reduce - but will not eliminate - the risk for rubella" (89). The Handbook suggests 20ml of NHIG in divided doses if it is to be used.

State guidelines for rubella control differ. In Queensland, guidelines recommend referral of the non-immune exposed pregnant woman to her obstetrician for “frank” discussion of the risks and possible benefits of NHIG within 72 hours of exposure (90). Victorian guidelines suggest considering immunoglobulin after exposure to rubella in early pregnancy as “it may modify abnormalities in the baby” (91). New South Wales guidelines state that immunoglobulin has not been demonstrated to be of value post-exposure (84).

The UK Immunoglobulin Handbook indicates the use of NHIG for post-exposure rubella prophylaxis in non-immune pregnant women when termination of pregnancy for proved rubella infection is unacceptable (79). The Handbook suggests that NHIG “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”. It refers to guidelines on rashes in pregnancy for further information, but these guidelines do not contain any information about the use of NHIG in relation to rubella in pregnancy (92). UK Immunisation guidelines, “Immunisation against infectious disease – ‘The Green Book’”, offer similar conflicting advice, stating that: “It is not recommended for the protection of pregnant women exposed to rubella. It should only be considered when termination of pregnancy is unacceptable. Serological follow-up of recipients is essential…..To prevent or attenuate an attack: Dose: 750mg” (65 p359). This dose is approximately 5ml (79).
The NZ Immunisation Handbook suggests: “The routine use of immunoglobulin (IG) for post-exposure prophylaxis of rubella in early pregnancy is not recommended. It may be considered if termination of the pregnancy is not an option, but termination must be discussed for documented maternal infection. Although IG has been shown to reduce clinically apparent infection in the mother, there is no guarantee that foetal infection will be prevented” (80 p241). A recommended dose is not given.

The US Centres for Disease Control (CDC) suggest: “Immunoglobulin (IG) does not prevent rubella or mumps infection after exposure and is not recommended for that purpose. Administration of IG after exposure to rubella will not prevent infection or viremia, but might modify or suppress symptoms and create an unwarranted sense of security. Therefore, IG is not recommended for routine post-exposure prophylaxis of rubella in early pregnancy or any other circumstance. Infants with congenital rubella have been born to women who received IG shortly after exposure. Administration of IG should be considered only if a pregnant woman who has been exposed to rubella will not consider termination of pregnancy under any circumstances. In such cases, intramuscular administration of 20 mL of IG within 72 hours of rubella exposure might reduce --- but will not eliminate --- the risk for rubella” (67 p19).

1.7 Possible reasons for differences in practice circa 2013

Australia, NZ, UK and the US are similar countries in many ways (see Tables 1 and 2). They are all in the top 30 countries as listed by gross domestic product (GDP) per capita by the World Bank (93). They are all grouped as ‘high income’ countries by the World Health Organization for burden of disease reporting (94). The UK, Australia and NZ have similar spending on health, both as a percentage of GDP and per capita, according to Organisation for Economic Co-Operation and Development (OECD) data (95). The United States spends roughly twice that of these other countries on health. Population health status, as measured by life expectancy at birth (95), infant mortality (95) and rates of all cause disability adjusted life years (96) is similar. The contribution of communicable and non-communicable diseases to each country’s burden of disease is also similar (96).

However, the health systems differ considerably, particularly in terms of financing and the roles of government (97, 98). The populations also differ in terms of ethnic groups and their proportions, although the majority of each country’s population is white (99). While there is no evidence to suggest that ethnicity should be a factor in the efficacy or
safety of post-exposure passive immunisation, these differences may have some implications in terms of applying some evidence in a local setting. Generally though, it seems reasonable to conclude that these countries have common relevant medical literature with regards to the public health management of communicable diseases.

Table 1. Expenditure on Health of Four Developed Countries, 2009 (95)

<table>
<thead>
<tr>
<th>Health Expenditure</th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Percentage of Gross Domestic Product</td>
<td>9.1</td>
<td>9.8</td>
<td>17.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Per capita (US$)</td>
<td>3670</td>
<td>3379</td>
<td>7990</td>
<td>2923</td>
</tr>
</tbody>
</table>

Table 2. Overall Population Health of Four Developed Countries

<table>
<thead>
<tr>
<th>Marker of Population Health</th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Life expectancy at birth (F/M) 2010 (95)</td>
<td>84.0 / 79.5</td>
<td>82.6 / 78.6</td>
<td>81.1 / 76.2</td>
<td>82.8 / 79.1</td>
</tr>
<tr>
<td>Infant mortality (deaths per 1000 live births) 2009 (95)</td>
<td>4.3</td>
<td>4.6</td>
<td>6.4</td>
<td>5.2</td>
</tr>
<tr>
<td>Age standardised DALYs per 100 000 all causes 2004 (96)</td>
<td>9894</td>
<td>11012</td>
<td>12844</td>
<td>10642</td>
</tr>
<tr>
<td>Age standardised DALYs per 100 000 Infectious and parasitic diseases 2004 (96)</td>
<td>155</td>
<td>187</td>
<td>330</td>
<td>144</td>
</tr>
<tr>
<td>Age standardised DALYs per 100 000 non-communicable diseases 2004 (96)</td>
<td>8222</td>
<td>9576</td>
<td>10481</td>
<td>8831</td>
</tr>
</tbody>
</table>

Available evidence suggests that access to NHIG is also similar. Each of these countries has one or more national blood collection programs (100-104) and collection rates are all at least 30 donations per 1000 population (105), although, the UK imports plasma for the production of NHIG because of the theoretical risk of bovine spongiform encephalitis transmission (106, 107). Two different practice manuals in the UK suggest NHIG is readily available from pharmacies and through the Health Protection Agency (76, 106). A June 2012 presentation to the Advisory Committee on Immunization Practices Meeting suggested that intramuscular immunoglobulin is readily available in the US, although distribution is sometimes an issue (108). New Zealand reports self-sufficiency in terms of blood and plasma products (107, 109). Australia too, is able to meet demands for NHIG locally (107, 110).
Other possible reasons for the differences in the practice of passive immunisation for controlling these communicable diseases may include: differing incidences of disease resulting in different public health resource implications; differing levels of immunity to the particular diseases in the population resulting in different public health resource implications; practice based on local expert opinion rather than the evidence because of a lack of available systematic reviews of the evidence or a lack of evidence of sufficient quality; differing local evidence of the cost effectiveness of the intervention for one or more of the diseases; or, differing levels of disease-specific antibodies in the blood product/s used for passive immunisation having practical implications at the point of delivery. Each of these possible reasons is examined below.

Firstly, Australia, NZ, US and UK all have low incidences of these diseases (37, 78, 80, 82, 88, 111) (Table 3). While some variation in rates exists across countries, and from year to year within countries, the differences do not appear to be large enough to impact significantly on the resources required for the public health management of these conditions in these affluent countries.

Secondly, differences in population immunity are unlikely to contribute to differing public health management recommendations for these diseases.

Each of these countries has a similar immunisation schedule for these diseases, with the exception of the US where Hepatitis A vaccine is included on the childhood immunisation schedule for all children in addition to the MMR vaccine (Table 3) (80, 112-114). MMR vaccine coverage rates are high in each country at around 90% of the target population (111).

Hepatitis A population immunity is similar (Table 3), with low proportions of children and higher proportions of adults seropositive, but many adults still susceptible (51). A study estimating overall seroprevalence in 2005 based on published figures reported very similar age-specific seroprevalence distributions across these countries (115).

Measles immunity is similar, with 94% of the Australian population immune in 2002 (116), 96% of the US population aged 6 to 49 years immune in 1999-2004 (117), 94% of the NZ population aged 6 to 44 years immune in 2009 (118), and more than 90% of UK adults immune in 2000 (119). Age-specific seroprevalence distributions are also similar, with high proportions of all age groups immune subsequent to the second MMR scheduled dose.
Rubella immunity is similar with 94% of the Australian adults aged 19 to 49 years immune in 1997-1998 (69) and 94% of Victorians age 1 to 55 years immune in 2002 (120), 91% of the US population aged 6 to 49 years immune in 1999-2004 (121), 92% of the NZ population aged 6 to 44 years immune in 2009 (118), and over 90% of the UK population aged greater than 3 years immune in 1994-1998 (122). Age-specific and sex-specific seroprevalence distributions (when available) were also similar, with lower proportions of adult males than females immune, but high proportions of all age groups immune subsequent to the second MMR scheduled dose.
<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>0.31/10</td>
<td>0.71/10</td>
<td>0.023/10</td>
<td>0.98/10</td>
</tr>
<tr>
<td>Vaccine Schedule</td>
<td>12 mths &amp; 4 yrs</td>
<td>13 mths &amp; 3-5 yrs</td>
<td>12 mths &amp; 4 yrs</td>
<td>12 mths &amp; 4 yrs</td>
</tr>
<tr>
<td>Vaccine Coverage</td>
<td>88% 2 vaccines</td>
<td>90% 1 vaccine</td>
<td>91% 1 vaccine</td>
<td>91% 1 vaccine</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>88% 2 vaccines</td>
<td>90% 1 vaccine</td>
<td>91% 1 vaccine</td>
<td>91% 1 vaccine</td>
</tr>
<tr>
<td>Serosurvey Evidence of Immunity</td>
<td>94% (all ages) 1998</td>
<td>30.7% (all ages) in England 1996</td>
<td>34.9% (6+ yrs) 1999-2006</td>
<td>27.9% (adults 18+ yrs) 1996</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>94% (all ages) 1998</td>
<td>30.7% (all ages) in England 1996</td>
<td>34.9% (6+ yrs) 1999-2006</td>
<td>27.9% (adults 18+ yrs) 1996</td>
</tr>
<tr>
<td>Antibody Level in NHIG</td>
<td>≥100 IU/mL as per European Pharmacopeia (pers comm D. Maher, CSL)</td>
<td>60.3-68.8 IU/ml (68)</td>
<td>≥100 IU/mL as per European Pharmacopeia (pers comm D. Maher, CSL)</td>
<td>2100 IU/ml as per European Pharmacopeia</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>Australia</th>
<th>UK</th>
<th>USA</th>
<th>NZ</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serosurvey Evidence of Immunity</td>
<td>18-24 mths (113) high risk areas at 18-4 yrs</td>
<td>All children at 18 mths</td>
<td>Not on Childhood Immunisation Schedule (8)</td>
<td>Indigenous children in high risk areas at 12 &amp; 18-24 mths (113)</td>
</tr>
</tbody>
</table>

### Table 3: Comparison of Four Developed Countries on Disease-Specific Possible Reasons for Differences in Passive Immunisation Practices

- **Measles**
- **Hepatitis A**
- **Rubella**
<table>
<thead>
<tr>
<th>Antibody level in</th>
<th>NHIC Immunity evidence of Serosurvey</th>
</tr>
</thead>
<tbody>
<tr>
<td>1997-98 (69)</td>
<td>94% aged 19-44 yrs</td>
</tr>
<tr>
<td>1994-98 (122)</td>
<td>91% aged 6-49 yrs</td>
</tr>
<tr>
<td>1999-2009 (118)</td>
<td>&lt; 90% aged ≥3 yrs</td>
</tr>
<tr>
<td>2009</td>
<td>≥92% aged 6-44 yrs</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
<tr>
<td>Unknown</td>
<td>Unknown</td>
</tr>
</tbody>
</table>
Evidence for the effectiveness and cost effectiveness of passive immunisation for the prevention of measles, hepatitis A and rubella

There is a lack of systematic review evidence of the effectiveness of passive immunisation for the prevention of measles. Ramsay et al (75) cite a number of observational studies and one controlled study as evidence of the effectiveness of post-exposure prophylaxis with NHIG for preventing measles. So too, Zingher’s presentation to the Pediatrics Section of the New York Academy of Medicine in 1924 cites a number of early studies (9). Neither of these publications claims to be a systematic review and certainly not all current relevant studies are included. For example, Harper et al (133) report on an observational study of children aged one to six years demonstrating increasing efficacy of post-exposure passive immunisation with shorter duration between exposure and intervention. And Sheppeard et al (134) assessed the effectiveness of post-exposure prophylaxis during a measles outbreak in Australia in 2006, finding the effectiveness of NHIG to be 75.8%. In addition, critical appraisal of the evidence is essential to form appropriate conclusions. For example, Ramsay et al (75) cited King et al (135) and their finding that post-exposure NHIG had an efficacy of only 8% during the 1990 measles epidemic in the US, but did not consider that their analysis was based on observational data comparing children with an average age of 9 months who did not receive NHIG to children with an average age of 11 months who did receive NHIG. While the difference in mean age between the groups was not statistically significant, it requires consideration that persisting maternal antibodies in the control group may have decreased the attack rate in that group, artificially decreasing the calculated efficacy. While it is generally accepted that post-exposure prophylaxis with NHIG for measles is effective, a systematic review would help to clarify the degree of effectiveness and may help to answer the question of a minimum effective dose.

There is a lack of systematic review evidence of the effectiveness of passive immunisation for the prevention of rubella. Further, the evidence on which public health practice is based with regard to non-immune pregnant rubella contacts is limited and somewhat contradictory. The UK guidelines do not reference the statement that “there is no evidence that it is effective” (referring to using NHIG for post-exposure prophylaxis for pregnant women) (65 p359). The Australian Immunisation Handbook references the US guidelines for each of the statements about post-exposure passive immunisation for rubella (89). These Australian guidelines state that post-exposure passive immunisation "does not prevent infection in non-immune contacts" (89).
Whereas, the NZ guidelines state that “IG has been shown to reduce clinically apparent infection in the mother”, but do not reference this statement (80 p241). The US guidelines provide two references at the end of the paragraph on post-exposure passive immunisation against rubella (74). 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 (136). The other is a book chapter that does not include in-text citations (137). It states that: “Immune globulin may reduce clinical findings, but does not prevent viraemia”. There is no indication of the dose of immune globulin, anti-rubella IgG concentration, or timing of administration to which this statement is referring. The statement conflicts with the study by Schiff (136) (the other reference used in the US guidelines) that concluded viraemia was prevented with high dose immunoglobulin. Waagner’s book chapter (137) 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 immune globulin given post-exposure won’t prevent viraemia, the author reasons that asymptomatic infection may occur in the mother post immune globulin, anti-rubella antibody titres in immune globulin vary, and there have been infants born with CRS despite post-exposure prophylaxis with immune globulin. Again, each of these points is unreferenced. The author does not consider the possibility of detecting asymptomatic infection in the women post immune globulin 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 NHIG or immunoglobulins generally for preventing rubella in non-immune exposed pregnant women. Schiff and other literature from the 1970s and earlier draws varying conclusions, but may indicate a degree of efficacy (1, 136, 138-146). Small numbers of participants in each of these studies, and the varying conclusions highlight the benefits that would be gained from a systematic review on the topic. As in Schiff’s study, levels of rubella-specific antibodies in NHIG will need to be considered when forming conclusions, as they are likely to be lower in today’s product given the much lower current-day disease incidence.

Two systematic reviews of passive immunisation for the prevention of hepatitis A have been published. Liu et al (147) completed a Cochrane review on immunoglobulins for
preventing hepatitis A published in 2009. They looked at passive immunisation for both pre and post-exposure prophylaxis. They included only randomised controlled trials, of which there were two examining post-exposure prophylaxis. Mosley et al (148) examined two different immunoglobulin products from the same manufacturer, produced at different times, versus placebo, finding one to be effective and the other not. The anti-HAV IgG content of the products was not identified. Victor et al (149) compared immunoglobulin and vaccine, finding both were equally efficacious for susceptible contacts aged two to 40 years. Again, the anti-HAV IgG content of the blood product used was not identified. However, this information is published in the UK hepatitis A public health guidelines (150). That document identifies that the immunoglobulin product used in the trial by Victor et al contained 18.83 IU/mL of anti-HAV IgG. The two included trials in this Cochrane review (147) were clearly unable to be combined in meta-analysis.

Bianco et al (151), published a review in 2004 that also examined immunoglobulins for both pre and post-exposure prevention of hepatitis A. They included only randomised controlled trials, of which there were two examining post-exposure prophylaxis. These authors also included Mosley et al’s study (148). The second included study was a quasi-randomised multi-centre controlled trial that reported post-exposure prophylaxis with British immunoglobulin to be effective (152). Again, the anti-HAV IgG content of the blood product used was not identified. The review by Bianco et al combined these two trials in meta-analysis to give an overall effectiveness estimate of 69% (151). Considering when the two trials were published, however, the products used in the interventions may have contained higher concentrations of anti-HAV IgG than today’s NHIG.

The UK guidelines for the public health management of hepatitis A include a summary of the evidence base for post-exposure prophylaxis with NHIG (88). This is not identified as a systematic review. The guidelines cite a number of randomised and non-randomised controlled trials and observational studies. Critique of the methods of these studies is not included. The guidelines point out the varying estimates of effectiveness of post-exposure NHIG for the prevention of hepatitis A from early studies, but go on to estimate the efficacy of NHIG using data from Victor et al’s recent study (149) at 84%. The NHIG used in that study had a hepatitis A antibody concentration of 18.83 IU/mL and was administered at dose 0.02 mL/kg. However, the UK guidelines note that the minimum effective dose of hepatitis A antibodies for preventing infection is unknown.
Given the lack of systematic review evidence of post-exposure passive immunisation for the prevention of measles and rubella, it is not surprising that the cost effectiveness of this intervention for these diseases has not been considered in the medical literature. One study estimated the costs of the public health response to a single measles case who had flown in a passenger aircraft whilst infectious at US$142 452 (153). The response in this case was not reported to include passive immunisation. No estimate of cost per case prevented was given. A health service reported measles containment costs additional to those of case hospitalisation during a community outbreak of measles to be AU$10 339 for the 17 patients (12 episodes) seen at their facility (154). They estimated AU$825 for “readmitting patients and administering immunoglobulin”. Again, no cost per case prevented was calculated, or could be calculated from the information given.

More consideration has been given to the cost effectiveness of post-exposure passive immunisation for preventing hepatitis A, although evidence is limited from US, UK, NZ or Australian settings. Analysis of a cohort of visitors to a National Park in the US where drinking water had been contaminated by sewage revealed an attack rate of hepatitis A of 0.23% in those who did not receive post-exposure immune globulin and 0% for those who did (155). The authors extrapolated these figures, and estimated costs to consider the cost benefit of providing immune globulin to all park visitors possibly exposed during the contamination. They determined that this would not have been cost-beneficial. Pavia et al (156) reported on the effects and costs of a mass campaign to passively immunise the residents in a religious community in the US during a hepatitis A outbreak. The attributable risk reduction measured post intervention was 33.8 / 1000 over a seven-month period. In the intervention group of 2 249 people, the number of cases prevented was therefore 76, and the cost per case prevented can be calculated as US$47.63. The costs reported did not include staffing costs as immunisers mostly worked on a volunteer basis. Gillis et al (157) compared the cost effectiveness of the Israeli Defence Forces program of passive immunisation against hepatitis A, that includes both pre and post-exposure prophylaxis, with active hepatitis A vaccination. The cost per case prevented by passive immunisation depended on the incidence of disease assumed, the duration of service, and the state of living conditions. It ranged from US$48.53 to US$810.78. A cost-benefit analysis of passive immunisation of children and pregnant women in Israel in response to faecal contamination of a water supply did not support the practice (158). The cost to prevent one child case was estimated as US$362.50, and the cost to prevent one case among
pregnant women was estimated as US$11,514. Particularly notable in this study was the assumptions made about the attack rates in the subject populations and the accompanying lack of sensitivity analysis.

The most recent of these investigations was published in 2000, and no examination of the cost effectiveness of post-exposure passive immunisation for the prevention of hepatitis A has been undertaken in Australia, NZ or the UK.

**Disease-specific levels of antibodies in NHIG and IVIG**

World Health Organization guidelines recommend measuring antibody levels against one species of bacteria and one virus in each batch of immunoglobulins produced to ensure adequate efficacy (22).

The Australian product information for NHIG indicates the product contains 160 mg/mL of human plasma proteins, mainly immunoglobulin G (IgG). However, the disease-specific levels of IgG in NHIG are not listed. CSL Behring Australia Ltd. (pers comm: Darryl Maher, Senior Director, Medical and Research, CSL Behring Australia) confirmed that NHIG is manufactured to the European Pharmacopeia standard for Hepatitis A antibodies of 100 IU/mL (159). Blood donors with likely high levels of hepatitis A antibodies are specifically selected for the NHIG pool. Each batch of NHIG is tested to ensure the concentration of anti-hepatitis A antibodies is at least 100 IU/mL. The average anti-hepatitis A antibody levels in Australian NHIG have varied over time as seen in Figure 1. Testing and production processes have not changed over this time, so variation is most likely to be due to variation in anti-hepatitis A antibody levels in the donor pools used (pers comm: Joe Bertolini, Research and Development Manager, CSL Behring Australia). Measles and rubella antibody levels are not routinely measured in the product (pers comm: Darryl Maher, Senior Director, Medical and Research, CSL Behring Australia).
CSL Behring Australia Ltd. also manufactures NHIG for NZ, using NZ plasma donations. The manufacturing process is identical to that of Australian NHIG and the European Pharmacopeia standard for hepatitis A antibodies is applied (pers. comm. Darryl Maher, Senior Director, Medical and Research, CSL Behring Australia). The NHIG product used for hepatitis A post-exposure prophylaxis in the UK was determined to contain anti-hepatitis A antibody levels between 60.3 and 86.8 IU/mL in 2008 (88). The UK report altering the public health guidelines for the management of hepatitis A in response to this (88). The anti-hepatitis A antibody levels in US NHIG has been reported to vary by batch, but no range was given (82). Changes to US hepatitis A recommendations were made in 2007 in light of new evidence about post-exposure vaccination, but not hepatitis A antibody levels in NHIG (81, 82).

The UK and NZ published measles-specific antibody levels in their NHIG products in 2009 and 2011, with concentrations of 23 to 39 IU/mL and 14-16 IU/mL respectively (75, 83). The UK measured antibody levels by plaque neutralisation, while the methodology for measuring the NZ antibody levels is not identified. Different testing methods may account for some of the difference between countries (160). Both the UK and at least one NZ region report adjusting the public health management of measles
in response to this (75, 83). They base their adjusted dosage recommendations on the study by Endo et al that identified anti-measles antibody levels between 16 and 45 IU/mL as measured by haemagglutination inhibition in commercially available preparations of NHIG in Japan in 1999 and 2000 (87). The US manufactures NHIG standardised to a reference lot for measles antibodies (123).

No published levels of anti-rubella antibodies in NHIG were identified. Further, no published levels of disease-specific antibodies in Australian or NZ IVIG were identified. A number of researchers have measured disease-specific antibodies in IVIG products elsewhere.

Matejtschuk et al (161) report varying anti-rubella antibodies in a number of IVIG products as measured by a commercially available enzyme-linked immunosorbent assay (ELISA) kit. Those derived from UK donors contained an average of 1055 IU/mL, whereas those derived from US donors averaged between 630 and 670 IU/mL. Three other products of unidentified origin contained average anti-rubella antibody levels of 303-1319 IU/mL.

Levels of anti-hepatitis A antibodies in IVIG products vary considerably by region, but seem to have declined over time. Matejtschuk et al (161) used commercial ELISA kits to measure anti-hepatitis A antibodies in IVIG manufactured from UK donors at 32 IU/mL, and manufactured from US donors at 20-24 IU/mL. These authors also examined disease-specific antibody levels in three other IVIG products of unidentified origin, reporting anti-hepatitis A antibodies of between 29 and 46 IU/mL. The year of sample collection is not given, but the results were submitted for publication in 2001. Simon and Spath (162) report average anti-hepatitis A antibody levels in IVIG derived from European donors at 30.2 IU/mL and derived from US donors at 15.8 IU/mL. The method of measurement is not identified, nor is the year the samples were obtained. The results were reported in 2003. Farcet et al (163) used ELISA to measure anti-hepatitis A antibodies in IVIG derived from European donors at 22.91 IU/mL and derived from US donors at 14.6 IU/mL. The samples tested were manufactured between 2005 and 2007.

Anti-measles antibody levels in IVIG are also highly variable. Matejtschuk et al (161) report average anti-measles antibodies in IVIG derived from UK donors of 27 IU/mL, and in IVIG derived from US donors of 16-19 IU/mL. The three other IVIG products (of unidentified origin), also tested by ELISA, had average anti-measles antibody levels of
Simon and Spath report average anti-measles antibody levels in IVIG derived from European donors of 32.8 IU/mL, and derived from US donors of 31.1 IU/mL (162). The method of measurement is not identified. Products from three different manufacturers used in the UK were found to contain anti-measles antibodies between four and 34 IU/mL as measured by plaque neutralisation in 2009 (75).

1.8 Conclusions circa 2013

Passive immunisation still plays an important role in the control of communicable diseases in the developed world, including in Australia. There are current differences in practice with respect to passive immunisation for measles, hepatitis A and rubella between Australia and other developed countries.

It seems likely that relevant medical literature, and access to NHIG are similar across Australia, NZ, the UK and the USA. Disease incidence and population immunity levels are unlikely to account for the differences in the practice of passive immunisation for the public health management of these diseases. As very limited global evidence exists about the cost effectiveness of post-exposure passive immunisation for preventing these diseases, it is also unlikely that local evidence of cost effectiveness accounts for the differences in practice. Each of the countries guidelines that have been examined already recommend passive immunisation post-exposure for these diseases, inherently indicating passive immunisation effectiveness and cost effectiveness is already accepted in these settings. However, the remaining gaps in evidence in these areas may lead to reliance on expert opinion to some extent and this may be one of the drivers behind practice differences.

In relation to the evidence of effectiveness, systematic review evidence on the effectiveness of passive immunisation for preventing hepatitis A exists, but there is no systematic review evidence of the effectiveness of passive immunisation for preventing measles or rubella. Questions about the minimum effective doses of NHIG as post-exposure prophylaxis for each disease are also unanswered.

The disease-specific antibody content of NHIG varies considerably across these countries and over time and may be another driver of passive immunisation practice differences. Decreasing levels of some disease-specific antibody levels in NHIG has been reported to be the reason behind some recent changes to practice in the UK and
NZ. Anti-measles IgG and anti-rubella IgG levels in Australian NHIG are currently unknown.

Together with the practical implications of differences in the health system structures, incomplete evidence of effectiveness including a lack of evidence on minimum effective doses, and the disease-specific antibody concentrations in local NHIG products could well account for the differences in practice across these countries.

The studies within this thesis will therefore seek to fill the gaps in the evidence base for the effectiveness of post-exposure passive immunisation for the prevention of measles, and rubella, measure the anti-measles and anti-rubella IgG levels in Australian NHIG, and estimate the minimum effective doses of disease-specific antibodies required to prevent these diseases; ultimately providing evidence-based recommendations and associated cost implications for national public health practice in Australia.

1.9 Aims and Objectives

Aim: To inform public health practice recommendations in Australia with regards to passive immunisation for contacts of measles, hepatitis A and rubella.

Objectives:

1. To systematically review the existing evidence for the effectiveness of passive immunisation as used in the public health management of measles, and rubella.
2. To ascertain the current levels of IgG against measles and rubella in the blood products NHIG and IVIG in Australia.
3. To estimate the minimum effective doses of disease-specific antibodies when injected to prevent each disease.
4. To identify the quantity of NHIG used for the public health management of communicable disease in Queensland and Australia over the past decade.
5. To identify the cost implications of any changes to practice recommended in light of fulfilment of objectives 1-4.

1.10 Methodology

Detailed methods for each study are presented in the relevant chapters. The following is an overview of the methodologies used to meet the above objectives.
1. Systematic reviews were conducted according to the Cochrane methodology on the effectiveness of passive immunisation in the public health management of measles, and rubella.

2. In collaboration with CSL Behring (Australia) Pty Ltd anti-measles and anti-rubella antibody levels in samples of NHIG and IVIG were measured using the plaque-reduction neutralisation test and a chemiluminescent immunoassay respectively.

3. Published data on the pharmacokinetics of IgG, and information gained on the concentrations of disease-specific antibodies in Australian NHIG were used to model the minimum effective doses of injected disease-specific antibodies for preventing each disease. The model was compared to interim data from a randomised controlled clinical trial that measured serum concentrations of hepatitis A antibodies after dosing according to current practice and dosing according to the model.

4. Routinely collected data were analysed to describe the use of NHIG in the public health management of communicable diseases in Queensland over a decade. National NHIG order data were obtained from the National Blood Authority according to availability. This was for the time period June 2014 to December 2016 inclusive. These data were also descriptively analysed and compared to the Queensland data.

5. Estimates of the cost of production and distribution of NHIG and IVIG were sourced from publicly available documents and CSL Behring (Australia) Pty Ltd. A budget impact analysis was conducted for the recommended changes to practice that were based on the results from objectives 1 to 3, given the information obtained under objective 4.

Ethical approval was sought and granted for studies under objectives 3 and 4. The Griffith University Human Research Ethics Committee and the Red Cross Blood Service Ethics Committee approved the clinical trial that contributed to objective 3. Letters of approval are found in Appendix 1. The Griffith University Human Research Ethics Committee and the Queensland Health Ethics Committee approved the descriptive study that contributed to objective 4. Letters of approval are found in Appendix 1.
Chapter 2  The effectiveness of passive immunisation for preventing measles

Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Drafting the protocol and finalising the protocol together with my co-authors. Obtaining copies of the studies and selecting studies for inclusion in the review independently from a co-author then coming to consensus with my co-author on included studies; extracting the data from included studies and assessing the risk of bias in the studies independently from a co-author and then coming to consensus with my co-author; entering the data and, with my co-author, analyzing and interpreting the analysis. Drafting the review manuscript and with my co-authors completing the final review.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
As one of the potential drivers of differences in post-exposure passive immunisation practice among high income countries was identified as the lack of systematic review evidence of effectiveness and the lack of evidence of minimum effective doses of immunoglobulin for this purpose, the following Cochrane review was conducted. It examined the existing evidence of effectiveness of post-exposure passive immunisation for the prevention of measles among contacts of cases.
Post-exposure passive immunisation for preventing measles
(Review)

Young MK, Nimmo GR, Cripps AW, Jones MA

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2014, Issue 4

http://www.thecochranelibrary.com

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
# TABLE OF CONTENTS

- **HEADER** ......................................................... 1
- **ABSTRACT** .................................................... 1
- **PLAIN LANGUAGE SUMMARY** .................................. 2
- **SUMMARY OF FINDINGS FOR THE MAIN COMPARISON** ....... 4
- **BACKGROUND** .................................................. 8
- **OBJECTIVES** ................................................... 9
- **METHODS** .................................................... 9
- **RESULTS** ........................................................ 12
  - Figure 1. ....................................................... 14
  - Figure 2. ....................................................... 17
- **ADDITIONAL SUMMARY OF FINDINGS** ......................... 21
- **DISCUSSION** .................................................. 26
- **AUTHORS' CONCLUSIONS** ..................................... 26
- **ACKNOWLEDGEMENTS** .......................................... 27
- **REFERENCES** .................................................. 30
- **characteristics of studies** ................................... 48
- **Data and analyses** ............................................. 49
  - Analysis 1.1. Comparison 1 Immunoglobulin versus no treatment, Outcome 1 Measles cases. ................. 49
  - Analysis 1.2. Comparison 1 Immunoglobulin versus no treatment, Outcome 2 Measles cases. ................. 50
  - Analysis 1.3. Comparison 1 Immunoglobulin versus no treatment, Outcome 3 Measles cases. ................. 52
  - Analysis 1.4. Comparison 1 Immunoglobulin versus no treatment, Outcome 4 Mortality due to measles. .... 53
  - Analysis 1.5. Comparison 1 Immunoglobulin versus no treatment, Outcome 5 Complications due to measles. 54
  - Analysis 2.1. Comparison 2 Gamma globulin versus serum, Outcome 1 Measles cases. ......................... 55
- **APPENDICES** .................................................... 55
- **Contributions of authors** ..................................... 58
- **Declarations of interest** ....................................... 58
- **Sources of Support** ............................................ 58
- **Differences between protocol and review** .................... 59

---

Post-exposure passive immunisation for preventing measles (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
[Intervention Review]

Post-exposure passive immunisation for preventing measles

Megan K Young1, Graeme R Nimmo2, Allan W Cripps3, Mark A Jones4

1School of Medicine, Griffith Health Institute, Griffith University, Meadowbrook, Australia. 2Department of Microbiology, Pathology Queensland, Brisbane, Australia. 3Griffith Health, Griffith University, Gold Coast, Australia. 4School of Population Health, The University of Queensland, Brisbane, Australia

Contact address: Megan K Young, School of Medicine, Griffith Health Institute, Griffith University, University Drive, Meadowbrook, Queensland, 4121, Australia. megan.young@griffith.edu.au.

Editorial group: Cochrane Acute Respiratory Infections Group.


Review content assessed as up-to-date: 14 August 2013.

Citation: Young MK, Nimmo GR, Cripps AW, Jones MA. Post-exposure passive immunisation for preventing measles. Cochrane Database of Systematic Reviews 2014, Issue 4. Art. No.: CD010056. DOI: 10.1002/14651858.CD010056.pub2.

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

A B S T R A C T

Background
Measles outbreaks continue to occur in countries with high vaccination coverage. Passive immunisation is generally considered to prevent measles in someone who is not immune and has been exposed to infection. Estimates of effectiveness have varied and no minimum effective dose has been determined.

Objectives
To assess the effectiveness and safety of intramuscular injection or intravenous infusion of immunoglobulins (passive immunisation) for preventing measles when administered to exposed susceptible people before the onset of symptoms.

Search methods

Selection criteria
We included randomised controlled trials (RCTs), quasi-RCTs and prospective, controlled (cohort) studies if: participants were susceptible and exposed to measles, polyclonal immunoglobulins derived from human sera or plasma were administered intramuscularly or intravenously as the only intervention in at least one group and the number of subsequent measles cases was measured. We excluded studies of other sources of immunoglobulins.

Data collection and analysis
Two authors independently extracted data and critically appraised the included studies. We attempted to contact study authors for missing information. We described the results of studies not included in meta-analyses.

Main results
We included one RCT, two quasi-RCTs and 10 cohort studies (3925 participants). No studies were rated as low risk of bias for all criteria. Critical appraisal was constrained by a lack of information in most studies. The overall quality of the evidence was moderate. Seven studies (1432 participants) assessed cases of measles after immunoglobulin versus no treatment. Heterogeneity was explained by subgrouping according to the blood product used as an approximation of dose of immunoglobulin. When given within seven days of
exposure, immunoglobulins were effective at preventing measles: gamma globulin (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.08 to 0.36), convalescent serum (RR 0.21, 95% CI 0.15 to 0.29 to RR 0.49, 95% CI 0.44 to 0.54) and adult serum (RR 0.52, 95% CI 0.45 to 0.59). The differences in the effectiveness of different blood products were supported by studies not included in the meta-analysis and by two studies (702 participants) that found gamma globulin more effective than serum (RR 0.56, 95% CI 0.46 to 0.69).

Based on three studies (893 participants) immunoglobulin was effective at preventing death due to measles compared to no treatment (RR 0.24, 95% CI 0.13 to 0.44).

Two studies included measles vaccine alone among the intervention groups. Meta-analysis could not be undertaken. Both studies suggested the vaccine was more effective than gamma globulin.

No serious adverse events were observed in any of the included studies, although reporting of adverse events was poor overall. Non-serious adverse events included transient fever, rash, muscle stiffness, local redness and induration.

**Authors’ conclusions**

Passive immunisation within seven days of exposure is effective at preventing measles, with the risk for non-immune people up to 83% less than if no treatment is given. Given an attack rate of 45 per 1000 (per the control group of the most recent included study), gamma globulin compared to no treatment has an absolute risk reduction (ARR) of 37 per 1000 and a number needed to treat to benefit (NNTB) of 27. Given an attack rate of 759 per 1000 (per the attack rate of the other included study assessing gamma globulin), the ARR of gamma globulin compared to no treatment is 629 and the NNTB is two.

It seems the dose of immunoglobulin administered impacts on effectiveness. A minimum effective dose of measles-specific antibodies could not be identified.

Passive immunisation is effective at preventing deaths from measles, reducing the risk by 76% compared to no treatment. Whether the benefits of passive immunisation vary among subgroups of non-immune exposed people could not be determined.

Due to a paucity of evidence comparing vaccine to passive immunisation, no firm conclusions can be drawn regarding relative effectiveness.

The included studies were not specifically designed to detect adverse events.

Future research should consider the effectiveness of passive immunisation for preventing measles in high-risk populations such as pregnant women, immunocompromised people and infants. Further efforts should be made to determine the minimum effective dose of measles-specific antibodies for post-exposure prophylaxis and the relative effectiveness of vaccine compared to immunoglobulin.

**PLAIN LANGUAGE SUMMARY**

Antibodies for preventing measles after exposure

People who have had measles, or measles vaccine, have antibodies against the virus in their blood that protect them from developing measles should they come into contact with it. These antibodies can be extracted from blood donated by these individuals.

If people without antibodies come into contact with someone who is contagious with measles, they are likely to contract the disease. Measles is usually debilitating and can have serious consequences including death, so preventing it is desirable. One way of preventing measles in this group, when they do come into contact with a contagious person, is to inject them with antibodies that have been extracted from blood donations. This has been practised since the 1920s, but measures of its effectiveness have varied and the minimum amount of antibodies that we can give to prevent measles is unknown.

Based on seven studies (1432 people), of overall moderate quality, injecting antibodies into a muscle of people who came into contact with measles, but lacked their own antibodies, was effective at preventing them catching the disease compared to those who received no treatment. Using the modern day antibody preparation, people were 83% less likely to develop measles than those who were not treated. It was very effective at preventing them developing complications if they did contract measles and very effective at preventing death. The included studies generally did not intend to measure possible harms from the injections. Minor side effects were reported, such as muscle stiffness, redness around the injection site, fever and rash. Importantly, only two studies compared the measles vaccine with the antibody injection in this group of people, so no firm conclusions could be drawn about the relative effectiveness of these interventions.
The antibody injection is often recommended for pregnant women, infants and immunocompromised people (if they do not have their own antibodies to measles and come into contact with someone who is contagious with measles). The included studies did not include these groups of people, so it is unknown whether the effectiveness of antibody injections is different for them. We were also unable to identify the minimum dose of antibodies required as only one study measured the specific amount of measles antibodies in the injections and one other study estimated this figure; the results of these two studies were not consistent.

The evidence is current to August 2013.
### Summary of Findings for the Main Comparison

**Immunoglobulin compared to no treatment for preventing measles**

**Patient or population:** Susceptible people exposed to measles

**Settings:** Community and hospitals

**Intervention:** Immunoglobulin

**Comparison:** No treatment

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>Measles cases - convalescent serum</td>
<td></td>
<td>RR 0.21</td>
<td>181 per 1000 (129 to 250)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.15 to 0.29</td>
<td>(3 studies)</td>
<td>⬤⃝moderate (1, 3, 5, 6)</td>
<td></td>
</tr>
<tr>
<td>Measles cases - adult serum</td>
<td></td>
<td>RR 0.52</td>
<td>447 per 1000 (387 to 507)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.45 to 0.59</td>
<td>(2 studies)</td>
<td>⬤⃝moderate (1, 7, 9)</td>
<td></td>
</tr>
<tr>
<td>Measles cases - gamma globulin</td>
<td></td>
<td>RR 0.17</td>
<td>472 per 1000 (408 to 535)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.08 to 0.36</td>
<td>(2 studies)</td>
<td>⬤⃝moderate (3, 11, 12)</td>
<td></td>
</tr>
<tr>
<td>Mortality due to measles</td>
<td></td>
<td>RR 0.24</td>
<td>34 per 1000 (19 to 62)</td>
<td>High (1, 7)</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.13 to 0.44</td>
<td>(3 studies)</td>
<td>⬤⃝moderate (1, 7, 13)</td>
<td></td>
</tr>
<tr>
<td>Complications due to measles</td>
<td></td>
<td>RR 0.18</td>
<td>10 per 1000 (5 to 18)</td>
<td>Moderate</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>0.05 to 0.6</td>
<td>(3 studies)</td>
<td>⬤⃝moderate (3, 4, 5, 6)</td>
<td></td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td>Not estimable</td>
<td>0 (0)</td>
<td>See comment</td>
<td></td>
</tr>
</tbody>
</table>

Adverse events were poorly reported or not measured in all but one study comparing immunoglobulins and no treatment. No serious adverse events were reported.13
Post-exposure passive immunisation for preventing measles

The effect size in this case. We rated measurement bias as low risk for confounding would have decreased the effect size. We rated measurement bias as unclear for one study and this may have increased the effect size, measurement bias may have increased the effect size and so warrants a downgrade in quality here.

Downgraded one level for risk of bias. We pooled one quasi-randomised trial and two cohort studies to give this estimate. Two further cohort studies also assessed convalescent serum versus no treatment for the prevention of measles. These latter studies had heterogeneous results that may have resulted from differences in methodology and so were not included. We rated no studies at high risk of measurement bias, but lack of information about blinding and assessment of the outcome typically resulted in unclear risk.

While any uncontrolled confounding would have decreased the effect size, measurement bias may have increased the effect size and so warrants a downgrade in quality here.

Downgraded one level for risk of bias. The two cohort studies that assessed convalescent serum versus no treatment, which were left out of this pooled estimate, had heterogeneous results, although still indicated a significant benefit of this intervention.

Publication bias strongly suspected. The studies in this analysis were all published in the first half of the 20th century. Not as many journals existed and reporting standards were not as rigorous at that time. It is very likely that many small studies were not published.

Upgraded for dose-response gradient. Convalescent serum was one subgroup of three in an analysis that examined the effect of an approximation of dose on the results. An apparent dose response could be seen across the three subgroups.

Upgraded for dose-response gradient. Adult serum was one subgroup of three in an analysis that examined the effect of an approximation of dose on the results. An apparent dose response could be seen across the three subgroups.

Downgraded one level for risk of bias. We pooled one quasi-randomised trial and two cohort studies to give this estimate. Two further cohort studies also assessed convalescent serum versus no treatment for the prevention of measles. These latter studies had heterogeneous results that may have resulted from differences in methodology and so were not included. We rated no studies at high risk of measurement bias, but lack of information about blinding and assessment of the outcome typically resulted in unclear risk.

While any uncontrolled confounding would have increased the effect size, measurement bias may have increased the effect size and so warrants a downgrade in quality here.

Downgraded two levels for risk of bias. Both of the studies contributing to this estimate were cohort studies. Any uncontrolled confounding would have decreased the effect size. We rated measurement bias as unclear for one study and this may have increased the effect size in this case. We rated measurement bias as low risk for the other study, but attrition bias was high risk for this study. Overall, a downgrading of two levels is warranted.

Publication bias strongly suspected. Although one study in the analysis of this subgroup was published recently, the other was published in the first half of the 20th century. Not as many journals existed and reporting standards were not as rigorous at that time. It is very likely that many small studies were not published.

Upgraded for dose-response gradient. Gamma globulin was one subgroup of three in an analysis that examined the effect of an approximation of dose on the results. An apparent dose response could be seen across the three subgroups.

One study recording ‘vaccine reactions’ reported ‘fever and rash’ at rates of 5% in the gamma globulin group, 4% in the vaccine group and 1% in the no treatment group. The differences between groups were not statistically significant. This study reported loss to follow–up exceeding 20%.

Further research is very unlikely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

GRADE Working Group grades of evidence

High quality: Further research is very unlikely to change our confidence in the estimate of effect.

Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

Very low quality: We are very uncertain about the estimate.
BACKGROUND

Before vaccination against measles was available, annual case numbers were estimated at 130 million (WHO 1999) and the disease caused between five and eight million deaths globally each year (Moss 2009). With the introduction of the vaccine, the worldwide number of cases began to decline (WHO 1999) and this trend continued with increasing vaccination coverage (WHO 2009a). However, the number of measles cases worldwide exceeded 300,000 in 2010 (WHO 2013), with the highest incidence occurring in the World Health Organization (WHO) African region at 238 cases per million population (WHO 2012). Measles is still an important cause of global mortality as identified by the joint WHO and United Nations International Children’s Emergency Fund (UNICEF) Global Immunization Vision and Strategy 2005 to 2015 (WHO 2015). One of the strategy’s goals is measles mortality reduction. In 2008, measles caused around 164,000 deaths (WHO 2009b).

Further to mortality reduction, most WHO regions have set measles elimination goals and reported on progress towards these (Castillo-Solorzano 2011; Martin 2011; Sniadack 2011; WHO 2008). Many countries have noted continued reductions in incidence (WHO 2012) and even elimination of endemic transmission (Parker Fiebelkorn 2010). In 2010, the incidence in the WHO region of the Americas was just 0.3 cases per million population (WHO 2012). However, the WHO cautions that failure to maintain high vaccination coverage in all areas of a country results in resurgence of the disease (WHO 2009a). Certainly, there are many recent published reports of measles outbreaks among countries with high vaccination coverage (CDC 2011a; Delaporte 2011; DVD CDC 2011; Hoskins 2011; Parker Fiebelkorn 2010; Smithson 2010; Takimoto 2011; Vainio 2011) and the WHO confirms that the incidence of measles worldwide increased in 2010 because of large outbreaks in some regions (WHO 2012).

In countries with low incidences of measles, elimination strategies typically include an urgent response to a single reported case, including confirmation of the diagnosis, contact tracing and post-exposure prophylaxis (CDC 1998; CDNA 2009; NZ MoH 2011; UK DoH 2010). Post-exposure prophylaxis may be a vaccination, which seems to be effective at preventing disease onset if administered within 72 hours of exposure (Barraque 2011), or may involve passive immunisation with immunoglobulin, particularly if outside this 72-hour window (Heymann 2008).

Description of the intervention

The practice of passive immunisation against measles has been used since the 1920s (Haas 1926). Polyclonal immunoglobulins are administered parenterally to susceptible individuals, who have been in contact with an infectious case of measles, in an attempt to prevent the onset of disease or modify disease expression (Keller 2000).

A number of different immunoglobulin preparations have been used in the prophylaxis of measles. The serum or plasma of people recovering from measles or of adults who have previously suffered from the disease, whole blood from the same sources, the serum fluid obtained from placentas, ascites fluid and animal sera have all been tried (Barenberg 1939; Karelitz 1937; Morales 1930; Thalhimmer 1939; Zingher 1924). In the 1940s, methods were devised for concentrating the antibodies in human plasma and today the process of fractionation continues to be used to produce the blood product human immune globulin from pooled donated human plasma (Gonik 2011). Both intramuscular and intravenous preparations are in use. Product names vary from country to country; so too the concentration of disease-specific immunoglobulins in the products will generally reflect circulating antibody levels in the donating populations (Sawyer 2000). However, in some countries, minimum neutralising antibody concentrations to measles may be regulated (Sawyer 2000).
Current recommendations for dose calculations vary by country, although they are all calculated according to body weight (CDC 2011b; CDNA 2009; ID HPA 2009; NZ MoH 2011). Regardless of the dose recommended, passive immunisation is not currently recommended if more than six days have elapsed since exposure to measles (CDC 2011b; CDNA 2009; ID HPA 2009; NZ MoH 2011).

How the intervention might work
Whether injected or infused, the administered immunoglobulins distribute throughout the recipient’s body (Birdsall 2009). The mechanism by which the recipient is protected from disease involves interaction between the immunoglobulins, the invading measles 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). In general, measles-specific antibodies bind to invading measles virus particles and this may prevent their entry into cells directly, or trigger other immune mechanisms that result in neutralisation or destruction of the virus (Birdsall 2009; Keller 2000; Reading 2007).

Why it is important to do this review
The effectiveness of post-exposure prophylaxis against measles with immunoglobulins is generally accepted (ATAGI 2008; CDC 1998; NZ MoH 2011; Ramsay 2009). However, effectiveness rates vary considerably among identified reports (King 1991; Ordman 1944; Sheppeard 2009; Stokes 1944). Further, national recommendations for the use of post-exposure immunoglobulins for measles differ across a number of countries (Best 2011; CDC 1998; CDNA 2009; ID HPA 2009; NZ MoH 2011; Ramsay 2009) where disease incidences (WHO 2014), immunisation schedules (ATAGI 2008; Gustavo 2008; HPA 2011; NZ MoH 2011), measles-containing vaccine coverage (WHO 2014) and relevant literature are similar. Differences in immunoglobulin dosage recommendations among these countries may reflect differences in the minimum levels of measles-specific antibodies in intramuscular preparations (Best 2011; Ramsay 2009; Sawyer 2000).

We could not identify any systematic review evidence of the effectiveness of post-exposure passive immunisation against measles, nor any systematic review evidence of the minimum effective dosage of immunoglobulin for post-exposure prophylaxis against measles. Recent guidance from the United Kingdom on the required dosage of intramuscular immunoglobulin is based on a single study (Endo 2001; Ramsay 2009).

This review aimed to clarify the effectiveness rate, assess the evidence for a minimum effective dose and identify differences in benefit or harm across population groups. These outcomes would be valuable to guide public health practice in countries with low incidences of measles.

OBJECTIVES
To assess the effectiveness and safety of intramuscular injection or intravenous infusion of immunoglobulins for preventing measles when administered to exposed susceptible people before the onset of symptoms.

METHODS
Criteria for considering studies for this review
Types of studies
We included randomised controlled trials (RCTs), quasi-RCTs and prospective non-RCTs (cohort studies), irrespective of blinding, publication status, language or unit of randomisation. We included prospective non-RCTs given that more recent studies, using current immunoglobulin preparations, were likely to be non-randomised for ethical reasons. The intervention has been part of public health practice since the 1920s and, as such, any RCTs are likely to have been conducted at a time when the antibody levels of blood donors were due to infection with measles rather than vaccination. To inform practice appropriately, any evidence of the effectiveness of current immunoglobulin preparations should be included.

Types of participants
People of any age, sex or ethnic origin who were susceptible (no history of measles and not vaccinated against measles and/or measles immunoglobulin G (IgG) negative) and exposed to measles, or exposed to someone diagnosed with measles and who were asymptomatic at the time of intervention or control administration. The primary study’s definition of ‘exposed’ was accepted.

Types of interventions
1. Intervention: intramuscular injection of polyclonal immunoglobulins; intravenous infusion of polyclonal immunoglobulins. Only interventions using immunoglobulins derived from human sera or plasma were included.
2. Control: no intervention or placebo or live attenuated measles virus vaccine.
We also included studies assessing different brands or preparations of polyclonal immunoglobulins or different dosages of immunoglobulins. We only included studies where the intervention (and control) were administered to participants after exposure to measles and before the participants developed measles symptoms.

**Types of outcome measures**

**Primary outcomes**

1. Cases of measles. The diagnosis may be made by detection or isolation of measles virus in urine or respiratory secretions; by serological detection of immunoglobulin M (IgM) to measles in the absence of vaccination eight days to eight weeks prior to testing; by IgG seroconversion or by a fourfold or greater rise in titre to measles virus in the absence of vaccination eight days to eight weeks prior to testing; or by symptoms consistent with measles (fever, a red blotchy rash, conjunctivitis, runny nose and cough) or modified measles (prolonged incubation period, milder fever, cough, runny nose, conjunctivitis and sparse discrete rash of short duration).

2. Mortality due to measles.

**Secondary outcomes**

1. Prevention of measles outbreak (higher than expected incidence) as identified by active surveillance.
2. Cessation of measles outbreak (return to expected incidence) as identified by active or passive surveillance (or both).
3. Complications due to measles such as otitis media, pneumonia or encephalitis.
4. Occurrence and type of adverse events. We proposed to analyse two types of adverse events: serious adverse events and non-serious adverse events. A serious adverse event was defined as “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). We classified all other events as non-serious. We specifically sought to extract data on: blood-borne virus infection; anaphylaxis; generalised hypersensitivity and injection site reactions. We also included any other adverse event reported as such by study authors.

**Search methods for identification of studies**

**Electronic searches**

We searched the Cochrane Central Register of Controlled Trials (CENTRAL) (2012, Issue 7), which contains the Cochrane Acute Respiratory Infections (ARI) Group’s Specialised Register, MEDLINE (via OVID) (1946 to July week 4, 2012), CINAHL (via EBSCO) (1981 to August 2012) and EMBASE (1974 to August 2012). We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We adapted the strategy for EMBASE (Appendix 2) and CINAHL (Appendix 3). We combined the MEDLINE and EMBASE searches with the filter for study type in Appendix 4 as we considered the search results retrieved too large to be manageable. We updated the electronic searches on 14 August 2013 by searching CENTRAL (2013, Issue 7) from 2011 to 2013, MEDLINE from 1 June 2012 to July week 5 2013, CINAHL after June 2012 and EMBASE from 1 July 2012 to August 2013.

**Searching other resources**

We searched reference lists of identified relevant studies and reviews. We searched www.clinicaltrials.gov and WHO ICTRP (19 August 2013) using the search term ‘measles’. To locate further published or unpublished studies, we attempted to contact companies manufacturing immunoglobulin products for countries with low measles incidences and attempted to contact the corresponding author of any included studies.

**Data collection and analysis**

**Selection of studies**

Two review authors (MY, GN) independently inspected each full article. If identified by either review author as potentially relevant, we retrieved the full article. One author (MY) searched the reference lists of the relevant retrieved studies and retrieved the full articles of those that could not be excluded based on title (and abstract where available).

Both review authors independently inspected each full article using an eligibility checklist based on the inclusion criteria, to determine inclusion in the review. We resolved any disagreements through discussion. We excluded studies not meeting the eligibility criteria and stated the reasons for exclusion. We did not identify any duplicate publications.

**Data extraction and management**

Two review authors (MY, AC) independently extracted data from the included studies using pre-designed electronic data extraction forms. We resolved disagreements by discussion. We attempted to contact study authors for clarification or further information as necessary.

We attempted to extract the following data:

1. The study
Collaboration’s tool for assessing ‘Risk of bias’ (sources of bias. We reported the risk of bias using The Cochrane incomplete outcome data; selective reporting and other potent ment; blinding of participants, personnel and outcome assess assessed: randomisation sequence generation; allocation concea cussion. For randomised and quasi-randomised studies, we as-

Two review authors (MY, AC) independently assessed the risk of bias of included studies. We resolved any disagreements by dis-

For randomised and quasi-randomised studies, we as-

We assessed: blinding of participants, personnel and outcome assessors; incomplete outcome data; selective reporting and other potential sources of bias. We reported the risk of bias using The Cochrane Collaboration’s tool for assessing ‘Risk of bias’ (Higgins 2011). For non-randomised studies, we allocated randomisation sequence generation and allocation concealment (selection bias) ‘high risk’. We assessed: blinding of participants, personnel and outcome as-

We made the decision to include ‘Summary of findings’ ta-

Measures of treatment effect

Outcomes, as identified above, are dichotomous. We expressed these outcomes as risk ratios (RRs) and calculated 95% confidence intervals (CIs) for each.

Unit of analysis issues

No cluster-randomised trials were identified for inclusion in the review.

For studies with multiple intervention groups, for example different doses or preparations of immunoglobulins compared to control, we split the shared group and included the relevant pair-wise comparisons in the meta-analysis (Higgins 2011).

Dealing with missing data

We attempted to contact the trial authors for any missing data. Where missing data exceeded 20% (one study - Glyn-Jones 1972), or where data were missing in different proportions in the treat-

The main paper and enter the data for meta-analysis once only.

Our protocol indicated that we would assess publication bias by exam-

Our protocol indicated the secondary outcome ‘serious adverse events’ among those for meta-analysis. However, this outcome was not reported in any included study.

Assessment of reporting biases

We examined each included study for indications that outcomes assessed had not been reported.

Our protocol indicated that, had multiple publications of the same study been retrieved, we would list the subsequent papers with the main paper and enter the data for meta-analysis once only.

However, we did not identify multiple publications of the same study.

Our protocol indicated that we would assess publication bias by examining funnel plots if sufficient studies (at least 10) were included. However, the maximum number of studies included in meta-analyses was seven.
**Data synthesis**

We calculated the RR and 95% CI for each outcome measured in each study. We used a fixed-effect model in meta-analysis of each primary outcome and the secondary outcome 'complications due to measles' and examined the forest plots to assess heterogeneity. We explored possible reasons for apparent heterogeneity via subgroup and sensitivity analyses and reported the results of these using fixed-effect models.

We reported the results of the secondary outcome ‘adverse events’ descriptively.

**Subgroup analysis and investigation of heterogeneity**

Our protocol listed the following subgroup analyses that we were unable to perform because of insufficient available information from the included studies:
- proportion of high-risk individuals;
- dose of measles-specific immunoglobulins.

Further, the following subgroup analyses were not relevant to the review:
- route of administration of immunoglobulins (all included studies administered immunoglobulins intramuscularly);
- timing of administration of intervention in relation to exposure (included studies generally administered immunoglobulins within seven days of exposure where this was reported. Only Stillerman 1944 administered immunoglobulins within eight days, although Salomon 1923 and Wesselhoeft 1928 did not report the timing of the intervention in relation to exposure. Hence, rather than subgroup analysis, we undertook sensitivity analysis, by excluding each of these studies in turn and together. In addition, there were insufficient studies assessing the effect of the timing of the intervention (within seven days of exposure) on the prevention of measles to undertake a separate analysis);
- differences in the primary study definition of exposed (with the exception of Cockburn 1950, Endo 2001 and Sheppeard 2009, all included studies had similar definitions of ‘exposed’. Endo 2001 was not included in meta-analyses. Cockburn 1950 was included with only one other study in a meta-analysis. Thus we undertook sensitivity analysis, by excluding Sheppeard 2009, rather than subgroup analysis, to assess the impact of the difference in this study’s exposure definition).

We undertook the following subgroup analyses:
- study type (quasi-RCTs and cohort type studies);
- age of participants (although sufficient information was not available to divide the data as we had intended (infants/children/adults/combination), we grouped studies according to age as follows: “included infants less than six months of age” and “did not include infants less than six months of age”);
- dose of immunoglobulins (studies generally reported administering a range of volumes of immunoglobulins and these were not uniform, hence studies were grouped by the type of intervention blood product (convalescent serum, adult serum and gamma globulin) as an approximation of dose).

**Sensitivity analysis**

Our protocol specified that we would undertake sensitivity analysis based on the risk of bias in included studies and studies with imputed missing data. We examined the effect of the risk of bias of included studies on the results of meta-analyses by excluding Sheppeard 2009 from the relevant outcome because of the high risk of attrition bias in this study. The risk of bias was otherwise similar across included studies. We did not impute missing data for any study.

**Post-protocol sensitivity analyses**

As indicated above, because most included studies identified the intervention dose of immunoglobulin by total volume and the ranges administered were not uniform between studies, we grouped the studies by the blood product used as an approximation of immunoglobulin dose. The rationale for this was: gamma globulin is manufactured as a concentrated preparation of immunoglobulins and is thus likely to have the highest concentration of measles-specific antibodies per unit volume; the acute immune response following disease means that convalescent serum will contain the next highest concentration of measles-specific antibodies per unit volume; and adult serum will contain the lowest concentration of measles-specific antibodies per unit volume as disease would most likely have occurred in childhood for the donors of the serum at the time of the included studies. Given this approximation of dose, we undertook sensitivity analyses by excluding Stillerman 1944 as the outlier (largest volume range and highest volume) within the convalescent serum group and by excluding Salomon 1923 from the convalescent serum group as the volume of serum administered was not reported. Volume ranges within the subgroups were otherwise similar.

As indicated above, we also excluded Stillerman 1944, Salomon 1923 and Wesselhoeft 1928 alone and together to examine the impact of definite (Stillerman 1944) and possible (Salomon 1923; Wesselhoeft 1928) differences in the maximum time between exposure and intervention. We also excluded Sheppeard 2009 alone to assess the impact of this study’s definition of exposure.

**R E S U L T S**

**Description of studies**
Results of the search

Searches of MEDLINE, EMBASE, CENTRAL and CINAHL on 6 August 2012 identified 2369 unique records, of which we retrieved 55 full-text articles resulting in five included studies. We updated the electronic searches on 14 August 2013 and identified 102 unique records, of which we retrieved two full-text articles. No further studies met the inclusion criteria. Searching the reference lists of relevant retrieved full-text articles identified a further 133 unique papers, of which we retrieved 89 full-text articles resulting in eight included studies (Figure 1). Searching www.clinicaltrials.gov returned 158 records but no additional relevant studies. Searching WHO ICTRP returned 182 records but no additional relevant studies. We sent electronic written requests to 13 separate companies that manufacture immunoglobulin products (Appendix 5) and the Australian Technical Advisory Group on Immunisation (ATAGI). Four companies and the ATAGI responded. No additional studies were identified. The age of the included studies and absent up-to-date contact details for authors meant that we were only able to contact the authors of one study. No additional studies were identified as a result of this communication.
Figure 1. Flow diagram of retrieval, selection and exclusion of studies.

2936 records identified through database searching

477 additional records identified through other sources

2944 records after duplicates removed

2944 records screened

2798 records excluded

146 full-text articles assessed for eligibility

133 full-text articles excluded, with reasons

13 studies included in qualitative synthesis

9 studies included in at least one quantitative synthesis (meta-analysis)
Included studies

A total of 13 studies were included in the review: one RCT, two quasi-RCTs and 10 prospective, non-randomised, controlled (cohort) studies (see Characteristics of included studies table). Included studies were published between 1920 and 2009. No unpublished studies were included.

Studies were undertaken in seven different countries: United States (Berkovich 1963; Ordman 1944; Stillerman 1944; Toomey 1926; Wesselhoeft 1928), Japan (Endo 2001), United Kingdom (Cockburn 1950; Hartley 1948), Australia (Sheppeard 2009), Germany (Degkwitz 1920; Salomon 1923), Zimbabwe (Glyn-Jones 1972) and Puerto Rico (Morales 1930). A total of 3925 participants were recruited from hospitals, child care facilities and the community. Sample sizes ranged from 11 to 921.

Only one study included adults among the participants (Sheppeard 2009), although four studies (Berkovich 1963; Degkwitz 1920; Endo 2001; Wesselhoeft 1928) did not report the age of participants and five studies (Hartley 1948; Ordman 1944; Salomon 1923; Sheppeard 2009; Toomey 1926) did not report a clear age range. Two of these latter studies included participants less than six months of age (Hartley 1948; Salomon 1923). Ordman 1944 and Sheppeard 2009 specified that participants were aged six months and over. Toomey 1926 identified participants as 'children'. Participants of the remaining four included studies were aged no younger than six months, with maximum ages ranging from 35 months to 15 years (Cockburn 1950; Glyn-Jones 1972; Morales 1930; Stillerman 1944).

The only study reporting gender distribution noted similar proportions of males and females in both the intervention and control groups (intervention 53% males; control 51% males) (Cockburn 1950).

The proportions of participants at high risk of measles complications were also poorly reported. Glyn-Jones 1972 reported that between 40% and 50% of participants were aged less than 12 months, while this group was approximately one-quarter of the participants of Hartley 1948, approximately 10% of the participants of Stillerman 1944 and around 5% of the participants of Cockburn 1950. No information was available on high-risk groups in the other studies.

With the exception of Cockburn 1950, Endo 2001 and Sheppeard 2009, participants were exposed to measles either by living with someone diagnosed with measles or being in the same hospital ward as a person with measles. Cockburn 1950 defined 'intimate', 'close' and 'remote' contact. (Intimate - played with and enrolled in the same section of the nursery as the primary care; close - exposed for short periods at play or meals but enrolled in a different section of the nursery; remote - contact usually confined to exposure in the entrance hall in the morning or evening or out of doors during the day). Endo 2001 defined close contact as: a household member with measles, exposure to a schoolmate or playmate with measles lasting at least one hour, or exposure to a person with measles in a medical facility. Sheppeard 2009 defined exposure as: anyone who was in the same room as the case, or the same room for up to two hours after the case, during the infectious period.

The interval between exposure and intervention or control was within seven days for 10 studies, within eight days for Stillerman 1944 and not reported for the other two studies (Salomon 1923; Wesselhoeft 1928). The intervention was convalescent serum given intramuscularly in six studies (Degkwitz 1920; Morales 1930; Salomon 1923; Stillerman 1944; Toomey 1926; Wesselhoeft 1928). Morales 1930 and Salomon 1923 also trialled adult serum intramuscularly. Doses ranged from 2.5 ml to 20 ml.

The remaining seven studies trialled gamma globulin intramuscularly. With the exception of Glyn-Jones 1972, whose participants received 2 ml every three weeks until discharge, studies trialling gamma globulin varied the single administered dose usually in response to participants' weight or age.

With the exception of Degkwitz 1920, all studies trialling convalescent serum included a 'no treatment' control group. Degkwitz examined 3 ml compared to 2.5 ml of convalescent serum both on day four after exposure in one trial and examined 6 ml to 7 ml of convalescent serum on day six after exposure compared to 7 ml to 8 ml of convalescent serum on day seven after exposure in a second trial.

Three studies trialling gamma globulin included 'no treatment' control groups (Glyn-Jones 1972; Ordman 1944; Sheppeard 2009). Three studies administered measles vaccine to a control group (Berkovich 1963; Glyn-Jones 1972; Sheppeard 2009), although Berkovich 1963 administered gamma globulin as well as vaccine to the same individuals. Hartley 1948 administered convalescent serum of doses between 2.5 ml and 5 ml or more to the control group. Cockburn 1950 administered adult serum or reconstituted dried plasma to the control group at a dose of 5 ml. Endo 2001 used four lots of gamma globulin, each with a different measles-specific antibody titre (16 IU/ml, 33 IU/ml, 40 IU/ml and 15 IU/ml). The dose administered was 0.33 ml/kg for each participant.

All included studies assessed the number of measles cases in each group as the primary outcome. Five studies assessed complications due to measles in each study group (Cockburn 1950; Glyn-Jones 1972; Morales 1930; Ordman 1944; Wesselhoeft 1928). One study ceased follow-up of the 'no treatment' control group upon onset of rash and hence only assessed complications in the intervention group (Stillerman 1944). None of these studies described the criteria for determining that complications were due to measles. Four studies assessed mortality due to measles (Glyn-Jones 1972; Morales 1930; Salomon 1923; Wesselhoeft 1928). None
of these studies described the process for attributing participants’ deaths to measles rather than another cause.

Adverse events were not considered in the majority of the included studies and only Glyn-Jones 1972 specified adverse events as an outcome measure in the methods, but under the premise of reactions to measles vaccine rather than gamma globulin. However, Cockburn 1950 and Morales 1930 also reported on adverse events amongst their participants and Hartley 1948, Ordman 1944 and Toomey 1926 made mention of adverse events in their experience with passive immunisation more generally.

The effectiveness of passive immunisation for the prevention or cessation of measles outbreaks was not assessed by any included study.

**Excluded studies**

Out of the 146 full-text papers retrieved, 108 were not prospective controlled studies. They included case reports, case series, reviews, retrospective designs and two studies where it was not clear that the comparison group originated from the same population as the intervention group. Another 21 of those excluded were studies where either the participants were not susceptible and exposed to measles or this was unclear. Three studies did not examine intramuscular or intravenous polyonal immunoglobulins derived from human serum or plasma. One study did not assess the number of participants who developed measles.

The reasons for exclusion of individual studies where these were discussed by the authors, after comparison of their independent assessments, are given in the Characteristics of excluded studies table. For brevity, we have not listed studies where authors’ independent assessments were in agreement.

**Risk of bias in included studies**

None of the included studies was determined to have a low risk of bias for all criteria (see Figure 2 and Characteristics of included studies table).
Figure 2. 'Risk of bias' summary: review authors' judgement about each risk of bias item for each included study.
Allocation
The one included RCT described the random sequence generation in insufficient detail and we deemed it to have unclear risk of bias for this criterion (Cockburn 1950). All other studies were at high risk of bias for this criterion as they were either quasi-randomised or non-randomised studies. Glyn-Jones 1972 seemed to allocate participants to interventions using third parties with no knowledge of the participants. However, this was not explicitly stated and hence we deemed it to be unclear risk in terms of allocation concealment. The other studies, including the RCT, were at high risk of bias regarding the allocation of participants to interventions.

Blinding
The intervention, administration of polyclonal immunoglobulin, is very unlikely to be subject to variation due to performance and, as such, we deemed all studies at low risk of performance bias. We assessed detection bias for the outcomes: cases of measles, complications due to measles, mortality due to measles and adverse events. With the exception of adverse events, each of these outcomes is objective provided appropriate pre-study definitions are adopted. Unfortunately, sufficient information was rarely provided to determine whether pre-study definitions had been set. Similarly, very limited information on blinding was provided in nearly all included studies.

Given this, we deemed the risk of detection bias to be unclear for the majority of included studies in relation to measles cases. We deemed Cockburn 1950, Glyn-Jones 1972 and Sheppeard 2009 to have a low risk of detection bias with respect to cases of measles. Cockburn 1950 and Glyn-Jones 1972 adequately described blinding procedures despite the lack of information on their case definition of measles and Sheppeard 2009 provided a very clear pre-study case definition that was applied uniformly. The outcome ‘complications due to measles’ was assessed by six studies. As for cases of measles, Cockburn 1950 and Glyn-Jones 1972 were at low risk of detection bias. Stillerman 1944 assessed only the intervention group for complications due to measles as the study ceased follow-up of controls upon the onset of rash. This study was clearly at high risk of detection bias for this outcome. The other three studies did not provide sufficient information and we deemed them at unclear risk (Morales 1930; Ordman 1944; Wesselhoeft 1928).

The outcome ‘mortality due to measles’ was assessed by four studies. Glyn-Jones 1972 was again at low risk. The other three studies did not provide sufficient information and we deemed them at unclear risk (Morales 1930; Salomon 1923; Wesselhoeft 1928). Glyn-Jones 1972 was the only study to specify adverse events as an outcome measure in the methods, although Cockburn 1950 and Morales 1930 also reported on adverse events amongst their participants. As Cockburn 1950 and Glyn-Jones 1972 were adequately blinded, these studies were at low risk of detection bias for this outcome. Morales 1930 did not provide sufficient information and was at unclear risk.

Incomplete outcome data
Most studies reported complete follow-up for the primary outcome measures and were at low risk of attrition bias. Glyn-Jones 1972 reported a loss to follow-up of 20.6% overall, with rates of 19.4% to 22.4% across the three study groups. We considered this a high risk of bias and we excluded the study from meta-analysis. Endo 2001 did not specify whether parents who did not report illness in their child were actively followed up and the authors could not be contacted. We therefore deemed this study to be at unclear risk of attrition bias. The author of Sheppeard 2009 provided information that passive surveillance was the means of participant follow-up. As such we deemed this study to be at high risk of attrition bias, although no loss to follow-up was reported.

Selective reporting
Toomey 1926 presented some adverse event case series data but this outcome was not reported in relation to the cohort study participants. We therefore deemed this study to be at high risk of reporting bias. Each of the other included studies reported on all outcomes specified in the methods sections and we deemed them to be at low risk of reporting bias.

We did not identify multiple publications of the same study. As the maximum number of studies included in meta-analysis was seven, we did not have sufficient studies to examine publication bias using funnel plots.

Other potential sources of bias
Ten of the included studies were non-randomised ‘cohort type’ studies. Confounding was not well addressed in any of these studies and was typically not addressed at all. Confounding is therefore a likely source of bias in each of these studies and we deemed each to be at high risk for this criterion.

Effects of interventions
See: Summary of findings for the main comparison Immunoglobulin compared to no treatment for preventing measles; Summary of findings 2 Gamma globulin compared to serum for preventing measles

Three included studies could not be included in meta-analysis because of heterogeneity among the comparison groups
(Berkovich 1963; Degkwitz 1920; Endo 2001). One included study (Glyn-Jones 1972) could not be included in meta-analyses as per protocol because loss to follow-up exceeded 20%.

Primary outcomes

1. Cases of measles

Seven included studies that examined the effect of immunoglobulin versus no treatment for the prevention of measles were included in a meta-analysis of the primary outcome ‘cases of measles’ (Morales 1930; Ordman 1944; Salomon 1923; Sheppeard 2009; Stillerman 1944; Toomey 1926; Wesselhoeft 1928). Although all results favoured the intervention group, statistical heterogeneity was visually obvious upon examination of the initial forest plot (Analysis 1.1) and indeed the I² statistic was 87%. The sensitivity analyses conducted by excluding Salomon 1923, Sheppeard 2009, Stillerman 1944 and Wesselhoeft 1928 in turn did not alter these results.

There was no significant difference in the results of the subgroup which included infants younger than six months of age compared to the subgroup that did not include infants younger than six months of age (test for subgroup differences: Chi² test = 0.36, df = 1 (P value = 0.55); I² statistic = 0%). No other subgroup analyses were able to examine possible differences in the benefit of the intervention.

Subgroup analyses examining study type and participant age did not explain the observed heterogeneity (Analysis 1.2). However, the subgroup analysis examining the blood product used, as an approximation of dose, revealed homogenous results for the adult serum group (risk ratio (RR) 0.52, 95% confidence interval (CI) 0.45 to 0.59; heterogeneity: Chi² test = 0.02, df = 1 (P value = 0.88); I² statistic = 0%) and gamma globulin group (RR 0.17, 95% CI 0.08 to 0.36; heterogeneity: Chi² test = 0.34, df = 1 (P value = 0.56); I² statistic = 0%), although not the convalescent serum group (RR 0.49, 95% CI 0.44 to 0.54; heterogeneity: Chi² test = 49.53, df = 4 (P value < 0.001); I² statistic = 92%) (Analysis 1.2). Excluding Sheppeard 2009 from the gamma globulin group left only one study in this subgroup and only minimally altered the risk ratio from 0.17 to 0.15.

Sensitivity analyses that excluded Stillerman 1944, Salomon 1923 and Wesselhoeft 1928, in turn and together, demonstrated that the former two studies contributed most of the heterogeneity to the results for the convalescent serum subgroup (Analysis 1.3). The RR for this subgroup was 0.49 (95% CI 0.44 to 0.54) when the five eligible studies were included. Excluding Salomon 1923 did not alter the RR (0.49, 95% CI 0.45 to 0.55) and heterogeneity remained high (Chi² test = 46.69, df = 3 (P value < 0.001); I² statistic = 94%). Excluding Stillerman 1944 affected the RR considerably and also decreased the heterogeneity, although this was still significant (RR 0.26, 95% CI 0.21 to 0.33; heterogeneity: Chi² test = 11.40, df = 3 (P value = 0.010); I² statistic = 74%). Excluding Wesselhoeft marginally altered the RR 0.50 (95% CI 0.45 to 0.56) but again heterogeneity remained high (heterogeneity: Chi² test = 2.11, df = 2 (P value = 0.35); I² statistic = 5%) (Analysis 1.3). Excluding Wesselhoeft as well altered the RR minimally (RR 0.19, 95% CI 0.12 to 0.28) and resulted in a further small reduction of heterogeneity (Chi² test = 0.01, df = 1 (P value = 0.90); I² statistic = 0%). Irrespective of these sensitivity analyses, differences in the subgroup estimates of effect were significant (I² statistic < 0.001 to 0.02; I² statistic = 93.8% to 75.3%).

Two studies that examined the effect of gamma globulin compared to a comparison group administered serum (either convalescent or adult serum) for the prevention of measles were included in a meta-analysis of the primary outcome ‘cases of measles’ (Cockburn 1950; Hartley 1948). Heterogeneity was not significant either visually or statistically (heterogeneity: Chi² test = 3.03, df = 2 (P value = 0.22); I² statistic = 34%). Similar to the comparison of immunoglobulin to no treatment, the result favoured gamma globulin (RR 0.56, 95% CI 0.46 to 0.69) (Analysis 2.1).

The results of studies which could not be included in the meta-analyses also supported the impact of the dose of immunoglobulins upon effectiveness. Endo 2001 reported that eight of 14 participants administered gamma globulin with a measles-specific antibody concentration of 16 IU/ml developed measles as compared to one of six participants administered gamma globulin with a measles-specific antibody concentration of 33 IU/ml and none of 13 participants administered gamma globulin with a measles-specific antibody concentration of 40 IU/ml or more. This is a RR of 0.29 (95% CI 0.05 to 1.85) for the group given 33 IU/ml gamma globulin compared to the group given 16 IU/ml gamma globulin. Degkwitz 1920 reported that three of seven participants administered 2.5 ml of convalescent serum developed measles as compared to none of 12 participants administered 3 ml of convalescent serum. A RR could not be calculated for this comparison. Degkwitz 1920 also examined the effect of the time since exposure on the effectiveness of immunoglobulins for preventing measles. None of eight participants administered 6 ml to 7 ml of convalescent serum at six days post-exposure compared to one of three cases administered 7 ml to 8 ml of convalescent serum at seven days post-exposure developed measles. Again, a RR could not be calculated for this comparison.

Berkovich 1963 compared measles vaccine and gamma globulin at 0.02 ml per pound of body weight to gamma globulin alone at 0.1 ml per pound of body weight and reported that nine of 14 participants given vaccine and gamma globulin and two of four participants given gamma globulin alone developed measles. This suggests less risk of developing measles in the gamma globulin only group but the RR was not statistically significant (RR 0.78, 95% CI 0.31 to 1.90; heterogeneity: I² statistic = 79%).
2. Mortality due to measles

Three studies were included in the meta-analysis of the primary outcome 'mortality due to measles' (Morales 1930; Salomon 1923; Wesselhoeft 1928). The results were homogenous and favoured the intervention group (RR 0.24, 95% CI 0.13 to 0.44; heterogeneity: Chi² test ² = 1.23, df = 3 (P value = 0.75); I² statistic = 0%) (Analysis 1.4). Glyn-Jones 1972, not included in the meta-analysis due to loss to follow-up in excess of 20%, reported that three of 68 participants in the gamma globulin group, 12 of 73 participants in the no treatment group and two of 70 participants in the gamma globulin group died as a result of measles. Thus gamma globulin reduced mortality compared to no treatment (RR 0.18, 95% CI 0.05 to 0.60; heterogeneity: Chi² test = 0.27, df = 1 (P value = 0.60)) (Analysis 2).

Glyn-Jones 1972 compared the effectiveness of gamma globulin, 2 ml every three weeks, with measles vaccine and no treatment. Twenty-four of 68 participants who received gamma globulin, seven of 70 participants who received vaccine and 58 of 73 participants who received no measles prophylaxis developed measles. Thus, among those for whom data were available, the risk of measles was greater in the gamma globulin group than the vaccine group (RR 3.53, 95% CI 1.63 to 7.65) and less in the gamma globulin group than the no treatment group (RR 0.44, 95% CI 0.32 to 0.63).

In addition to comparing gamma globulin to no treatment, Sheppard 2009 included a vaccine only group. None of the 82 participants who received vaccine within three days of exposure developed measles compared to two of the 183 participants who received gamma globulin within seven days and 13 of the 288 participants who received no treatment. A RR could not be calculated for comparison of vaccine to the other groups.

Secondary outcomes

1. Prevention of measles outbreak

No included studies assessed the outcome 'prevention of measles outbreak'.

2. Cessation of measles outbreak

No included studies assessed the outcome 'cessation of measles outbreak'.

3. Complications due to measles

Three studies were included in the meta-analysis of the secondary outcome 'complications due to measles' (Morales 1930; Ordman 1944; Wesselhoeft 1928). Stillerman 1944 was excluded from the analysis because of complete missing data in the control group. The results were homogenous and favoured the intervention group (RR 0.18, 95% CI 0.05 to 0.60; heterogeneity: Chi² test = 1.23, df = 3 (P value = 0.75); I² statistic = 0%) (Analysis 1.5).

Two studies not included in the meta-analysis because of heterogeneous comparison groups also reported on 'complications from measles'. Cockburn 1950 reported that two of 212 participants given gamma globulin compared to five of 215 participants given adult serum developed complications from measles. This is a RR of 0.39 (95% CI 0.13 to 1.17); RR for gamma globulin versus no treatment 0.39 (95% CI 0.39 to 10.87)).

4. Occurrence and type of adverse events

Of the included studies that mentioned or recorded adverse events, no 'serious adverse events' were reported. Glyn-Jones 1972 recorded adverse event rates of 5% in the gamma globulin group, 4% in the vaccine group and 1% in the no treatment group. These 'probable vaccine reactions' were described as rash and fever. The differences between groups were not statistically significant. Glyn-Jones 1972 also noted no statistically significant differences in mortality rates due to presenting illness, or in exacerbations of presenting illness, between these groups of children who were hospital inpatients. Morales 1930 noted that two participants in the intervention group given convalescent serum had a slight fever and urticarial rash. The control group for this study was 'no treatment' and data on adverse events were not collected or reported. Cockburn 1950 noted a few cases (intervention group unspecified) of transient limb stiffness lasting one or two hours among participants. Referring to their experience within and beyond the included study, Ordman 1944 noted no severe adverse reactions to gamma globulin, with less than 5% of recipients experiencing mild reactions of slight muscle stiffness, local redness and induration. One recipient of 'several hundred' experienced fever two days after gamma globulin administration. Hartley 1948, also referring to observations within and beyond the included study, noted no...
Toomey 1926, reporting on recipients of convalescent serum over a two-year period prior to the included study, noted no local reactions, although reported that mild fever within 24 hours of administration and lasting not more than 24 hours was common.

**ADDITIONAL SUMMARY OF FINDINGS**

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Assumed risk</td>
<td>Corresponding risk</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Serum</td>
<td>Gamma globulin</td>
<td>RR 0.56 (0.46 to 0.69)</td>
<td>702 (2 studies)</td>
<td>⊕⊕⊕⊕</td>
<td></td>
</tr>
<tr>
<td>Measles cases Study population</td>
<td>464 per 1000 260 per 1000 (214 to 320) Moderate</td>
<td>310 per 1000 (265 to 362) Moderate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality due to measles Study population</td>
<td>Not estimable 0 (0)</td>
<td>See comment See comment</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Measles cases**

<table>
<thead>
<tr>
<th>Study population</th>
<th>RR 0.56 (0.46 to 0.69)</th>
<th>Moderate</th>
</tr>
</thead>
<tbody>
<tr>
<td>464 per 1000</td>
<td>260 per 1000 (214 to 320) Moderate</td>
<td></td>
</tr>
<tr>
<td>545 per 1000</td>
<td>310 per 1000 (265 to 362) Moderate</td>
<td></td>
</tr>
</tbody>
</table>

**Mortality due to measles**

<table>
<thead>
<tr>
<th>Study population</th>
<th>Not estimable 0 (0)</th>
<th>See comment</th>
</tr>
</thead>
</table>

- The basis for the assumed risk is the median control group risk across studies. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).
- CI: confidence interval; RCT: randomised controlled trial; RR: risk ratio
- GRADE Working Group grades of evidence
  - High quality: Further research is very unlikely to change our confidence in the estimate of effect.
  - Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
  - Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
  - Very low quality: Were very uncertain about the estimate.

1. Not downgraded for risk of bias. One of the studies contributing to this estimate is a randomised controlled trial, the other is a cohort study. Any uncontrolled confounding would have decreased the effect size. Measurement bias was low-risk for the RCT and unclear for the cohort study. Overall, the downgrade of quality already applied for including cohort studies is all that is warranted.
2. Publication bias strongly suspected. Both studies were published in the first half of the 20th century. Not as many journals existed and reporting standards were not as rigorous. It is likely that many small studies would not have been published.
3. Upgraded for large effect size. Effect size is large and precise.
4. Upgraded as plausible confounding would reduce the demonstrated effect.
Upgraded for dose-response gradient. Two doses of gamma globulin were used by the RCT. The higher dose was a smaller group and the confidence intervals overlap with that of the lower dose from this study, but the estimates of effect are consistent with a dose response.
Summary of main results

A total of 13 studies were included in the review: one randomised controlled trial (RCT), two quasi-RCTs and 10 prospective, non-randomised, controlled (cohort) studies. No unpublished studies were included.

Seven studies were included in meta-analysis of immunoglobulin versus no treatment for measles cases. Heterogeneity was explained by subgrouping studies according to the blood product used as an approximation of the dose of immunoglobulin and then excluding two studies among the convalescent serum group thought to have different dosing and intervention timing to the other studies. Gamma globulin was most effective at preventing measles (risk ratio (RR) 0.17, 95% confidence interval (CI) 0.08 to 0.36), followed by convalescent serum (RR 0.21, 95% CI 0.15 to 0.29 to RR 0.49, 95% CI 0.44 to 0.54) and then adult serum (RR 0.52, 95% CI 0.45 to 0.59).

One study was particularly influential on the convalescent serum group estimate of effect (Stillerman 1944). This study had a very large sample size and diverged from the other studies in this group on some points of methodology, namely the volume range of convalescent serum administered was the largest (5 ml to 20 ml) and the intervention was administered up to eight days post-exposure to measles rather than up to seven days. The estimate of effect of this study was smaller than the other studies in this group. Factors contributing to this may have included: the delay between exposure and intervention for some participants; the fact that although the maximum volume of serum administered was much larger than the other studies, the volume range was not applied uniformly according to age or weight and was not applied consistently across the duration of the study; and the serum was collected from convalescents up to four months after illness (average two months), which is longer than for other studies where this was reported (Toomey 1926: eighth day after the rash began to disappear; Morales 1930: fifth to tenth day of convalescence). The results of the blood product subgroup analyses were supported by a meta-analysis of gamma globulin versus serum (either convalescent or adult serum) including two studies. Gamma globulin was more effective than serum at preventing measles (RR 0.56, 95% CI 0.46 to 0.69). The apparent dose-effect was further supported by studies not included in the meta-analyses. However, only two studies provided sufficient information to calculate the dose of measles-specific antibodies administered to participants and at the attack rates in their intervention groups were not congruous, no minimum effective dose could be concluded.

Three studies were included in meta-analysis of immunoglobulin versus no treatment for mortality due to measles. Immunoglobulin was effective at preventing death due to measles (RR 0.24, 95% CI 0.13 to 0.44).

Three studies were included in meta-analysis of immunoglobulin versus no treatment for complications due to measles. Immunoglobulin was effective at preventing complications due to measles (RR 0.18, 95% CI 0.05 to 0.60). Only two studies included vaccine only comparison groups. Their results suggested greater effectiveness of vaccine given within three days of exposure compared to gamma globulin given within seven days of exposure, but meta-analysis could not be undertaken.

No serious adverse events were observed in any of the included studies. Non-serious adverse events reported included: transient fever, rash, muscle stiffness, local redness and induration.

Overall completeness and applicability of evidence

The ethnic diversity of the populations of the included studies supports the generalisability of the results. However, ‘high-risk individuals’ were not well represented and, in particular, pregnant women and immunocompromised people were not identified among study participants. Further, only one included study identified adults among their participants. While it is highly likely that passive immunisation would also be effective for these groups, no conclusions can be drawn about possible differences in the magnitude of effect.

Our investigation of the influence of age on the effectiveness of immunoglobulins compared to no treatment was limited to sub-grouping studies that included infants younger than six months of age among participants and those that did not. No difference in the magnitude of effect was observed between these subgroups. Two included studies were conducted this century and therefore examined gamma globulin that was likely to contain concentrations of measles-specific antibodies similar to those used in current practice. These were the only two studies that provided sufficient information to allow calculation of the dose of measles-specific antibodies administered to participants. One of these studies administered gamma globulin of different measles-specific antibody concentrations to different groups and did not include a no treatment group (Endo 2001). The other obtained an estimate of the measles-specific antibody concentration from the manufacturer and included a no treatment group (Sheppeard 2009). Despite overlapping estimates of the administered doses of measles-specific antibody, no conclusions about the minimum effective dose could be drawn as the attack rates in these intervention groups across the two studies were not consistent with a unified dose-response relationship. There are a number of possible reasons for this. Firstly, as mentioned, Sheppeard 2009 did not measure measles-specific antibody levels in the blood product used for passive immunisation but reported an estimate from the manufacturer. Secondly, the intervention group sizes were very small in Endo 2001. Thirdly, study methodology was different across these studies and Sheppeard 2009, in particular, was known to be at high risk of attrition bias and may have underestimated the number of measles cases.
cases in the group administered gamma globulin if this led to modified measles which was not identified as such.

Only two studies examined the effectiveness of active vaccination alone compared to passive immunisation (Glyn-Jones 1972; Sheppeard 2009). We were unable to combine these studies in meta-analysis as per our protocol because the loss to follow-up in Glyn-Jones 1972 exceeded 20%. Both studies suggested vaccination was more effective at preventing measles cases than passive immunisation when administered within three days of exposure. However, study quality, low event rates in Sheppeard 2009 and the questionable external validity of Glyn-Jones 1972 limit the conclusions that can be drawn.

No studies specifically examined measles outbreak prevention or cessation and this is perhaps not unexpected given that we did not include interrupted time series study designs in the review. In retrospect, the question of the impact of passive immunisation (and vaccination) on measles outbreaks is distinct from the individual focus of the questions we asked and may be better posed in a separate review.

Quality of the evidence

We rated no included studies at a low risk of bias for all criteria. Critical appraisal was constrained by a lack of information in most studies, yet study authors could not be contacted to supplement the information reported, mostly because of the age of the studies. Despite these limitations, we have rated the overall quality of the evidence as moderate (see Summary of findings for the main comparison; Summary of findings 2). This is for the following reasons:

- Although only one study randomised participants and none of the non-randomised studies adequately controlled for confounders, all prespecified confounders, if present and not controlled for would be expected to cause an underestimation of effect. The prespecified confounders were: dose according to weight, time between exposure and intervention, ‘high risk’ of poor outcome (immunosuppression, pregnancy, infancy), other comorbidity and age. For comparison with no treatment, dose according to weight and time between exposure and intervention are not applicable. Non-random allocation to groups would likely distribute those at ‘high risk’, including those with comorbidity or of particularly susceptible age, into the treatment group because of the tendency to present for preventive treatment and because of the clinician’s desire for a good outcome. If we consider that this group is most likely to become ill with measles, random allocation would have increased the estimate of the effect of treatment. The non-randomised study included in the comparison of gamma globulin and serum controlled for time between exposure and intervention by restriction, and demonstrated even distribution according to age group between treatment groups. As gamma globulin was thought to be the better product as outlined in the study’s introduction, those at ‘high risk’, including participants with comorbidity, would have a tendency to be allocated to the gamma globulin group, meaning that random allocation would result in an increased estimate of effect. Similarly, as gamma globulin was thought to be ‘more potent’, the study shows that the proportion of older children who were given the smallest volume of gamma globulin was larger than the proportion of older children given the smallest volume of serum. Confounding because of failing to dose per unit of weight is thus likely (more of the gamma globulin group would have received a smaller dose per unit weight), but would result in an underestimate of the effect of gamma globulin.

- The other important point of potential bias for these studies was measurement bias in relation to the outcome. There was only one study that we assessed as at high risk of bias under this criterion and this was for the outcome ‘measles complications’. All other studies were at low or unclear risk of bias. Lack of information usually resulted in the unclear rating. For most studies, measles was diagnosed by a physician but blinding to treatment group was unknown. The age of the studies meant that the diagnosis was not usually confirmed by laboratory testing. If the assessors were not blind, there may be a bias operating that would overestimate the effect of passive immunisation. However, the effect size was very large and therefore likely still to be significant even if this bias was realised.

- The gamma globulin estimates of effect are particularly pertinent to current practice. Meta-analytic comparison of gamma globulin compared to another immunoglobulin preparation for the outcome ‘measles cases’ consisted of two studies, one at low risk of measurement bias and the other at unclear risk. In this comparison, the study at unclear risk had a smaller estimate of effect than the one at low risk. Meta-analytic comparison of gamma globulin compared to no treatment consisted of two studies, again one at low risk of measurement bias in relation to the outcome ‘measles cases’ and one at unclear risk. In this comparison, the study at unclear risk did have a slightly larger effect size but the results of both studies were still homogenous.

- Acknowledging that dose was approximately, an apparent dose effect was observed, increasing confidence in the results.

Potential biases in the review process

We used a filter for study design to reduce the results of the electronic searches to a manageable number. However, the use of the filter may have excluded relevant studies.

We were unable to contact the study authors of many of the retrieved studies, therefore we necessarily relied on reported information. We therefore may have excluded relevant studies because of the lack of information reported about participant exposure and/or susceptibility and/or the populations from which participants (mainly controls) were selected.

Post-exposure passive immunisation for preventing measles (Review)
Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
We were not aware, prior to retrieving studies, that immunoglobulins had been sourced from other than human sera or plasma in the early days of passive immunisation and this resulted in a narrowing of the intervention inclusion criteria during the review process.

It may be argued that the inclusion of non-randomised studies introduces a bias into the review. However, as outlined above, non-even distribution of confounders between study groups is likely to have underestimated rather than overestimated the effect size in this case.

In the absence of reported doses of measles-specific immunoglobulins administered to intervention groups, we used blood product as an approximation of dose, acknowledging the inherent imprecision.

Agreements and disagreements with other studies or reviews

No previous systematic reviews have examined passive immunisation for the prevention of measles. Ramsay 2009 presented an account of some studies that have contributed to the field, noting the varying estimates of effectiveness. Some of the studies cited by Ramsay 2009 were included in our review (Endo 2001; Ordman 1944), while others did not meet our inclusion criteria (Black 1960; King 1991; Stokes 1944). Ramsay 2009 also suggested that the dose of measles-specific antibody is important to the estimates of effect.

Authors' conclusions

Implications for practice

Compared to no treatment, passive immunisation is of benefit for preventing measles up to seven days after exposure. Considering the results for gamma globulin (the current immunoglobulin preparation used in practice) and the attack rate of measles in the control group of the most recent included study (45 per 1000) (Sheppeard 2009), the absolute risk reduction for passive immunisation is 37 and the number needed to treat to benefit (NNTB) is 27 compared to no treatment. Adopting the attack rate of the control group of the other study comparing gamma globulin to no treatment (759 per 1000) (Ordman 1944), the absolute risk reduction would be 629 and the NNTB would be two.

The data for a dose-response effect in our review has come from subgroup estimates of the different blood products used in the included studies for preventing measles. There is insufficient evidence to conclude a minimum effective dose of measles-specific antibodies.

There is insufficient evidence to make firm conclusions regarding the relative effectiveness of passive immunisation compared to vaccination at this time.

Implications for research

With the evidence available (of moderate quality), it is clear that passive immunisation has a large protective effect against measles for those who are exposed and not immune. However, the available evidence does not include pregnant women nor people who are immunocompromised and does not adequately distinguish infants from older participants. This 'high-risk' group are particularly mentioned in existing public health recommendations about passive immunisation from countries with low incidences of measles. Future research should consider the effectiveness of passive immunisation for preventing measles in this defined 'high-risk' population and include careful recording of any potential adverse events.

As a dose effect is clearly observed, further efforts should be made to determine the minimum effective dose of measles-specific antibodies. If sufficient information exists, this may be possible to do via retrospective cohort studies. In the absence of routinely collected data that include the measles-specific antibody level of any immunoglobulin administered, ethical considerations would likely limit this avenue of study to in vitro experiments.

In this era where measles vaccination is recommended for post-exposure prophylaxis for those not at 'high risk', future studies should also consider the comparative effectiveness of measles vaccine if possible.

Acknowledgements

We would like to thank Liz Dooley and Clare Dooley for their support and assistance. We also wish to thank the following people for commenting on the draft protocol: Theresa Wrangham, Sushil Kabra, Segun Bello, Viviana Rodriguez and Taixiang Wu. Finally we thank the following people for commenting on the draft review: Theresa Wrangham, Sushil Kabra, Segun Bello, Robert Ware and Taixiang Wu.
Post-exposure passive immunisation for preventing measles (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.

References to studies included in this review

Berkovich 1963 (published data only)

Cockburn 1950 (published data only)

Degkwitz 1920 (published data only)

Endo 2001 (published data only; unpublished sought but not used)

Glyn-Jones 1972 (published data only)

Hartley 1948 (published data only)

Morales 1930 (published data only)

Ordman 1944 (published data only)

Salomon 1923 (published data only)

Sheppeard 2009 (published and unpublished data)

Stillerberg 1944 (published data only)

Toomey 1926 (published data only)

Wesselhoeft 1928 (published data only)

References to studies excluded from this review

Barenberg 1930 (published data only)

Benson 1927 (published data only)

Blackfan 1923 (published data only)

Christensen 1953 (published data only)

Gunn 1928 (published data only)

Haas 1926 (published data only)

Karelitz 1938 (published data only)

King 1991 (published data only)
Kingsbury 1927 [published data only]

Laning 1935 [published data only]

LeBlanc 2012 [published and unpublished data]

Lempiäri 1939 [published data only]

McGuinness 1943 [published data only]

Monnet 1954 [published data only]

Rivera 1991 [published data only (unpublished sought but not used)]

Weaver 1924 [published data only]

Zingher 1924 [published data only]

Additional references

ATAGI 2008

Barrabéig 2011

Best 2011

Birdsell 2009

Black 1960

Castillo-Solorzano 2011

CDC 1998

CDC 2011a

CDC 2011b

CDNA 2009

Delaporte 2011

DVD CDC 2011

EMEA 1995

Gonik 2011

GRADEpro 2008

Gustavo 2008

Heymann 2008

Karelitz 1937

Keller 2000

Martin 2011

Moss 2009

NZ MoH 2011

Parker Fiebelkorn 2010

Ramsay 2009

Reading 2007

Sawyer 2000

Smithson 2010

Sniadack 2011

Stokes 1944

Takimoto 2011

Thalheimer 1939
UK DoH 2010

Vainio 2011

WHO 1999

WHO 2005

WHO 2008

WHO 2009a

WHO 2009b

WHO 2012

WHO 2013

WHO 2014

* Indicates the major publication for the study
## CHARACTERISTICS OF STUDIES

### Characteristics of included studies [ordered by study ID]

#### Berkovich 1963

<table>
<thead>
<tr>
<th>Methods</th>
<th>Non-RCT undertaken in December 1961</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Tuberculous patients housed together in a children’s ward of a New York hospital, USA and exposed to a symptomatic case of measles on the ward. Age and gender not reported</td>
</tr>
</tbody>
</table>
| Interventions | 1. Commercially produced gamma globulin of 512 neutralising measles titre intramuscularly at 0.1 ml/pound of body weight  
2. Ender’s live measles virus vaccine and same lot of commercially produced gamma globulin at 0.02 ml/pound body weight intramuscularly at separate sites |
| Outcomes | Cases of measles |
| Total length of follow up | 20 days |
| Notes | - |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Those with parental consent received live virus vaccine while those without consent for the vaccine received gamma globulin only</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of both interventions is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not clear who assessed the participants for signs of measles and no standard definition of measles was reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in the results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>
Berkovich 1963  (Continued)

<table>
<thead>
<tr>
<th>Confounding</th>
<th>High risk</th>
<th>No measurement of or control for potential confounders</th>
</tr>
</thead>
</table>

Cockburn 1950

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT undertaken in early 1949</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Children aged between 6 and 60 months of age who attended or resided at child care institutions in England and Scotland. Around 5% were under the age of 1 year. Just over half the participants were male</td>
</tr>
</tbody>
</table>
| Interventions        | 1. 225 mg to 450 mg of freeze-dried gamma globulin dissolved in 3 ml to 6 ml of sterile, distilled water immediately before intramuscular injection  
2. 5 ml adult serum containing 0.5% phenol or reconstituted dried plasma intramuscularly |
| Outcomes             | Cases of measles  
Complications due to measles  
Adverse events |
| Total length of follow up | 21 days |
| Notes                | Adverse events not specified as an outcome in the methods but reported for both groups collectively: “Apart from transient limb stiffness lasting one or two hours in a few cases, no local reactions were observed in the globulin or adult-serum groups. One child in the globulin group developed, three days after inoculation, an urticarial rash which disappeared in twenty-four hours” (pg 735) |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>A person who was not giving the injections provided for each study locality a list of pairs of letters, “G” for gamma globulin and “A” for adult serum. The order in which the letters appeared in the pair was determined by “random sampling numbers”. No further information was reported on how numbers were generated</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Person giving injections made a list of all eligible consenting contacts, dividing them into groups according to predefined “intimacy of exposure” levels. Within each subgroup participants were listed in order of increasing age. From the top of the list, those in each pair were then allocated based on the letter list. Once used, the pair of letters was crossed off the list</td>
</tr>
</tbody>
</table>
### Cockburn 1950 (Continued)

<table>
<thead>
<tr>
<th>Bias Type</th>
<th>Risk Assessment</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>Performance bias: The nature of the interventions means they are not subject to variation due to performance</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Detection bias: The details of the intervention were recorded and then filed away, with subsequent clinical observations recorded on a separate sheet (pg 733). While the doctors who gave the injections were the assessors of the outcomes, the authors tested recall of which child had which intervention in a preliminary study and “it was practically impossible for the observer to remember after inoculating the children whether a particular child had been given gamma globulin or adult serum”</td>
</tr>
<tr>
<td>Cases of measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Detection bias: As with cases of measles outcome</td>
</tr>
<tr>
<td>Complications from measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Detection bias: As with cases of measles outcome</td>
</tr>
<tr>
<td>Adverse events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data</td>
<td>Low risk</td>
<td>Attrition bias: No loss to follow-up apparent. Each child was observed for 21 days at the child care institutions. If the child was absent, they were visited at their home. If no cases of measles occurred in the contacts within 21 days, the trial at that institution was closed</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting</td>
<td>Low risk</td>
<td>Reporting bias: No outcomes specified that were not reported</td>
</tr>
<tr>
<td>(reporting bias)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Degkwitz 1920

<table>
<thead>
<tr>
<th>Method</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>Non-RCT. Year study undertaken not known</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Children aged 8 months to 13.5 years, exposed to measles in a hospital in Germany</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>1. Convalescent serum administered on day 4 after exposure, 3 ml versus 2.5 ml as control</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2. Convalescent serum 6 ml to 7 ml administered on day 6 after exposure versus day 7 after exposure as control</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Measles cases</td>
<td></td>
</tr>
<tr>
<td>Total length of follow up</td>
<td>Not reported</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Article in German - assessment based on translation form information</td>
<td></td>
</tr>
</tbody>
</table>
### Degkwitz 1920 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Not reported how participants were allocated to groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Not clear who assessed the participants for signs of measles and no standard definition of measles was reported</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants accounted for in the results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
<tr>
<td>Confounding</td>
<td>High risk</td>
<td>No measurement of or control for potential confounders</td>
</tr>
</tbody>
</table>

**Endo 2001**

**Methods**

Non-RCT undertaken in 1999 to 2000

**Participants**

Susceptible infants and toddlers in Japan, of average age 1.5 years, who had close contact with someone with measles and whose parents consented to participate in the study. 24 boys and 9 girls were enrolled

**Interventions**

Intramuscular immunoglobulin 0.33 ml/kg within 5 days of exposure. 4 different lots of commercially obtained immunoglobulins were used. The concentrations of measles-specific antibody in each were: 16 IU/ml, 33 IU/ml, 40 IU/ml, 45 IU/ml

**Outcomes**

Cases of measles

**Total length of follow up**

14 days

**Notes**

Adverse events not reported
### Endo 2001 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. It is not reported how participants were allocated to the different lots of immunoglobulin</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Parents were asked to report fever or rash over the 2 weeks subsequent to intervention. Upon report, a physician examined the child to confirm the diagnosis. It is not reported whether the physician was aware of which lot of IG was administered</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Unclear risk</td>
<td>It is not clear whether those parents who did not report illness of their child were actively followed up although the results suggest follow-up was complete</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
<tr>
<td>Confounding</td>
<td>High risk</td>
<td>Comparison is made between the 9 children with clinical measles and the 24 children without clinical measles over the follow-up period in terms of age, body weight, interval between exposure and intervention, dose of IG in ml/kg and measles-specific antibody titre, suggesting no difference in these characteristics between the 2 groups apart from the mean measles-specific antibody titre administered. There is no control for confounding according to lot of IG administered</td>
</tr>
</tbody>
</table>

### Glyn-Jones 1972

<table>
<thead>
<tr>
<th>Methods</th>
<th>Quasi-RCT undertaken in 1968 to 1969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Susceptible children aged 6 to 35 months admitted to the paediatric unit at Mpilo Hospital in Zimbabwe ('Rhodesia' at the time of the study) who were alive the day after admission</td>
</tr>
</tbody>
</table>
### Interventions
- 1. Human immune globulin 2 ml intramuscularly on the day after admission, repeated at 3-weekly intervals until discharge
- 2. No treatment
- 3. Measles vaccine, 1 dose intramuscularly on the day after admission

### Outcomes
- Cases of measles
- Deaths due to measles
- Complications from measles
- Adverse events - measles vaccine reactions

### Total length of follow up
At least 2 weeks after discharge from hospital

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Assigned sequentially according to admission order</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Treatment group assigned by author’s colleague and given to senior ward nurses who administered the treatment (pg 4). Unclear if the colleague was involved in the care of the participants</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the interventions means they are not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Low risk</td>
<td>All assessment of participants carried out by author who was not aware of group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Complications from measles</td>
<td>Low risk</td>
<td>All assessment of participants carried out by author who was not aware of group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Deaths due to measles</td>
<td>Low risk</td>
<td>All assessment of participants carried out by author who was not aware of group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Adverse events</td>
<td>Low risk</td>
<td>All assessment of participants carried out by author who was not aware of group allocation</td>
</tr>
<tr>
<td>Bias</td>
<td>Authors’ judgement</td>
<td>Support for judgement</td>
</tr>
<tr>
<td>------------------------------------------------</td>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Not reported how contacts were allocated to intervention group</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the interventions means they are not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not reported who assessed the participants for signs of measles and measles is not defined for the purposes of the study</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in the results</td>
</tr>
</tbody>
</table>
**Selective reporting (reporting bias)** | Low risk | No outcomes specified in the methods that were not reported |
---|---|---|
**Confounding** | High risk | Did not dose according to weight and did not account for 'high risk' of illness or other comorbidity. Restricted based on time between exposure and intervention and stratified by dose of gamma globulin/serum, age and place of exposure |

### Morales 1930

**Methods** | Quasi-RCT undertaken in 1928 to 1929 |
**Participants** | Susceptible children aged 6 months to 15 years old in Porto Rico exposed to a household case of measles |
**Interventions** | 1. “Injection” of 4 ml to 6 ml pooled convalescent serum obtained from the 5th to 10th day of convalescence  
2. “Injection” of 10 ml to 40 ml pooled serum from adult donors with a history of measles between 1 and 10 years ago  
3. No treatment |
**Outcomes** | Cases of measles  
Complications due to measles  
Deaths due to measles  
Adverse events |
**Total length of follow up** | 8 weeks following exposure |
**Notes** | Adverse events very poorly reported: “Among more than 500 who received injections of serum, only 2 children showed reactions; they had slight fever, accompanied by an urticarial rash” (pg 1218) |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>“Every third child was regarded as a control and received no treatment, while each of the remainder received an injection of either convalescent or immune serum” (pg 1216)</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not reported who allocated participants to groups or whether the person allocating had any knowledge of participant characteristics</td>
</tr>
</tbody>
</table>
### Morales 1930 (Continued)

<table>
<thead>
<tr>
<th>Blinding of participants and personnel (performance bias) All outcomes</th>
<th>Low risk</th>
<th>The nature of the interventions means they are not subject to variation due to performance</th>
</tr>
</thead>
<tbody>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Inspectors visited the participants at home at regular intervals and reported illness to one author who then visited the participant immediately to determine the cause of illness. Not reported whether the author was blinded to intervention group</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Complications from measles</td>
<td>Unclear risk</td>
<td>No definition of complications from measles is reported for the purposes of study. Not reported who assessed participants for complications or whether they were blind to intervention group</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Deaths due to measles</td>
<td>Unclear risk</td>
<td>Unclear whether the author who confirmed measles diagnosis was blind to intervention status. Unclear whether the deaths reported are only those felt to be connected to measles or all deaths</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Adverse events</td>
<td>Unclear risk</td>
<td>Inspectors visited the participants at home at regular intervals and reported illness to one author who then visited the participant immediately to determine the cause of illness. Not reported whether the author was blinded to intervention group</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

### Ordman 1944

<table>
<thead>
<tr>
<th>Methods</th>
<th>Non-RCT undertaken in 1942 to 1943</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Susceptible children 6 months of age and older living in Boston, USA exposed to a household member with measles</td>
</tr>
<tr>
<td>Interventions</td>
<td>1. Single batch of gamma globulin prepared by Cohn cold ethanol fractionation 2 ml to 5 ml IM in the gluteal region 2. No treatment</td>
</tr>
</tbody>
</table>
Outcomes

Cases of measles
Complications due to measles

Total length of follow up

3 weeks after intervention

Notes

Adverse reactions not specified as an outcome in the methods, poorly reported and not specific for this cohort. “No severe reactions have been observed in the several hundred individuals inoculated with it. In less than 5 per cent of these, mild reactions occurred. With a single exception, the reactions consisted of a slight feeling of stiffness in the muscle injected or a little local erythema and induration. In one case, the individual had a rise in temperature to 102°F 2 days after inoculation but no other systemic or local manifestation. Whether or not this febrile reaction was due to the globulin cannot be stated” (pg 547)

Risk of bias

Bias | Authors’ judgement | Support for judgement
---|---|---
Random sequence generation (selection bias) | High risk | Not randomised
Allocation concealment (selection bias) | High risk | “When there were 2 or more susceptible contacts in a family, they were divided into 2 groups composed of persons as nearly alike as possible with respect to age and degree of exposure. Children over 15 years of age were placed in the control group” (pg 542)
Blinding of participants and personnel (performance bias) | Low risk | The nature of the intervention means it is not subject to variation due to performance
Blinding of outcome assessment (detection bias) | Unclear risk | Family was visited by one of the authors at each follow-up. Not reported whether assessors were different to those who had given the interventions or whether they were blinded to intervention group
Incomplete outcome data (attrition bias) | Low risk | All participants accounted for in results
Selective reporting (reporting bias) | Low risk | No outcomes specified in the methods that were not reported
<table>
<thead>
<tr>
<th><strong>Confounding</strong></th>
<th><strong>High risk</strong></th>
<th>Adjusted dose to age as in methodological protocol but no other measurement or control for confounding</th>
</tr>
</thead>
</table>

**Salomon 1923**

<table>
<thead>
<tr>
<th><strong>Methods</strong></th>
<th>Non-RCT. Year study undertaken not reported</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants</strong></td>
<td>Children aged older than 3 months in a hospital in Germany</td>
</tr>
</tbody>
</table>
| **Interventions** | 1. Convalescent serum (dose not reported)  
2. Adult serum 10 ml to 15 ml  
3. No treatment |
| **Outcomes** | Measles cases  
Death due to measles |
| **Total length of follow up** | Not reported |
| **Notes** | Article in German. Assessment based on translation form information |

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Interventions administered sequentially in blocks of time according to availability</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not clear who assessed the participants for signs of measles and no standard definition of measles was reported</td>
</tr>
<tr>
<td>Cases of measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not clear who assessed the participants regarding death due to measles or whether they were blind to group allocation</td>
</tr>
<tr>
<td>Deaths due to measles</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### Salomon 1923 (Continued)

<table>
<thead>
<tr>
<th>Risk of bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Allocation determined by length of time from exposure at point of contact with participant</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the interventions means they are not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Low risk</td>
<td>Case of measles defined for the purposes of the study, criteria objective and likely assessed by other than the authors</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Follow-up by passive surveillance</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

### Sheppeard 2009

<table>
<thead>
<tr>
<th>Methods</th>
<th>Non-RCT undertaken in 2006</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Susceptible contacts (aged 6 months to 40+ years) of confirmed cases of measles notified to New South Wales public health units</td>
</tr>
<tr>
<td>Interventions</td>
<td>1. MMR if within 3 days of exposure 2. Normal human immunoglobulin (gamma globulin) within 7 days of exposure, 0.2 ml/kg up to 15 ml 3. No treatment</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Cases of measles</td>
</tr>
<tr>
<td>Total length of follow up</td>
<td>Passive surveillance until 2 incubation periods after the last notified case</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Allocation determined by length of time from exposure at point of contact with participant</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the interventions means they are not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Low risk</td>
<td>Case of measles defined for the purposes of the study, criteria objective and likely assessed by other than the authors</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>High risk</td>
<td>Follow-up by passive surveillance</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>
### Confounding

<table>
<thead>
<tr>
<th></th>
<th>High risk</th>
<th>No control of potential confounders. Measured setting of exposure only</th>
</tr>
</thead>
</table>

### Stillerman 1944

#### Methods

Non-RCT undertaken in 1938-1941

#### Participants

Healthy, susceptible children living in New York city, USA, aged 6 months to 15 years who were exposed to a family member in their household who had been diagnosed with measles

#### Interventions

1. Pooled convalescent serum (collected from adolescents and adults up to 4 months after the onset of measles) 5 ml to 20 ml administered IM into the upper outer aspect of the buttock or the thigh
2. No treatment

#### Outcomes

Cases of measles
Complications from measles

#### Total length of follow up

Up to 23 days after exposure

#### Notes

- 

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Not reported how participants were allocated to groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Unclear risk</td>
<td>Not reported who assessed participants for measles or whether they were blind to group allocation</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>High risk</td>
<td>Complications only reported for intervention group. Control only followed up until rash onset if they became ill</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results for cases of measles</td>
</tr>
</tbody>
</table>
Selective reporting (reporting bias) | Low risk | No outcomes specified that were not reported
---|---|---
Confounding | High risk | Restricted against 'high-risk' contacts in terms of comorbidity. Measured most prespecified confounders but only undertook univariate analyses. Did not dose according to weight

**Toomey 1926**

Methods | Non-RCT undertaken in 1925
Participants | Cohort of susceptible 'children' exposed on the same hospital ward in the 2 days prior. Age and gender not reported
Interventions | 1. Convalescent serum (obtained 8 days after the rash began to disappear) 2.5 ml to 5 ml administered intramuscularly 2. No treatment
Outcomes | Cases of measles
Total length of follow up | 60 days
Notes | Some children had a second exposure Adverse reactions not specified as an outcome in the methods, poorly reported and not specific for this cohort. "There was no local reaction to the injection. In most instances there was a rise in temperature of from 1 to 1.5°C, beginning within twenty-four hours after the injection and lasting rarely longer than twenty-four hours. In six susceptible subjects, diarrhea was noted" (pg 401)

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised. Not reported how participants allocated to groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Not reported who assessed participants for signs of measles or whether they were blind to group allocation; no standard definition of measles was reported</td>
</tr>
</tbody>
</table>
Toomey 1926  (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised, Not reported how participants were allocated to groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Not reported who assessed participants for signs of measles or whether they were blind to group allocation and no standard definition of measles was reported</td>
</tr>
</tbody>
</table>

Wesselhoeft 1928

<table>
<thead>
<tr>
<th>Methods</th>
<th>Non-RCT undertaken in 1928</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Susceptible children exposed to measles in the diptheria and scarlet fever wings of a hospital in Boston, USA. Age and gender not reported</td>
</tr>
</tbody>
</table>
| Interventions                    | 1. Convalescent serum (collected from older children and adults) 5 ml administered intramuscularly  
                                      2. No treatment |
| Outcomes                         | Cases of measles  
                                      Complications due to measles  
                                      Deaths due to measles |
| Total length of follow up        | Not reported |
| Notes                            | - |

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>High risk</td>
<td>Not randomised</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>High risk</td>
<td>Not randomised, Not reported how participants were allocated to groups</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of measles</td>
<td>Unclear risk</td>
<td>Not reported who assessed participants for signs of measles or whether they were blind to group allocation and no standard definition of measles was reported</td>
</tr>
</tbody>
</table>
### Characteristics of excluded studies  
*ordered by study ID*

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Barenberg 1930</td>
<td>Unclear whether all participants were exposed</td>
</tr>
<tr>
<td>Benson 1927</td>
<td>Intervention and control groups not recruited over similar and overlapping time periods</td>
</tr>
<tr>
<td>Blackfan 1923</td>
<td>Unclear whether all participants were susceptible</td>
</tr>
<tr>
<td>Christensen 1953</td>
<td>Unclear whether all controls were susceptible and placental and plasma globulin were combined as one intervention (results for each not separable)</td>
</tr>
<tr>
<td>Gann 1928</td>
<td>No definable control group for intervention of relevance</td>
</tr>
<tr>
<td>Haas 1926</td>
<td>Unclear whether all controls were susceptible</td>
</tr>
<tr>
<td>Karelitz 1938</td>
<td>Unclear whether all participants susceptible</td>
</tr>
<tr>
<td>King 1991</td>
<td>Retrospective cohort study</td>
</tr>
<tr>
<td>Kingsbury 1927</td>
<td>Unclear whether all participants exposed and unclear whether all susceptible</td>
</tr>
</tbody>
</table>

---

**Wesselhoeft 1928 (Continued)**

| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported who assessed participants for complications due to measles or whether they were blind to group allocation |
| Blinding of outcome assessment (detection bias) | Unclear risk | Not reported who assessed participants regarding death due to measles or whether they were blind to group allocation |
| Incomplete outcome data (attrition bias)        | Low risk     | All participants accounted for in results                                                  |
| Selective reporting (reporting bias)            | Low risk     | No outcomes specified that were not reported                                              |
| Confounding                                     | High risk    | No measurement of or control for potential confounders                                   |

RCT = randomised controlled trial  
IG = immunoglobulin  
IM = intramuscularly  
MMR = measles, mumps and rubella vaccine
We retrieved 144 full-text articles for assessment and excluded 131 of these from the review. Studies included in the above table are those that were discussed by the authors, after comparison of their independent assessments, because either one or both authors listed the study as ‘unsure’ for inclusion or because there was disagreement in the results of independent assessment.

<table>
<thead>
<tr>
<th>Author</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Laning 1935</td>
<td>Immunoglobulin used was derived from placentas</td>
</tr>
<tr>
<td>LeBlanc 2012</td>
<td>Communication from author that study was retrospective</td>
</tr>
<tr>
<td>Lempriere 1939</td>
<td>Unclear whether all participants were exposed</td>
</tr>
<tr>
<td>McGuinness 1943</td>
<td>Unclear whether control group were comparable and unclear whether all were susceptible</td>
</tr>
<tr>
<td>Monnet 1954</td>
<td>Intervention and control groups not recruited over similar and overlapping time periods</td>
</tr>
<tr>
<td>Rivera 1991</td>
<td>Unable to contact study author for further details. Review authors agreed retrospective study from published details</td>
</tr>
<tr>
<td>Weaver 1924</td>
<td>Unclear whether controls came from the same exposed population as the intervention group</td>
</tr>
<tr>
<td>Zingher 1924</td>
<td>Unclear whether all were susceptible</td>
</tr>
</tbody>
</table>
## Data and Analyses

Comparison 1. Immunoglobulin versus no treatment

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Measles cases</td>
<td>7</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Totals not selected</td>
</tr>
<tr>
<td>2 Measles cases</td>
<td>7</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>2.1 Quasi-RCTs</td>
<td>1</td>
<td>696</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.38 [0.32, 0.45]</td>
</tr>
<tr>
<td>2.2 Cohort type studies</td>
<td>6</td>
<td>1575</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.52 [0.48, 0.57]</td>
</tr>
<tr>
<td>2.3 Included infants &lt; 6 months of age</td>
<td>1</td>
<td>194</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.46 [0.38, 0.56]</td>
</tr>
<tr>
<td>2.4 Did not include infants &lt; 6 months of age</td>
<td>5</td>
<td>2001</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.49 [0.45, 0.54]</td>
</tr>
<tr>
<td>2.5 Convalescent serum</td>
<td>5</td>
<td>1140</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.49 [0.44, 0.54]</td>
</tr>
<tr>
<td>2.6 Adult serum</td>
<td>2</td>
<td>586</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.52 [0.45, 0.59]</td>
</tr>
<tr>
<td>2.7 Gamma globulin</td>
<td>2</td>
<td>545</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.17 [0.08, 0.36]</td>
</tr>
<tr>
<td>3 Measles cases</td>
<td>6</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>3.1 Convalescent serum</td>
<td>3</td>
<td>301</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.21 [0.15, 0.29]</td>
</tr>
<tr>
<td>3.2 Adult serum</td>
<td>2</td>
<td>586</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.52 [0.45, 0.59]</td>
</tr>
<tr>
<td>3.3 Gamma globulin</td>
<td>2</td>
<td>545</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.17 [0.08, 0.36]</td>
</tr>
<tr>
<td>4 Mortality due to measles</td>
<td>3</td>
<td>893</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.24 [0.13, 0.44]</td>
</tr>
<tr>
<td>5 Complications due to measles</td>
<td>3</td>
<td>832</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.18 [0.05, 0.60]</td>
</tr>
</tbody>
</table>

Comparison 2. Gamma globulin versus serum

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Measles cases</td>
<td>2</td>
<td>702</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.56 [0.46, 0.69]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Immunoglobulin versus no treatment, Outcome 1 Measles cases.

Review: Post-exposure passive immunisation for preventing measles

Comparison: 1 Immunoglobulin versus no treatment

Outcome: 1 Measles cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 1930</td>
<td>166/393</td>
<td>74/92</td>
<td>0.53 [ 0.45, 0.61 ]</td>
</tr>
<tr>
<td>Morales 1930</td>
<td>18/120</td>
<td>75/92</td>
<td>0.18 [ 0.12, 0.28 ]</td>
</tr>
<tr>
<td>Chalmers 1944</td>
<td>5/45</td>
<td>22/29</td>
<td>0.15 [ 0.06, 0.34 ]</td>
</tr>
<tr>
<td>Salmon 1923</td>
<td>25/62</td>
<td>30/30</td>
<td>0.41 [ 0.30, 0.56 ]</td>
</tr>
<tr>
<td>Salmon 1923</td>
<td>36/72</td>
<td>30/30</td>
<td>0.51 [ 0.40, 0.64 ]</td>
</tr>
<tr>
<td>Shepeard 2009</td>
<td>2/183</td>
<td>13/288</td>
<td>0.24 [ 0.06, 1.06 ]</td>
</tr>
<tr>
<td>Stillman 1944</td>
<td>252/502</td>
<td>195/245</td>
<td>0.63 [ 0.57, 0.70 ]</td>
</tr>
<tr>
<td>Tookey 1926</td>
<td>17/19</td>
<td>6/6</td>
<td>0.20 [ 0.05, 0.87 ]</td>
</tr>
<tr>
<td>Wesselhoeft 1928</td>
<td>14/51</td>
<td>25/25</td>
<td>0.28 [ 0.18, 0.44 ]</td>
</tr>
</tbody>
</table>

0.002 0.1 1 10 500
Favours immunoglobulin  Favours no treatment

Post-exposure passive immunisation for preventing measles (Review)

Copyright © 2014 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 1.2. Comparison 1 Immunoglobulin versus no treatment, Outcome 2 Measles cases.

Review: Post-exposure passive immunisation for preventing measles

Comparison: 1 Immunoglobulin versus no treatment

Outcome: 2 Measles cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>1 Quasi-RCTs</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>18/120</td>
<td>75/92</td>
<td>41.4 %</td>
<td>0.18 [0.12, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>166/393</td>
<td>74/91</td>
<td>58.6 %</td>
<td>0.52 [0.45, 0.60]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>513</strong></td>
<td><strong>183</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.38 [0.32, 0.45]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>184 (Immunoglobulin), 149 (No treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 26.75, df = 1 (P&lt;0.00001); I² = 96%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 11.60 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

2 Cohort type studies

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Ordman 1944</td>
<td>5/45</td>
<td>22/29</td>
<td>6.3 %</td>
<td>0.15 [0.06, 0.34]</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>36/72</td>
<td>30/30</td>
<td>10.1 %</td>
<td>0.51 [0.40, 0.64]</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>25/62</td>
<td>30/30</td>
<td>9.7 %</td>
<td>0.41 [0.30, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Sheppeard 2009</td>
<td>2/183</td>
<td>13/288</td>
<td>2.4 %</td>
<td>0.24 [0.16, 0.36]</td>
<td></td>
</tr>
<tr>
<td>Stillerman 1944</td>
<td>252/502</td>
<td>195/245</td>
<td>61.9 %</td>
<td>0.63 [0.57, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Tomsen 1926</td>
<td>1/7</td>
<td>6/6</td>
<td>1.6 %</td>
<td>0.20 [0.05, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Weissehoft 1928</td>
<td>14/51</td>
<td>25/25</td>
<td>8.0 %</td>
<td>0.28 [0.18, 0.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>922</strong></td>
<td><strong>653</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.52 [0.48, 0.57]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>335 (Immunoglobulin), 321 (No treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 32.75, df = 6 (P = 0.00001); I² = 82%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 13.51 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

3 Included infants < 6 months of age

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>25/62</td>
<td>30/30</td>
<td>48.8 %</td>
<td>0.41 [0.30, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>36/72</td>
<td>30/30</td>
<td>51.2 %</td>
<td>0.51 [0.40, 0.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>134</strong></td>
<td><strong>60</strong></td>
<td><strong>100.0 %</strong></td>
<td><strong>0.46 [0.38, 0.56]</strong></td>
<td></td>
</tr>
<tr>
<td>Total events:</td>
<td>61 (Immunoglobulin), 60 (No treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity:</td>
<td>Chi² = 1.21, df = 1 (P = 0.27); I² = 17%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 8.08 (P &lt; 0.00001)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

4 Did not include infants < 6 months of age

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 1930</td>
<td>166/393</td>
<td>74/91</td>
<td>23.5 %</td>
<td>0.52 [0.45, 0.60]</td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>18/120</td>
<td>75/92</td>
<td>16.6 %</td>
<td>0.18 [0.12, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Ordman 1944</td>
<td>5/45</td>
<td>22/29</td>
<td>5.2 %</td>
<td>0.15 [0.06, 0.34]</td>
<td></td>
</tr>
</tbody>
</table>

Continued...
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sheppeard 2009</td>
<td>2/183</td>
<td>13/288</td>
<td>2.0 % 0.24 [0.06, 1.06]</td>
<td></td>
</tr>
<tr>
<td>Stillerman 1944</td>
<td>252/502</td>
<td>195/245</td>
<td>5.13 % 0.63 [0.57, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Toomey 1926</td>
<td>1/7</td>
<td>6/6</td>
<td>1.4 % 0.20 [0.05, 0.87]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1250</strong></td>
<td><strong>751</strong></td>
<td><strong>100.0 % 0.49 [0.45, 0.54]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>5 Convalescent serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>18/120</td>
<td>75/92</td>
<td>19.8 % 0.18 [0.12, 0.28]</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>25/62</td>
<td>30/30</td>
<td>9.5 % 0.41 [0.30, 0.56]</td>
<td></td>
</tr>
<tr>
<td>Stillerman 1944</td>
<td>252/502</td>
<td>195/245</td>
<td>6.11 % 0.63 [0.57, 0.70]</td>
<td></td>
</tr>
<tr>
<td>Toomey 1926</td>
<td>1/7</td>
<td>6/6</td>
<td>1.6 % 0.20 [0.05, 0.87]</td>
<td></td>
</tr>
<tr>
<td>Wesselhoeft 1928</td>
<td>14/51</td>
<td>25/25</td>
<td>7.9 % 0.28 [0.18, 0.44]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>742</strong></td>
<td><strong>398</strong></td>
<td><strong>100.0 % 0.49 [0.44, 0.54]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>6 Adult serum</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>166/193</td>
<td>74/91</td>
<td>73.7 % 0.52 [0.45, 0.60]</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>36/72</td>
<td>30/30</td>
<td>26.3 % 0.51 [0.45, 0.64]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>465</strong></td>
<td><strong>121</strong></td>
<td><strong>100.0 % 0.52 [0.45, 0.59]</strong></td>
<td></td>
</tr>
<tr>
<td><strong>7 Gamma globulin</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ordman 1944</td>
<td>5/45</td>
<td>22/29</td>
<td>72.6 % 0.15 [0.06, 0.34]</td>
<td></td>
</tr>
<tr>
<td>Sheppeard 2009</td>
<td>2/183</td>
<td>13/288</td>
<td>27.4 % 0.24 [0.06, 1.06]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>228</strong></td>
<td><strong>317</strong></td>
<td><strong>100.0 % 0.17 [0.08, 0.36]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 50.61, df = 5 (P=0.00001); I^2 =90\%
Test for overall effect: \( Z = 15.18 \) (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events: 444 (Immunoglobulin), 385 (No treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>1250</strong></td>
<td><strong>751</strong></td>
<td><strong>100.0 % 0.49 [0.45, 0.54]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 49.53, df = 4 (P=0.00001); I^2 =92\%
Test for overall effect: \( Z = 14.04 \) (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events: 310 (Immunoglobulin), 331 (No treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>742</strong></td>
<td><strong>398</strong></td>
<td><strong>100.0 % 0.49 [0.44, 0.54]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 4.95, df = 4 (P=0.00001); I^2 =33\%
Test for overall effect: \( Z = 10.14 \) (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events: 202 (Immunoglobulin), 104 (No treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>465</strong></td>
<td><strong>121</strong></td>
<td><strong>100.0 % 0.52 [0.45, 0.59]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 2.02, df = 1 (P = 0.16); I^2 =0.0\%
Test for overall effect: \( Z = 10.14 \) (P < 0.00001)

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total events: 7 (Immunoglobulin), 35 (No treatment)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>228</strong></td>
<td><strong>317</strong></td>
<td><strong>100.0 % 0.17 [0.08, 0.36]</strong></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: \( \chi^2 = 0.34, df = 1 (P = 0.56); I^2 =0.0\%
Test for overall effect: \( Z = 4.63 \) (P < 0.00001)
Analysis 1.3. Comparison 1 Immunoglobulin versus no treatment, Outcome 3 Measles cases.

Review: Post-exposure passive immunisation for preventing measles.
Comparison: 1 Immunoglobulin versus no treatment
Outcome: 3 Measles cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Convalescent serum</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>18/120</td>
<td>75/92</td>
<td>0.18 [0.12, 0.28]</td>
<td>67.5%</td>
<td></td>
</tr>
<tr>
<td>Toomey 1926</td>
<td>1/7</td>
<td>6/6</td>
<td>0.20 [0.05, 0.87]</td>
<td>5.5%</td>
<td></td>
</tr>
<tr>
<td>Wesselhoeft 1928</td>
<td>14/51</td>
<td>25/25</td>
<td>0.28 [0.18, 0.44]</td>
<td>27.0%</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>178</td>
<td>123</td>
<td>0.21 [0.15, 0.29]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 33 (Immunoglobulin), 106 (No treatment)
Heterogeneity: $\chi^2 = 2.11, df = 2 \ (P = 0.35), I^2 = 0%
Test for overall effect: Z = 9.59 (P < 0.00001)

2 Adult serum
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 1930</td>
<td>166/393</td>
<td>74/91</td>
<td>0.52 [0.45, 0.60]</td>
<td>73.7%</td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>36/72</td>
<td>39/30</td>
<td>0.51 [0.40, 0.64]</td>
<td>26.3%</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>465</td>
<td>121</td>
<td>0.52 [0.45, 0.59]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 202 (Immunoglobulin), 104 (No treatment)
Heterogeneity: $\chi^2 = 0.02, df = 1 \ (P = 0.88), I^2 = 0%
Test for overall effect: Z = 10.14 (P < 0.00001)

3 Gamma globulin
<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin n/N</th>
<th>No treatment n/N</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed,95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ordman 1944</td>
<td>5/45</td>
<td>22/29</td>
<td>0.15 [0.06, 0.34]</td>
<td>72.6%</td>
<td></td>
</tr>
<tr>
<td>Sheppeard 2009</td>
<td>2/183</td>
<td>13/288</td>
<td>0.24 [0.06, 1.06]</td>
<td>27.4%</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>228</td>
<td>317</td>
<td>0.17 [0.08, 0.36]</td>
<td>100.0%</td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7 (Immunoglobulin), 35 (No treatment)
Heterogeneity: $\chi^2 = 0.14, df = 1 \ (P = 0.56), I^2 = 0%
Test for overall effect: Z = 3.63 (P < 0.00001)
Test for subgroup differences: $\chi^2 = 32.43, df = 2 \ (P = 0.00001), I^2 = 94%
### Analysis 1.4. Comparison 1 Immunoglobulin versus no treatment, Outcome 4 Mortality due to measles.

**Review:** Post-exposure passive immunisation for preventing measles

**Comparison:** 1 Immunoglobulin versus no treatment

**Outcome:** 4 Mortality due to measles

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 1930</td>
<td>0/120</td>
<td>1/92</td>
<td>4.1% 0.26 [0.01, 6.22]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>0/393</td>
<td>1/91</td>
<td>5.9% 0.08 [0.00, 1.90]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>4/25</td>
<td>17/30</td>
<td>37.5% 0.28 [0.11, 0.73]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Salomon 1923</td>
<td>5/36</td>
<td>18/30</td>
<td>47.6% 0.23 [0.10, 0.55]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wesselhoeft 1928</td>
<td>0/51</td>
<td>1/25</td>
<td>4.9% 0.17 [0.01, 3.35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>625</strong></td>
<td><strong>268</strong></td>
<td><strong>100.0% 0.24 [0.13, 0.44]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 9 (Immunoglobulin), 38 (No treatment)

Heterogeneity: Chi² = 0.65, df = 4 (P = 0.96); I² = 0.0%

Test for overall effect: Z = 4.67 (P < 0.00001)

Test for subgroup differences: Not applicable
### Analysis 1.5. Comparison 1 Immunoglobulin versus no treatment, Outcome 5 Complications due to measles.

**Review:** Post-exposure passive immunisation for preventing measles

**Comparison:** 1 Immunoglobulin versus no treatment

**Outcome:** 5 Complications due to measles

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Immunoglobulin</th>
<th>No treatment</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Morales 1930</td>
<td>0/393</td>
<td>2/91</td>
<td>27.6 % 0.05 [0.00,0.96]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morales 1930</td>
<td>0/120</td>
<td>2/92</td>
<td>19.3 % 0.15 [0.01,3.16]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ordman 1944</td>
<td>0/17</td>
<td>6/43</td>
<td>25.7 % 0.19 [0.01,3.17]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wesselhoeft 1928</td>
<td>2/51</td>
<td>3/25</td>
<td>27.4 % 0.33 [0.06,1.83]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>581</strong></td>
<td><strong>251</strong></td>
<td><strong>100.0 % 0.18 [0.05,0.60]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 2 (Immunoglobulin), 13 (No treatment)

Heterogeneity: $\chi^2 = 1.23, df = 3 (P = 0.75), I^2 = 0.0$

Test for overall effect: $Z = 2.81$ ($P = 0.0049$)

Test for subgroup differences: Not applicable
Analysis 2.1. Comparison 2 Gamma globulin versus serum, Outcome 1 Measles cases.

Review: Post-exposure passive immunisation for preventing measles
Comparison: 2 Gamma globulin versus serum
Outcome: 1 Measles cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma globulin</th>
<th>Serum</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Cockburn 1950</td>
<td>8/37 (0.33 [0.17, 0.63])</td>
<td>25/118 (15.2 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cockburn 1950</td>
<td>59/175 (0.61 [0.48, 0.78])</td>
<td>98/177 (59.9 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hartley 1948</td>
<td>24/139 (0.59 [0.38, 0.92])</td>
<td>40/136 (24.9 %)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>351 (100.0 %)</td>
<td>351 (0.56 [0.46, 0.69])</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 91 (Gamma globulin), 163 (Serum)
Heterogeneity: Chi² = 3.03, df = 2 (P = 0.22); I² = 34%
Test for overall effect: Z = 5.50 (P < 0.00001)
Test for subgroup differences: Not applicable

APPENDICES

Appendix 1. CENTRAL and MEDLINE (OVID) search strategy
1 exp Measles/ (12564)
2 exp Measles virus/ (5522)
3 measles.tw. (17121)
4 (rubeola or rubeolla).tw. (280)
5 or/1-4 (20953)
6 exp Immunoglobulins/ (703484)
7 (immunoglobulin* or immuno-globulin* or immun* globulin*).tw,nm. (282301)
8 (gammaglobulin* or gamma-globulin* or gamma globulin*).tw,nm. (24894)
9 exp Immunization, Passive/ (27269)
10 (passiv* adj2 (immunotherap* or immuni*)).tw. (4143)
11 (passiv* transfer* adj2 antibod*).tw. (294)
12 passive antibody transfer.rw. (35)
13 Post-Exposure Prophylaxis/ (255)
14 ((post exposur* or post-exposur* or postexposur*) adj2 (prophyla* or prevent*)).tw. (1708)
15 or/6-14 (755709)
16 5 and 15 (4922)
Appendix 2. Embase.com search strategy

#16 #5 AND #15 1938
#15 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 298227
#14 (postexposure* OR post exposure' OR 'post-exposure') NEAR/2 (prophyla* OR prevent*):ab,ti 1589
#13 post exposure prophylaxis/exp 279
#12 (passiv* NEAR/2 (immunother* OR immuni*)):ab,ti 3659
#11 'passive antibody transfer':ab,ti 35
#10 (antibod* NEAR/2 'passive transfer'):ab,ti OR (antibod* NEAR/2 'passively transferred'):ab,ti OR (antibod* NEAR/2 'passively transfer'):ab,ti 251
#9 'passive immunization'/de 5281
#8 gammaglobulin*:ab,ti OR gamma-globulin*:ab,ti OR gamma-globulins:ab,ti OR (gamma NEXT/1 globulin*):ab,ti 5413
#7 immunoglobulin*:ab,ti OR immuno-globulin*:ab,ti OR immuno-globulins:ab,ti OR (immun* NEXT/1 globulin*):ab,ti 1110314
#6 'immunoglobulin'/exp 252149
#5 #1 OR #2 OR #3 OR #4 16468
#4 rubeola:ab,ti OR rubeolla:ab,ti 240
#3 measles:ab,ti 12401
#2 'measles virus'/de 5656
#1 'measles'/de 9241

Appendix 3. CINAHL (EBSCO) search strategy

S14 S4 and S13 108
S13 S5 or S6 or S7 or S8 or S9 or S10 or S11 or S12 8108
S12 TI (((post exposur* or post-exposur* or postexposur*) N2 (prophyla* or prevent*))) OR AB (((post exposur* or post-exposur* or postexposur*) N2 (prophyla* or prevent*))) 413
S11 (MH "Postexposure Follow-Up") 952
S10 TI passive antibody transfer OR AB passive antibody transfer 6
S9 TI passiv* transfer* N2 antibod* OR AB passiv* transfer* N2 antibod* 11
S8 TI (passiv* N2 (immunotherap* or immuni*)) OR AB (passiv* N2 (immunotherap* or immuni*)) 82
S7 TI (gammaglobulin* or gamma-globulin* or gamma globulin*) OR AB (gammaglobulin* or gamma-globulin* or gamma globulin*) 97
S6 TI (immunoglobulin* or immuno-globulin* or immun* globulin*) OR AB (immunoglobulin* or immuno-globulin* or immun* globulin*) 3229
S5 (MH "Immunoglobulin") 5000
S4 S1 or S2 or S3 1902
S3 TI (rubeola or rubeolla ) OR AB ( rubeola or rubeolla ) 17
S2 TI Measles OR AB Measles 1512
S1 (MH "Measles") 1276

Appendix 4. EMBASE and MEDLINE filter for study type

We combined 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 tripel*) 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 Quasisperiment* 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 adj5 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.ab.
49. (or/1-46) not (47 or 48)
Appendix 5. Companies manufacturing immunoglobulin products contacted for unpublished studies

- Bayer Healthcare Pharmaceuticals
- BDI Pharma (a business unit of Baxter Healthcare corporation)
- Bio Products Laboratory*
- CSL Behring
- Grifols*
- Haffkine Bio-Pharmaceutical Corporation Ltd
- Kedrion Biopharma
- LFB Biotechnologies
- Link Medical Products Pty Ltd
- Mirren*
- Octapharma*
- Sanofi Aventis*
- Taj Pharmaceuticals Limited

Companies contacted using details available publicly on their websites in October 2012.

*Companies that responded indicated with an asterisk.

CONTRIBUTIONS OF AUTHORS

Dr Megan Young (MY) and Prof Graeme Nimmo (GN) obtained copies of the studies and selected studies for inclusion in the review. MY and Prof Allan Cripps (AC) extracted the data and assessed the risk of bias in the studies. MY and Dr Mark Jones (MJ) entered and analysed the data and interpreted the analysis. All authors completed 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 measles and a PhD student whose thesis topic is the effectiveness and efficiency of passive immunisation with NHIG (normal human immunoglobulin) for the public health management of communicable disease. She 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.

Prof Allan Cripps and Prof Graeme Nimmo are PhD supervisors for Dr Megan Young.

Dr Mark Jones has no known conflicts of interest.

SOURCES OF SUPPORT
Internal sources
- Griffith University, Australia.
  In-kind employee time
- The University of Queensland, Australia.
  In-kind employee time
- Queensland Health, Australia.
  In-kind employee time

External sources
- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
We had not identified in the protocol that we would search www.clinicaltrials.gov or WHO ICTRP.

We recognised during the search and retrieval of studies that a number of different sources of immunoglobulin had been studied in the early practice of passive immunisation. GN and MY collectively decided to include only studies where the immunoglobulins used were sourced from human sera or plasma and exclude studies of immunoglobulins from other sources. This decision was made as these interventions were felt to be analogous to the current practice of using a blood product manufactured from human plasma, whereas the other sources are not comparable to current practice.

We recognised during the application of the inclusion criteria, particularly to older studies where no further information was going to be obtainable from authors, that we needed to increase the specificity of the criteria for inclusion so that they could be applied consistently. GN and MY discussed the criteria and collectively determined that to be considered a prospective non-RCT (cohort) study, the intervention and control groups of relevance needed to be recruited over the same (or similar and overlapping) timeframe and from the same exposed population. Further, to be included, the study must specify that the intervention and control populations of relevance had been exposed to measles and were susceptible to measles. If any of these points could not be determined from the information available, either in the publication or from the authors, the study was excluded.

We found that in at least one study with multiple intervention groups the risk ratio for each intervention group compared to control was clearly heterogenous. We therefore chose, for studies with multiple intervention groups, to split the control group and add each pair-wise comparison to the relevant meta-analyses rather than calculate a weighted average of the relevant pair-wise comparisons as we had outlined in the protocol.

We had not listed the secondary outcome 'complications from measles' among the outcomes for meta-analysis in the protocol but found this was warranted given the available evidence.

We undertook a number of sensitivity analyses that were not listed in the protocol in response to our inability to undertake subgroup analyses that were specified in the protocol.

We made the decision to include 'Summary of findings' tables in the review along with the eligible outcomes for the tables post-protocol.
With the conclusion that moderate quality evidence demonstrated the effectiveness of passive immunisation for the prevention of measles up to seven days post-exposure, with an apparent dose response effect, the review contributed to thesis objective 1: To systematically review the existing evidence for the effectiveness of passive immunisation as used in the public health management of measles, and rubella. The question of the minimum effective dose of immunoglobulin for preventing measles was unable to be answered by the review.
Chapter 3  The effectiveness of passive immunisation for preventing rubella

Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Drafting the protocol and finalising the protocol together with my co-authors. Obtaining copies of the studies and selecting studies for inclusion in the review independently from a co-author then coming to consensus with my co-author on included studies; extracting the data from included studies and assessing the risk of bias in the studies independently from a co-author and then coming to consensus with my co-author; entering the data and, with my co-author, analyzing and interpreting the analysis. Drafting the review manuscript and with my co-authors completing the final review.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
The lack of systematic review evidence of effectiveness and the lack of evidence of the minimum effective dose of immunoglobulin for preventing rubella were identified as potential drivers of practice differences across high income countries in relation to the public health management of this condition. The following Cochrane review aimed to redress these deficits by examining the existing evidence of effectiveness of post-exposure passive immunisation for the prevention of rubella among contacts of cases and for the prevention of congenital rubella syndrome among pregnant contacts of cases.
Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)

Young MK, Cripps AW, Nimmo GR, van Driel ML

This is a reprint of a Cochrane review, prepared and maintained by The Cochrane Collaboration and published in The Cochrane Library 2015, Issue 9

http://www.thecochranelibrary.com

WILEY
# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Section</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>HEADER</td>
<td>1</td>
</tr>
<tr>
<td>ABSTRACT</td>
<td>1</td>
</tr>
<tr>
<td>PLAIN LANGUAGE SUMMARY</td>
<td>2</td>
</tr>
<tr>
<td>SUMMARY OF FINDINGS FOR THE MAIN COMPARISON</td>
<td>4</td>
</tr>
<tr>
<td>BACKGROUND</td>
<td>7</td>
</tr>
<tr>
<td>OBJECTIVES</td>
<td>9</td>
</tr>
<tr>
<td>METHODS</td>
<td>9</td>
</tr>
<tr>
<td>RESULTS</td>
<td>13</td>
</tr>
<tr>
<td>Figure 1.</td>
<td>14</td>
</tr>
<tr>
<td>Figure 2.</td>
<td>17</td>
</tr>
<tr>
<td>Figure 3.</td>
<td>18</td>
</tr>
<tr>
<td>DISCUSSION</td>
<td>21</td>
</tr>
<tr>
<td>AUTHORS' CONCLUSIONS</td>
<td>22</td>
</tr>
<tr>
<td>ACKNOWLEDGEMENTS</td>
<td>23</td>
</tr>
<tr>
<td>REFERENCES</td>
<td>23</td>
</tr>
<tr>
<td>CHARACTERISTICS OF STUDIES</td>
<td>32</td>
</tr>
<tr>
<td>DATA AND ANALYSES</td>
<td>50</td>
</tr>
<tr>
<td>Analysis 1.1. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 1 Rubella cases.</td>
<td>51</td>
</tr>
<tr>
<td>Analysis 1.2. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 2 Rubella cases.</td>
<td>52</td>
</tr>
<tr>
<td>Analysis 1.3. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 3 Rubella cases.</td>
<td>53</td>
</tr>
<tr>
<td>Analysis 1.4. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 4 Rubella cases.</td>
<td>54</td>
</tr>
<tr>
<td>Analysis 1.5. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 5 Rubella cases.</td>
<td>55</td>
</tr>
<tr>
<td>Analysis 1.6. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 6 Rubella cases.</td>
<td>56</td>
</tr>
<tr>
<td>Analysis 1.7. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 7 Rubella cases.</td>
<td>57</td>
</tr>
<tr>
<td>Analysis 1.8. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 8 Rubella cases.</td>
<td>59</td>
</tr>
<tr>
<td>Analysis 1.9. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 9 Rubella cases.</td>
<td>60</td>
</tr>
<tr>
<td>APPENDICES</td>
<td>60</td>
</tr>
<tr>
<td>CONTRIBUTIONS OF AUTHORS</td>
<td>66</td>
</tr>
<tr>
<td>DECLARATIONS OF INTEREST</td>
<td>66</td>
</tr>
<tr>
<td>SOURCES OF SUPPORT</td>
<td>66</td>
</tr>
<tr>
<td>DIFFERENCES BETWEEN PROTOCOL AND REVIEW</td>
<td>67</td>
</tr>
</tbody>
</table>

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

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
ABSTRACT

Background
Control of rubella is desired because infection in early pregnancy can result in miscarriage, foetal death or congenital abnormality. Primary studies examining the effectiveness of immunoglobulins for post-exposure prophylaxis of rubella have small sample sizes and varying results. National public health recommendations suggest a degree of effectiveness.

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.

Search methods

Selection criteria
For the outcome 'preventing cases of rubella', we included randomised controlled trials (RCTs) and quasi-RCTs. We found several studies addressing this outcome where the design was a controlled clinical trial (CCT) (with exposure to rubella virus controlled by the investigators) but the method of allocation of participants to groups was not reported. We found an alternative report of one of these studies that indicated participants were assigned to groups randomly. We therefore included such studies as meeting criteria for RCTs or quasi-RCTs and undertook sensitivity analyses. For the outcomes, 'congenital rubella infection' and 'congenital rubella syndrome', we included RCTs, quasi-RCTs and prospective controlled (cohort) studies. Participants were necessarily susceptible and exposed to rubella. Polyclonal immunoglobulins derived from human sera or plasma must have been administered intramuscularly or intravenously as the only intervention in at least one group.
Data collection and analysis

We used the standard methodological procedures expected by The Cochrane Collaboration.

Main results

We included 12 studies (430 participants) in the review: seven RCTs and five CCTs where it was not clear whether participants were randomly allocated to groups. We did not include any unpublished studies. Participants included children and adults of both sexes. Only one study included pregnant women. All studies were conducted in high-income countries.

The quality of the 11 studies in the initial meta-analysis was moderate, although we classified no study as having a low risk of bias on all criteria.

We included 11 studies in the initial meta-analysis of gamma-globulin (concentrated polyclonal immunoglobulins) versus control (saline or no treatment) for rubella cases. The result favoured the intervention group (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.45 to 0.83) but was heterogenous (Chi² test = 36.59, df = 10 (P value < 0.0001); I² statistic = 73%). Heterogeneity was explained by subgrouping studies according to the estimated volume of gamma-globulin administered per pound of bodyweight and then removing those studies where the intervention was administered more than five days after participant exposure to rubella (post hoc analysis). The test of subgroup differences demonstrated heterogeneity between subgroups according to our protocol definition (P value < 0.1; I² statistic > 60%) and there appeared to be greater effectiveness of the intervention when a greater volume of gamma-globulin was administered (‘0.027 to 0.037 ml/lb’ RR 1.60 (95% CI 0.57 to 4.52); ‘0.1 to 0.15 ml/lb’ RR 0.53 (95% CI 0.29 to 0.99); ‘0.2 to 0.5 ml/lb’ RR 0.20 (95% CI 0.04 to 1.00)).

None of the studies reported the outcome ‘congenital rubella infection’. One included study reported on congenital rubella syndrome, with no cases among participants who were fewer than nine weeks pregnant at enrolment and who were randomised to one of two gamma-globulin groups (‘high’ or ‘low’ rubella titre). However, the study did not report how congenital rubella syndrome was measured and did not report the length of follow-up according to intervention group. This study did not include a non-treatment group.

No included study measured adverse events.

Authors’ conclusions

Compared to no treatment, polyclonal immunoglobulins seem to be of benefit for preventing rubella. The available evidence suggests that this intervention may be of benefit up to five days after exposure, and that effectiveness is dependent on dose. Considering the attack rate for rubella cases in the control group of the highest volume gamma-globulin subgroup (333 per 1000), the absolute risk reduction (calculated from the RR) for this volume of gamma-globulin was 266 (95% CI 0 to 320) and the number needed to treat to benefit is four (95% CI 3 to incalculable).

The included studies did not measure rubella-specific antibodies in the immunoglobulin products used in a standard way and thus estimation of the dose of rubella-specific antibodies in international units administered was not possible. As the concentration of rubella-specific antibodies in today’s polyclonal immunoglobulin products may vary from those products used in the studies in the review, the volume required per pound of bodyweight to produce similar results may also vary.

There is insufficient evidence to make direct conclusions about the effectiveness of polyclonal immunoglobulins for preventing congenital rubella syndrome. This is an area requiring further research.

Plain Language Summary

Passive immunisation (giving antibodies) for preventing rubella (German measles) after contact with it

Background and review question

People who have had rubella (German measles), or rubella vaccine, have antibodies against the virus in their blood. These antibodies protect them from getting rubella should they come into contact with it again. These antibodies can be extracted from blood donated by these people.

If people without antibodies come into contact with someone who is contagious with rubella, they can contract it. Rubella can be serious. The baby of a woman who is infected with rubella, especially early in pregnancy, may be born with a range of birth defects including heart, eye and hearing problems. One way of preventing rubella in people who come into contact with a contagious person...
is to inject them with antibodies that have been extracted from blood donations. This was done in the 1950s and 1960s and is still recommended for rubella control in some circumstances in some countries. Whether this is effective is unclear. We sought to answer this question.

**Study characteristics**

The evidence is current to August 2014. We included 12 studies (430 participants). People of all ages were included in the studies, which were conducted in high-income countries.

**Key results and quality of the evidence**

Eleven studies (389 participants) compared injecting antibodies into the muscle or vein of participants to injecting salt water or giving no treatment. The study participants did not have their own antibodies. They had been in contact with rubella between one and 28 days prior to receiving the antibodies. The antibodies seemed to be effective at preventing participants from catching rubella, with those receiving antibodies 39% less likely to develop rubella than those not given antibodies. In an analysis of the seven studies (89 participants) where participants had been in contact with rubella only up to five days earlier, people given the highest doses used in the studies were 80% less likely to develop rubella than those not given antibodies. The studies assessing the prevention of rubella were of moderate quality because of some methodological issues and the fairly small number of participants. It is important to consider that the amount of rubella antibodies in today's blood donations may differ from those used in the studies. Therefore, doses given today may need to vary from those of the studies in order to obtain the same effect.

Only one study included pregnant women. All of the women were given one of two different doses of antibodies. They did not measure whether the babies born to the women were infected with rubella, but did consider whether birth defects that may be related to rubella were present. Key details about the study methods were missing and unobtainable, so the quality of this study was unclear. None of the babies born to these women were identified as having birth defects related to rubella. However, we cannot draw direct conclusions from this single study about the effectiveness of injecting antibodies after contact with rubella for preventing rubella-related birth defects in pregnant women. This is an area that needs further research.

The included studies did not report adverse events. Future studies should report this outcome.
### SUMMARY OF FINDINGS FOR THE MAIN COMPARISON (Explanation)

Gamma-globulin compared to control (saline or no treatment) for preventing rubella or congenital rubella syndrome

**Patient or population:** susceptible people exposed to rubella

**Settings:** community, different residential institutions, universities and medical settings

**Intervention:** gamma-globulin

**Comparison:** saline or no treatment

#### Outcomes

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Illustrative comparative risks* (95% CI)</th>
<th>Relative effect (95% CI)</th>
<th>No of participants (studies)</th>
<th>Quality of the evidence (GRADE)</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rubella cases</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Control (saline or no Gamma-globulin treatment)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Initial meta-analysis</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Study population</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-273 per 1000</td>
<td>166 per 1000 (123 to 226)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Moderate</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>-571 per 1000</td>
<td>348 per 1000 (257 to 474)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
| Subgroup: rubella cases Estimated dose 0.027 to 0.037 ml/lb
Clinical diagnosis by 2 physicians
Follow-up: 3 to 8 weeks | | | | | |
| Study population | | | | | |
| -333 per 1000 | 533 per 1000 (190 to 1000) | | | | |
| Moderate | | | | | |
| -571 per 1000 | 514 per 1000 (325 to 1000) | | | | |
| Subgroup: rubella cases Estimated dose 0.1 to 0.15 ml/lb
Clinical diagnosis by 2 physicians
Follow-up: 6 to 8 months | | | | | |
| Study population | | | | | |
| -765 per 1000 | 495 per 1000 (312 to 757) | | | | |
| Moderate | | | | | |
| -571 per 1000 | 303 per 1000 (166 to 500) | | | | |
| Subgroup: rubella cases Estimated dose 0.2 to 0.5 ml/lb
Serology +/- virus isolation +/- clinical signs
Follow-up: 3 to 6 weeks | | | | | |
| Study population | | | | | |
| -333 per 1000 | 67 per 1000 (13 to 333) | | | | |
| Moderate | | | | | |
| -571 per 1000 | 114 per 1000 (23 to 571) | | | | |
| **Cases of congenital rubella infection - not measured** | | | | | |
| See comment | See comment | Not estimable | - | See comment | No included studies measured the outcome congenital rubella infection |
| **Cases of congenital rubella syndrome - not measured** | | | | | |
| See comment | See comment | Not estimable | - | See comment | No included studies of gamma-globulin versus control measured the outcome congenital rubella syndrome |
| **Adverse events - not measured** | | | | | |
| See comment | See comment | Not estimable | - | See comment | No included studies measured adverse events |

*The basis for the assumed risk is the median control group risk across studies included in the initial meta-analysis. The corresponding risk (and its 95% confidence interval) is based on the assumed risk in the comparison group and the relative effect of the intervention (and its 95% CI).

CI: confidence interval; RR: risk ratio

---

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

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Grade Working Group grades of evidence

**High quality:** Further research is very unlikely to change our confidence in the estimate of effect.

**Moderate quality:** Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

**Low quality:** Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.

**Very low quality:** We are very uncertain about the estimate.

---

1. Downgraded one level for risk of bias. Most information was from studies at low and unclear risk of bias. Two studies were at high risk of detection bias only. Three studies were at high risk of selective reporting only, and this was unlikely to affect their results.

2. Downgraded one level for inconsistency. The studies’ results were statistically heterogeneous.

3. Upgraded one level for plausible confounding would reduce the measure of effect. The plausible confounding factors we listed a priori were: dose, time between exposure and intervention, immunosuppression, age and gestation. No studies in this meta-analysis included pregnant women or identified immunosuppressed individuals. Subgroup analysis by age showed no difference between the subgroups. This analysis includes studies where the intervention was administered longer than five days after exposure and includes studies that administered lower volumes of immunoglobulin per unit weight than others. Both of these factors would reduce the measure of effect.

4. Downgraded one level for risk of bias. The sole study in this subgroup was at high risk of detection bias as the outcome was assessed subjectively and there was no reported blinding of outcome assessors.

5. Downgraded two levels for imprecision. The sole study in this subgroup had a small sample size and the resulting confidence interval is wide.

6. Upgraded one level for apparent dose response effect. While there is overlap in the confidence intervals, there appeared to be heterogeneity across estimated dose subgroups (P value = 0.07; I² = 62.4%) and the estimates of effect seemed to indicate greater effectiveness with greater estimated dose.

7. Downgraded one level for imprecision. Each trial in this subgroup was of small sample size and the overall sample size for the subgroup is small. However, the confidence interval does not include one.

8. Downgraded one level for risk of bias. Two of the three studies in this subgroup had a high risk of selective reporting bias.

9. Downgraded two levels for imprecision. The trials in this subgroup were small, the overall sample size of the subgroup was small and the confidence interval of the pooled estimate of effect extended to 1.00.

10. Upgraded one level for large effect estimate. The pooled estimate of effect for this subgroup was 0.2.

11. One study included in the review compared a ‘high’ titre gamma-globulin with a ‘low’ titre gamma-globulin control group. This study did not identify any cases of congenital rubella syndrome among any of the infants born to participants although the means of assessment was not reported and the length of follow-up was not given by study group.
**BACKGROUND**

Global rubella control has progressed since the introduction of rubella vaccine (Usónis 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; Usónis 2011; WHO 2011). Though vaccination is available in these countries, rates are not sufficiently high to achieve adequate rubella control (Muscat 2012; Usónis 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 (Catts 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 childbearing 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) (Caïdi 2009), India (12% to 23% between 2000 to 2008) (Dowan 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 for the prevention of CRS at the population level, there is little in the way of preventive measures for the individual exposed at the time of pregnancy. Before rubella vaccine became available, passive immunisation was investigated as a means of preventing rubella infection, with mixed results (Green 1965a; Green 1965b; Green 1965c; McDonald 1965). 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) and New Zealand (NZ) 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 (CDC 1998; CDC 2001; IDHPA 2009; NZMoH 2014; PHE 2015). Australian recommendations are similar but do not include consideration of termination of pregnancy (ATAGI 2013). The rationales for these recommendations 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 fetal infection will be prevented” (NZMoH 2014 p452); and the Australian Immunisation Handbook states that IG may prolong the incubation period, which may reduce the risk to the foetus (ATAGI 2013). 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 (where applicable) 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 (Usónis 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; Patison 1975). When present, symptoms include fever, headache, a generalised red blotchy rash, tender enlarged lymph nodes, joint pain and mild conjunctivitis (Usónis 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 (Usónis 2011). An infant born with any of the com-
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 (Banarvala 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 immunoglobulins) derived from either pooled extracts from human placentas, pooled blood from human placentas or pooled human blood (McDonagh 1966). 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 (Burnout 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; Burston 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 (Burston 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) (IDHQA 2009 p359). The Australian Immunisation Handbook references the US guidelines for each of the statements about post-exposure passive immunisation for rubella (ATAGI 2013). These Australian guidelines state that post-exposure passive immunisation "does not prevent infection in non-immune contacts" (ATAGI 2013 p396), 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 2014 p452). 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 1990a). The other is a book chapter that does not include in-text citations (Waagner 1993). It states that "Immune globulin 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 1990a (the other reference used in the US guidelines) that concluded viraemia was prevented with high-dose IG. Waagner's book chapter 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 (Waagner 1993). 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 unrefereced. 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 1965a; Green 1965b; Green 1965c; Macrae 1968; McCallin 1972; Neumann-Haefelin 1975; Petersen 1978; Schiff 1969d). 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 provides 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.

**METHODS**

**Criteria for considering studies for this review**

**Types of studies**

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

We included randomised controlled trials (RCTs) and quasi-RCTs that examined this outcome, irrespective of blinding, publication status, language or unit of randomisation. (*To note: We found several studies addressing this outcome where the design was a controlled clinical trial (with exposure to rubella virus controlled by the investigators) but the method of allocation of participants to groups was not reported. We found an alternative report of one of these studies that indicated participants were assigned to groups randomly. We therefore included such studies as meeting the criteria for RCTs or quasi-RCTs and undertook sensitivity analyses.*)

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

We included RCTs, quasi-RCTs and prospective controlled studies (cohort studies) that examined either or both of these outcomes, irrespective of blinding, publication status, language or unit of randomisation. We included 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 needed to be recruited over the same (or similar and overlapping) timeframe and from the same population and the study must have specified 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 excluded the study if any of these points could not be determined from the information available either in the publication or from the study authors.

To assess adverse events:

We included data on adverse events from any of the studies included in the review as above.

**Types of participants**

Participants were 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. We accepted the primary study's definition of exposed and explored any differences 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 have originated from human plasma or serum. We excluded 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 have been 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 have been 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, meningoencephalitis, 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 was defined as “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). We classified all other events as non-serious.

We specifically extracted 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. We also included any other adverse event reported as such by study authors.

Search methods for identification of studies

Electronic searches
We searched the Cochrane Central Register of Controlled Trials (CENTRAL 2014, Issue 7), which contains the Cochrane Acute Respiratory Infections (ARI) Group’s Specialised Register, MEDLINE (OVID) (1946 to August week 2, 2014), CINAHL (1981 to August 2014), EMBASE (1974 to August 2014), EMBASE, LILACS (1982 to August 2014) and Web of Science (1955 to August 2014). We used the search strategy in Appendix 1 to search MEDLINE and CENTRAL. We adapted the strategy for EMBASE (Appendix 2), CINAHL (Appendix 3), LILACS (Appendix 4) and Web of Science (Appendix 5). We combined the MEDLINE and EMBASE searches with the filter for study type in Appendix 6.

Searching other resources
We searched the reference lists of retrieved relevant studies and reviews. To locate further published or unpublished studies, we attempted to contact companies manufacturing IG products for countries with low rubella incidences and also attempted to contact the corresponding author of any included studies. We searched the reference lists of published national public health guidelines on rubella control. We searched ClinicalTrials.gov and the World Health Organization International Clinical Trials Registry (WHO ICTRP) using the terms “rubella” OR (“German” AND “measles”) on 16 October 2014.

Data collection and analysis

Selection of studies
Two review authors (MY, GN) independently inspected the title and abstract (as available) of each reference identified by the electronic searches and determined the potential relevance of each article. If identified by either review author as potentially relevant, we retrieved the full article. One review author (MY) searched the
Data extraction and management

Two review authors (MY, AC) independently extracted data from the included studies using pre-designed data extraction forms. We resolved disagreement by discussion. We attempted to contact study authors for clarification or further information as necessary.

We listed duplicate publications with the main publication for each retrieved abstract. We removed duplicates of full-text articles, leaving the main publication for each retrieved full-text article.

We resolved disagreements through discussion. We excluded studies not meeting the eligibility criteria and stated the reasons for exclusion. Among the articles retrieved in full text, we found several studies where the design was a controlled clinical trial (CCT) (with exposure to rubella virus controlled by the investigators) but the method of allocation of participants to groups was not reported. An alternative report of one of these studies indicated participants were assigned to groups randomly, therefore we mutually agreed to include such studies and then undertake sensitivity analysis.

We extracted 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: RCT, quasi-RCT, CCT 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) independently assessed the risk of bias for included studies. We resolved any disagreements by discussion. We extracted the following data.

The 12 included studies were either RCTs or controlled clinical trials (CCTs) where the means of allocation of participants to groups was not reported. An alternative report of one of these latter studies indicated that participants were assigned to groups randomly, therefore we included such studies as meeting the criteria for RCTs/quasi-RCTs.

We therefore assessed 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 reported the risk of bias using The Cochrane Collaboration’s tool for assessing ‘Risk of bias’ (Higgins 2011).

We conducted sensitivity analyses based on the study type and the risk of bias of included studies. We reported these results descriptively.

Measures of treatment effect

We undertook data analyses in RevMan 5.3 (RevMan 2014). Outcomes, as identified above, are dichotomous. We expressed these outcomes as risk ratios (RR) and calculated 95% confidence intervals (CIs) for each.

Unit of analysis issues

Our protocol specified that should cluster-randomised trials be included in the review, we would attempt to extract RRs and 95% CIs resulting from analyses that have accounted for the clustering directly from the article/s. If this had been possible, we would have proceeded to meta-analyse the data using the inverse variance method. If this had not been possible, we would have extracted 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 proceeded 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). However, we did not identify any cluster-randomised trials that met our inclusion criteria.

Our protocol specified that should studies with multiple intervention groups, for example, different doses of immunoglobulins compared to control, be included in the review, we would initially split the shared group/s and include the relevant pair-wise comparisons in the meta-analysis (Higgins 2011). Then, if there was no significant heterogeneity between the different interventions/controls from the same study, we would combine the groups and include the single intervention and single control group in the final meta-analysis, or if significant heterogeneity existed, we would explore the differences in subgroup analyses. However, we did not identify any studies with multiple intervention groups, for
example, different doses of immunoglobulins compared to control, which met our inclusion criteria.

Dealing with missing data
Our protocol specified that we would attempt to contact the trial authors for any missing data. Then, for remaining missing data we would analyse using the intention-to-treat (ITT) principle with all missing data considered treatment failures. If we undertook ITT analysis, we would undertake 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). However, for all included studies, follow-up of participants was complete.

Assessment of heterogeneity
We considered heterogeneity firstly by considering the populations, settings, methods and outcomes of the different studies. We were not able to undertake meta-analysis for the primary outcomes 'congenital rubella infection' (no studies assessed this outcome) and 'congenital rubella syndrome' (only one study assessed this outcome). We described the results of the study assessing congenital rubella syndrome descriptively. We did not identify clinically important heterogeneity that would have required reporting results descriptively for the primary outcome 'rubella cases', so we inspected the forest plot for this outcome. As per our protocol, we considered an I² statistic estimate of 60% or more, alongside a test P value of 0.1 or less to indicate important heterogeneity.

Assessment of reporting biases
In the event of multiple publications of the same study, we listed the subsequent articles with the main article and only entered data once. Our protocol indicated that we would assess publication bias by examining funnel plots if sufficient studies (at least 10) were included. However, our final meta-analysis included only seven studies. Further, all included studies had fairly small sample sizes. The largest study was of 179 participants.

Data synthesis
We calculated the RRs and 95% CI for each outcome measured in each study. We initially included all studies relevant to the outcome subject to meta-analysis and examined the forest plot to assess heterogeneity. We explored possible reasons for apparent heterogeneity via subgroup and sensitivity analyses. As per our protocol, we pooled the results using a fixed-effect model. We reported the results of those outcomes where meta-analysis was not undertaken descriptively. We reported the results of the secondary outcomes descriptively.

Subgroup analysis and investigation of heterogeneity
Our protocol listed the following subgroup analysis that we were unable to perform:
- dose of rubella-specific immunoglobulins (most studies reported rubella-specific antibody titres for the immunoglobulin product/s used, however, none of the included studies reported the rubella-specific antibody concentration in international units or reported using an internationally recognised standard control when assessing this measure. It was thus not possible to compare and categorise the products used into similar rubella-specific antibody concentrations.)

Further, the following subgroup analyses were not relevant to the review:
- stage of gestation (trimester of pregnancy) (none of the studies included in meta-analyses included pregnant participants);
- route of administration of immunoglobulins (all except Martin du Pan 1972 administered IG via the intramuscular route);
- per protocol versus ITT analysis (to account for missing data) (participant follow-up was complete for all studies).

We undertook the following subgroup analyses as identified in our protocol:
- study type (CCT and RCT);
- age of participants (children, adults, mixed) (adults were defined using the widely accepted, legal 'age of majority' definition for most countries (World Law Direct 2009; Zeldin 2007), 18 years and over);
- dose of immunoglobulins (0.027 to 0.037 ml/lb; 0.1 to 0.15 ml/lb; 0.2 to 0.5 ml/lb). In those studies where the same volume was administered to each adult participant and participant weights were not reported (Martin du Pan 1972; Petersen 1978; Schiff 1969b), the volume administered by weight was estimated using 70 kg (154 lb) as the weight of an adult. Similarly, the 50th percentile weight for age for males according to current Australian growth charts (NSW Health 2014) was used (126 to 150 lb) for the study where participants were adolescent boys aged 15 to 18 years in Australia but no participant weights were reported (Anderson 1953b). We then determined dose categories by visually assessing the number and range of volumes per pound administered in the different studies. We excluded McDonald 1963 because the amount of IG given was given in milligrams instead of as a volume;
- timing of administration of intervention in relation to exposure (exposure 24 hours to five days prior to IG; and exposure up to eight to 28 days prior to IG) (we excluded Green...
1965c and McDonald 1963 because the timing of the intervention in relation to exposure was not reported);

- differences in primary study definitions of ‘exposed’ (artificial exposure; controlled exposure to an infected person; household contact with a diagnosed case) (we excluded McDonald 1963 because the nature of exposure was not reported);

- differences in primary study measurement of outcomes (laboratory-confirmed; and cases defined on clinical grounds only) (we excluded McDonald 1963 because no information was reported on how rubella cases were assessed);

- funder (those with potential conflict of interest (gamma-globulin provided by a company); and no known conflict of interest) (we included Martin du Pan 1972; McDonald 1963; Petersen 1978 in the subgroup “no known conflict of interest” but we noted that the funding source was not reported).

**Sensitivity analysis**

We performed sensitivity analyses as per our protocol to assess the impact of heterogeneity and risk of bias on the pooled estimate/s of meta-analyses. For heterogeneity, we gradually removed single trials that seemed to contribute to heterogeneity upon inspection of the forest plots. For risk of bias, we pooled the studies with the lowest risk of bias and then gradually added the studies assessed as having a higher risk of bias.

We undertook additional sensitivity analyses because of the inclusion of controlled clinical trials where the means of allocation of participants was not reported and because we noted some included studies used history only to assess susceptibility for rubella whereas the majority identified those susceptible according to serology. We gradually removed the controlled clinical trials from the analysis firstly in order of the magnitude of the effect estimate (largest to smallest) and then separately in order of the size of the trial (largest to smallest). We simultaneously removed the three studies that used history only to assess susceptibility of participants to rubella at the beginning of the respective trials.

**Overall quality of the evidence**

We used the GRADE approach to assess the overall quality of the evidence (GRADE Working Group 2004). One author (MY) entered the information into GRADEpro (GRADEpro 2015) and produced the ‘Summary of findings’ table for the primary outcomes and adverse events (Summary of findings for the main comparison). For the primary outcome ‘Rubella cases’, we included both the initial meta-analysis and the final (subgroup analysis that explained heterogeneity) meta-analysis results.

**RESULTS**

**Description of studies**

**Results of the search**

The number of search results obtained from each database prior to duplicate removal was CENTRAL (168), MEDLINE (1664), EMBASE (747), CINAHL (78), LILACS (120) and Web of Science (563). Of these, we retrieved 71 full-text articles resulting in eight included studies. Searching the reference lists of relevant retrieved full-text articles identified a further 79 unique records, of which we retrieved 69 full-text articles resulting in four additional included studies (Figure 1).
Figure 1. Study flow diagram.

3340 records identified through database searching

299 additional records identified through other sources

2798 records after duplicates removed

2798 records screened

2658 records excluded

140 full-text articles assessed for eligibility

129 full-text articles excluded, with reasons

12 studies (11 articles) included in qualitative synthesis

11 studies included in quantitative synthesis (meta-analysis)
searching ClinicalTrials.gov returned 108 records and WHO ICTRP returned 157 records. We did not identify any additional relevant studies.

We sent electronic written requests to 13 separate companies that manufacture immunoglobulin products (Appendix 8) and the Australian Technical Advisory Group on Immunisation (ATAGI). Six companies and ATAGI responded. We did not identify any additional relevant studies.

We searched the reference lists of 18 documents we identified as published national public health guidelines on rubella control (Appendix 9). We did not identify any additional relevant studies.

The age of the included studies and absent up-to-date contact details for authors meant that we were not able to contact the authors of any included studies.

Included studies

We included 12 studies in the review: seven RCTs and five presumed RCTs (see Characteristics of included studies). In these last five studies, susceptible participants were intentionally exposed to rubella virus by the investigators. Included studies were published between 1953 and 1978. We included no unpublished studies. Included studies were undertaken in five different countries: the United States (Doerge 1967; Green 1965a; Green 1965b; Green 1965c; Schiff 1969a; Schiff 1969b; Schiff 1969c), United Kingdom (McCallin 1972), Germany (Petersen 1978), Switzerland (Martin du Pan 1972), and Australia (Anderson 1953a; Anderson 1953b). A total of 430 participants were recruited from the community, different residential institutions, universities and medical settings. Sample sizes ranged from seven to 179.

Six studies included only adult participants (Anderson 1953a; Martin du Pan 1972; McCallin 1972; Petersen 1978; Schiff 1969b; Schiff 1969b), and four studies included only children (Green 1965a; Green 1965b; Green 1965c; McDonald 1963). One study included adolescents (aged 15 to 18 years) (Anderson 1953b).

One study included children and adults (Doerge 1967). The entire study population for this study included participants aged three to 50 years, however only results from those who were known to be susceptible to rubella were included in the review. This group was aged three to 19 years.

Three studies included only male participants (Anderson 1953b; Schiff 1969b; Schiff 1969b), two studies included only female participants (Anderson 1953a; McCallin 1972), and the remainder did not report the gender distribution of their participants. Participants in one of the all-female studies were fewer than nine weeks pregnant (McCallin 1972).

Susceptibility was defined as no history of rubella infection by three studies (Anderson 1953a; Anderson 1953b; McDonald 1963).

The remainder determined susceptibility by serology. Participants were artificially exposed to rubella virus in five studies (Anderson 1953a; Martin du Pan 1972; Petersen 1978; Schiff 1969b; Schiff 1969b). In three studies, participants were exposed under controlled conditions to children who had been artificially exposed and were known to be infected with rubella virus (Green 1965a; Green 1965b; Green 1965c).

In two studies, participants were living with diagnosed cases of rubella (Anderson 1953b; Doerge 1967). Participants self-reported exposure in one study (McCallin 1972) and in one study, no detail was given on the means of exposure (McDonald 1963).

The time between exposure and intervention ranged from 24 hours to five days in the studies where exposure was via inoculation with the virus (Anderson 1953a; Martin du Pan 1972; Petersen 1978; Schiff 1969a; Schiff 1969b). Green 1965b controlled the time of exposure to a known case and administered immunoglobulin 24 hours after exposure. The interval between exposure and intervention was much less precise (up to 11 days - Anderson 1953b; up to eight days - Green 1965a; up to four weeks - Doerge 1967) and unknown or not reported (Green 1965c; McCallin 1972; McDonald 1963) for the other studies.

The intervention was gamma-globulin given intramuscularly in 10 studies (Anderson 1953a; Anderson 1953b; Green 1965a; Green 1965b; Green 1965c; McCallin 1972; McDonald 1963; Petersen 1978; Schiff 1969a; Schiff 1969b). Gamma-globulin was given intravenously in one study (30 ml to 60 ml diluted in 200 ml saline) (Martin du Pan 1972), and ‘poliomyelitis immune globulin’ with a rubella antibody concentration of 1:300 was given intramuscularly in one study (at 0.5 ml per unit of bodyweight - unit not specified) (Doerge 1967). Of those administering gamma-globulin, one study reported a rubella antibody titre as assessed by neutralisation assay (Green 1965a; Green 1965b; Green 1965c) at 0.15 ml to 0.2 ml per pound, three studies administered 20 ml (McCallin 1972; Schiff 1969a; Schiff 1969b), two studies administered 4 ml (Anderson 1953a; Anderson 1953b), one study administered 15 ml after giving 20 ml six weeks earlier to the same participants (Petersen 1978), and one study administered 250 mg (McDonald 1963).

None of the included studies reported antibody titres of the immunoglobulin products used in international units. The rubella antibody titre of the immunoglobulin product used was not reported in three studies (Anderson 1953a; Anderson 1953b; McDonald 1963). Three studies reported a rubella antibody titre as assessed by hemagglutination inhibition: one had a titre of 512 (McCallin 1972), one had a titre of 1000 (Martin du Pan 1972), and one had a titre of 2560 (Petersen 1978). Five studies reported rubella antibody titre as assessed by neutralisation assay: one had a titre of 1024/0.1 ml (Schiff 1969a), one had a titre of 256/0.1 ml (Schiff 1969b), two had titres of 64 (Green 1965b; Green 1965c), and one had a titre of 32 (Green 1965a). One study reported rubella antibody titre but did not report the means by which it was assessed. The reported titre was 1:300 (Doerge 1967).
Of the studies trialing intramuscular gamma-globulin, six used ‘no treatment’ control groups (Anderson 1953a; Green 1965a; Green 1965b; Green 1965c; McDonald 1963; Petersen 1978), three gave saline of the same volume as the intervention intramuscularly to the control group (Anderson 1953b; Schiff 1969a; Schiff 1969b), and one gave gamma-globulin intramuscularly in the same volume but of a lower rubella antibody titre (McCallin 1972). The study trialing intravenous gamma-globulin used a ‘no treatment’ control group (Martin du Pan 1972), as did the study trialing ‘poliomyelitis immune globulin’ (Doege 1967).

All included studies assessed the number of rubella cases in each group as the primary outcome. Serological survey with or without other laboratory testing was undertaken to determine rubella infection in all but three studies (Anderson 1953a; Anderson 1953b; McDonald 1963). Cases were determined on clinical grounds only by two of these studies (Anderson 1953a; Anderson 1953b). McDonald 1963 did not report how participants were assessed for rubella infection. One study assessed cases of congenital rubella syndrome (McCallin 1972). No studies assessed cases of congenital rubella infection. No studies assessed or reported on adverse events.

In three studies, the intervention product used was supplied by a company. These were: Red Cross Blood Transfusion Service and CSL, Australia (Anderson 1953a; Anderson 1953b), and Parker, Davis & Co, Detroit (Doege 1967). The study by Doege 1967 was also supported by a US Public Health Service infectious diseases training grant. Green 1965a, Green 1965b and Green 1965c were funded by a grant from the National Institute of Allergy and Infectious Diseases, US Public Health Service and a contract with the US Army Medical Research and Development Command, Office of the Surgeon General. Schiff 1969a and Schiff 1969b were supported by the ‘National Foundation’ and a ‘Career Research Development Award from the National Institutes of Health’. Martin du Pan 1972, McCallin 1972, McDonald 1963 and Petersen 1978 did not report any sources of funding.

Excluded studies

We excluded 129 of the 140 articles retrieved in full text. The reasons for exclusion of individual articles are given in the Characteristics of excluded studies table.

Risk of bias in included studies

Five studies where exposure to rubella was controlled by the investigators did not specify that participants were allocated randomly to groups (Green 1965a; Green 1965b; Green 1965c; Martin du Pan 1972; Petersen 1978). However, an alternative report of a study initially categorised with these studies did specify that participants were assigned to groups randomly and hence we included these studies in the review as meeting criteria for RCTs/quasi-RCTs. No study was at low risk of bias for all criteria (Figure 2; Figure 3; Characteristics of included studies). The quality of the 11 studies in the initial meta-analysis was moderate (Summary of findings for the main comparison).
Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.
Allocation
Random sequence generation and the means of allocation concealment was not reported in any included study. We thus assessed all to have unclear risk of bias for this criteria.

Blinding
The intervention, administration of polyclonal immunoglobulins, is very unlikely to be subject to variation due to performance and, as such, we deemed all studies at low risk of performance bias. We assessed detection bias for the outcomes cases of rubella and cases of congenital rubella syndrome, as no study examined the outcome cases of congenital rubella infection. The study that assessed cases of congenital rubella syndrome did not report whether participants or outcome assessors were blinded, although the control group was given gamma-globulin of a lower rubella antibody titre at the same volume as the intervention group (McCallin 1972). There was no reported definition of congenital rubella syndrome nor method of assessment of the infants of participants. Infants of participants were followed up for between six months and three years but it was not reported whether there was a difference in average length of follow-up between groups. Due to the lack of information on the methodology, we assessed the study as at an unclear risk of detection bias for cases of congenital rubella syndrome. The same study defined cases of maternal rubella syndrome nor method of assessment of the infants of participants. We deemed two studies at high risk of detection bias in relation to cases of rubella (Anderson 1953a; McDonald 1963). This was because no blinding was reported and the outcome was assessed by means of clinical signs. We deemed Anderson 1953b at low risk of detection bias for rubella cases. Although the outcome was measured clinically, both the participants and the outcome assessor were blinded. We assessed the remaining studies as at low risk of detection bias for cases of rubella because, irrespective of blinding, the outcome was objectively measured.

Incomplete outcome data
All studies reported complete follow-up for cases of rubella. Doege 1967 had complete clinical follow-up and complete follow-up of the subset of participants from whom oropharyngeal swabs were collected but did report collection of paired sera on 43 of the 47 participants in the subgroup (91.5%). McCallin 1972 reported complete follow-up for cases of congenital rubella syndrome. We deemed all studies at low risk of attrition bias.

Selective reporting
Among the three studies reported by Green et al, Green 1965a, Green 1965b and Green 1965c, is a comparison of the results of serum samples tested for viraemia on a subset of five intervention participants and five control participants. The methods indicate that nasopharyngeal swabs were collected from participants but do not include details of serum sampling. We deemed these studies at high risk of reporting bias. Each of the other included studies...
reported on all outcomes specified in the methods sections and we deemed them to be at low risk of reporting bias.

Other potential sources of bias
We were unable to examine a funnel plot to assess for publication bias as there were only seven studies in the analysis that explained the heterogeneity of the original pooled result. However, small study effects were unlikely in our review given the only study with an independently statistically significant result was the largest study.

Effects of interventions
See: Summary of findings for the main comparison Gamma-globulin compared to control (saline or no treatment) for preventing rubella or congenital rubella syndrome

Primary outcomes

I. Cases of rubella

We entered 11 of the 12 included studies into a meta-analysis of the primary outcome ‘cases of rubella’. The result favoured the intervention group (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.45 to 0.83) but was heterogeneous (Chi² test = 36.59, df = 10 (P value = 0.01); I² statistic = 79%) (Analysis 1.1). We excluded McCollin 1972 from this meta-analysis due to heterogeneity of the control group (a lower titre gamma-globulin was given to the controls) as compared to the other studies (do nothing or placebo in the form of saline). The result of this study also favoured the intervention group although it was not statistically significant (RR 0.70, 95% CI 0.13 to 3.76).

Subgroup analyses

Subgrouping studies by study type (Analysis 1.2) did not explain the heterogeneity (overall heterogeneity: Chi² test = 36.59, df = 10 (P value < 0.0001); I² statistic = 75%) and we found no difference between the subgroup estimates of effect (test for subgroup differences: Chi² test = 0.09, df = 1 (P value = 0.77), I² statistic = 0%).

Subgrouping studies according to age group (adults, children, mixed) (Analysis 1.3) did not explain the heterogeneity (overall heterogeneity: Chi² test = 36.59, df = 10 (P value < 0.0001); I² statistic = 73%) and we found no difference between the subgroup estimates of effect (test for subgroup differences: Chi² test = 1.09, df = 2 (P value = 0.58), I² = 0%).

Subgrouping studies according to categories of estimated dose of immunoglobulins (Analysis 1.4) somewhat reduced heterogeneity (overall heterogeneity: Chi² test = 21.92, df = 9 (P value = 0.009); I² statistic = 59%). The subgroup ‘estimated 0.1 to 0.15 ml/lb’ did not demonstrate significant heterogeneity, while the other two subgroups did (‘estimated 0.27 to 0.37 ml/lb’, heterogeneity: Chi² test = 5.07, df = 1 (P value = 0.08); I² statistic = 67%; ‘estimated 0.2 to 0.5 ml/lb’ heterogeneity: Chi² test = 16.68, df = 3 (P value = 0.0009); I² statistic = 82%). There was no difference in the estimates of effect between subgroups (test for subgroup differences: Chi² test = 0.12, df = 2 (P value = 0.94), I² statistic = 0%). The overall estimate of effect was smaller than the original meta-analysis (overall RR 0.70, 95% CI 0.52 to 0.95).

Subgrouping studies according to categories of time between exposure to rubella and intervention (Analysis 1.5) somewhat reduced heterogeneity (overall heterogeneity: Chi² test = 20.07, df = 8 (P value = 0.01); I² statistic = 60%). The subgroup ‘Exposure 24 hours to five days prior to IG’ did not demonstrate significant heterogeneity (heterogeneity: Chi² test = 7.84, df = 5 (P value = 0.17); I² statistic = 36%), while the subgroup ‘Exposure up to eight to 28 days prior to IG’ did (heterogeneity: Chi² test = 6.65, df = 2 (P value = 0.04); I² statistic = 70%). There was no difference in the estimates of effect between the subgroups (test for subgroup differences: Chi² test = 0.62, df = 1 (P value = 0.43), I² statistic = 0%). The overall estimate of effect was smaller than the original meta-analysis (overall RR 0.72, 95% CI 0.53 to 0.97).

Subgrouping studies according to the study definition of exposure (Analysis 1.6) somewhat reduced heterogeneity (overall heterogeneity: Chi² test = 21.92, df = 9 (P value = 0.009); I² statistic = 59%). No significant heterogeneity was demonstrated for the groups ‘Artificial exposure’ and ‘Controlled exposure to an infected person’. The subgroup ‘Household contact with a diagnosed case’ demonstrated significant heterogeneity (heterogeneity: Chi² test = 10.81, df = 1 (P value = 0.001); I² statistic = 91%). There was no difference in the estimates of effect between the subgroups (test for subgroup differences: Chi² test = 0.29, df = 2 (P value = 0.86), I² statistic = 0%). The overall estimate of effect was smaller than the original meta-analysis (overall RR 0.70, 95% CI 0.52 to 0.95).

Subgrouping studies according to the definition of rubella cases (Analysis 1.7) somewhat reduced heterogeneity (overall heterogeneity: Chi² test = 21.92, df = 9 (P value = 0.009); I² statistic = 59%), although both subgroups still demonstrated significant heterogeneity and there was no difference in the estimates of effect between subgroups (test for subgroup differences: Chi² test = 0.10, df = 1 (P value = 0.75), I² statistic = 0%). The overall estimate of effect was smaller than the original meta-analysis (overall RR 0.70, 95% CI 0.52 to 0.95).

Subgrouping studies according to funder (Analysis 1.8) demonstrated a difference between the subgroups (test for subgroup differences: Chi² test = 4.21, df = 1 (P value = 0.04), I² statistic = 76.3%), although both subgroups still demonstrated significant heterogeneity and there was no difference in the estimates of effect between subgroups ‘estimated 0.027 to 0.037 ml/lb’ heterogeneity: Chi² test = 4.52, df = 2 (P value = 0.10); I² statistic = 56%) and had a pooled estimate of effect of RR 0.87 (95% CI 0.57 to 1.33). The subgroup with no known
funder with a potential conflict of interest was heterogenous (heterogeneity: Chi² test = 17.58, df = 7 (P value = 0.01); I² statistic = 60%) and had a pooled estimate of effect of RR 0.46 (95% CI 0.29 to 0.72). Three studies included in the subgroup without known conflict of interest did not report funder information (Martin du Pan 1972; McDonald 1963; Petersen 1978). Excluding these studies reduced the difference between the subgroups so that it was no longer significant (test for subgroup differences: Chi² test = 1.25, df = 1 (P value = 0.26), I² statistic = 19.9%), but did not reverse the direction of the difference (no known conflict of interest subgroup RR 0.60, 95% CI 0.35 to 1.00).

Post hoc subgroup analysis

It is well established that the most important factors that impact on the effectiveness of post-exposure passive immunisation for other viral infections such as measles and hepatitis A are the dose of immunoglobulins administered and the time between exposure and intervention (Ramsay 2009; Thomas 2009). Given the variability in both of these factors across the included studies, we undertook a post hoc analysis to consider these simultaneously. The limited number of included studies meant that these factors could not be explored in a combined subgroup analysis. However, removing those studies where the time between exposure and intervention was up to eight to 28 days (Anderson 1953b; Doege 1967; Green 1965a) from the subgroup analysis that explored the impact of dose on effectiveness (Analysis 1.4) explained the heterogeneity within the subgroups and demonstrated a difference between subgroups (test for subgroup differences: Chi² test = 5.32, df = 2 (P value = 0.07), I² statistic = 62.4%). The estimates of effect were: ‘estimated 0.027 to 0.037 ml/lb’ RR 1.60 (95% CI 0.57 to 4.52); ‘estimated 0.1 to 0.15 ml/lb’ RR 0.53 (95% CI 0.29 to 0.99); and ‘estimated 0.2 to 0.5 ml/lb’ RR 0.20 (95% CI 0.04 to 1.00) (Analysis 1.9).

Sensitivity analyses

As seen in Figure 2, five studies were at a higher risk of bias than the others (Anderson 1953a; Green 1965a; Green 1965b; Green 1965c; McDonald 1963). We deemed each of these at high risk of bias for one item. Excluding these from the original pooled analysis marginally altered the estimate of effect away from the null (RR 0.58, 95% CI 0.40 to 0.83; heterogeneity: Chi² test = 30.82, df = 5 (P value < 0.0001), I² statistic = 84%). Retaining the three studies at high risk of selective reporting (Green 1965a; Green 1965b; Green 1965c) marginally altered this result toward the null (RR 0.62, 95% CI 0.45 to 0.86), while returning instead the two studies at high risk of detection bias (Anderson 1953a; McDonald 1963) did not alter the result (RR 0.58, 95% CI 0.41 to 0.81). Three studies assessed susceptibility to rubella on history alone (Anderson 1953a; Anderson 1953b; McDonald 1963). Removing these studies from the meta-analysis marginally reduced the size of the effect estimate (RR 0.68, 95% CI 0.50 to 0.92). Heterogeneity was still apparent (heterogeneity: Chi² test = 21.24, df = 7 (P value = 0.003); I² statistic = 67%).

Five studies did not specify how participants were allocated to groups (Green 1965a; Green 1965b; Green 1965c; Martin du Pan 1972; Petersen 1978). With all five studies removed, the results were unaltered (RR 0.59, 95% CI 0.41 to 0.86; heterogeneity: Chi² test = 32.12, df = 5 (P value < 0.0001), I² statistic = 84%). When sequentially removing these studies in order of effect size and then separately in order of study size, the pooled effect estimate ranged from RR 0.66 (95% CI 0.48 to 0.91) to RR 0.54 (95% CI 0.37 to 0.78).

During subgroup analyses, we noted the following subgroups to demonstrate significant heterogeneity while the other subgroups in the relevant analysis did not: ‘RCTs’, ‘children’ and ‘mixed (adult and child participants)’, ‘estimated 0.027 to 0.037 ml/lb’, ‘estimated 0.2 to 0.5 ml/lb’, ‘exposure up to 8 to 28 days prior to IG’ and ‘household contact with a diagnosed case’. The subgroups ‘mixed (adult and child participants)’, ‘estimated 0.27 to 0.37 ml/lb’ and ‘household contact with a diagnosed case’ contained only two studies each. We therefore listed each of these studies as seeming to contribute to heterogeneity and thus subject to the sensitivity analysis for the original meta-analysis. The other subgroups contained more than two studies. In each of these subgroups, we removed each study in turn to assess its impact on the heterogeneity of the subgroup. Where removal of the study resulted in an I² statistic proportion below 60% for the subgroup we listed it as seemingly contributing to heterogeneity and thus subject to the sensitivity analysis for the original meta-analysis. The studies thus listed for removal during sensitivity analyses were: Anderson 1953a; Anderson 1953b; Doege 1967; Green 1965a; and McDonald 1963. We removed studies in each analysis until overall heterogeneity did not meet our protocol specified definition of important heterogeneity (I² statistic < 60% and P value < 0.1). Removing the specified studies in order of the magnitude of the estimate of effect from lowest to highest resulted in removal of Anderson 1953a, Doege 1967 and Green 1965a (heterogeneity: Chi² test = 10.36, df = 7 (P value = 0.17); I² statistic = 32%) and RR 0.36 (95% CI 0.21 to 0.60). Removing these studies in order of the magnitude of the estimate of effect from highest to lowest resulted in removal of Anderson 1953b, Doege 1967 and McDonald 1963 (heterogeneity: Chi² test = 10.50, df = 7 (P value = 0.16); I² statistic = 33%) and RR 0.70 (95% CI 0.46 to 1.04). Removing the studies according to study size from largest to smallest resulted in removal of all five studies identified as seeming to contribute to heterogeneity (heterogeneity: Chi² test = 7.26, df = 3 (P value = 0.20); I² statistic = 31%) and RR 0.43 (95% CI 0.24 to 0.77). Removing the studies according to study size from smallest to largest resulted in removal of Anderson 1953a, Doege 1967 and Green 1965a (heterogeneity: Chi² test = 10.36, df = 7 (P value = 0.17); I² statistic = 32%) and RR 0.36 (95% CI 0.21...
2. Cases of congenital rubella infection

No included study measured the outcome cases of congenital rubella infection.

3. Cases of congenital rubella syndrome

One included study reported on cases of congenital rubella syndrome (McCallin 1972). This study did not identify any cases of congenital rubella syndrome among the infants born to the participants in either the 'high' titre (HI titre 512) intervention or the 'low' titre (HI titre 64) control group. The study reported that the rate of stillbirths (one of 83 participants) and spontaneous abortions (five of 83 participants) was within that expected, however the rates among those who were found to be susceptible to rubella prior to gamma-globulin administration was not reported (total of 41 of the original 83 participants). One of the five participants diagnosed as contracting rubella during their early pregnancy was the participant who suffered a stillbirth. The study did not report whether this participant had been in the high titre or low titre gamma-globulin group.

Secondary outcomes

1. Occurrence of serious adverse events.

No included studies measured or reported on adverse events.

2. Occurrence of non-serious adverse events.

No included studies measured or reported on adverse events.

**DISCUSSION**

**Summary of main results**

We included 12 studies in this review: seven randomised controlled trials (RCTs) and five controlled clinical trials (CCTs) where the means of allocation of participants was not reported. We did not include any unpublished studies. We included 11 studies in meta-analysis of gamma-globulin versus control (saline or no treatment) for rubella cases. The result favoured the intervention group (risk ratio (RR) 0.61, 95% confidence interval (CI) 0.45 to 0.83) but was heterogeneous (Chi² test = 36.59, df = 10 (P value < 0.0001); I² statistic = 73%). This result was robust to sensitivity analyses.

Heterogeneity was not explained by protocol specified subgroup analyses that considered a single factor, but was explained in a post hoc analysis that considered two of these factors simultaneously. We subgrouped studies according to the estimated volume of gamma-globulin administered per pound of bodyweight and then removed those studies where the intervention was administered more than five days after participant exposure to rubella. The test of subgroup differences demonstrated heterogeneity between subgroups according to our protocol definition and there appeared to be greater effectiveness of the intervention when a greater volume of gamma-globulin was administered (0.027 to 0.037 ml/lb: RR 1.6 (95% CI 0.57 to 4.52); '0.1 to 0.15 ml/lb' RR 0.53 (95% CI 0.29 to 0.99); '0.2 to 0.5 ml/lb' RR 0.2 (95% CI 0.04 to 1.00)). No studies measured the outcome congenital rubella infection. One included study reported on congenital rubella syndrome, reporting no cases among participants who were fewer than nine weeks pregnant at enrolment and who were randomised to one of two gamma-globulin groups ('high' or 'low' rubella titre). However, the study did not report how congenital rubella syndrome was measured and did not report the length of follow-up according to intervention group. This study did not include a non-treatment group. No included study measured adverse events.

**Overall completeness and applicability of evidence**

Pregnant women were not recruited in any of the studies included in meta-analyses and only one study attempted to assess the effect of post-exposure passive immunisation for preventing congenital rubella syndrome. The evidence is therefore insufficient to directly conclude the effectiveness of passive immunisation for preventing congenital rubella syndrome. The evidence for preventing rubella cases included participants with a range of ages and both genders. Included studies were undertaken in high-income countries with predominantly Caucasian populations. The health status of participants apart from their exposure to rubella was not reported but it is likely that most were otherwise healthy individuals. Given this, it seems reasonable to generalise the results to the susceptible, healthy, non-pregnant population of high-income countries. While it is likely that rubella could also be prevented by post-exposure passive immunisation of other susceptible individuals, no conclusions can be drawn about possible differences in the magnitude of effect.

None of the included studies measured adverse events associated with passive immunisation. Other literature must be examined in this respect.

**Quality of the evidence**
We rated no included studies at a low risk of bias for all criteria. Critical appraisal was constrained by a lack of information in most studies, yet study authors could not be contacted to supplement the information reported because of the age of the studies. Despite these limitations, we have rated the quality of the evidence as moderate based on the initial meta-analysis (see Summary of findings for the main comparison).

Subgrouping according to study type to account for those included studies where allocation of participants was not specified as random demonstrated that the subgroup of CCTs had an estimate of effect closer to the null than the subgroup of RCTs. Thus if these studies were not randomised trials, their inclusion has biased the overall effect estimate towards, rather than away from the null.

Subgrouping according to funder to examine those studies with potential conflicts of interest demonstrated that the subgroup where gamma-globulin was provided by a company had an estimate of effect closer to the null than the subgroup with no known potential conflicts of interest. While three studies included in those without known conflict of interest did not report funder information, excluding these studies reduced, but did not reverse the direction of the difference between the subgroups. Thus, the inclusion of studies with known potential conflicts of interest may underestimate rather than overestimate the effect size.

Sensitivity analyses also supported the overall beneficial result. The overall effect estimate was either unaltered or larger when we removed studies with a higher risk of bias. Removing studies seeming to contribute to heterogeneity in various sequences did not reverse the direction of effect and in three of the four analyses the estimate of effect increased rather than decreased.

Acknowledging that volume of gamma-globulin per pound of bodyweight was approximated for some studies, we observed an apparent dose effect when the time between exposure and intervention was simultaneously accounted for, increasing confidence in the results.

We specified the subgroup analyses to be conducted in our protocol, but were unable to define the specific subgroups for some of these: dose of immunoglobulins; dose of rubella-specific immunoglobulin; timing of administration of intervention in relation to exposure. This was because categories with clinical relevance had not been defined by the scientific or clinical communities. We therefore defined these categories based on the included studies.

When subgrouping studies by volume of immunoglobulin administered, we used standard weights for adults and adolescents to estimate the volume administered per pound of bodyweight where participant weights were not given. While this would have resulted in imprecision, it was unlikely to have resulted in misclassification between subgroups given there was a considerable degree of separation between the range of volumes defining each subgroup.

We undertook Analysis 1.9, which combined dose of immunoglobulin subgroups with time between exposure and intervention, post hoc based on immunological and clinical principles. This brought the number of subgroup analyses to eight, which may be felt to possibly result in false negative or false positive significance tests. However, the results of Analysis 1.9 are supported by the indirect evidence of the impact of dose and timing of the intervention in relation to post-exposure passive immunisation for preventing both measles (Ramsay 2009) and hepatitis A (Thomas 2009): the magnitude of the difference in the estimates of effect between subgroups within Analysis 1.9; and that this between-study relationship is replicated (although not statistically significantly) within McCallin 1972, which was not included in this meta-analysis.

Agreements and disagreements with other studies or reviews

No previous systematic review has examined passive immunisation for the prevention of rubella or congenital rubella syndrome.

**Potential biases in the review process**

We used a filter for study design to reduce the results of the electronic searches to a manageable number. However, the use of the filter may have excluded relevant studies. We were unable to contact the study authors of the retrieved studies, therefore we necessarily relied on reported information. We therefore may have excluded relevant studies because of the lack of information reported. Similarly, we may have over- or underestimated the potential bias in included studies.

Including studies that did not specify that they used a randomised process for allocating participants to subgroups may be seen as a bias in the review process. However, subgroup analysis and sensitivity analysis both reinforced that the studies included in the meta-analysis in that way reduced rather than increased the estimate of effect.

**A U T H O R S ’ C O N C L U S I O N S**

**Implications for practice**

Compared to no treatment, passive immunisation seems to be of benefit for preventing rubella. The available evidence suggests that this intervention may be of benefit up to five days after exposure, and that effectiveness is dependent on sufficient dose. Considering the attack rate for rubella cases in the control group of the highest volume gamma-globulin subgroup (333 per 1000), the absolute risk reduction (calculated from the risk ratio (RR) (Higgins 2011)) for this volume of gamma-globulin was 266 (95% CI 0 to 320) and the number needed to treat to benefit (NNTB) is four (95% confidence interval (CI) 3 to incalculable).

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

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
The included studies did not measure rubella-specific antibodies in the gamma-globulin products used in a standard way and thus estimation of the dose of rubella-specific antibodies in international units administered was not possible. As the concentration of rubella-specific antibodies in today’s gamma-globulin products may vary from those products used in the studies in the review (Barlinn 1953a, Vauloup-Fellous 2007), the volume required per pound of bodyweight to produce similar beneficial results may also vary.

There is insufficient evidence to make direct conclusions about the effectiveness of post-exposure passive immunisation for preventing congenital rubella syndrome.

The benefits of an intervention should always be weighed against the risks. While the studies included in this review did not measure or report adverse events, potential adverse events related to passive immunisation can be found in the published literature and product information (for example Ashwell 1997, CSL 2014, EMC 2014, EMEA 2002 and Sawyer 2000).

**Implications for research**

Preventing rubella infection among those susceptible after they have been exposed is most important for the subpopulation of exposed susceptible pregnant women. Given the paucity of evidence in this population, and because it would be unethical to design a study with an investigator-controlled placebo comparison group, observational studies comparing the infection status and pregnancy outcomes of exposed susceptible pregnant women with and without post-exposure passive immunisation would be of benefit. Studies should include careful recording of any potential adverse events. Given that dose appears to be important to the magnitude of effectiveness, studies should also include measurement of the concentration of rubella-specific antibodies in the blood product/s used.

**ACKNOWLEDGEMENTS**

We would like to thank Liz Dooley and Clare Dooley for their support and guidance on the development of the protocol. We would like to thank Sarah Thorning for her guidance on the electronic search strategies, running the searches and assisting with language translations. We would like to thank Dr Vittoria Lanje for assisting with Italian translations. We would like to thank the referees of the both the protocol and the review: Theresa Wrangham, Salie Bernard, Roger Thomas, Vittorio Demicheli, Mark Jones and Robert Ware. And finally to Susan Smith, the Contact Editor, for her guidance and support throughout the editorial process.

**REFERENCES**

References to studies included in this review

Anderson 1953a (published data only)

Anderson 1953b (published data only)

Doege 1967 (published data only)

Green 1965a (published data only)


Green 1965b (published data only)


Green 1965c (published data only)

McCallin 1972 (published data only)


McDonald 1963 (published data only)


Petersen 1978 (published data only)


Schiff 1969a (published data only)


Schiff 1969b (published data only)


Schiff 1970 (published data only)


Anon 1970 (published data only)


Anon 1975 (published data only)


Anon 1977 (published data only)


Anon 1993 (published data only)


Aurourse 1973 (published data only)


Badillet 1967 (published data only)


Balsamo 1963 (published data only)


Banatvala 2004 (published data only)


Barenberg 1942 (published data only)


Bass 1949 (published data only)


Beasley 1969 (published data only)


Braadstreet 1978 (published data only)


Brody 1965 (published data only)

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)
Lundstrom 1954 {published data only}

Krugman 1958 {published data only}

Krugman 1963 {published data only}

Krugman 1970 {published data only}

Lamprecht 1982 {published data only}

Lock 1961 {published data only}

Lundstrom 1953 {published data only}

Lundstrom 1956 {published data only}

Lundstrom 1961a {published data only}

Lundstrom 1961b {published data only}

Lundstrom 1962 {published data only}

Lundstrom 1965 {published data only}

Lundstrom 1969 {published data only}

Luthardt 1974 {published data only}

Macrae 1968 {published data only}

Macrae 1970 {published data only}

Magath 1957 {published data only}

Marshall 1976 {published data only}

Martin 1999 {published data only}

Martin du Pan 1960 {published data only}

Martin du Pan 1971 {published data only}

Matzen 1970 {published data only}
Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)  


5. Skinner 1961


7. Spiteri 2008


9. Stokes 1947


11. Straussburg 1981


13. Strauss 1980


15. Uqquhart 1978


17. Valheri 1972


19. Ward 1956


21. Watson 1969


23. WHO 2000


25. WHO 2002


27. Additional references

28. Ang 2010


30. Ashwell 1997


32. ATAGI 2008


34. ATAGI 2013


36. Barlinn 2014


38. Best 2007


40. Birdauss 2009


42. BMJ Clinical Evidence 2012


44. Burnout 2007


46. Burton 2002


48. Caidi 2009


50. CDC 1998

51. Centers for Disease Control and Prevention. Measles, mumps, and rubella - vaccine use and strategies for

CDC 2001

CSL 2014

Cutts 1999

De Santis 2006

Dewan 2012

EMC 2014

EMEA 1995

EMEA 2002

Furlan 2006
Furlan AD, Irvin E, Bombardier C. Limited search strategies were effective in finding relevant nonrandomized studies. Journal of Clinical Epidemiology 2006;59(12):1303–11.

Goodson 2011

GRADE Working Group 2004

GRADEpro 2015

Heymann 2008

Higgins 2011

Himman 2002

IDHPA 2009

Law 2008

Lefebvre 2011

McDonagh 1966

Muscat 2012

Nardone 2008

Nessa 2008
Nessa A, Islam MN, Táboasum S, Munshi SU, Ahmed M, Karim R. Seroprevalence of rubella among urban and rural Bangladeshi women emphasises the need for rubella...
Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)  

Schiff 1969d  

SIGN 2012  

Simon 2003  

Song 2012  

Strebel 2010  

Thomas 2009  

University of Texas 2012  

Usonis 2011  

Vauloup-Fellous 2007  

WHO 1994  
WHO 2011

World Law Direct 2009

Zeldin 2007

References to other published versions of this review
Young 2013

* Indicates the major publication for the study
### Characteristics of included studies [ordered by study ID]

#### Anderson 1953a

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Female university students (sample size 24) aged 18 to 26 from Victoria, Australia, with no history of rubella, exposed artificially with virus obtained from rubella sufferers and processed to a solution of 500 Oxford units per millilitre. The viral solution was administered to the volunteers by atomised spray into the throat (0.1 ml) and dropped into each nostril during inhalation (0.1 ml)</td>
</tr>
<tr>
<td>Interventions</td>
<td>70 hours after exposure, 4 ml (0.03 to 0.04 ml/lb) gamma-globulin (rubella antibody titre not reported) IM versus no intervention</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rubella cases diagnosed after examination by 2 physicians. Follow-up duration: 21 days plus</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: intervention product supplied by Red Cross Blood Transfusion Service and CSL, Australia</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of rubella</td>
<td>High risk</td>
<td>Blinding not reported. Outcome assessed subjectively</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>
### Anderson 1953b

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adolescent boys (sample size 91) aged 15 to 18 years from Victoria, Australia with no history of rubella living together with other boys diagnosed with rubella in the preceding 4 days</td>
</tr>
<tr>
<td>Interventions</td>
<td>On day 5 since the first case was diagnosed, 4 ml gamma-globulin (rubella antibody titre not reported) IM versus 4 ml normal saline IM</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rubella cases diagnosed by a physician Follow-up duration: 21 days plus</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: intervention product supplied by Red Cross Blood Transfusion Service and CSL, Australia</td>
</tr>
</tbody>
</table>

#### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>Participants and outcome assessors blinded: “Both the globulin and the saline were given by the same physicians and the boys had no knowledge of which they received. From May 19 to June 3 the 91 boys were inspected daily by one of the authors (SGA), who at the time of inspection did not know who had received saline and who globulin” p184</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

### Doege 1967

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Residents (sample size 17) aged 3 to 19 with rubella antibody neutralisation titres &lt; 1:4 who lived in 1 wing of an institution for mentally handicapped people in Seattle, USA where diagnosed cases also resided</td>
</tr>
</tbody>
</table>
**Doege 1967** (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>3 weeks after the first case and 6 days after the most recent case in the wing was diagnosed, 0.5 ml per unit bodyweight (unit not specified) ‘poliomyelitis immune globulin’ with rubella neutralisation titre 1:300 IM versus no intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Rubella cases: clinical signs, virus isolates from oropharyngeal or nasopharyngeal swabs, change in rubella neutralisation titre Follow-up duration: 3 months</td>
</tr>
<tr>
<td>Notes</td>
<td>Data were presented in the publication on a wider range of participants but we have included only those the authors determined to be susceptible to rubella (which the authors based on rubella neutralisation titre &lt; 1:4) Funding: intervention product supplied by Parke, Davis &amp; Co, Detroit. Study supported by US Public Health Service infectious diseases training grant</td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Means of random sequence generation not reported. Of 47 participants randomised from 1 wing, we have included only the 17 deemed by the authors as susceptible</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Cases of rubella</td>
<td>Low risk</td>
<td>Virus isolation and serology measures objective. Participants with “suspicious rashes” were examined by one of the authors who was blind to group allocation: “Children of both wings were observed by competent nurses and attending physicians and persons with suspicious rashes were examined by one of us (TCD) without knowledge of their group” p105</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

**Green 1965a**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Controlled clinical trial with unclear randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Mentally handicapped children (sample size 13) aged 1 to 10 years residing at an institution on Staten Island, USA, with rubella neutralisation titres at baseline &lt; 1:4 who were living with a child with clinical rubella after that child’s artificial infection</td>
</tr>
</tbody>
</table>
Green 1965a (Continued)

<table>
<thead>
<tr>
<th>Interventions</th>
<th>24 hours after the appearance of rash on the infected child, 0.15 ml/lb of gamma-globulin with rubella neutralising titre of 1:32 IM versus no intervention</th>
</tr>
</thead>
<tbody>
<tr>
<td>Outcomes</td>
<td>Rubella cases: significant neutralising antibody titre rise +/- clinical signs +/- virus isolation from serum or pharynx Follow-up: 53 days</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: grant from the National Institute of Allergy and Infectious Diseases, US Public Health Service and a contract with the US Army Medical Research and Development Command, Office of the Surgeon General</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of rubella</td>
<td>Low risk</td>
<td>No blinding reported but outcome measured objectively using serology</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants accounted for in the results regarding the outcome rubella cases</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Viraemia outcome presented for 5 intervention and 5 control participants only of all participants in Green 1965a, b, and c. Results of swab/serum virus isolation for other participants not reported</td>
</tr>
</tbody>
</table>

Green 1965b

<table>
<thead>
<tr>
<th>Methods</th>
<th>Controlled clinical trial with unclear randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Mentally handicapped children (sample size 10) aged 1 to 10 years residing at an institution on Staten Island, USA, with rubella neutralisation titres at baseline &lt; 1:4 who were living with a child with clinical rubella from onset of rash on that child</td>
</tr>
<tr>
<td>Interventions</td>
<td>24 hours after initial exposure to the child with rash, 0.2 ml/lb of gamma-globulin with rubella neutralising titre 1:64 IM versus no intervention</td>
</tr>
</tbody>
</table>
Green 1965b  (Continued)

<table>
<thead>
<tr>
<th>Outcomes</th>
<th>Rubella cases: significant neutralising antibody titre rise +/- clinical signs +/- virus isolation from serum or pharynx Follow-up: 53 days</th>
</tr>
</thead>
</table>

| Notes | Funding: grant from the National Institute of Allergy and Infectious Diseases, US Public Health Service and a contract with the US Army Medical Research and Development Command, Office of the Surgeon General |

| Risk of bias |
|---|---|---|
| Bias | Authors' judgement | Support for judgement |
| Random sequence generation (selection bias) | Unclear risk | Means of allocation to groups not reported |
| Allocation concealment (selection bias) | Unclear risk | Means of allocation to groups not reported |
| Blinding of participants and personnel (performance bias) All outcomes | Low risk | The nature of the intervention means it is not subject to variation due to performance |
| Blinding of outcome assessment (detection bias) Cases of rubella | Low risk | No blinding reported but outcome measured objectively using serology |
| Incomplete outcome data (attrition bias) All outcomes | Low risk | All participants accounted for in the results regarding the outcome rubella cases |
| Selective reporting (reporting bias) | High risk | Viraemia outcome presented for 5 intervention and 5 control participants only of all participants in Green 1965a, b and c. Results of swab/serum virus isolation for other participants not reported |

Green 1965c

<table>
<thead>
<tr>
<th>Methods</th>
<th>Controlled clinical trial with unclear randomisation</th>
</tr>
</thead>
</table>

<table>
<thead>
<tr>
<th>Participants</th>
<th>Mentally handicapped children (sample size 11) aged 1 to 10 years residing at an institution on Staten Island, USA, with rubella neutralisation titres at baseline &lt; 1:4 who had brief contact (30 minutes but included ‘intimate oral contact’) with 2 children on the first day of their rubella rash</th>
</tr>
</thead>
</table>

| Interventions | At a time (not reported) after exposure, 0.2 ml/lb gamma-globulin with rubella neutralising titre 1:64 IM versus no intervention |
**Green 1965c** (Continued)

| Outcomes | Rubella cases: significant neutralising antibody titre rise +/- clinical signs +/- virus isolation from serum or pharynx  
| Follow-up: 53 days |

**Notes**  
Funding: grant from the National Institute of Allergy and Infectious Diseases, US Public Health Service and a contract with the US Army Medical Research and Development Command, Office of the Surgeon General

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>All outcomes</td>
<td>Low risk</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Cases of rubella</td>
<td>Low risk</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>All outcomes</td>
<td>Low risk</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>High risk</td>
<td>Viraemia outcome presented for 5 intervention and 5 control participants only of all participants in Green 1965a, b and c. Results of swab/serum virus isolation for other participants not reported</td>
</tr>
</tbody>
</table>

**Martin du Pan 1972**

<table>
<thead>
<tr>
<th>Methods</th>
<th>Controlled clinical trial with unclear randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>University student volunteers (sample size 7) from Geneva, Switzerland with no history of rubella and no rubella antibody at baseline on hemagglutinin inhibition (HI) testing, who were infected by intranasal administration of 1 ml solution containing 10 000 TCID50 (median tissue culture infective dose) rubella viruses of attenuated Brown strain</td>
</tr>
<tr>
<td>Interventions</td>
<td>5 days after infection, 30 ml to 60 ml of gamma-globulin with 1:1000 rubellatitre by HI diluted in 200 ml saline IV versus no intervention</td>
</tr>
</tbody>
</table>
| Outcomes | Rubella cases: significant rise in rubella serum titre by HI +/- clinical signs  
| Follow-up: 6 weeks |
Notes

**Funding:** no source reported

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>No blinding reported but outcome measured objectively using serology</td>
</tr>
<tr>
<td>Cases of rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

**McCallin 1972**

**Methods**

RCT

**Participants**

Women (sample size 41) registering at an antenatal clinic in Hawaii, USA who were fewer than 9 weeks pregnant, had no rubella antibody at baseline based on HI testing and self reported exposure to rubella during the first trimester of pregnancy

**Interventions**

On enrolment, 20 ml gamma-globulin with rubella HI titre 1:512 IM versus 20 ml gamma-globulin with rubella HI titre 1:64

**Outcomes**

Maternal rubella cases: seroconversion by HI. Follow-up: 2 months CRS: means of examination not reported. Infants “followed up for minimum 6 months and up to 3 years” p187

**Notes**

Publication reports on a 3rd study group given no intervention but this group was not randomly assigned

Funding: no source reported

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### McCallin 1972

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias) All outcomes</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of rubella</td>
<td>Low risk</td>
<td>No blinding reported but outcome measured objectively using serology</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias) Cases of congenital rubella syndrome</td>
<td>Unclear risk</td>
<td>No blinding reported. No reported definition of congenital rubella syndrome, no details on the means of examination of infants in each group, no reported average length of follow-up according to group</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias) All outcomes</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

### McDonald 1963

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Methods</td>
<td>RCT</td>
<td></td>
</tr>
<tr>
<td>Participants</td>
<td>Children (sample size 179) (age not further defined) in 5 wards in a hospital in London, UK with no past history of rubella who were &quot;exposed to infection&quot; p416</td>
<td></td>
</tr>
<tr>
<td>Interventions</td>
<td>At a time (not reported) after exposure, 250 mg gamma-globulin from 1 of 46 different batches (rubella antibody titre not reported) versus no intervention</td>
<td></td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rubella cases: outcome criteria not reported Excluded ‘cases’ from results where illness onset was within 3 days of the intervention time Follow-up: 35 days</td>
<td></td>
</tr>
<tr>
<td>Notes</td>
<td>Main portion of the publication reports on a case series, which is not a study design included in the review Funding: no source reported</td>
<td></td>
</tr>
</tbody>
</table>

**Risk of bias**

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
</tbody>
</table>
### McDonald 1963 (Continued)

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>(performance bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection</td>
<td>High risk</td>
<td>Blinding not reported. No mention of blood testing or other investigation for infection. Outcome likely to have been assessed subjectively</td>
</tr>
<tr>
<td>bias) Cases of rubella</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported although report was brief</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Petersen 1978

<table>
<thead>
<tr>
<th>Method</th>
<th>Controlled clinical trial with unclear randomisation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Medical student volunteers (sample size 16) in Germany with a mean age of 25 years who had no rubella antibody at baseline based on HI testing and were infected by administration of 0.25 ml of 1500 GKID50 (median tissue culture infective dose) rubella virus suspension into each nostril</td>
</tr>
<tr>
<td>Interventions</td>
<td>24 hours after exposure, 15 ml of gamma-globulin with rubella HI titre 1:2560 IM (intervention group had had 20 ml IM of same 6 weeks earlier) versus no intervention</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rubella cases: seroconversion as measured by HI +/- virus isolation +/- clinical signs Follow-up: 8 weeks</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: no source reported</td>
</tr>
</tbody>
</table>

### Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Means of allocation to groups not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>(performance bias)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Schiff 1969a

Methods  RCT

Participants  Adult male (sample size 10) (age not further defined) inmates of a correctional institution in Ohio, USA with no rubella neutralising antibody titre at baseline who were infected by dripping 0.5 ml of 100 TCID50 Gilchrist strain virus solution into each nostril after roughing the posterior pharynx with a cotton swab

Interventions  24 hours after exposure, 20 ml (0.12 ml/lb to 0.15 ml/lb) of gamma-globulin (called immune globulin in the publications) with rubella neutralisation titre of 1024 to 4096*/0.1 ml IM versus saline 20 ml IM

* (gamma-globulin original batch titre 4096/0.1 ml but on retesting after 3 years in storage titre was 1024/0.1 ml - unclear at what time in relation to testing of titre the study used the batch)

Outcomes  Rubella cases: seroconversion by neutralisation +/- virus isolation +/- clinical signs

Follow-up: 42 days

Notes  Funding; the 'National Foundation' and a 'Career Research Development Award from the National Institutes of Health'

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors’ judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>All outcomes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>No blinding reported but outcome measured objectively using serology</td>
</tr>
<tr>
<td>Cases of rubella</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Schiff 1969a (Continued)

<table>
<thead>
<tr>
<th>Incomplete outcome data (attrition bias)</th>
<th>Low risk</th>
<th>All participants accounted for in results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

Schiff 1969b

<table>
<thead>
<tr>
<th>Methods</th>
<th>RCT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Participants</td>
<td>Adult male (sample size 11) (age not further defined) inmates of a correctional institution in Ohio, USA with no rubella HI titre at baseline who were infected by dripping 0.5 ml of 100 TCID50 Gilchrist strain virus solution into each nostril after roughing the posterior pharynx with a cotton swab</td>
</tr>
<tr>
<td>Interventions</td>
<td>24 hours after exposure, 20 ml of gamma-globulin (called immune globulin in the publications) with rubella neutralisation titre of 256/0.1 ml IM versus saline 20 ml IM</td>
</tr>
<tr>
<td>Outcomes</td>
<td>Rubella cases: seroconversion by HI +/- virus isolation +/- clinical signs Follow-up: 42 days</td>
</tr>
<tr>
<td>Notes</td>
<td>Funding: the 'National Foundation' and a 'Career Research Development Award from the National Institutes of Health'</td>
</tr>
</tbody>
</table>

Risk of bias

<table>
<thead>
<tr>
<th>Bias</th>
<th>Authors' judgement</th>
<th>Support for judgement</th>
</tr>
</thead>
<tbody>
<tr>
<td>Random sequence generation (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Allocation concealment (selection bias)</td>
<td>Unclear risk</td>
<td>Not reported</td>
</tr>
<tr>
<td>Blinding of participants and personnel (performance bias)</td>
<td>Low risk</td>
<td>The nature of the intervention means it is not subject to variation due to performance</td>
</tr>
<tr>
<td>Blinding of outcome assessment (detection bias)</td>
<td>Low risk</td>
<td>No blinding reported but outcome measured objectively using serology</td>
</tr>
<tr>
<td>Incomplete outcome data (attrition bias)</td>
<td>Low risk</td>
<td>All participants accounted for in results</td>
</tr>
<tr>
<td>Selective reporting (reporting bias)</td>
<td>Low risk</td>
<td>No outcomes specified that were not reported</td>
</tr>
</tbody>
</table>

CRS: congenital rubella syndrome
HI: hemagglutinin inhibition
IM: intramuscular  
IV: intravenous  
RCT: randomised controlled trial

**Characteristics of excluded studies (ordered by study ID)**

<table>
<thead>
<tr>
<th>Study</th>
<th>Reason for exclusion</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adams 1997</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Alyswort 1971</td>
<td>Case study</td>
</tr>
<tr>
<td>Andre 1980</td>
<td>Letter - no primary study</td>
</tr>
<tr>
<td>Anon 1970</td>
<td>Letter - no primary study</td>
</tr>
<tr>
<td>Anon 1975</td>
<td>Question and answer - no primary study</td>
</tr>
<tr>
<td>Anon 1977</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Anon 1993</td>
<td>Does not appear to be a RCT or quasi-RCT. Immunoglobulin given prior to vaccination.</td>
</tr>
<tr>
<td></td>
<td>Outcome was seroconversion in relation to vaccine</td>
</tr>
<tr>
<td>Aurousse 1973</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Badillet 1967</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Balsamo 1963</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Banavala 2004</td>
<td>Review</td>
</tr>
<tr>
<td>Barenberg 1942</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Bass 1949</td>
<td>Participant susceptibility not known by investigators</td>
</tr>
<tr>
<td>Beasley 1969</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Bradstreet 1978</td>
<td>Laboratory study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Brody 1965</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Budai 1970</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Carne 1973</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>CDC 1964</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Reference</td>
<td>Study Type</td>
</tr>
<tr>
<td>--------------------</td>
<td>-----------------------</td>
</tr>
<tr>
<td>CDC 1978</td>
<td>Case study</td>
</tr>
<tr>
<td>CDC 1979</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>CDC 1980</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>CDC 1981a</td>
<td>Review</td>
</tr>
<tr>
<td>CDC 1981b</td>
<td>Review</td>
</tr>
<tr>
<td>CDC 1981c</td>
<td>Case series</td>
</tr>
<tr>
<td>CDC 1983</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>CDC 1986</td>
<td>No exposure - vaccination only. No immunoglobulin administered</td>
</tr>
<tr>
<td>Clarke 1975</td>
<td>Laboratory study</td>
</tr>
<tr>
<td>Connolly 1984</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Cradock-Watson 1973</td>
<td>Symptomatic participants. No immunoglobulin administered</td>
</tr>
<tr>
<td>Cradock-Watson 1976</td>
<td>Participants were infants with suspected or confirmed congenital rubella syndrome</td>
</tr>
<tr>
<td>Craig 1999</td>
<td>No comparison group</td>
</tr>
<tr>
<td>D'Agaro 2010</td>
<td>Outbreak description. No intervention</td>
</tr>
<tr>
<td>Darbois 1974</td>
<td>No comparison group. No immunoglobulin administered</td>
</tr>
<tr>
<td>DMPS 1973</td>
<td>Descriptive study. No intervention</td>
</tr>
<tr>
<td>Dudgeon 1974</td>
<td>Letter - no primary study</td>
</tr>
<tr>
<td>Fleigel 1982</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Forrest 1971</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Forrest 1973</td>
<td>Case study</td>
</tr>
<tr>
<td>Forrest 1974</td>
<td>Retrospective examination of cases</td>
</tr>
<tr>
<td>Frank 1969</td>
<td>Discussion at a conference/seminar - no primary study</td>
</tr>
<tr>
<td>Freestone 1972</td>
<td>Review</td>
</tr>
<tr>
<td>Furukawa 1970</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Author</td>
<td>Title and Description</td>
</tr>
<tr>
<td>-----------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Geursen 1982</td>
<td>Review</td>
</tr>
<tr>
<td>Gilberto 1988</td>
<td>Review</td>
</tr>
<tr>
<td>Giles 1965</td>
<td>Case series</td>
</tr>
<tr>
<td>Giraldi 2009</td>
<td>Symptomatic participants. No immunoglobulins administered</td>
</tr>
<tr>
<td>Gladstone 1981</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Goetz 1974</td>
<td>Question and answer - no primary study</td>
</tr>
<tr>
<td>Grayston 1959</td>
<td>Participants not identified as susceptible</td>
</tr>
<tr>
<td>Greaves 1982</td>
<td>Review</td>
</tr>
<tr>
<td>Greenberg 1947</td>
<td>Review. Some details of a primary study by the authors regarding rubella, but participants not identified as susceptible</td>
</tr>
<tr>
<td>Hahne 2009</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Haire 1970</td>
<td>Case series</td>
</tr>
<tr>
<td>Happe 1984</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Hillenbrand 1956</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Horstmann 1965</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Horstmann 1971</td>
<td>Review</td>
</tr>
<tr>
<td>Houser 1958</td>
<td>Immunoglobulin given pre-exposure</td>
</tr>
<tr>
<td>Huntley 1969</td>
<td>Examination of infant immunoglobulin levels</td>
</tr>
<tr>
<td>Hutchinson 1967</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Jackson 1993</td>
<td>No immunoglobulins administered</td>
</tr>
<tr>
<td>Just 1969</td>
<td>Conference proceedings on the vaccine</td>
</tr>
<tr>
<td>Kabat 1963</td>
<td>Review</td>
</tr>
<tr>
<td>Karchmer 1969</td>
<td>No exposure. No immunoglobulin administered</td>
</tr>
<tr>
<td>Karthikeyan 2012</td>
<td>Case study</td>
</tr>
<tr>
<td>Year</td>
<td>Reference</td>
</tr>
<tr>
<td>---------</td>
<td>--------------------</td>
</tr>
<tr>
<td>1952</td>
<td>Korns</td>
</tr>
<tr>
<td>1954</td>
<td>Krugman</td>
</tr>
<tr>
<td>1958</td>
<td>Krugman</td>
</tr>
<tr>
<td>1963</td>
<td>Krugman</td>
</tr>
<tr>
<td>1970</td>
<td>Krugman</td>
</tr>
<tr>
<td>1982</td>
<td>Lamprecht</td>
</tr>
<tr>
<td>1961</td>
<td>Lock</td>
</tr>
<tr>
<td>1953</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1956</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1961a</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1961b</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1962</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1965</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1969</td>
<td>Lundstrom</td>
</tr>
<tr>
<td>1974</td>
<td>Linhardt</td>
</tr>
<tr>
<td>1968</td>
<td>Macrae</td>
</tr>
<tr>
<td>1970</td>
<td>Macrae</td>
</tr>
<tr>
<td>1957</td>
<td>Magath</td>
</tr>
<tr>
<td>1976</td>
<td>Marshall</td>
</tr>
<tr>
<td>1999</td>
<td>Martin</td>
</tr>
<tr>
<td>1969</td>
<td>Martin du Pan</td>
</tr>
<tr>
<td>1971</td>
<td>Martin du Pan</td>
</tr>
<tr>
<td>1970</td>
<td>Matsen</td>
</tr>
<tr>
<td>Study</td>
<td>Design and Methodology</td>
</tr>
<tr>
<td>--------------------</td>
<td>----------------------------------------------------------------------------------------</td>
</tr>
<tr>
<td>McDonald 1967</td>
<td>No comparison group</td>
</tr>
<tr>
<td>McLorinan 1949</td>
<td>No comparison group</td>
</tr>
<tr>
<td>McLorinan 1950</td>
<td>No comparison group</td>
</tr>
<tr>
<td>Mele 1949</td>
<td>Not a RCT/quasi-RCT. Allocation based on availability of gamma-globulin</td>
</tr>
<tr>
<td>Mellinger 1995</td>
<td>Retrospective study</td>
</tr>
<tr>
<td>Miller 1967</td>
<td>Participant susceptibility not known by investigators</td>
</tr>
<tr>
<td>Millian 1971</td>
<td>Laboratory assessment of gamma-globulin</td>
</tr>
<tr>
<td>Morgan 1950</td>
<td>Report - no primary study</td>
</tr>
<tr>
<td>Neumann-Haefelin 1975</td>
<td>Not a RCT. Allocation based on organisation aspects and willingness of participants</td>
</tr>
<tr>
<td>Peckham 1974a</td>
<td>Participants symptomatic/diagnosed with rubella</td>
</tr>
<tr>
<td>Peckham 1974b</td>
<td>Letter - no primary study</td>
</tr>
<tr>
<td>Petersen 1982</td>
<td>No exposure - vaccination only</td>
</tr>
<tr>
<td>Plotinsky 2007</td>
<td>Case study</td>
</tr>
<tr>
<td>Polk 1980</td>
<td>Descriptive study. No immunoglobulin administered</td>
</tr>
<tr>
<td>Pollock 1970</td>
<td>Secondhand account of several primary studies</td>
</tr>
<tr>
<td>Reid 1967</td>
<td>Review</td>
</tr>
<tr>
<td>Sanchez 2010</td>
<td>Case study</td>
</tr>
<tr>
<td>Sandow 1978</td>
<td>Review</td>
</tr>
<tr>
<td>Schiff 1965a</td>
<td>Retrospective study. No comparison group</td>
</tr>
<tr>
<td>Schiff 1965b</td>
<td>Not all participants susceptible. No immunoglobulin administered</td>
</tr>
<tr>
<td>Schiff 1966</td>
<td>Review</td>
</tr>
<tr>
<td>Schiff 1969c</td>
<td>No immunoglobulin administered</td>
</tr>
<tr>
<td>Seglenieks 1974</td>
<td>Topic of study not rubella</td>
</tr>
<tr>
<td>Seth 1972</td>
<td>Seroprevalence study</td>
</tr>
</tbody>
</table>
Sever 1965a  Not all participants susceptible and cannot separate results for those who were
Sever 1965b  Descriptive study. No immunoglobulin administered
Skinner 1961  Review
Spiteri 2008  Descriptive study. No immunoglobulin administered
Stokes 1947  Review - topic not rubella
Strassburg 1981  No immunoglobulin administered
Strauss 1980  No immunoglobulin administered. Vaccine only
Urquhart 1978  No exposure - vaccine only
Vaheri 1972  Review regarding vaccination
Ward 1956  Participant susceptibility not known by investigators
Watson 1969  No immunoglobulin administered
WHO 2000  Review
WHO 2002  Descriptive study. No immunoglobulin administered

RCT: randomised controlled trial
### DATA AND ANALYSES

**Comparison 1. Gamma-globulin versus control (no treatment or saline)**

<table>
<thead>
<tr>
<th>Outcome or subgroup title</th>
<th>No. of studies</th>
<th>No. of participants</th>
<th>Statistical method</th>
<th>Effect size</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Rubella cases</td>
<td>11</td>
<td>389</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.45, 0.83]</td>
</tr>
<tr>
<td>2 Rubella cases</td>
<td>11</td>
<td>389</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.45, 0.83]</td>
</tr>
<tr>
<td>2.1 RCT</td>
<td>6</td>
<td>332</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.59 [0.41, 0.86]</td>
</tr>
<tr>
<td>2.2 Controlled clinical trial</td>
<td>5</td>
<td>57</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.38, 1.12]</td>
</tr>
<tr>
<td>3 Rubella cases</td>
<td>11</td>
<td>389</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.45, 0.83]</td>
</tr>
<tr>
<td>3.1 Adult participants</td>
<td>5</td>
<td>68</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.40, 1.07]</td>
</tr>
<tr>
<td>3.2 Child participants</td>
<td>4</td>
<td>213</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.46 [0.24, 0.91]</td>
</tr>
<tr>
<td>3.3 Mixed (adult and child participants)</td>
<td>2</td>
<td>108</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.71 [0.45, 1.12]</td>
</tr>
<tr>
<td>4 Rubella cases</td>
<td>10</td>
<td>210</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.70 [0.52, 0.95]</td>
</tr>
<tr>
<td>4.1 Estimated 0.027 to 0.037 ml/lb</td>
<td>2</td>
<td>115</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.77 [0.36, 1.67]</td>
</tr>
<tr>
<td>4.2 Estimated 0.1 to 0.15 ml/lb</td>
<td>4</td>
<td>50</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.69 [0.44, 1.08]</td>
</tr>
<tr>
<td>4.3 Estimated 0.2 to 0.5 ml/lb</td>
<td>9</td>
<td>199</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.67 [0.45, 0.99]</td>
</tr>
<tr>
<td>5 Rubella cases</td>
<td>6</td>
<td>78</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.63 [0.38, 1.04]</td>
</tr>
<tr>
<td>5.1 Exposure 24 hours to 5 days prior to IG</td>
<td>3</td>
<td>121</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.81 [0.56, 1.17]</td>
</tr>
<tr>
<td>6 Rubella cases</td>
<td>10</td>
<td>210</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.70 [0.52, 0.95]</td>
</tr>
<tr>
<td>6.1 Artificial exposure</td>
<td>5</td>
<td>68</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.65 [0.40, 1.07]</td>
</tr>
<tr>
<td>6.2 Controlled exposure to infected person</td>
<td>3</td>
<td>34</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.82 [0.42, 1.61]</td>
</tr>
<tr>
<td>6.3 Household contact with diagnosed case</td>
<td>2</td>
<td>108</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.71 [0.45, 1.12]</td>
</tr>
<tr>
<td>7 Rubella cases</td>
<td>10</td>
<td>210</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.70 [0.52, 0.95]</td>
</tr>
<tr>
<td>7.1 Cases defined on clinical grounds</td>
<td>2</td>
<td>115</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.77 [0.36, 1.67]</td>
</tr>
<tr>
<td>7.2 Laboratory-confirmed cases</td>
<td>8</td>
<td>95</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.68 [0.50, 0.92]</td>
</tr>
<tr>
<td>8 Rubella cases</td>
<td>11</td>
<td>389</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.61 [0.45, 0.83]</td>
</tr>
<tr>
<td>8.1 No known conflict of interest</td>
<td>8</td>
<td>257</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.46 [0.29, 0.72]</td>
</tr>
<tr>
<td>8.2 Potential conflict of interest</td>
<td>3</td>
<td>132</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.87 [0.57, 1.33]</td>
</tr>
<tr>
<td>9 Rubella cases</td>
<td>7</td>
<td></td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>Subtotals only</td>
</tr>
<tr>
<td>9.1 Estimated 0.027 to 0.037 ml/lb</td>
<td>1</td>
<td>24</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>1.6 [0.57, 4.52]</td>
</tr>
<tr>
<td>9.2 Estimated 0.1 to 0.15 ml/lb</td>
<td>3</td>
<td>37</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.53 [0.29, 0.99]</td>
</tr>
<tr>
<td>9.3 Estimated 0.2 to 0.5 ml/lb</td>
<td>3</td>
<td>28</td>
<td>Risk Ratio (M-H, Fixed, 95% CI)</td>
<td>0.20 [0.04, 1.00]</td>
</tr>
</tbody>
</table>
### Analysis 1.1. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 1 Rubella cases.

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

Comparison: 1 Gamma-globulin versus control (no treatment or saline)

Outcome: 1 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>6.7 % 1.60 [ 0.57, 4.52 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>14.1 % 0.38 [ 0.11, 1.35 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doose 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>15.9 % 1.00 [ 0.81, 1.24 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>8.2 % 1.17 [ 0.65, 2.10 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>2.7 % 0.33 [ 0.02, 6.65 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>2.9 % 0.29 [ 0.01, 5.79 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>5.9 % 0.10 [ 0.01, 1.49 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonald 1963</td>
<td>2/91</td>
<td>10/88</td>
<td>18.1 % 0.19 [ 0.04, 0.86 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>8.0 % 0.78 [ 0.29, 2.26 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>9.8 % 0.09 [ 0.01, 1.31 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>7.8 % 0.83 [ 0.41, 1.70 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td><strong>202</strong></td>
<td><strong>187</strong></td>
<td><strong>100.0 % 0.61 [ 0.45, 0.83 ]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 35 (Gamma-globulin), 51 (No treatment or saline)

Heterogeneity: $\chi^2 = 36.59$, df = 10 ($P = 0.0007$); $I^2 = 73%$

Test for overall effect: $Z = 3.15$ ($P = 0.0016$)

Test for subgroup differences: Not applicable
### Analysis 1.2. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 2 Rubella cases.

**Review:** Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome

**Comparison:** 1 Gamma-globulin versus control (no treatment or saline)

**Outcome:** 2 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>6.7 %</td>
<td>1.60 [ 0.57, 4.52 ]</td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>14.1 %</td>
<td>0.38 [ 0.11, 1.35 ]</td>
<td></td>
</tr>
<tr>
<td>Dooge 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>15.9 %</td>
<td>1.00 [ 0.81, 1.29 ]</td>
<td></td>
</tr>
<tr>
<td>McDonald 1963</td>
<td>2/91</td>
<td>10/88</td>
<td>18.1 %</td>
<td>0.19 [ 0.04, 0.86 ]</td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>9.8 %</td>
<td>0.09 [ 0.01, 1.31 ]</td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>7.8 %</td>
<td>0.83 [ 0.41, 1.70 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>171</strong></td>
<td><strong>161</strong></td>
<td><strong>72.3 %</strong></td>
<td><strong>0.59 [ 0.41, 0.86 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 26 (Gamma-globulin), 38 (No treatment or saline)

**Heterogeneity:** $\chi^2 = 32.12, df = 5 (P < 0.00001); I^2 = 84%$

**Test for overall effect:** $Z = 2.73 (P = 0.0063)$

### Controlled clinical trial

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>8.2 %</td>
<td>1.17 [ 0.65, 2.10 ]</td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>2.7 %</td>
<td>0.33 [ 0.02, 6.65 ]</td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>2.9 %</td>
<td>0.29 [ 0.01, 5.79 ]</td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>5.9 %</td>
<td>0.10 [ 0.01, 1.49 ]</td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>8.0 %</td>
<td>0.78 [ 0.29, 2.26 ]</td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>31</strong></td>
<td><strong>26</strong></td>
<td><strong>27.7 %</strong></td>
<td><strong>0.65 [ 0.38, 1.12 ]</strong></td>
<td></td>
</tr>
</tbody>
</table>

**Total events:** 9 (Gamma-globulin), 13 (No treatment or saline)

**Heterogeneity:** $\chi^2 = 6.17, df = 4 (P = 0.19); I^2 = 35%$

**Test for overall effect:** $Z = 1.56 (P = 0.12)$

### Total (95% CI)

<table>
<thead>
<tr>
<th></th>
<th>Total events: 35 (Gamma-globulin), 51 (No treatment or saline)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>202</strong></td>
</tr>
</tbody>
</table>

**Heterogeneity:** $\chi^2 = 36.59, df = 10 (P = 0.00007); I^2 = 73%$

**Test for overall effect:** $Z = 3.15 (P = 0.0016)$

**Test for subgroup differences:** $\chi^2 = 0.09, df = 1 (P = 0.77); I^2 = 0.0%$

---

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

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
## Analysis 1.3. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 3 Rubella cases.

**Review:** Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome

**Comparison:** 1 Gamma-globulin versus control (no treatment or saline)

**Outcome:** 3 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adult participants</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>6.7 %</td>
<td>1.60 [0.57, 4.52]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>5.9 %</td>
<td>0.10 [0.01, 1.49]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>8.0 %</td>
<td>0.78 [0.29, 2.06]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>9.8 %</td>
<td>0.09 [0.01, 1.31]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>7.8 %</td>
<td>0.83 [0.41, 1.70]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>40</td>
<td>28</td>
<td>38.2 %</td>
<td>0.65 [0.40, 1.07]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 16 (Gamma-globulin), 18 (No treatment or saline)

Heterogeneity: $\text{Chi}^2 = 7.41, \text{df} = 4 (P = 0.12), I^2 = 46%$

Test for overall effect: $Z = 1.68 (P = 0.093)$

<table>
<thead>
<tr>
<th>Child participants</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>8.2 %</td>
<td>1.17 [0.65, 2.10]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>2.7 %</td>
<td>0.33 [0.02, 6.65]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>2.9 %</td>
<td>0.29 [0.01, 5.79]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonald 1963</td>
<td>2/91</td>
<td>10/88</td>
<td>18.1 %</td>
<td>0.19 [0.04, 0.86]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>108</td>
<td>105</td>
<td>31.8 %</td>
<td>0.46 [0.24, 0.91]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 7 (Gamma-globulin), 17 (No treatment or saline)

Heterogeneity: $\text{Chi}^2 = 10.85, \text{df} = 3 (P = 0.02), I^2 = 72%$

Test for overall effect: $Z = 2.25 (P = 0.025)$

<table>
<thead>
<tr>
<th>Mixed (adult and child participants)</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>14.1 %</td>
<td>0.38 [0.11, 1.35]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doege 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>15.9 %</td>
<td>1.00 [0.81, 1.24]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>54</td>
<td>54</td>
<td>30.0 %</td>
<td>0.71 [0.45, 1.12]</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 12 (Gamma-globulin), 16 (No treatment or saline)

Heterogeneity: $\text{Chi}^2 = 10.81, \text{df} = 1 (P = 0.001), I^2 = 91%$

Test for overall effect: $Z = 1.47 (P = 0.14)$

<table>
<thead>
<tr>
<th>Total (95% CI)</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight M-H,Fixed</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>202</td>
<td>187</td>
<td>100.0 %</td>
<td>0.61 [0.45, 0.83]</td>
</tr>
</tbody>
</table>

Total events: 35 (Gamma-globulin), 51 (No treatment or saline)

Heterogeneity: $\text{Chi}^2 = 36.59, \text{df} = 10 (P = 0.0007), I^2 = 73%$

Test for overall effect: $Z = 3.15 (P = 0.0016)$

Test for subgroup differences: $\text{Chi}^2 = 1.09, \text{df} = 2 (P = 0.58), I^2 = 0.0%$
### Analysis 1.4. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 4 Rubella cases.

**Review:** Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome

**Comparison:** 1 Gamma-globulin versus control (no treatment or saline)

**Outcome:** 4 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Estimated 0.027 to 0.037 ml/lb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>8.1 % 1.60 [0.57, 4.52]</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>17.2 % 0.38 [0.11, 1.35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>60</strong></td>
<td><strong>55</strong></td>
<td><strong>25.3 % 0.77 [0.36, 1.67]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Estimated 0.1 to 0.15 ml/lb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>10.0 % 1.17 [0.65, 2.10]</td>
<td>0.08</td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>9.8 % 0.78 [0.29, 2.66]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>11.9 % 0.09 [0.01, 1.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>9.5 % 0.83 [0.41, 1.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>26</strong></td>
<td><strong>24</strong></td>
<td><strong>41.2 % 0.69 [0.44, 1.08]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Estimated 0.2 to 0.5 ml/lb</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doege 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>19.4 % 1.00 [0.81, 1.24]</td>
<td>0.47</td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>3.3 % 0.33 [0.02, 6.65]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>3.5 % 0.29 [0.01, 5.79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>7.2 % 0.10 [0.01, 1.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>25</strong></td>
<td><strong>20</strong></td>
<td><strong>33.4 % 0.67 [0.45, 0.99]</strong></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Total events: 111 (Gamma-globulin), 11 (No treatment or saline)

Heterogeneity: $\chi^2 = 16.48$, $df = 3$ ($P = 0.00090$), $I^2 = 82$

Test for overall effect: $Z = 2.28$ ($P = 0.023$)

**Test for subgroup differences:** $\chi^2 = 0.12$, $df = 2$ ($P = 0.94$), $I^2 = 0$

---

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)  
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
Analysis 1.5. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 5 Rubella cases.

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

Comparison: 1 Gamma-globulin versus control (no treatment or saline)

Outcome: 5 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>1 Exposure 24 hours to 5 days prior to IG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>0/5</td>
<td>1/5</td>
<td>3.4 % 0.33 [ 0.02, 6.65 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>7.5 % 0.10 [ 0.01, 1.49 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>8.4 % 1.60 [ 0.57, 4.52 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>9.8 % 0.83 [ 0.41, 1.70 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>10.1 % 0.78 [ 0.29, 2.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>12.4 % 0.09 [ 0.01, 1.31 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>45</td>
<td>33</td>
<td>51.7 % 0.63 [ 0.38, 1.04 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 16 (Gamma-globulin), 19 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 7.84$, df = 5 ($P = 0.17$); $I^2 = 36%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.82$ ($P = 0.068$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Exposure up to 8 to 28 days prior to IG</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>10.4 % 1.17 [ 0.65, 2.10 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>17.8 % 0.38 [ 0.11, 1.35 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doege 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>20.1 % 1.00 [ 0.81, 1.24 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td>60</td>
<td>61</td>
<td>48.3 % 0.81 [ 0.56, 1.17 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 17 (Gamma-globulin), 21 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 6.65$, df = 2 ($P = 0.04$); $I^2 = 70%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.13$ ($P = 0.26$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>105</td>
<td>94</td>
<td>100.0 % 0.72 [ 0.53, 0.97 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 33 (Gamma-globulin), 40 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 20.07$, df = 8 ($P = 0.01$); $I^2 = 60%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 2.14$ ($P = 0.032$)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2 = 0.62$, df = 1 ($P = 0.43$); $I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Analysis 1.6. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 6 Rubella cases.

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

Comparison: 1 Gamma-globulin versus control (no treatment or saline)

Outcome: 6 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed95% CI</td>
<td></td>
<td>M-H,Fixed95% CI</td>
</tr>
<tr>
<td>1 Artificial exposure</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>8.1 %</td>
<td>1.60</td>
<td>[ 0.57, 4.52 ]</td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>7.2 %</td>
<td>0.10</td>
<td>[ 0.01, 1.49 ]</td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>9.8 %</td>
<td>0.78</td>
<td>[ 0.29, 2.06 ]</td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>11.9 %</td>
<td>0.09</td>
<td>[ 0.01, 1.31 ]</td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>9.5 %</td>
<td>0.83</td>
<td>[ 0.41, 1.70 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>40</strong></td>
<td><strong>28</strong></td>
<td><strong>46.6 %</strong></td>
<td><strong>0.65</strong></td>
<td><strong>[ 0.40, 1.07 ]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Controlled exposure to infected person</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>10.0 %</td>
<td>1.17</td>
<td>[ 0.65, 2.10 ]</td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>3.3 %</td>
<td>0.33</td>
<td>[ 0.02, 6.65 ]</td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>3.5 %</td>
<td>0.29</td>
<td>[ 0.01, 5.79 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>17</strong></td>
<td><strong>17</strong></td>
<td><strong>16.8 %</strong></td>
<td><strong>0.82</strong></td>
<td><strong>[ 0.42, 1.61 ]</strong></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Household contact with diagnosed case</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>17.2 %</td>
<td>0.38</td>
<td>[ 0.11, 1.35 ]</td>
</tr>
<tr>
<td>Doege 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>19.4 %</td>
<td>1.00</td>
<td>[ 0.81, 1.24 ]</td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>54</strong></td>
<td><strong>54</strong></td>
<td><strong>36.6 %</strong></td>
<td><strong>0.71</strong></td>
<td><strong>[ 0.45, 1.12 ]</strong></td>
</tr>
</tbody>
</table>

Total events: 16 (Gamma-globulin), 18 (No treatment or saline)
Heterogeneity: $\chi^2 = 7.41$, df = 4 ($P = 0.12$), $I^2 = 46$
Test for overall effect: $Z = 1.68$ ($P = 0.093$)

Total events: 5 (Gamma-globulin), 7 (No treatment or saline)
Heterogeneity: $\chi^2 = 2.19$, df = 2 ($P = 0.34$), $I^2 = 10$
Test for overall effect: $Z = 0.58$ ($P = 0.56$)

Total events: 12 (Gamma-globulin), 16 (No treatment or saline)
Heterogeneity: $\chi^2 = 10.81$, df = 1 ($P = 0.001$), $I^2 = 91$

(Continued ...)

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)  56
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 1.7. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 7 Rubella cases.

**Review:** Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome

**Comparison:** 1 Gamma-globulin versus control (no treatment or saline)

**Outcome:** 7 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin (n/N)</th>
<th>No treatment or saline (n/N)</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H, Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td>111</td>
<td>99</td>
<td></td>
<td>100.0%</td>
<td>0.70 [ 0.52, 0.95 ]</td>
</tr>
<tr>
<td>Total events: 33 (Gamma-globulin), 41 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: $\chi^2 = 21.92, df = 9 (P = 0.01); I^2 = 59%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: $Z = 1.47 (P = 0.14)$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2 = 0.29, df = 2 (P = 0.86); I^2 = 0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### 1 Cases defined on clinical grounds

- Anderson 1953a: 8/15 (3/9) 8.1% 1.60 [0.57, 4.52]
- Anderson 1953b: 3/45 (8/46) 17.2% 0.38 [0.11, 1.35]

Subtotal (95% CI): 60/55 25.3% 0.77 [0.36, 1.67]

Total events: 11 (Gamma-globulin), 11 (No treatment or saline)

- Doege 1967: 9/9 (8/8) 19.4% 1.00 [0.81, 1.24]
- Green 1965a: 5/6 (5/7) 10.0% 1.17 [0.65, 2.10]
- Green 1965b: 0/5 (1/5) 3.3% 0.33 [0.02, 6.65]
- Green 1965c: 0/6 (1/5) 3.5% 0.29 [0.01, 5.79]

(Continued...)
### Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)

**Study or subgroup** | Gamma-globulin | No treatment or saline | Risk Ratio | Weight | Risk Ratio |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed,95% CI</td>
<td></td>
<td>M-H,Fixed,95% CI</td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>7.2 % 0.10 [ 0.01, 1.49 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>9.8 % 0.78 [ 0.29, 2.06 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>11.9 % 0.09 [ 0.01, 1.31 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>9.5 % 0.83 [ 0.41, 1.70 ]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>51</strong></td>
<td><strong>44</strong></td>
<td><strong>74.7 % 0.68 [ 0.50, 0.92 ]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 22 (Gamma-globulin), 30 (No treatment or saline)</td>
<td>Heterogeneity: $\chi^2 = 21.24, df = 7 (P = 0.003); I^2 = 67%$</td>
<td>Test for overall effect: $Z = 2.48 (P = 0.013)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>111</strong></td>
<td><strong>99</strong></td>
<td><strong>100.0 % 0.70 [ 0.52, 0.95 ]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total events: 33 (Gamma-globulin), 41 (No treatment or saline)</td>
<td>Heterogeneity: $\chi^2 = 21.92, df = 9 (P = 0.01); I^2 = 59%$</td>
<td>Test for overall effect: $Z = 2.28 (P = 0.023)$</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: $\chi^2 = 0.10, df = 1 (P = 0.73); I^2 = 0.0%$</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Favours gamma-globulin | Favours control

Continued...
### Analysis 1.8. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 8 Rubella cases.

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

Comparison: 1 Gamma-globulin versus control (no treatment or saline)

Outcome: 8 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin n/N</th>
<th>No treatment or saline n/N</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
<th>Weight</th>
<th>Risk Ratio M-H,Fixed 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 No known conflict of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965a</td>
<td>5/6</td>
<td>5/7</td>
<td>8.2 % 1.17 [0.65, 2.10]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>2.7 % 0.33 [0.02, 6.65]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>2.9 % 0.29 [0.01, 5.79]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>5.9 % 0.10 [0.01, 1.49]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>McDonald 1963</td>
<td>2/9</td>
<td>10/88</td>
<td>18.1 % 0.19 [0.04, 0.86]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>8.0 % 0.78 [0.29, 2.06]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>9.8 % 0.09 [0.01, 1.31]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>7.8 % 0.83 [0.41, 1.70]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>133</strong></td>
<td><strong>124</strong></td>
<td><strong>63.3 % 0.46 [0.29, 0.72]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>15 (Gamma-globulin), 32 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>χ² = 17.58, df = 7 (P = 0.01), I² = 60%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 3.41 (P = 0.00065)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Potential conflict of interest</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td>8/15</td>
<td>3/9</td>
<td>6.7 % 1.60 [0.57, 4.52]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anderson 1953b</td>
<td>3/45</td>
<td>8/46</td>
<td>14.1 % 0.38 [0.11, 1.35]</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Doege 1967</td>
<td>9/9</td>
<td>8/8</td>
<td>15.9 % 1.00 [0.81, 1.24]</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Subtotal (95% CI)</strong></td>
<td><strong>69</strong></td>
<td><strong>63</strong></td>
<td><strong>36.7 % 0.87 [0.57, 1.33]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>20 (Gamma-globulin), 19 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>χ² = 4.52, df = 2 (P = 0.01), I² = 54%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 0.63 (P = 0.53)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>202</strong></td>
<td><strong>187</strong></td>
<td><strong>100.0 % 0.61 [0.45, 0.83]</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Total events:</strong></td>
<td>35 (Gamma-globulin), 51 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Heterogeneity:</strong></td>
<td>χ² = 36.59, df = 10 (P = 0.00007), I² = 73%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for overall effect:</strong></td>
<td>Z = 3.15 (P = 0.0016)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Test for subgroup differences:</strong></td>
<td>χ² = 4.21, df = 1 (P = 0.04), I² = 76%</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

---

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)  
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
### Analysis 1.9. Comparison 1 Gamma-globulin versus control (no treatment or saline), Outcome 9 Rubella cases.

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

Comparison: 1 Gamma-globulin versus control (no treatment or saline)

Outcome: 9 Rubella cases

<table>
<thead>
<tr>
<th>Study or subgroup</th>
<th>Gamma-globulin</th>
<th>No treatment or saline</th>
<th>Risk Ratio</th>
<th>Weight</th>
<th>Risk Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>n/N</td>
<td>M-H,Fixed 95% CI</td>
<td></td>
<td>M-H,Fixed 95% CI</td>
</tr>
<tr>
<td>1 Estimated 0.027 to 0.037 ml/l</td>
<td>8/15</td>
<td>3/9</td>
<td>100.0 %</td>
<td>1.60 [ 0.57, 4.52 ]</td>
<td></td>
</tr>
<tr>
<td>Anderson 1953a</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Petersen 1978</td>
<td>4/9</td>
<td>4/7</td>
<td>31.3 %</td>
<td>0.78 [ 0.29, 2.06 ]</td>
<td></td>
</tr>
<tr>
<td>Schiff 1969a</td>
<td>0/5</td>
<td>5/5</td>
<td>38.3 %</td>
<td>0.09 [ 0.01, 1.31 ]</td>
<td></td>
</tr>
<tr>
<td>Schiff 1969b</td>
<td>4/6</td>
<td>4/5</td>
<td>30.4 %</td>
<td>0.83 [ 0.41, 1.70 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>15</td>
<td>9</td>
<td>100.0 %</td>
<td>1.60 [ 0.57, 4.52 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 8 (Gamma-globulin), 13 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: not applicable</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 0.89 (P = 0.37)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2 Estimated 0.1 to 0.15 ml/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965b</td>
<td>0/5</td>
<td>1/5</td>
<td>23.3 %</td>
<td>0.33 [ 0.02, 6.65 ]</td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>25.0 %</td>
<td>0.29 [ 0.01, 5.79 ]</td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>51.7 %</td>
<td>0.10 [ 0.01, 1.49 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>20</td>
<td>17</td>
<td>100.0 %</td>
<td>0.53 [ 0.29, 0.99 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 8 (Gamma-globulin), 13 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 3.79, df = 2 (P = 0.15); I² = 47%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.99 (P = 0.047)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3 Estimated 0.2 to 0.5 ml/l</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Green 1965c</td>
<td>0/6</td>
<td>1/5</td>
<td>25.0 %</td>
<td>0.29 [ 0.01, 5.79 ]</td>
<td></td>
</tr>
<tr>
<td>Martin du Pan 1972</td>
<td>0/5</td>
<td>2/2</td>
<td>51.7 %</td>
<td>0.10 [ 0.01, 1.49 ]</td>
<td></td>
</tr>
<tr>
<td>Subtotal (95% CI)</td>
<td>16</td>
<td>12</td>
<td>100.0 %</td>
<td>0.20 [ 0.04, 1.00 ]</td>
<td></td>
</tr>
<tr>
<td>Total events: 0 (Gamma-globulin), 4 (No treatment or saline)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heterogeneity: Chi² = 4.42, df = 2 (P = 0.01); I² = 0%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for overall effect: Z = 1.96 (P = 0.050)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Test for subgroup differences: Chi² = 5.32, df = 2 (P = 0.07); I² = 62%</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

0.01 0.1 1 10 100
Favours gamma-globulin Favours control

---

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

Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
APPENDICES

Appendix 1. MEDLINE and CENTRAL search strategy

1. exp Rubella/ (7373)
2. Rubella virus/ (3235)
3. (rubella or rubeole).tw. (10177)
4. german measles.tw. (194)
5. or/1-4 (12092)
6. exp Immunoglobulin* or immuno-globulin* or immum* globulin*.tw,nm. (305857)
7. (gammaglobulin* or gamma-globulin* or gamma globulin*).tw,nm. (24893)
8. exp Immunization, Passive/ (29747)
9. (passiv* adj2 (immuni* or antibody transfer* or prophyla*)).tw. (4067)
10. Post-Exposure Prophylaxis/ (386)
11. ((post exposure* or post-exposure* or postexposur*) adj2 (prophyla* or prevent* or immuni*)):ab,ti AND [embase]/lim
12. 'post exposure prophylaxis'/de AND [embase]/lim
13. 'adoptive immunotherapy'/de AND [embase]/lim
14. 'adoptive transfer'/de AND [embase]/lim
15. 'passive immunization'/de AND [embase]/lim
16. 'adoptive immunotherapy'/de AND [embase]/lim
17. gamma globulin*:ab,ti OR 'gamma-globulin':ab,ti OR 'gamma-globulins':ab,ti OR (gamma NEXT/1 globulin*):ab,ti AND [embase]/lim
18. immunoglobulin*:ab,ti OR 'immuno-globulin':ab,ti OR 'immuno-globulins':ab,ti OR (immun* NEXT/1 globulin*):ab,ti AND [embase]/lim
19. 'german measles':ab,ti AND [embase]/lim
20. rubella:ab,ti OR rubeole:ab,ti AND [embase]/lim
21. 'congenital rubella syndrome'/de AND [embase]/lim
22. 'rubella'/de AND [embase]/lim
23. or/1-24 (61706)

Appendix 2. EMBASE (Elsevier) search strategy

#1.1 exp Immunoglobulin* or immuno-globulin* or immum* globulin*.tw,nm. (305857)
#1.2 exp Immunization, Passive/ (29747)
#1.3 exp Immunization, Passive/ (29747)
#1.4 exp Immunization, Passive/ (29747)
#1.5 exp Immunization, Passive/ (29747)
#1.6 exp Immunization, Passive/ (29747)
#1.7 exp Immunization, Passive/ (29747)
#1.8 exp Immunization, Passive/ (29747)
#1.9 exp Immunization, Passive/ (29747)
#1.10 exp Immunization, Passive/ (29747)
#1.11 exp Immunization, Passive/ (29747)
#1.12 exp Immunization, Passive/ (29747)
#1.13 exp Immunization, Passive/ (29747)
#1.14 exp Immunization, Passive/ (29747)
#1.15 exp Immunization, Passive/ (29747)
#1.16 exp Immunization, Passive/ (29747)
#1.17 exp Immunization, Passive/ (29747)
#1.18 exp Immunization, Passive/ (29747)
#1.19 exp Immunization, Passive/ (29747)
#1.20 exp Immunization, Passive/ (29747)
#1.21 exp Immunization, Passive/ (29747)
#1.22 exp Immunization, Passive/ (29747)
#1.23 exp Immunization, Passive/ (29747)
#1.24 exp Immunization, Passive/ (29747)

Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)
Appendix 3. CINAHL (Ebsco) search strategy

S12 S4 AND S11 76
S11 S5 OR S6 OR S7 OR S8 OR S9 OR S10 9,435
S10 TI ((post exposur* or post-exposur* or postexposur*) N2 (prophyla* or prevent* or immuni*)) OR AB ((post exposur* or post-exposur* or postexposur*) N2 (prophyla* or prevent* or immuni*)) 438
S9 (MH "Postexposure Follow-Up") 987
S8 TI (passiv* N2 (immuni* or antibody transfer* or prophyla*)) OR AB (passiv* N2 (immuni* or antibody transfer* or prophyla*)) 75
S7 TI (gammaglobulin* or gamma-globulin* or gamma globulin*) OR AB (gammaglobulin* or gamma-globulin* or gamma globulin*) 73
S6 TI (immunoglobulin* or immuno-globulin* or immuno globulin*) OR AB (immunoglobulin* or immuno-globulin* or immuno globulin*) 3,511
S5 TI german measles OR AB german measles 11
S4 S1 OR S2 OR S3 1,096
S3 TI (rubella or rubeole) OR AB (rubella or rubeole) 886
S1 (MH "Rubella") 382

Appendix 4. LILACS (BIREME) search strategy


Appendix 5. Web of Science (Thomson Reuters) search strategy

<table>
<thead>
<tr>
<th>#</th>
<th>521</th>
<th>#5 AND #1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases=SCI-EXPANDED, CPCI-S Timepan=All years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>138,097</th>
<th>#4 OR #3 OR #2</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases=SCI-EXPANDED, CPCI-S Timepan=All years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>1,770</th>
<th>Topic=I((&quot;post exposur*&quot; or post-exposur* or postexposur*) NEAR/2 (prophyla* or prevent* or immuni*))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases=SCI-EXPANDED, CPCI-S Timepan=All years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>#</th>
<th>4,580</th>
<th>Topic=I((passiv* NEAR/2 (immuni* or &quot;antibody transfer*&quot; or prophyla*)))</th>
</tr>
</thead>
<tbody>
<tr>
<td>Databases=SCI-EXPANDED, CPCI-S Timepan=All years</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Appendix 6. MEDLINE and EMBASE filter for study type

The Cochrane Highly Sensitive Search Strategy for identifying randomised trials (Lefebvre 2011) was used for the initial search in the MEDLINE database. The MEDLINE search was then repeated replacing the randomised trial filter with the following filter (adapted from filters for non-randomised studies provided by the Cochrane Effective Practice and Organisation of Care Group and the Cochrane Public Health Group and these publicly available filters: BMJ Clinical Evidence 2012; Furlan 2006; SIGN 2012; University of Texas 2012) to identify non-randomised prospective intervention studies (not before and after and not time series studies). These two searches were combined to give the search results for MEDLINE. This process was repeated for the EMBASE database, adapting the filter as needed.

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.
Appendix 7. 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 the 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.

Appendix 8. Companies manufacturing immunoglobulin products contacted for unpublished studies

Bayer Healthcare Pharmaceuticals
BDI Pharma (a business unit of Baxter Healthcare corporation)
Bio Products Laboratory*
CSL Behring*
Grifols*
Haffkine Bio-Pharmaceutical Corporation Ltd
Kedrion Biopharma
LFB Biotechnologies
Link Medical Products Pty Ltd
Mirren*
Octapharma*
Sanofi Aventis*
Taj Pharmaceuticals Limited

Companies contacted using details available publicly on their websites in October 2012.
*Companies that responded indicated with an asterisk.

Appendix 9. Published national public health guidelines on rubella control where reference list was searched


Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome (Review)
Copyright © 2015 The Cochrane Collaboration. Published by John Wiley & Sons, Ltd.
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.

Dr Megan Young (MY) and Prof Graeme Nimmo (GN) obtained copies of the studies and selected studies for inclusion in the review.

MY and Prof Allan Cripps (AC) extracted the data and assessed the risk of bias in the studies.

MY entered the data.

Prof Mieke van Driel (MVD) and MY analysed the data and interpreted the analysis.

All authors completed 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.

Prof Allan Cripps has been a consultant to Probiotec Pty Ltd, has received grant funding for a clinical trial on probiotics from Danisco, and holds stock of Bioxyne. None of these activities relate to the current review. He is Dr Megan Young’s PhD supervisor.

Prof Graeme Nimmo has been a sponsored speaker for bioMerieux P/L, has served on advisory boards for Wyeth, Pfizer and AstraZeneca, and has co-ordinated a study for Quotient Bioresearch. He is Dr Megan Young’s PhD supervisor.

Prof Mieke van Driel has no known conflicts of interest.

SOURCES OF SUPPORT
Internal sources
- Griffith University, Australia.
- In-kind employee time
- University of Queensland, Australia.
- In-kind employee time
- Queensland Health, Australia.
- In-kind employee time

External sources
- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW
We found several studies where the design was a controlled clinical trial (with exposure to rubella virus controlled by the investigators) but the method of allocation of participants to groups was not reported. We found an alternative report of one of these studies that indicated that participants were assigned to groups randomly. We therefore included such studies and undertook sensitivity analysis by gradually removing them from the analysis firstly in order of the magnitude of the effect estimate (largest to smallest) and then separately in order of the size of the trial (largest to smallest).

A number of the studies assessed participant susceptibility by means of history only and up to 50% of rubella infections are asymptomatic, therefore we undertook sensitivity analysis by excluding those studies using only history of rubella as the means of assessing susceptibility.

Given variability among the studies with respect to the time between exposure and intervention and the dose of immunoglobulins administered, and that these factors are most likely to impact on effectiveness, we conducted a post hoc meta-analysis that considered both simultaneously. We subgrouped studies according to estimated dose and then removed studies where the intervention was administered up to eight to 28 days after exposure.
Concluding that insufficient evidence existed to determine if passive immunisation is effective at preventing congenital rubella syndrome, but that moderate quality evidence supported the efficacy of passive immunisation for preventing rubella, the review contributed to thesis objective 1: to systematically review the existing evidence for the effectiveness of passive immunisation as used in the public health management of measles, and rubella. The question of the minimum effective dose of immunoglobulin for preventing rubella was unable to be answered by the review.

While a robust body of direct evidence of the effectiveness of passive immunisation for preventing congenital rubella syndrome was not available, it was concluded, after conducting the review, that post-exposure passive immunisation should be recommended for non-immune pregnant women within five days of exposure to rubella in the absence of contraindication to NHIG. The rationale for this conclusion was as follows:

• the systematic review evidence indicated efficacy for preventing rubella in susceptible adults and children up to five days after exposure (164), so it is biologically plausible that efficacy also extends to the prevention of congenital rubella syndrome,
• while there were known failures of gamma-globulin when given to non-immune pregnant women in the 1960s, an insufficient dose and/or delay in administration may have been responsible for the failures (140),
• administration of intramuscular and intravenous immunoglobulin in high-income countries has an excellent safety profile (18), meaning the risk of adverse events is low, and
• alternative interventions with a similar low risk of adverse events do not exist for non-immune pregnant women exposed to rubella.
Chapter 4  Disease-specific antibody levels in Australian NHIG and IVIG

Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Conceptualising the paper, undertaking the statistical analyses, drafting the manuscript and finalising the manuscript with my co-authors.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Conceptualising the paper, undertaking the statistical analyses, drafting the manuscript and finalising the manuscript with my co-authors.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
The systematic reviews presented in Chapters 2 and 3 established the effectiveness of passive immunisation for preventing measles, and the efficacy of passive immunisation for preventing rubella, but were unable to answer the questions of the minimum effective doses of NHIG for preventing these conditions. Quantifying the minimum effective doses requires understanding of the concentration of disease-specific antibodies in the available blood product/s. The studies in this chapter therefore aimed to measure the measles and rubella antibody concentrations in Australian NHIG and IVIG samples.

4.1 Anti-measles antibody levels in Australian plasma products

The following study used the plaque-reduction neutralization test and an enzyme immunoassay to measure the anti-measles antibody concentration in Australian NHIG and IVIG.

This is the authors accepted manuscript of an article published as the version of record in Human Vaccines & Immunotherapeutics © 2017, republished by permission of Informa UK Limited, trading as Taylor & Francis Group, available online https://www.tandfonline.com/doi/full/10.1080/21645515.2016.1234554
Do Australian immunoglobulin products meet international measles antibody titre standards?

Megan K Young1
Corresponding author – School of Medicine, Griffith University, Gold Coast Campus, Parklands Drive, Southport Qld 4222; megan.young@griffith.edu.au; ph +61 7 5678 0704

Joseph Bertolini2
joe.bertolini@cslehring.com.au

Pushpa Kotharu2
pushpa.kotharu@cslehring.com.au

Darryl Maher2
Darryl.Maher@cslehring.com.au

Allan W Cripps1
allan.cripps@griffith.edu.au

1. School of Medicine and Menzies Health Institute Queensland, Griffith University
2. CSL Behring (Australia) Pty Ltd
Abstract

The effectiveness of passive immunisation post-exposure to measles appears subject to a dose-response effect. New Zealand and the United Kingdom have increased the recommended dose of polyclonal human immunoglobulin for post-exposure prophylaxis within the last decade in response to concerns about decreasing levels of measles antibodies in these products. This study used the plaque-reduction neutralization test (PRNT) to measure the titre of measles-specific antibodies in Australian immunoglobulin products for post-exposure prophylaxis and compared the utility of an enzyme-linked immunosorbent assay (ELISA) to the PRNT in available Australian and international samples: Australian intramuscular (n=10), Australian intravenous (n=28), New Zealand intramuscular (n=2), Hizentra (subcutaneous)(USA) (n=3), and Privigen (intravenous)(USA) (n=2). Measles titres in Australian IM and IV immunoglobulins ranged from 51 to 76 IU/mL and 6 to 24 IU/mL respectively, as measured by PRNT calibrated to the WHO 3rd international standard. ELISA titres were variable but higher than PRNT titres in all tested samples. Measles antibody titres in Australian immunoglobulin products meet consensus-prescribed international thresholds. Development of a convenient, standardized, readily accessible assay for determination of measles titres in immunoglobulin products would be useful for future studies and facilitate international comparisons.

Keywords: measles, immunoglobulin, Australia, blood products, prevention

Measles has been targeted for elimination by the World Health Organisation (WHO).(1) However, even in countries with high vaccination coverage where elimination has been declared, outbreaks still occur, usually as a result of imported cases.(2-5) In recent years, the global burden of measles has increased rather than decreased and elimination targets are under threat.(6)

In high-income countries, post-exposure prophylaxis for measles typically consists of either active immunisation within three days of exposure, or passive immunisation within six days of exposure.(7,10) Hence, passive immunisation plays an important role in measles control.(11) A recent systematic review confirmed that passive immunisation is effective up to seven days after exposure to measles.(12) The review noted that included studies were mostly conducted in the pre-vaccine era, when the concentration of measles antibodies in the blood products tested were the result of immunity following infection rather than immunisation. In fact, the final meta-analysis included only one study from the post-vaccine era. It has been shown that immunisation results in lower antibody titres when compared to measles infection.(13) Further, the review supported a likely dose response effect with respect to post-exposure passive immunisation.(12) Thus, the concentration of measles antibodies in current immunoglobulin products may impact on their effectiveness for preventing measles.

Levels of measles-specific antibodies in the intramuscular (IM) immunoglobulin products that are used for passive immunisation post-exposure to measles in New Zealand and the United Kingdom have been published.(10, 14) Within the last decade, these countries have increased the recommended volume of immunoglobulin to be administered for post-exposure prophylaxis based on those reported levels.(10, 14, 15) New Zealand increased the recommended dose from 0.2mL/kg to 0.6mL/kg.(14) Because the recommended volume, dependent on an individual’s weight, may then be considerable, New Zealand have also recommended that intravenous (IV) rather than IM immunoglobulin be considered in certain cases.(14, 15)

In the United States of America (US) immunoglobulins must meet a specified measles antibody level.(16) Due to the decreasing titre in donor plasma, the Food and Drug Administration, with advice
from the Blood Products Advisory Committee, lowered the required concentration of measles antibodies in US IV and subcutaneous immunoglobulin products in 2007, though not in IM products.\(^{(17)}\) However, an increase in the dose of IM immunoglobulin was recommended for immunocompetent people and, because of the large volume then required, IV immunoglobulin was recommended for immunocompromised people and pregnant women for post-exposure prophylaxis.\(^{(7)}\)

Australia does not require the routine measurement of the concentration of measles antibodies in immunoglobulin products. The volume currently recommended for immunocompetent individuals for post-exposure prophylaxis in Australia is 0.2mL/kg\(^{[9]}\); lower than that used in the United Kingdom (0.6mL/kg for infants under 9 months)\(^{[18]}\), US (0.5mL/kg)\(^{(7)}\) or New Zealand (0.6mL/kg).\(^{(8)}\)

This study aimed to establish the current titre of measles-specific antibodies in the IM and IV immunoglobulin products produced in Australia and available for post-exposure prophylaxis against measles. Antibody titre was established by the pharmacopoeia prescribed plaque reduction neutralization test (PRNT).\(^{(19)}\) Although PRNT is a clinically relevant assay, measuring biologically active neutralising antibodies, it is more labour-intensive and less readily available than ELISA. Thus, a further aim was to establish the utility of an ELISA for quantitating measles antibody titres in immunoglobulin products by comparing the results of the PRNT with those obtained by ELISA using immunoglobulin products from Australia, New Zealand and the US.

**Results**

Measles titres in the Australian IM immunoglobulins ranged from 51 to 76 IU/mL as measured by PRNT calibrated to the WHO 3\(^{rd}\) international standard (Figure 1). When standardised to protein concentration, values were 0.32 to 0.48 IU/mg of IgG. The GMT±GMSD was 6.1± 1.12 IU/mL (0.39 ± 1.12 IU/mg) for all 16 samples, and 6.2± 1.15 IU/mL (0.39 ± 1.15 IU/mg) for the 10 samples also tested by ELISA.

Measles titres in the Australian IV immunoglobulins ranged from 6 to 24 IU/mL as measured by PRNT calibrated to the WHO 3rd international standard (Figure 2). When standardised to protein concentration, values were 0.10 to 0.40 IU/mg of IgG. The GMT±GMSD was 14 ± 1.34 IU/mL (0.24 ± 1.34 IU/mg).

There was a statistically significant difference between the geometric mean measles titres of Australian IM immunoglobulin and Australian IV immunoglobulin obtained by PRNT (p<0.001).

When titres were expressed relative to Lot 176 CBER standard, Australian IM and IV immunoglobulin values ranged from 1.54 to 2.31, and 0.46 to 1.94 times the standard respectively (Figures 1 and 2). One CBER unit equated to 0.2 IU/mg of IgG.

Pearson’s correlation co-efficients (r) for Australian IM and IV products respectively were -0.156 (p=0.666) and 0.317 (p=0.1). There was a statistically significant difference between the geometric mean measles titres obtained by PRNT compared to those obtained for the same product by ELISA for Australian IM and IV products (Table 1).

Measles titres in New Zealand and US products were also lower when measured by PRNT than ELISA (Table 2).
Discussion

Measles vaccination results in lower titres of measles antibodies compared to natural disease.\(^{(13)}\) As the plasma pools for immunoglobulin products become increasingly sourced from donor populations with predominantly vaccine-induced immunity to measles, there is a concern that the measles titre in these immunoglobulin products may be declining. This study aimed to establish the current titre of measles-specific antibodies in IM and IV immunoglobulin products produced in Australia. The current recognised test for measles titre quantitation, the PRNT, is complex and not readily available. Therefore, the opportunity was taken to also test samples with an ELISA to investigate the utility of this alternative assay across a range of available Australian and international products.

The range of titres of measles-specific antibodies in Australian IM immunoglobulin was 51 - 76 IU/mL when measured by PRNT calibrated to the WHO 3\(^{rd}\) international standard, and 1.5-2.3 times the CBER standard (lot 176). The US minimum requirement for measles antibodies in immunoglobulins is 0.6 times the CBER standard for IM products and 0.48 times the CBER standard for IV products.\(^{(17)}\) Thus the results for Australian IM immunoglobulin would exceed US specifications.

The Australian IV immunoglobulin values ranged from 6 - 24 IU/mL when measured by PRNT calibrated to the WHO 3\(^{rd}\) international standard and 0.5 – 1.9 times the CBER standard (lot 176). The PRNT results for Australian IV immunoglobulin as compared to the CBER standard exceeded US specifications for all but one sample that was manufactured in 2011.

The measles titre in Australian IV immunoglobulin was statistically significantly higher than that in Australian IV immunoglobulin. The difference in Australian products is likely due to the manufacturing process as both products are derived from the same plasma pool.

The titre of measles-specific antibodies in Australian IM and IV immunoglobulin was higher when measured by ELISA, at 105-272 IU/mL and 9-59 IU/mL respectively, than by PRNT. The differences noted between results for the same product according to the method of testing did not seem unique to Australian immunoglobulin products. Measles antibodies were between 1.48 and 3.56 times higher when measured using the Enzygnost anti measles virus/IgG ELISA (Seimens, Germany) compared to PRNT for New Zealand, and US samples, however, given the small sample sizes, these results were not statistically compared.

Others have previously reported higher ELISA results as compared to PRNT.\(^{(20, 21)}\) Siennicka et al found a ratio of 3.18 : 1 using the same commercial ELISA kit compared to PRNT when testing samples of the WHO 3\(^{rd}\) international standard anti-measles preparation.\(^{(20)}\) Terletksaia-Ladwig et al found ELISA results were 4.76 and 2.28 times higher using the same commercial ELISA kit compared to PRNT when testing samples of pooled human sera and an immunoglobulin product respectively.\(^{(21)}\)

ELISA and PRNT results for Australian IM and IV products did not significantly correlate. Indeed, ELISA results in this study exhibited considerable variability that did not seem to be mirrored in the PRNT results. This is likely due in part to the inherent differences between the tests, in that PRNT measures biologically active neutralising antibodies, where ELISA measures total antibodies and thus the ratio between the two measures is not consistent across batches of IG. While it requires further investigation, it is also possible this reflects differing sensitivity and signal response ratios between the two assays.

A limitation of this study is the unknown effect that long-term storage of immunoglobulin samples may have had on quantitation of antibody levels. However, PRNT results were consistent across the
chronological order of manufacture of the product batches and the ratio of ELISA:PRNT did not appear to increase with the age of the samples. It should be noted that the oldest samples available were manufactured in 2010. A lack of historical product available to test does limit conclusions about time trends in antibody titres to the period of available samples. Similarly, the lack of availability of international product samples restricts international comparisons.

The results of this study do allow estimation of the dose of measles-specific antibodies offered for post exposure prophylaxis under current national recommendations. Australian guidelines recommend 0.2mL/kg of intramuscular immunoglobulins to immunocompetent people and 0.5mL/kg to immunocompromised people to a maximum of 15 mL. Considering the lowest PRNT result for Australian IM immunoglobulin (51 IU/mL), this is equivalent to at least 10.2IU/kg measles antibodies for immunocompetent individuals and 25.5IU/kg for immunocompromised individuals.

New Zealand guidelines recommend 0.6mL/kg intramuscular immunoglobulins (to a maximum of 5mL for infants and a maximum of 15mL for pregnant women and immunocompromised people). Best et al reported the measles titre range for New Zealand intramuscular immunoglobulin as 14-16 IU/mL. The two NZ batches tested by PRNT in this study had titres of 39 and 47 IU/mL. The reason for the discrepancy between the measured values and those reported by Best et al is not known. Possible reasons include a rise in measles-specific antibody titre in New Zealand plasma pools following large outbreaks of measles in New Zealand, the small number of New Zealand samples tested in this study, and differences in test methodology. Best et al did not indicate the methodology employed to obtain the reported results. At a dose of 0.6mL/kg, the lower concentration quoted by Best et al equates to 8.4IU/kg measles antibodies, whereas, the lower result as measured in this study equates to 23.4 IU/kg.

The US recommends 0.5mL/kg intramuscular immunoglobulins to a maximum of 15mL. IM products in the US must have a minimum titre of 0.6 CBER. Based on data from this study, 0.6 CBER equates to 0.12IU/mg. Considering a 15%-18% solution as is available for measles IM post-exposure prophylaxis in the US, this equates to 9-10.8 IU/kg measles antibodies.

There is a lack of evidence for what constitutes a protective dose of measles antibody when administered as post exposure prophylaxis. A single study undertaken by Endo et al in 1999 suggested 10.9 IU/kg as an optimal dose. However, it is noteworthy that Endo et al quantified the measles antibody concentration in the immunoglobulin used in their study by haemagglutination inhibition rather than the PRNT. Further, it does not appear that participants were allocated randomly to receive the various doses of measles antibodies administered and it is unclear whether any of the participants were immunocompromised. Further studies addressing this topic are required. Though randomised clinical studies of post exposure prophylaxis are ethically and logistically difficult, pharmacokinetic simulation studies using published data may assist to quantify the confidence in the results of Endo et al.

In the absence of other studies, United Kingdom guidelines cite 11 IU/kg as an optimal dose of measles antibodies for post exposure prophylaxis. The results of the current study suggest Australian guidelines typically meet this suggested target, as do US and New Zealand guidelines.

Unlike other countries, measles antibody titres in Australian immunoglobulin products do not appear to have decreased over the timespan of the samples available to this study (2010-2015). However, given the significant decreases in these other countries that have led to revision of policy around immunoglobulins for post-exposure prophylaxis, it would be pertinent to regularly measure measles antibodies in Australian immunoglobulin products in the future, at least once per generation.
This study and associated literature clearly shows that ELISA cannot be immediately substituted for the PRNT assay for determination of measles titre in immunoglobulin products. The development of a convenient, standardized, readily accessible assay for determination of measles titre in immunoglobulin products would be valuable for future studies and facilitate international comparisons.

**Methods**

Samples from 16 batches of IM and 28 batches of IV Australian immunoglobulin products, manufactured between 2010 and 2015 were obtained from CSL Behring (Australia) Pty Ltd. The IM product was manufactured by the Cohn-Oncley ethanol precipitation procedure, while the IV product was manufactured using a chromatographic-based process. The formulated products differ with respect to protein concentration, pH and excipient [IM (16% w/v; pH 6.6; glycine); IV (6% w/v; pH 4.25; Maltose)].

PRNT was performed as described by Cohen et al. The proportion of infectious foci within a well of a Vero cell culture was calculated to generate a quantitative result. Results were expressed calibrated to the WHO 3rd international reference standard and Lot 176 CBER standard.

The geometric mean titre (GMT) and geometric standard deviation (GSD) for each product was calculated. The measles titres of the Australian IM and IV products obtained by PRNT were compared using the Mann-Whitney U test. A nonparametric test was chosen because of the small sample sizes.

Six of the sixteen samples of Australian IM immunoglobulin were not tested by ELISA because of insufficient sample volume. The remainder were tested using the Enzygnost anti measles virus/IgG ELISA kit (Siemens, Germany) according to the manufacturer’s instructions. The solid phase antigen in the Enzygnost kit is permanent simian kidney cells infected with measles virus. Testing was performed by the Victorian Infectious Disease Research Laboratory (VIDRL). Initial results demonstrated the need for dilution to minimise the matrix effects of the samples. Dilution was performed with the diluent provided with the kit. In accordance with the results of the dilution study, testing of samples was performed in duplicate at 1:20 and 1:40 for IM immunoglobulin products, and at 1:16 and 1:32 for IV immunoglobulin products. Results were expressed in international units (IU) using the WHO 3rd international reference standard. The titre of the sample was the average of the two results. Inter-assay precision was 10.5%.

ELISA values were plotted against PRNT values to ensure the assumptions of Pearson’s correlation co-efficient were met before this test was carried out. The geometric mean titre (GMT) and geometric standard deviation (GSD) for each product was calculated. Geometric mean measles titres obtained by ELISA were compared to those obtained by PRNT using the Wilcoxon signed-rank test because of the small sample sizes.

Available samples of the following immunoglobulin products were also tested with both PRNT and the Enzygnost anti measles virus/IgG ELISA kit (Siemens, Germany): New Zealand IM immunoglobulin (16% w/v) (CSL Behring (Australia) Pty Ltd), Hizentra (20% w/v) (CSL Behring AG), and Privigen (10% w/v) (CSL Behring AG). While small sample numbers prevented statistical hypothesis testing, individual sample measles titre results and GMT±GMSD are presented for qualitative comparison.

Ethical approval was not required for this study.
Statement of financial support

This study was not grant funded. In kind support was provided by CSL Behring (Australia) Pty Ltd and Griffith University.

Competing interests statements

Megan Young is a PhD student examining the effectiveness and efficiency of normal human immunoglobulin for the public health management of communicable diseases. She is also a public health physician practising in Queensland.

Joseph Bertolini, Pushpa Kotharu and Darryl Maher are employees of CSL Behring (Australia) Pty Ltd and provided in-kind support for this study. Joseph Bertolini and Daryl Maher own shares in CSL Limited. All the immunoglobulin products investigated were manufactured by the CSL Behring group of companies.

Allan Cripps is the supervisor of Megan Young’s PhD.

References


### Table 1. ELISA compared to PRNT measles-specific antibody results for Australian immunoglobulin products

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of samples</th>
<th>Measles titre (IU/mg)</th>
<th>Wilcoxon signed rank test p value</th>
<th>Ratio ELISA:PRNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>Australian IM immunoglobulin (16% w/v)</td>
<td>10</td>
<td>0.97 ±1.38</td>
<td>0.005</td>
<td>2.49:1</td>
</tr>
<tr>
<td>(CSL Behring (Australia) Pty Ltd)</td>
<td></td>
<td>0.39 ±1.15</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Australian IV immunoglobulin (6% w/v)</td>
<td>28</td>
<td>0.62 ±1.62</td>
<td>&lt;0.001</td>
<td>2.58:1</td>
</tr>
<tr>
<td>(CSL Behring (Australia) Pty Ltd)</td>
<td></td>
<td>0.24 ±1.34</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### Table 2. ELISA compared to PRNT measles-specific antibody results for New Zealand and United States of America immunoglobulin products

<table>
<thead>
<tr>
<th>Product</th>
<th>Number of samples</th>
<th>Measles titre (IU/mg)</th>
<th>Ratio ELISA:PRNT</th>
</tr>
</thead>
<tbody>
<tr>
<td>New Zealand IM immunoglobulin (16% w/v)</td>
<td>2</td>
<td>1.28 0.73</td>
<td>3.56:1</td>
</tr>
<tr>
<td>(CSL Behring (Australia) Pty Ltd)</td>
<td></td>
<td>0.29 0.24</td>
<td></td>
</tr>
<tr>
<td>Hizentra (20% w/v) for subcutaneous</td>
<td>3</td>
<td>0.34 0.30 0.40</td>
<td>1.48:1</td>
</tr>
<tr>
<td>administration (CSL Behring AG) (US plasma</td>
<td></td>
<td>0.20 0.17 0.37</td>
<td></td>
</tr>
<tr>
<td>derived)</td>
<td></td>
<td>0.34 0.16 0.51</td>
<td></td>
</tr>
<tr>
<td>Privigen (10% w/v) for IV administration</td>
<td>2</td>
<td>0.24 0.58</td>
<td>1.60:1</td>
</tr>
<tr>
<td>(CSL Behring AG) (US plasma derived)</td>
<td></td>
<td>0.19 0.29</td>
<td></td>
</tr>
</tbody>
</table>

|                                         |                   | 0.37 ±1.87            |                  |
|                                         |                   | 0.23 ±1.35            |                  |
Figure 1. Measles antibody concentrations in Australian intramuscular immunoglobulin products by ELISA and PRNT and expressed as times CBER units
Figure 2. Measles antibody concentrations in Australian intravenous immunoglobulin products by ELISA, PRNT and expressed as times CBER units.
The study contributed to thesis objective 2: to ascertain the current average levels of IgG against measles and rubella in the blood products NHIG and IVIG in Australia; noting that in samples manufactured between 2010 and 2015, Australian NHIG contained a minimum of 51 IU/mL measles antibodies, and Australian IVIG contained a minimum of 6 IU/mL measles antibodies. The average concentrations (geometric mean titres) of measles antibodies in NHIG and IVIG were 61 IU/mL and 15 IU/mL respectively.
4.2 Anti-rubella antibody levels in Australian plasma products

The following study measured the anti-rubella antibody titres in Australian NHIG and IVIG using a chemiluminescent immunoassay.
Rubella antibodies in Australian immunoglobulin products

Megan K Young¹
Corresponding author – School of Medicine, Griffith University, Gold Coast Campus, Parklands Drive, Southport Qld 4222; megan.young@griffith.edu.au; ph +61 7 5678 0704

Joseph Bertolini²
joe.bertolini@cslbehring.com.au

Pushpa Kotharu²
pushpa.kotharu@cslbehring.com.au

Darryl Maher²
Darryl.Maher@cslbehring.com.au

Allan W Cripps¹
allan.cripps@griffith.edu.au

1. School of Medicine and Menzies Health Institute Queensland, Griffith University

2. CSL Behring (Australia) Pty Ltd
Abstract

Rubella antibodies are not routinely measured in immunoglobulin products and there is a lack of information on the titre in Australian products. To facilitate future studies of the effectiveness of passive immunisation for preventing rubella and congenital rubella syndrome, this study measured the concentration of rubella-specific antibodies in Australian intramuscular (IM) and intravenous (IV) human immunoglobulin products suitable for post-exposure prophylaxis using a chemiluminescent immunoassay. The GMT ± GSD for the IM product was 19 ± 1.2 IU/mg (2980 ± 1.2 IU/mL). The GMT ± GSD for the IV product was 12 ± 1.5 IU/mg (729 ± 1.5 IU/mL). At present, Australian guidelines recommend offering non-immune pregnant women exposed to rubella 20 mL of intramuscular immunoglobulin within 72 hours of exposure. This equates to 42,160 IU of rubella antibodies if the lowest titre obtained for the Australian IM product is considered. The same dose would be delivered by 176 mL of the Australian IV product at the lowest measured rubella-specific antibody titre.

Keywords: rubella, immunoglobulin, Australia, blood products, titres
Congenital rubella syndrome, manifesting as heart and eye abnormalities and sensorineural deafness is devastating for families and causes significant burden to health systems (1-4). Prevention of congenital rubella syndrome is best achieved by pre-pregnancy vaccination. For pregnant women who are non-immune, vaccination is contra-indicated (5), so if they are exposed to rubella, passive immunisation is the only alternative to either a watch and wait approach and/or termination of pregnancy. Passive immunisation as post-exposure prophylaxis for rubella for non-immune pregnant women is a part of the disease control guidelines in a number of countries, but is recommended only in certain circumstances (5-9).

Recommendations about passive immunisation for post-exposure prophylaxis are inconsistent across different national guidelines, and this most likely stems from the paucity of evidence of effectiveness (10). A systematic review noted the lack of recent evidence on this intervention, but found studies from the 1950s - 1970s seemed to indicate effectiveness for preventing rubella in non-pregnant subjects when given up to five days post-exposure (10). The review concluded that further evaluation of the intervention should be undertaken, and highlighted the need for the concentration of rubella-specific antibodies in immunoglobulin products to be available so that definition of an effective dose could be determined.

Rubella antibodies are not routinely measured in immunoglobulin products and there is a lack of information on the titre in Australian products. This study aimed to measure the concentration of rubella-specific antibodies in Australian intramuscular
and intravenous human immunoglobulin products suitable for post-exposure prophylaxis, to facilitate future studies of the effectiveness of this intervention.

**Results**

The GMT ± GSD for the IM product was 19 ± 1.2 IU/mg (2980 ± 1.2 IU/mL). The GMT ± GSD for the IV product was 12 ± 1.5 IU/mg (729 ± 1.5 IU/mL) (Figure 1).

There was a statistically significant difference between the GMT of Australian IM immunoglobulin and Australian IV immunoglobulin (p<0.001).

**Discussion**

The aim of this study was to establish the rubella titre in two Australian immunoglobulin products. Rubella titres in Australian IM and IV immunoglobulin products were found to range from 4 to 26 IU/mg. Geometric mean titres were significantly different for the intramuscular and intravenous products (p<0.001). The difference is likely due to the manufacturing process (Bertolini, unpublished data) as both products are derived from the same plasma pool.

Enzyme Immunoassay (EIA) calibrated against the WHO international standard, as reported in this and a number of other studies, is well accepted as the test of choice for quantitating rubella antibodies (11). Variability of results has been noted when the same sample of serum has been tested with different commercial EIA kits (11, 12). No published studies comparing rubella antibody titres in immunoglobulin products across different EIA kits were identified. The magnitude of variation
reported upon testing a single serum sample on multiple assays was small, but clinically significant at the lower titres found in serum (11). A similar magnitude of variation (up to approximately 100 IU/mL) when applied to rubella titres measured in immunoglobulin products would not impact greatly on the conclusions drawn from this study as 100 IU/mL is within the GSD of the results.

Few other studies have quantitated rubella antibodies in immunoglobulin products. Krause et al (13) found between 4.5 and 6.2 EIA units/mL of rubella antibodies in five different intravenous immunoglobulin products from Italy, Israel, Switzerland and the United States of America. In the absence of a common unit of measurement, it is not possible to compare these results to the current study. Wu et al (14) tested four different intravenous products from Taiwan and the United States of America with different protein concentrations. The product from Taiwan had a rubella titre of 260.2 IU/mL (4.3 IU/mg). The products from the United States of America had rubella titres ranging from 351.6 - 786.3 IU/mL (7.0-7.9 IU/mg) (IgG concentrations of the products tested were obtained by personal communication with DY Wang). Matejtschuk et al (15) analysed two intravenous products derived from plasma from the United States of America, one intravenous product derived from United Kingdom plasma and three products for which the source of plasma was either the United States of America or Europe, but for which the specific origin was unknown. The United Kingdom product had a rubella titre of 1,055 IU/mL or 21.1 IU/mg. The products from the United States of America had rubella titres of 670 and 630 IU/mL or 13.4 and 12.6 IU/mg respectively. In the three products of unknown specific origin, rubella titres were 1,319, 828 and 303 IU/mL or 26.4, 16.6 and 6.1 IU/mg
respectively (IgG concentration of the products tested were obtained by personal communication with J More). The results of this study fall within the range of results reported by these latter two studies.

At present, Australian guidelines recommend offering non-immune pregnant women exposed to rubella 20 mL of intramuscular immunoglobulin within 72 hours of exposure (5). This equates to 42,160 IU of rubella antibodies if the lowest titre obtained for the Australian IM product is considered. The same dose would be delivered by 176 mL of the Australian IV product at the lowest measured rubella-specific antibody titre.

Only two studies were identified that measured rubella antibodies serially in the serum of non-immune recipients of immunoglobulins (16, 17). du Pan et al (17) infused three healthy non-immune volunteers with either 40 or 60 mL of a solution of immunoglobulins. The haemagglutination inhibition (HI) titre of the product was 1:2048 in one instance and 1:1024 in the other two instances. The protein concentration of neither the product nor the solution used for infusion was reported. These authors noted serum rubella HI titres peaked at five minutes after infusion and were still detectable two weeks post-infusion. One volunteer (infused with 60 mLs of solution containing immunoglobulins with 1:2048 rubella antibody titre) maintained an ‘immune’ titre of HI 1:8 at two weeks.

Field et al (16) reported titres at or in excess of the ‘immune’ level (HI 1:8) for five previously non-immune recipients of 3,000 mg of immunoglobulins for at least two
weeks after injection. This dose of immunoglobulins is equivalent to the Australian recommendation (20 mLs of immunoglobulins with protein content of 16 mg/mL). However, it is not clear whether the dose of rubella antibodies recommended under Australian guidelines is equivalent to that used in Field et al’s study. That study does report that the product used had a measured rubella HI titre of between 1:1600 and 1:12,800 (16), but, as with du Pan et al (17), there is no information on assay standardisation. Without this knowledge it is not possible to convert the doses of rubella antibodies used in these studies into international units (18) and further compare them to current Australian recommendations.

As rubella vaccine is widely and freely available in Australia, it would be unethical to repeat similar studies here. Future observational or pharmacokinetic modeling studies, with the assistance of the data provided by this study, may help to further investigate the effectiveness of passive immunisation, including the optimal dose of immunoglobulins, for preventing rubella in non-immune pregnant women post-exposure.

Methods
Samples of 14 batches of intramuscular (IM) and 18 batches of intravenous (IV) immunoglobulins, manufactured between 2011 and 2013, were obtained from CSL Behring (Australia) Pty Ltd. The IM product was manufactured by the Cohn-Oncley ethanol precipitation procedure, while the IV product was manufactured using a chromatographic-based process. The formulated products differ with respect to
protein concentration, pH and excipient [IM (16% w/v; pH 6.6; glycine); IV (6% w/v; pH 4.25; maltose)].

Rubella testing was performed using a chemiluminescent immunoassay (CLIA) (Access Rubella IgG reagent (Beckman Coulter Catalogue no 34430) using the Access Immunoassay System). Testing was performed in duplicate at 1:50 and 1:100 on the IM product samples and at 1:10 and 1:20 on the IV product samples. The titre of the sample was the average of the results obtained at the two dilutions. Inter-assay precision was 8.2%.

The geometric mean titres (GMT) and geometric standard deviations (GSD) were calculated for each product. The titres of the products were compared using the Mann-Whitney U test. A nonparametric test was chosen because of the small sample sizes.

Ethical approval was not required for this study.
Statement of financial support

This study was not grant funded. In kind support was provided by CSL Behring (Australia) Pty Ltd and Griffith University.

Competing interests statements

Megan Young is a PhD student examining the effectiveness and efficiency of normal human immunoglobulin for the public health management of communicable diseases. She is also a public health physician practising in Queensland. Joseph Bertolini, Pushpa Kotharu and Darryl Maher are employees of CSL Behring (Australia) Pty Ltd and provided in-kind support for this study. Joseph Bertolini and Daryl Maher own shares in CSL Limited. All the immunoglobulin products investigated were manufactured by the CSL Behring group of companies. Allan Cripps is the supervisor of Megan Young’s PhD.
References


Figure 1. Rubella antibody titres in Australian intramuscular and intravenous immunoglobulin product samples by year of manufacture
The study contributed to thesis objective 2: to ascertain the current average levels of IgG against measles and rubella in the blood products NHIG and IVIG in Australia; concluding that in samples of Australian NHIG and IVIG manufactured between 2011 and 2013, the average concentrations (geometric mean titre) of rubella antibodies were 2980 IU/mL and 729 IU/mL respectively. The minimum concentration of rubella antibodies measured in Australian NHIG was 2108 IU/mL, while in Australian IVIG it was 268 IU/mL.
Chapter 5  Minimum effective NHIG dosing

Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Conceptualising the paper, contributing to the statistical analyses, interpreting the analyses, drafting the manuscript and finalising the manuscript with my co-authors.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
Having established the concentrations of anti-measles and anti-rubella antibodies in Australian NHIG and IVIG in Chapter 4 and knowing that Australian NHIG is manufactured to the European Pharmacopoeia standard of 100IU/mL for hepatitis A antibodies, the remaining information required to estimate the minimum effective doses of immunoglobulin for post-exposure prophylaxis for these diseases was pharmacokinetic.

Pharmacokinetics is defined as the mechanisms of drug absorption, distribution and elimination within the human body (165). Modelling the pharmacokinetics of intramuscular immunoglobulin was determined to be the optimal methodology for estimating the minimum effective doses of NHIG for preventing measles, hepatitis A and rubella based on the following rationale:

- it would be unethical to conduct a clinical trial intentionally exposing people to any of these diseases to find the minimum effective dose of immunoglobulin and therefore potentially cause infection when effective vaccines exist;
- it is not logistically feasible to enrol sufficient contacts requiring passive immunisation in a timely fashion for an observational trial as the timeline for injection of NHIG after exposure is short, and contacts requiring NHIG for hepatitis A (which is the only routinely measured disease-specific antibody in NHIG batches in Australia) number approximately 24 around the country per year (see Chapter 6); and
- insufficient studies exist to allow a synthesis of relevant clinical pharmacokinetic trial data. Only one study of the pharmacokinetics of disease-specific antibodies (hepatitis A, measles or rubella) after intramuscular injection of polyvalent immunoglobulin that reported results in international units and considered antibody concentrations to an incubation period was identified. This was an examination of the elimination of hepatitis A and B antibodies in subjects injected with one of two formulations of NHIG in a dose that was approximately three or more times the current Australian recommendation for hepatitis A post-exposure prophylaxis (166).

Pharmacokinetic models were therefore built using the parameters for intramuscular immunoglobulin reported in Mould et al (166) and other published clinical pharmacokinetic studies of intramuscular polyvalent immunoglobulin. From the built models, the minimum effective dose per kilogram bodyweight of Australian NHIG for the prevention of each disease was estimated.
The first studies in this Chapter detail the pharmacokinetic modelling processes and results. The final study in the Chapter presents preliminary results from a randomised controlled trial that administered Australian NHIG to healthy volunteers (without disease exposure) and was designed to validate and/or optimise the pharmacokinetic models. The Chapter concludes with recommendations for changes to current Australian passive immunisation practice post-exposure to measles, rubella and hepatitis A; made utilising the evidence obtained in this and the preceding Chapters.

5.1 Pharmacokinetic modelling to determine the minimum effective doses of disease-specific antibodies and Australian NHIG for preventing measles and rubella

The following study adapted Dubois et al’s equation for a two compartment model with first order absorption (167) to estimate the minimum effective doses of disease-specific antibodies for the prevention of measles and rubella post-exposure. The measured concentrations of disease-specific antibodies in Australian NHIG as determined in chapter 4 were utilised to estimate the volumes required for effective and efficient post-exposure prophylaxis.

This is the authors accepted manuscript of an article published as the version of record in Expert Opinion on Drug Metabolism & Toxicology © 2018, republished by permission of Informa UK Limited, trading as Taylor & Francis Group, available online https://www.tandfonline.com/doi/abs/10.1080/17425255.2018.1484449
The optimal dose of disease-specific antibodies for post-exposure prophylaxis of measles and rubella in Australia: new guidelines recommended

Megan K Young1,2.

Shu-Kay Ng1

Graeme R Nimmo1,3

Allan W Cripps1

1. School of Medicine and Menzies Health Institute – Queensland, Griffith University, Southport, Queensland, Australia

2. Metro North Public Health Unit, Metro North Hospital and Health Service, Brisbane, Queensland, Australia

3. Pathology Queensland, Queensland Health, Brisbane, Queensland, Australia

Corresponding author:

Megan Young

Griffith University School of Medicine

Gold Coast Campus

Southport QLD 4215

Ph. +61 7 5678 0624

Email: megan.young@griffith.edu.au
Abstract

Background: It is unclear whether recommended doses of intramuscular polyvalent immune globulin are optimal for both effectiveness and efficiency of disease prevention when administered post-exposure to measles and rubella.

Methods: The peak concentration and decay of disease-specific antibodies after intramuscular dosing of polyvalent immune globulin in adults was modelled using published pharmacokinetic parameters and product disease-specific antibody concentrations. Models simulated dosing according to current Australian guidelines, then adjusted the dose in clinically relevant increments to estimate the optimal dose of disease-specific immunoglobulins for post-exposure prophylaxis of non-immune individuals against measles and rubella. Optimal dosing assumed a target serum concentration of disease-specific antibodies of the correlate of protection plus a 10% margin of error at an incubation period.

Results: Current Australian guidelines appeared to underdose a measles naive subpopulation. The optimal dose of measles-specific antibodies was 17.5 IU/kg assuming 75% bioavailability and 25.5 IU/kg assuming 50% bioavailability. Current Australian guidelines recommend 520 IU/kg rubella antibodies for an 80kg individual. This model suggests that 13 IU/kg is more than sufficient.
Conclusions: The recommended dose of intramuscular polyvalent immune globulin should be increased following measles exposure and decreased following rubella exposure for recommended subgroups. These models may be adapted for use internationally.

Key words: immunoglobulin, measles, passive immunisation, pharmacokinetics, post-exposure prophylaxis, rubella

Key Issues:

- Current recommended doses of polyvalent immune globulin for post-exposure prophylaxis of measles and rubella in Australia are not based on a target serum antibody concentration.
- This pharmacokinetic modelling study estimated the optimal dose of intramuscular disease-specific antibodies required to reach and maintain target serum antibody concentrations for an incubation period for measles and rubella.
- Current Australian guidelines appeared to underdose a measles naïve subpopulation.
- Current Australian guidelines appeared to overdose a rubella naïve population.
- Optimal doses of disease-specific antibodies and the corresponding volumes of Australian polyvalent immune globulin for post-exposure prophylaxis according to the models are recommended.
- The models presented may be adapted for use internationally.
1. Introduction

Active immunisation with measles, mumps, rubella (MMR) vaccine can prevent measles if given to a non-immune person within three days of exposure, however, it is contraindicated in some population groups. Particularly for subpopulations at highest risk of complications from this disease, passive immunisation therefore plays an important role in post-exposure prevention [1]. While not routinely used in practice, a recent systematic review has also found that passive immunisation may be effective for preventing rubella if given early enough after an exposure [2].

The national guidelines of Australia and other similar countries include recommended doses of intramuscular immune globulin for the purposes of post-exposure prophylaxis to measles and rubella (the latter in certain circumstances) [1]. Recommended doses differ between countries. One possible reason for this discrepancy is differences in the concentrations of disease-specific antibodies in the immune globulin products used in different countries.

Certainly, measles and rubella antibody concentrations in the immune globulin product funded for use for post-exposure prophylaxis in Australia were unknown until recently. The availability of these data now provide crucial information on the current doses of disease-specific antibodies recommended for post-exposure prophylaxis in this country [3, 4].

Yet, it is still unclear whether these recommended doses are optimal for both effectiveness and efficiency of disease prevention. Endo et al [5] examined the effectiveness of different measles-specific antibody doses administered as intramuscular polyvalent immune globulin for post-exposure prophylaxis and recommended 10.9 IU measles-specific antibody/kg as the
optimal dose. With this exception, no other studies provide evidence of the optimal dose of
disease-specific antibodies prescribed in standardised units for preventing measles, or rubella,
post-exposure.

However, the correlates of protection for these diseases, often derived from active
immunisation studies, can provide a target for the desired serum concentration of disease-
specific antibodies after post-exposure passive immunisation. Table 1 outlines published
correlates of protection for these diseases.

Because the antibody titre required to prevent disease after passive immunisation may be
higher than for active immunisation [6], and considering individual and test variability, it is
desirable to add a margin of error to the above correlates when assigning a serum threshold of
protection to be reached for the purpose of post-exposure prophylaxis. A further consideration
regarding the optimal antibody doses for post-exposure prophylaxis is the length of protection
required from passive immunisation. To this end, maintaining serum antibody levels above the
correlate of protection for the duration of an incubation period for the particular disease seems
advisable.

Once such a target antibody concentration threshold is defined, pharmacokinetic studies may
be used to estimate the optimal dose of disease-specific antibodies required to reach and
maintain that concentration for an incubation period. However, pharmacokinetic studies of
measles-, and rubella-specific antibodies after immunoglobulin administration are sparse,
particularly in populations without immunocompromise.
A single such study was conducted by the British Public Health Laboratory Working Party on Rubella in the 1960s [7]. The study examined rubella titres in five seronegative volunteers after injection of 3000mg of polyclonal immunoglobulins manufactured at that time. Rubella antibody was detectable in serum two days after administration. Serum levels of HI titres of 1:8 or 1:16 were then maintained for 3 weeks. The HI titre of the immunoglobulin product used was 1:1600 – 1:12800.

The pharmacokinetics of immunoglobulins more broadly has been better reported. Absorption of immunoglobulins administered intramuscularly is thought to occur over hours with maximum plasma concentration achieved in one to eight days [8]. Some administered immunoglobulins may be degraded before reaching the blood stream, but this can be saturable. Bioavailability is said to therefore vary between 50-100%.

Extravasation from the bloodstream occurs and tissue binding can be substantial. Thus, the amount of immunoglobulin in the plasma is typically estimated at 20-50% of the total and the volume of distribution at 2.5 times the plasma volume [8].

Immunoglobulin clearance occurs predominantly via catabolism following first-order kinetics [9]. The rate of clearance of immunoglobulins is also increased when antibody-antigen complexes are metabolised as part of the immune response to a foreign antigen.

Lobo et al [8] reported an average endogenous IgG half-life among immunocompetent individuals of 23 days. Studies of immunoglobulins administered to healthy volunteers have suggested half-lives approximate that of endogenous IgG. A single dose of one of three formulations of intravenous immune globulin at 0.6 g/kg administered to 30 healthy individuals
resulted in measured half-lives between 24 and 28 days [10]. A single dose of intravenous Anthrax immunoglobulin administered to 90 healthy individuals resulted in measured half-lives between 22 and 25 days [11]. A single 250 ug dose of anti-D immunoglobulin administered intramuscularly to 16 pregnant women demonstrated a median half-life of 23 days [12]. A single dose of hepatitis B immunoglobulin at 30IU/kg administered intramuscularly to 15 healthy volunteers resulted in a mean half-life of 23 days [13].

Using these and other published pharmacokinetic parameters of immune globulin and disease-specific antibodies, where available, this study modelled the peak concentration and decay of disease-specific antibodies after intramuscular dosing in adults. Initial models for each disease simulated dosing according to current Australian guidelines and evaluated serum concentrations at an incubation period against the specified target threshold. Subsequent models adjusted the dose of disease-specific antibodies in clinically relevant increments to estimate the optimal dose of disease-specific immunoglobulins for post-exposure prophylaxis of non-immune individuals against measles and rubella using Australian intramuscular polyvalent immune globulin (NHIG).

2. Methods

Published data on the pharmacokinetics of parenterally administered immune globulin was sought by searching Medline, Cinahl and Cochrane databases using the search strategy in Box 1.
Medical subject heading (MeSH) terms were used as well as key word searches. Results were limited to those in the English language. Results were assessed by title and abstract and relevant articles were retrieved in full-text.

The following data was then extracted:

- absorption rate constant and/or time to maximum concentration and/or absorption half-life
- volume of central compartment and volume of peripheral compartment and/or volume of distribution
- time to equilibrium between compartments and/or equilibration constant
- intercompartmental clearance
- total clearance measures (AUC, half-life, calculated clearance)
- study participant characteristics: Age range, weight range, sex ratio, gestation if applicable
- dose of immunoglobulins and route of administration
- the measure of variation about mean values and/or range as applicable for each of the above.

Published data on the disease-specific antibody concentrations of measles and rubella in Australia immune globulin were also utilised [3, 4].
It was assumed that the published correlate of protection, with a margin of error of 10% was the optimal threshold concentration of disease-specific antibodies to be maintained for the duration of the incubation period for the particular disease. Incubation periods used were as per current Australian guidelines for the respective diseases [14, 15].

2.1 Analysis

The two compartment, first order absorption model for a single intramuscular dose as detailed in Dubois et al was utilised for this study (Figure 1 and Box 2) [16].

In the absence of published measured values of central and peripheral compartments, the volume of the central compartment was defined as:

\[ V_1 = 70 \times \text{weight} \times (1 - \text{haematocrit})/1000 \] [17]

where haematocrit was generated from a normal distribution with mean 0.43 (standard deviation 0.03) based on the pathology reference range for adults [18].

The volume of the peripheral compartment was defined as:

\[ V_2 = \frac{k_{12}}{k_{21}} \times V_1 \]

where the ratio \( k_{12}/k_{21} \) was generated from a uniform distribution between 1.22 (55% : 45%) and 1.33 (57% : 43%) [17, 19].

The total volume of distribution was checked to ensure it was within published values for this parameter.
k was generated from a lognormal distribution with a location parameter of ln(0.77) and a scale parameter of ln(1.13), corresponding to a half-life of about 0.7-1.3 days [20].

k was generated from a lognormal distribution with a location parameter of ln(0.028) and a scale parameter of ln(1.06), corresponding to a half-life of about 20-30 days [12, 13, 20, 21].

k12 was generated from a lognormal distribution with a location parameter of ln(0.04) and a scale parameter of ln(1.07), corresponding to a half-life of about 13-23 days. This was based on a distribution phase of 5 days at a rate of 0.56 per day [22] followed by an elimination phase estimated at 179 days (to total eight half-lives) at a rate of 0.026 per day (equivalent to k).

The concentration of antibodies prior to dosing was generated from a lognormal distribution with a range corresponding to levels that would generate a negative result on commercial serology testing for rubella [23] and a range below the published threshold of protection for measles [6]. The published threshold of protection was chosen instead of commercial serology testing limits for measles because commercial tests utilise enzyme immunoassay methodology, whereas the immunity threshold and measles titres in Australian immune globulin are both the result of plaque reduction neutralisation assays. Further, the mean and variation of the concentration of antibodies prior to dosing was sourced from published studies [24, 25]. For both measles and rubella, two ‘non-immune’ subpopulations were noted [24, 25]; a naïve subpopulation with very low disease-specific antibody levels, and a subpopulation who were likely non-naïve, but in whom antibody levels had waned below protective thresholds. Each of these subpopulations was modelled separately.

Bioavailability was set at 75%, with sensitivity analyses at 50% and 100% [8].
Initial intramuscular dose of measles antibodies was based on the minimum measured concentration in Australian NHIG batches [3] and the recommended volume of 0.2 mL/kg to a maximum of 15 mL as per national guidelines [15]. The measured geometric mean titre of Australian NHIG batches was then substituted. In each of these models, the maximum dose of measles-specific antibodies was capped equivalent to the maximum recommended volume as per national guidelines.

The initial intramuscular dose of rubella antibodies was based on the minimum measured concentration in Australian NHIG batches [4] and the recommended volume of 20mL as per the advice in the Australian Immunisation Handbook [26]. The measured geometric mean titre of Australian NHIG batches was then substituted.

To identify the optimal dose in each circumstance, dose was input as dose per kilogram body weight, commencing with a dose equivalent to the national guideline calculated for an 80kg person using the minimum measured disease-specific antibody concentration in Australian NHIG. The dose per kilogram body weight was multiplied by weight where weight was randomly selected from a normal distribution with mean 80kg (standard deviation 13kg) based on approximation of Australian Bureau of Statistics data [27]. Dose per kilogram was then adjusted incrementally in steps of one international unit per kilogram for measles until the lower 95% confidence interval of the mean serum concentration at day 18 was as close as possible, but above, the correlate of protection plus a 10% margin of error (132mIU/mL). Dose per kilogram was adjusted incrementally for rubella until the lower 95% confidence interval of the mean serum concentration at day 21 was as close as possible, but above, the correlate of
protection plus a 10% margin of error (11IU/mL). Adjustments for rubella considered the equivalent of the following volumes of NHIG for an 80kg individual: 5, 2, 1 and 0.5mL. Volumes smaller than 0.5mL were felt to be clinically insignificant.

Ethical approval was not required for this study.

3. Results

3.1 Measles

Modelling the minimum measured concentration of measles antibodies in NHIG [3] as administered according to national guidelines [15] at 75% bioavailability resulted in an average serum concentration in naïve contacts of 95 mIU/mL (95% CI 74-116 IU/mL) at day 18 after injection (Table 2). Using the measured geometric mean titre of measles antibodies in NHIG, at 75% bioavailability, serum concentration was 108 mIU/mL (95% CI 84-133 IU/mL) in this group at day 18.

For a naïve population, given 75% bioavailability, the dose at which the lower 95% CI of the mean serum concentration at day 18 was above the correlate of protection plus a 10% margin of error (132mIU/mL) was 17.5IU/kg (Table 3). In a non-naïve population, the current dose administered under national guidelines to an 80kg individual is sufficient to keep the serum concentration above the correlate of protection at day 18 at 50% bioavailability.

3.2 Rubella
Modelling the existing national recommended dose of NHIG for post-exposure prophylaxis of rubella [26] resulted in serum concentrations at day 21 post intramuscular injection that exceeded the correlate of protection plus a 10% margin of error (11IU/mL) by at least 120 fold even at 50% bioavailability (Table 4). Bioavailability of 100% was therefore not modelled.

For a naïve population, given 50% bioavailability, the equivalent dose per kilogram for an 80kg person to receive 0.5mL NHIG was still sufficient for serum concentration of rubella antibodies to substantially exceed 11IU/mL even using the minimum measured concentration of rubella antibodies in NHIG [4]. This dose was 13IU/kg. At this dose per kilogram, the average serum concentration of rubella antibodies at 21 days was 60 IU/mL (95% CI 51-69 IU/mL). Further reductions in dose were not modelled.

4. Discussion

Pharmacokinetic modelling of disease specific antibodies administered intramuscularly identified current Australian guidelines for post-exposure prophylaxis against measles may underdose a naïve subpopulation. Current guidelines recommend a maximum of 765 IU assuming the minimum measured measles antibody concentration in Australian NHIG [3]. This equates to 9.6 IU/kg for an 80kg individual. According to this model, the optimal dose of measles specific antibodies was 17.5 IU/kg with 75% bioavailability or 25.5 IU/kg with 50% bioavailability.
This contrasts with the results of pharmacokinetic modelling of disease specific antibodies for rubella post-exposure prophylaxis. According to this model, under current Australian guidelines, the dose of NHIG recommended for non-immune pregnant women far exceeds that required to maintain a serum correlate of protection plus a 10% margin of error for 21 days post administration. Current Australian guidelines recommend a minimum of 41600 IU of rubella antibodies [4]. This equates to 520 IU/kg for an 80kg individual. This model suggests that 13 IU/kg is more than sufficient.

The limitations of predictive modelling should be considered when interpreting these results and it should be noted that results have been recorded from a single iteration of each simulation scenario. In particular to this model, it is unlikely the volume of distribution of immunoglobulins varies with weight in a linear fashion [28] and our model was unable to account for this. The estimates of optimal doses of disease specific antibodies generated from these models are therefore likely to be conservative.

However, the authors of this study are aware of several unpublished case reports where contacts of people with measles developed the disease despite administration of NHIG according to current Australian guidelines. The United Kingdom and New Zealand have increased the dose of immunoglobulin recommended for post-exposure prophylaxis within the last decade [29, 30], and a recent study examining the effectiveness of passive immunisation for preventing measles in Canada has also concluded that NHIG doses may need to be increased in that country [31].
Further, given ethical and logistic difficulties, it is unlikely any methodologically robust in vivo studies of the optimal dose of polyvalent immunoglobulins for post-exposure prophylaxis of either measles or rubella will be conducted.

Thus, these limitations notwithstanding, the authors feel this study has a number of implications for the public health management of measles and rubella. Regarding measles, it is recommended to alter Australian guidelines by increasing the dose of NHIG used for post-exposure prophylaxis. According to the results of the models presented here, it is recommended to remove the maximum intramuscular volume and replace the current dose with one equivalent to 25.5 IU/kg. For Australian NHIG, this is 0.5mL/kg. As this equates to 40mL of NHIG for an 80kg individual, which is clinically impractical and likely to be distressing for the person, it is further recommended to consider altering Australian guidelines to include the option of intravenous IG dosing where calculated doses are large. The dose of intravenous immunoglobulin (IVIG) should be based on further modelling, as intravenous dosing will result in a higher maximum serum concentration and then a faster rate of decay. Because intravenous dosing will likely require administration in a hospital setting, it is further recommended that consideration be given to altering Australian guidelines to recommend passive immunisation as post-exposure prophylaxis only for those who are non-immune and most vulnerable to measles complications. This includes infants, pregnant women and people with immunosuppression. Each of these recommendations would bring Australian public health guidelines for measles more in line with those of the United Kingdom [32], the United States [33] and New Zealand [34].
Regarding rubella, it is recommended to alter Australian guidelines by decreasing the current recommended dose of 20mL NHIG for post-exposure prophylaxis of non-immune pregnant women. According to the results of the model presented here, it is recommended that a dose of 0.5mL NHIG would be sufficient for a woman up to 160kg. For someone exceeding this weight, a dose of 1mL would be appropriate. International guidelines are highly variable regarding post-exposure prophylaxis of non-immune pregnant contacts of rubella. This is likely to be due in part to the relative paucity of evidence specific to this intervention [1], with the first systematic review on the topic completed only recently [2]. This recommendation would see Australian guidelines more closely aligned with those of the United Kingdom where a dose of approximately 5mL is recommended [35].

5. Conclusions

Post-exposure passive immunisation is the only means of preventing infection with measles or rubella for certain vulnerable subpopulations. This study provides estimates of the doses of intramuscular NHIG likely to be most effective and efficient for this purpose. Thorough and holistic consideration of the following suggests that these results should inform future Australian public health practice: the available evidence of effectiveness of passive immunisation for post-exposure prophylaxis of measles and rubella, what is known about the pharmacokinetics of immunoglobulins, the national guidelines of other countries similar to Australia for control of these diseases, opportunity to carry out experimentation in this area (which is particularly limited given ethical and logistic barriers), and the limitations of this study.
(which are likely to result in conservative estimates of the doses of immunoglobulin required).

The models presented here may also be utilised internationally to assist evaluation of current dosing recommendations and aid calculation of optimal dose volumes of intramuscular polyvalent immune globulins for the post-exposure prophylaxis of measles and rubella.

**Financial and competing interests**

This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

The authors report no conflicts of interest.

**Author contributions**

MY was responsible for conception of the study, assisted with the design and data collection, interpreted the results and drafted the paper.

SKN assisted with the design and data collection, was responsible for data analysis, and critically revised the paper for intellectual content.

GN assisted with interpretation of the results and critically revised the paper for intellectual content.

AC assisted with design of the study, and interpretation of results and critically revised the paper for intellectual content.

All authors agree to be accountable for all aspects of the work.
6. References

   This paper was the first to publish measured measles-specific antibodies in Australian immunoglobulin products.
   This paper was the first to publish measured rubella-specific antibodies in Australian immunoglobulin products.
   An excellent overview of antibody pharmacokinetics.
This is one of the few experimental pharmacokinetic studies examining disease-specific antibody levels after intramuscular injection of polyvalent immunoglobulin.
This paper established the current correlate of protection for measles.


Table 1. Published correlates of protection for measles and rubella.

<table>
<thead>
<tr>
<th>Correlate of protection</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Measles</strong></td>
<td></td>
</tr>
<tr>
<td>PRN titre &gt;120 (no unit given)</td>
<td>Chen et al [24]</td>
</tr>
<tr>
<td>PRN &gt;120 mIU/mL</td>
<td>World Health Organization [6] p7</td>
</tr>
<tr>
<td>Microneutralisation 120 mIU/mL</td>
<td>Plotkin [36]</td>
</tr>
<tr>
<td>HAI 200 mIU/mL</td>
<td>Siber et al [37]</td>
</tr>
<tr>
<td>Microneutralisation 120-200 mIU/mL</td>
<td>Thakur et al [38]</td>
</tr>
<tr>
<td>Nt-EIA 500 mIU/mL</td>
<td>Lee et al [39]</td>
</tr>
<tr>
<td><strong>Rubella</strong></td>
<td></td>
</tr>
<tr>
<td>EIA 10 IU/mL</td>
<td>World Health Organization [40] p13</td>
</tr>
<tr>
<td>Immunoprecipitation 10-15 IU/mL</td>
<td>Plotkin [36]</td>
</tr>
<tr>
<td>Immunoprecipitation 10-15 IU/mL</td>
<td>Thakur et al [38]</td>
</tr>
<tr>
<td>HAI 10-15 IU/mL</td>
<td>Skendzel [41]</td>
</tr>
</tbody>
</table>

PRN – plaque reduction neutralisation
HAI – hemagglutination inhibition
Nt-EIA – neutralisation enzyme immunoassay
EIA – enzyme immunoassay
Table 2. Serum concentration of measles antibodies at day 18 after intramuscular dosing of Normal Human Immunoglobulin according to current Australian guidelines

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pre-dose serum antibody concentration</th>
<th>Serum concentration at day 18 (mIU/mL)</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1) 0.2mL/kg to max 15mL; minimum measured measles antibody concentration</td>
<td>Naïve – 23mIU/mL (Range 13-42)</td>
<td>71</td>
<td>55-87</td>
</tr>
<tr>
<td></td>
<td>Non-naïve - 98mIU/mL (Range 83-114)</td>
<td>146</td>
<td>129-163</td>
</tr>
<tr>
<td>1) 0.2mL/kg to max 15mL; GMT measured measles antibody concentration</td>
<td>Naïve – 23mIU/mL (Range 13-42)</td>
<td>80</td>
<td>62-99</td>
</tr>
<tr>
<td></td>
<td>Non-naïve - 98mIU/mL (Range 83-114)</td>
<td>155</td>
<td>136-174</td>
</tr>
<tr>
<td>2) 0.2mL/kg to max 15mL; minimum measured measles antibody concentration</td>
<td>Naïve – 23mIU/mL (Range 13-42)</td>
<td>95</td>
<td>74-116</td>
</tr>
<tr>
<td></td>
<td>Non-naïve - 98mIU/mL (Range 83-114)</td>
<td>170</td>
<td>147-192</td>
</tr>
<tr>
<td>2) 0.2mL/kg to max 15mL; GMT measured measles antibody concentration</td>
<td>Naïve – 23mIU/mL (Range 13-42)</td>
<td>108</td>
<td>84-133</td>
</tr>
<tr>
<td></td>
<td>Non-naïve - 98mIU/mL (Range 83-114)</td>
<td>183</td>
<td>158-208</td>
</tr>
<tr>
<td>3) 0.2mL/kg to max 15mL; minimum</td>
<td>Naïve – 23mIU/mL (Range 13-42)</td>
<td>118</td>
<td>90-146</td>
</tr>
</tbody>
</table>
Table 3. Minimum dose of measles antibodies required to achieve a serum concentration above 132mIU/mL at day 18 after intramuscular dosing

<table>
<thead>
<tr>
<th>Pre-dose serum antibody concentration</th>
<th>Bioavailability (%)</th>
<th>Minimum dose required (IU/kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Naïve – 23mIU/mL (95% CI 13-42)</td>
<td>50</td>
<td>25.5</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>17.5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>13.5</td>
</tr>
<tr>
<td>Non-naïve - 98mIU/mL (95% CI 83-114)</td>
<td>50</td>
<td>9.5</td>
</tr>
<tr>
<td></td>
<td>75</td>
<td>6.5</td>
</tr>
<tr>
<td></td>
<td>100</td>
<td>5.5</td>
</tr>
</tbody>
</table>
Table 4. Serum concentration of rubella antibodies at day 21 after intramuscular dosing of Normal Human Immunoglobulin according to current Australian guidelines

<table>
<thead>
<tr>
<th>Dose</th>
<th>Pre-dose antibody concentration</th>
<th>Serum concentration at day 21 (IU/mL)</th>
<th>95% Confidence intervals</th>
</tr>
</thead>
<tbody>
<tr>
<td>1^20mL; minimum measured rubella antibody concentration</td>
<td>Naïve – 1 IU/mL (Range 0.2–4.4)</td>
<td>2434</td>
<td>1357-3512</td>
</tr>
<tr>
<td></td>
<td>Non-naive – 9 IU/mL (Range 6.5 – 10)</td>
<td>2455</td>
<td>1355-3554</td>
</tr>
<tr>
<td>1^20mL; GMT measured rubella antibody concentration</td>
<td>Naïve - 1 IU/mL (Range 0.2-4.4)</td>
<td>3499</td>
<td>1958-5040</td>
</tr>
<tr>
<td></td>
<td>Non-naive - 9 IU/mL (Range 6.5 – 10)</td>
<td>3511</td>
<td>1945-5078</td>
</tr>
<tr>
<td>2^20mL; minimum measured rubella antibody concentration</td>
<td>Naïve – 1 IU/mL (Range 0.2-4.4)</td>
<td>3646</td>
<td>2024-5269</td>
</tr>
<tr>
<td></td>
<td>Non-naive – 9 IU/mL (Range 6.5 – 10)</td>
<td>3659</td>
<td>2003-5315</td>
</tr>
<tr>
<td>2^20mL; GMT measured rubella antibody concentration</td>
<td>Naïve - 1 IU/mL (Range 0.2-4.4)</td>
<td>5235</td>
<td>2855-7615</td>
</tr>
<tr>
<td></td>
<td>Non-naive - 9 IU/mL (Range 6.5 – 10)</td>
<td>5266</td>
<td>2872-7660</td>
</tr>
</tbody>
</table>

^1bioavailability 50%

^2bioavailability 75%
BOX 1. Search strategy used to retrieve articles from which pharmacokinetic parameters were extracted

1 (Healthy OR pregnant OR infant OR neonate) AND
2 Immunoglobulin* AND
3 (intramuscular OR intravenous) AND
4 (pharmacokinetics OR uptake OR absorption rate OR maximum concentration OR central compartment OR peripheral compartment OR intravascular OR extravascular OR volume of distribution OR equilibrium or equilibration constant OR intercompartmental OR clearance OR area under the curve OR half-life)
5 (rat or rats or cow or cows or chicken* or horse or horses or mice or mouse or bovine or animal*).ti OR exp animals/ not humans.sh
6 #1 AND #2 AND #3 AND #4
7 #6 NOT #5
BOX 2. Model formulae (adapted from Dubois et al 2011 with permission of the authors) (16)

\[ C(t) = D \left( A e^{-\alpha(t-t_D)} + B e^{-\beta(t-t_D)} - (A + B) e^{-k_a(t-t_D)} \right) \]

Where:

- \( C(t) \) is the concentration in the central compartment at time \( t \) after the dose was given
- \( t_0 \) is the time at which the dose was given
- \( D \) is dose multiplied by bioavailability
- \( k_a \) is the absorption rate constant

\[ A = \frac{k_u}{V} \frac{k_{21} - \alpha}{(k_a - \alpha)(\beta - \alpha)} = \frac{k_u}{V_1} \frac{Q}{V_2} - \frac{\alpha}{(k_a - \alpha)(\beta - \alpha)} \]

\[ B = \frac{k_u}{V} \frac{k_{21} - \beta}{(k_a - \beta)(\alpha - \beta)} = \frac{k_u}{V_1} \frac{Q}{V_2} - \frac{\beta}{(k_a - \beta)(\alpha - \beta)} \]

\[ \alpha = \frac{k_{21}k}{\beta} = \frac{Q}{V_2} \frac{CL}{V_1} \]

\[ \beta = \left\{ \begin{aligned} &\frac{1}{2} \left[ k_{12} + k_{21} + k - \sqrt{(k_{12} + k_{21} + 2)^2 - 4k_{21}k} \right] \\ &\frac{1}{2} \left[ \frac{Q}{V_1} + \frac{Q}{V_2} + \frac{CL}{V_1} - \sqrt{\left( \frac{Q}{V_1} + \frac{Q}{V_2} + \frac{CL}{V_1} \right)^2 - 4\frac{Q}{V_2} \frac{CL}{V_1}} \right] \end{aligned} \right. \]

- \( k \) is the elimination rate constant
- \( k_{12} \) is the distribution rate constant from compartment 1 (central) to compartment 2 (peripheral)
- \( k_{21} \) is the distribution rate constant from compartment 2 (peripheral) to compartment 1 (central)
- \( V_1 \) is the volume of distribution in the central compartment
- \( V_2 \) is the volume of distribution in the peripheral compartment
- \( Q \) is the inter-compartmental clearance
- \( CL \) is the clearance rate
Figure 1. Schematic of a two compartment model (adapted from Dubois et al. 2011 with permission of the authors [16]).

Legend:

V1 is the volume of distribution in the central compartment
V2 is the volume of distribution in the peripheral compartment
Q is the inter-compartmental clearance
CL is the clearance rate
kₐ is the absorption rate constant
Concluding that 0.5 mL/kg NHIG is required for effective and efficient measles post-exposure prophylaxis and that 0.5-1 mL of NHIG is required for effective and efficient rubella post-exposure prophylaxis, this study contributed to thesis objective 3: to estimate the minimum effective doses of disease-specific antibodies when injected to prevent each disease. The minimum effective dose of disease-specific antibodies for hepatitis A was estimated using similar methodology and that model is described in the following section of the Chapter.
Statement of contribution to Section 5.2

My contribution to this section involved:

Conceptualising the study, contributing to the statistical analyses, interpreting the analyses, drafting the section and finalising the section with editorial input from my primary supervisor and Associate Professor Shu-Kay Ng.

(Signed)
Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
5.2 Pharmacokinetic modelling to determine the minimum effective dose of disease-specific antibodies for preventing hepatitis A

The following study again adapted Dubois et al’s equation for a two compartment model with first order absorption (167), though in this instance to estimate the minimum effective doses of disease-specific antibodies for the prevention of hepatitis A post-exposure. The study is presented here in the format of an unpublished paper.

5.2.1 Introduction of modelling the minimum effective dose of disease-specific antibodies for preventing hepatitis A

Hepatitis A vaccine is recommended for the post-exposure prophylaxis for most non-immune people, but passive immunisation with normal human immunoglobulin (NHIG) is an important means of prevention for subgroups most susceptible to complications, such as those who are immunocompromised (10). Although systematic review evidence concludes that passive immunisation is effective for preventing hepatitis A post-exposure, the minimum effective dose is unknown (147).

This may be a particular issue in Australia where: recommended dosing of NHIG is by weight category; the upper weight category begins at >50 kg (10); and an obesity epidemic is recognised (168). Without a known minimum effective dose, it is possible that Australian recommendations under-dose people over a certain weight. Other high-income countries currently recommend dosing by weight with no volume limit (169).

Efficacy or effectiveness studies that identify the minimum effective dose are unlikely as it is logistically difficult to conduct observational studies of people who require passive immunisation post-exposure to hepatitis A and it is unethical to conduct these sorts of exposure studies when effective pre-exposure prevention means exist.

An understanding of the expected serum concentrations of hepatitis A antibodies over time to an incubation period after post-exposure passive immunisation combined with an identified target threshold corresponding to the immune correlate of protection would be the next best means of identifying a minimum effective dose. The correlate of protection for hepatitis A is generally accepted as 10 mIU/mL (170, 171). However, existing clinical pharmacokinetic studies of hepatitis A-specific antibodies after immunoglobulin administration are few and only one was identified that measured serum concentrations of hepatitis A antibodies at or past an incubation period.
Mould et al (166) measured the hepatitis A antibody concentration in serum serially after IM injection of 750 mg (5 mLs) normal human immunoglobulin in one of two different formulations to several groups. The different formulations of NHIG contained different hepatitis A antibody concentrations, so participants who weighed between 51.5 – 100 kg received either 635 IU, 630 IU or 820 IU hepatitis A antibodies as a single intramuscular injection. At day 50 post injection (the upper range of the incubation period for hepatitis A), the mean serum concentration for each group well exceeded 10 mIU/mL, and the lower 95% confidence interval for the group with the lowest mean serum concentration appeared to be more than double this correlate of protection. Hence, while these doses seem effective for people who weigh 100 kg or less, they are not necessarily efficient, and the study still does not identify the minimum effective dose for hepatitis A post-exposure passive immunisation.

The doses of hepatitis A antibodies administered under Mould et al’s study are also potentially three or more times that administered under current Australian guidelines where adults weighing more than 50 kg are recommended 2 mL NHIG (10) (which by the manufacturing standard contains at least 100 IU/mL hepatitis A antibodies (172)). The question of whether Australian guidelines may under-dose certain groups is thus also still outstanding.

Recently, the minimum effective doses of NHIG for post-exposure prophylaxis for measles and rubella were estimated by means of pharmacokinetic modelling (173). In that study, the published correlates of protection served as the target for the serum disease-specific antibody concentration at an incubation period for the disease in question and published parameters were utilised to adapt and populate a two compartment, first order absorption, single dose model to give an understanding of the expected disease-specific antibody concentrations over time.

This study utilised the same methodology to explore the possible effect of bodyweight on disease-specific antibody concentrations at an incubation period under current NHIG dosing recommendations in Australia and to estimate the minimum effective dose per kilogram body weight of NHIG for the post-exposure prophylaxis of hepatitis A in non-immune individuals in Australia.
5.2.2 Methods of modelling the minimum effective dose of disease-specific antibodies for preventing hepatitis A

Published data on the pharmacokinetics of parenterally administered immune globulin as per Young et al (173) were utilised.

The minimum hepatitis A antibody concentration in Australian immune globulin was set at 100 IU/mL as Australian NHIG is manufactured to the European Pharmacopoeia standard of 100 IU/mL hepatitis A antibodies (172) (pers comm: Darryl Maher, Senior Director, Medical and Research, CSL Behring Australia).

It was assumed the published correlate of protection for hepatitis A of 10 mIU/mL (170, 171, 174), plus a margin of error of 10% to allow for individual and test variability was the optimal threshold concentration of disease-specific antibodies to be maintained for the duration of an incubation period. The incubation period used was 50 days, as per current Australian national guidelines for the public health management of hepatitis A (10).

The following adjustments were made to the previously published two-compartment, first-order absorption model for a single intramuscular injection (173) that was developed from the baseline equation of Dubois et al (167):

- The concentration of antibodies prior to dosing was generated from a lognormal distribution with a range corresponding to levels that would generate a negative result on commercial serology testing (<20 mIU/mL) (175, 176) with the mean and variation sourced from the participant group given standard NHIG in mould et al's study (166).
- The initial intramuscular dose of hepatitis A antibodies was set at 200 IU (the minimum dose that would be administered to an adult who weighed >50 kg under current Australian guidelines).
- Dose injected was multiplied by bioavailability which was set at 75%, with sensitivity analyses at 50 and 100% (177).
- The effect of weight on the serum concentration of hepatitis A antibodies at day 50 given an intramuscular dose of 200 IU was assessed by fixing weight in five-kilogram intervals.
- To identify the minimum effective dose, dose was input as dose per kilogram body weight, commencing with a dose equivalent to 200 IU for an 80 kg person and then adjusted incrementally in steps of 0.1 IU/kg until the lower 95% confidence interval of the mean serum concentration at day 50 was as close as
possible but above the correlate of protection plus a 10% margin of error (11 mIU/mL).

Ethics approval was not required for this study.

### 5.2.3 Results of modelling the minimum effective dose of disease-specific antibodies for preventing hepatitis A

Modelling an intramuscular dose of 200 IU for an Australian population at 75% bioavailability resulted in an average serum concentration at day 50 of 17 mIU/mL (95% CI 10 – 24 mIU/mL). At 50% bioavailability, the average was 14 mIU/mL (95% CI 8 – 20 mIU/mL), and at 100% bioavailability the average was 20 mIU/ml (95% CI 13 – 28 mIU/mL).

The average serum concentration of hepatitis A antibodies at day 50 decreased with increasing weight (Figure 2). At a weight of 85 kg, the lower 95% confidence interval of the mean serum concentration was at the defined optimal threshold of 11 mIU/mL under the assumption of 75% bioavailability. However, the estimated mean serum concentrations were all above the defined optimal threshold across the range of weights examined.

When dosing by weight, at 75% bioavailability, the dose at which the lower 95% confidence interval of the mean serum concentration of hepatitis A antibodies at day 50 was above the correlate of protection plus a 10% margin of error (11 mIU/mL) was 2.5 IU/kg. At 50% bioavailability, the optimal dose was 3.6 IU/kg, and at 100% bioavailability, the optimal dose was 1.9 IU/kg.
Discussion of modelling the minimum effective dose of disease-specific antibodies for preventing hepatitis A

Pharmacokinetic modelling of disease-specific antibodies administered intramuscularly identified that current Australian guidelines may under-dose some individuals who weigh more than 85 kg if the batch of NHIG used for post-exposure prophylaxis contains the minimum standard of hepatitis A antibodies of 100 IU/mL and is 75% bioavailable. When simulating a cohort with a range of weights similar to the Australian adult population, the lower 95% confidence intervals of the mean serum concentrations after a dose of 200 IU were also below the pre-defined threshold at both 75% and 50% bioavailability. The optimal dose according to the model was 2.5 IU/kg at 75% availability and 3.6 IU/kg at 50% bioavailability. This is equivalent to 0.025 mL/kg or 0.036 mL/kg of Australian NHIG respectively.

Recent guidance from the Centers for Disease Control in the United States suggests an optimal dose of at least 3.21 IU/kg (178, 179), similar to that suggested by the model under the assumption of 50% bioavailability. Guidance from the United Kingdom reports that a dose of 0.38 IU/kg was 84% effective at preventing hepatitis A in one published study, but recommends doses well in excess of this, at 3.77 IU/kg for
an 80kg individual based on the minimum concentration measured in the UK immunoglobulin product in 2008 (150, 180).

While Mould et al (166) did not dose by weight in their clinical pharmacokinetic study of single dose intramuscular immunoglobulin, the information provided on the doses administered and the weight ranges of individuals in the different study groups allows calculation that the doses of hepatitis A antibodies administered ranged from 6.35 IU/kg to 15.9 IU/kg, well in excess of the optimal doses suggested by the model in the current study.

The limitations of predictive modelling should be considered when interpreting the results of the current study for a practice setting, including that the results were recorded from a single iteration of each simulation scenario. As the model is unable to account for the fact that the volume of distribution of immunoglobulins is unlikely to vary in a linear fashion by weight (181), the estimates of the minimum effective dose are likely to be conservative.

While direct studies of the effectiveness of NHIG for the post-exposure prevention of hepatitis A (or other diseases) that enable calculation of a minimum effective dose are either difficult or impossible, confidence in the model of the current study would be enhanced by analytical comparison with raw clinical pharmacokinetic trial data. A study of healthy individuals administered a known dose of hepatitis A antibodies would be valuable to help validate and/or optimise the model presented here and would be possible in Australia where only a limited subgroup of the population are eligible for free hepatitis A vaccination.

In the interim, this study suggests that for the few individuals who are contacts of hepatitis A, recommended passive immunisation as post-exposure prophylaxis because they are at high risk of complications, and weigh in excess of 85kg, conservative management would include administering a dose of NHIG according to their weight at between 0.025 and 0.036 mL/kg (2.5-3.6 IU hepatitis A antibodies/kg).

Concluding that the minimum effective dose of Australian NHIG for preventing hepatitis A post-exposure is between 0.025 and 0.036mL/kg, this study contributed to thesis objective 3: to estimate the minimum effective doses of disease-specific antibodies when injected to prevent each disease. In line with the suggestion made in the
discussion section of the above study, the following section of the Chapter presents the preliminary findings of a randomised controlled trial that administered a known dose of hepatitis A antibodies to healthy non-immune individuals.
Statement of contribution to Section 5.3

My contribution to this section involved:

Conceptualising the study, designing the study and developing the protocol with advice from my primary supervisor, leading the application for ethical clearance and ensuring clearance was kept up to date, liaising with the Australian Red Cross Blood Service and Griffith Enterprise to draft the Collaborative Research Agreement, continuing to work with the Australian Red Cross Blood Service to fulfil the requirements of the CRA, registering the trial on the ANZCTR and keeping the registration up to date, recruiting participants, screening potential participants, undertaking required participant clinical measurements, administering the NHIG to participants, conducting the data analyses, interpreting the analyses, drafting the section and finalising the section with editorial input from my primary supervisor and Associate Professor Shu-Kay Ng.

(Signed)
Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
5.3 Validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A: a randomised controlled clinical trial

Following on from the conclusions of the pharmacokinetic modelling study estimating the minimum effective dose of NHIG for hepatitis A post-exposure prophylaxis, a randomised controlled clinical trial was implemented to validate and / or optimise the model. The trial was commenced in 2018, with anticipation of completion in the first months of 2019. However, despite many avenues of recruitment, enrolment in the trial has been significantly less than anticipated and necessitated an extension to the recruitment time frame. This has pushed completion of the trial outside the scope of this thesis. The interim results of the trial are presented here in the format of an unpublished paper.

5.3.1 Introduction of validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A: a randomised controlled clinical trial

While the mainstay of post-exposure prophylaxis for hepatitis A is vaccination, passive immunisation still plays an important role, particularly for subpopulations at highest risk of complications from the disease. Intramuscular injection of immunoglobulin is effective at preventing hepatitis A up to 14 days after exposure (150). However, the minimum dose required for efficacy is unknown.

Regarding post-exposure passive immunisation against hepatitis A, the national guidelines of Australia recommend 2mL of intramuscular immunoglobulin (NHIG) for individuals greater than 50 kg in weight (10). As Australia manufactures NHIG to the European Pharmacopoeia standard of hepatitis A antibodies of 100 IU/mL (pers comm: Darryl Maher, Senior Director, Medical and Research, CSL Behring Australia), the recommended volume equates to a dose of hepatitis A antibodies of at least 200 IU, and 3.92 IU/kg for someone weighing 51 kg, but the dose per kilogram declines as weight increases. Someone weighing 80 kg would receive 2.5 IU/kg for example. As available evidence suggests a dose-response relationship (147, 150), it is possible that Australia is under-dosing some subpopulations.

Volumes of NHIG recommended in other high income countries for the prevention of hepatitis A post-exposure vary considerably and given concerns about adequate dosing, this may be due to varying concentrations of hepatitis A antibodies in the blood products used (169). The United States have recently adopted recommendations based on a suggested optimal dose of hepatitis A antibodies of at least 3.21 IU/kg.
The United Kingdom recommendations equate to 3.77 IU/kg hepatitis A antibodies for an 80 kg individual based on the minimum concentration measured in the UK immunoglobulin product in 2008 (150, 180). Australian adults weigh approximately 80 kg on average (182), so both of these internationally recommended doses are considerably above Australian dosing guidelines for a large proportion of the local population.

To investigate the matter of a minimum effective dose of hepatitis A antibodies for post-exposure prophylaxis, a recent pharmacokinetic modelling study (unpublished at this time) utilised the correlate of protection for hepatitis A at an incubation period as the target serum concentration for effective dosing. The correlate of protection for hepatitis A is generally accepted as a serum antibody level of 10 mIU/mL as measured by ELISA (170, 171), and the incubation period for hepatitis A is up to 50 days (10). The modelling study suggested an optimal dose of hepatitis A antibodies after intramuscular injection of 2.5 IU/kg under the assumption of 75% bioavailability, or 3.6 IU/kg under the assumption of 50% bioavailability and supported the hypothesis that current Australian recommendations may under-dose some individuals weighing more than 85 kg (under the assumption of 75% bioavailability).

However, without clinical data, the modelling study results are untested. Yet, very few studies have examined quantitative serum hepatitis A antibody levels after administration of NHIG.

In a study comparing the quality of antibody response from active and passive immunisation, Lemon et al (174) found that both vaccination and passive immunisation with 0.06 ml/kg IG with unknown hepatitis A antibody titre resulted in approximately 40 mIU/ml geometric mean titre (GMT) hepatitis A antibodies at day 28 and day 7 respectively. This study did not measure antibody levels in those administered NHIG after day 7.

The only other study identified that quantitatively measured hepatitis A antibody concentrations in serum after NHIG injection was a study comparing solvent treated to non-solvent treated IG for safety and uptake (166). These authors measured hepatitis A antibody concentration in serum serially after intramuscular injection of 750 mg (5 mLs) normal human immunoglobulin to 36 immunocompetent adult subjects who the study classified as non-immune (pre-treatment serum antibody concentrations 4-60 mIU/mL). 635 IU of hepatitis A antibodies in standard NHIG administered to 12 participants resulted in a maximum mean serum concentration of 75.6 mIU/mL. At 50 days post administration, the mean serum concentration was approximately 29 mIU/mL.
in this group, whose pre-treatment serum antibody concentrations were all less than 20 mIU/mL. The weight of the 12 subjects ranged from 58 to 100 kg. 630 IU hepatitis A antibodies in solvent treated NHIG administered to 11 participants weighing 63-86 kg resulted in a maximum mean serum concentration of 92.6 mIU/mL; and 820 IU administered to 13 participants weighing 52-97 kg resulted in a maximum mean serum concentration of 123 mIU/mL. At 50 days post administration, the mean serum concentration of the latter two groups was consistent at approximately 38 mIU/mL. The mean and variation of the pre-dose hepatitis A serum concentrations of the participant group treated with standard NHIG was utilised as an input into the recent pharmacokinetic modelling study, but as the raw clinical trial data from Mould et al’s study (166) were not available, the pharmacokinetic model was unable be directly compared to their clinical trial results.

The current study therefore aimed to validate and/or allow optimisation of the pharmacokinetic model by administering one of two doses of NHIG (2 mL as per current Australian guidelines, or 2.5 IU/kg – the optimal dose at 75% bioavailability as suggested by the model) to healthy non-immune volunteers, measuring their serum hepatitis A antibody concentrations over time to an incubation period and comparing these to the same results predicted by the model. The optimal dose at 75% bioavailability, as opposed to the optimal dose at 50% bioavailability, as suggested by the model was chosen because consideration of the limitations of the model suggested the modelling results were likely to be conservative.

This randomised controlled trial is currently ongoing and remains registered as such on the Australian New Zealand Clinical Trials Registry (ANZCTR). The interim results from seven participants who completed the study in 2018 are presented here.

5.3.2 Methods of validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A

A randomised controlled trial methodology was used. Quantitative hepatitis A antibody levels were measured serially to an incubation period (50 days) post administration of one of two different doses (test dose (0.025 mL/kg) vs usual care (2 mL)) of NHIG to healthy volunteers who were not immune to hepatitis A on commercial serology testing. Quantitative serum hepatitis A antibody results were compared to the same results over time predicted by pharmacokinetic modelling.
Sample size calculation: Sample size for the trial was calculated by utilising the pharmacokinetic modelling study (unpublished at this time) based on published data. To identify a 10% difference in serum hepatitis A antibody titre between the groups at day 50 with 80% power required a sample size of 19 per arm. The study therefore attempted to screen 80 potential participants to allow for 50% drop out / ineligibility and result in recruitment of 20 participants per study group.

Participants: Volunteers were sought by way of

- the Griffith University e-news-sheet “Volunteer for Important Research Projects”.
- the Clinical Trials Unit register of volunteers for trials. (Anyone who may have been suitable was approached by email.)
- Flyers on noticeboards and pamphlets at the Clinical Trials Unit and in sitting areas around Griffith University Gold Coast campus (with permission from Campus Life Facilities Manager)
- an entry on the Clinical Trials Unit ‘current trials’ Griffith website with a link to the study flyer.
- (where agreed to by the relevant party) flyers and posters at GP surgeries and other institutions or businesses in the local area.

Healthy adult volunteers who provide informed consent, and met the following criteria were eligible:

- were not in another clinical trial within the 3 months prior to recruitment
- no history of hypersensitivity, or allergy to blood products or a serious haematological disorder
- had not received a blood product within the 3 months prior to recruitment
- had not been administered a live virus vaccine within the three weeks prior to NHIG administration
- were immune to measles and rubella according to a commercial serology test
- were not immune to hepatitis A according to a commercial serology test
o were not eligible for free hepatitis A vaccination and were unlikely to require hepatitis A vaccination during the course of study (ie no planned overseas travel to a country where pre-travel hepatitis A vaccine is recommended)

o were not pregnant

o weighed at least 51kg

Healthy 17-year olds who provided informed consent, met the same criteria, and whose parent or guardian also consented were also eligible.

Potential participants eligible on screening by history and weight measurement had an initial blood sample drawn for full blood count, measles, rubella and hepatitis A serology. These tests were done in a commercial pathology laboratory. If a low platelet count or abnormal results that had not been previously investigated were found on full blood count, the person was advised to see their usual medical practitioner for follow up and was excluded from the trial until such time as that medical practitioner deemed they were fit to participate. If measles and rubella serology did not demonstrate immunity, the person was advised to see their vaccine service provider for a free MMR vaccination and was excluded from the trial until such time as they were considered immune. Those who were immune to hepatitis A were excluded from the trial. The remainder were enrolled in the trial.

**Randomisation:** Participants were randomly allocated to either test dose or usual care group. Randomisation was undertaken by a person independent from the study using a random number table to assign the study group to sequentially numbered opaque envelopes. As a potential participant undertook blood screening, they were allocated the next envelope in numerical order. The envelope remained unopened until the day of immunoglobulin administration for that person. When a potential participant was deemed not eligible, the envelope remained unopened until the conclusion of the trial. Study staff performing the intervention were aware of group allocation for eligible participants. Those performing testing of quantitative hepatitis A antibody levels were blinded to group allocation. While participants were not advised of their group allocation, some may have become aware of this if they looked carefully at the syringe prior to NHIG administration. Single blinding was felt adequate for this study given the objective outcome measure.

**Intervention:** A research agreement was enacted between Griffith University and the Australian Red Cross Blood Service (ARCBS) for the trial. As part of this agreement, the ARCBS supplied the NHIG product that is registered and recommended in
Australia for post-exposure prophylaxis of hepatitis A (Normal Immunoglobulin VF). The product was sourced from CSL Behring Australia Ltd with permission from the National Blood Authority. The product was transported and stored according to manufacturer’s instructions at between 2 and 8 degrees Celsius and protected from light.

Both study groups received this NHIG product. The vials of the product used for the trial were all from the same production batch. Those in the test dose group received 0.025 mL/kg NHIG as a single IM dose. This dose was chosen based on the results of the modelling study at 75% bioavailability and equates to at least 2.5 IU/kg hepatitis A antibodies. The volume of NHIG administered to the test dose group did not exceed 5 mL. Those in the usual care group received 2 mL of NHIG as a single dose IM irrespective of weight, as per current Australian guidelines for post-exposure prophylaxis. This equates to at least 200 IU hepatitis A antibodies.

Prior to injection, participants had their weight, height and any regular medications recorded. Day 0 blood was drawn (baseline quantitative hepatitis A antibodies). Injection of NHIG was into the deltoid. A protocol for NHIG administration based on the advice in the Australian Immunisation Handbook (34) and the product information (183) was drawn up and followed. Participants returned for further blood sampling at days 1, 3, 7, 28, and 50 for quantitative hepatitis A antibody measurement by commercial ELISA kit. Allowance was made +/- 1 day in relation to day 3 and 7 blood sampling and +/- 3 days in relation to day 28 and 50 sampling to ensure maximal participation in the sampling schedule.

Participants were questioned about any adverse events potentially related to NHIG administration when they returned for blood sampling on / near days 1, 3 and 7. The following potential adverse events were specifically recorded in addition to any other events volunteered by the participant: local tenderness, erythema, muscle stiffness, pyrexia, malaise, drowsiness, urticaria, local swelling, headache, nausea, dizziness.

Recruitment, screening, clinical measurements, and NHIG administration was performed by Dr Megan Young. Phlebotomy and adverse event questioning was performed by qualified staff of the Griffith University Clinical Trials Centre.

**Outcome measurement:** Quantitative hepatitis A antibody testing was undertaken in the pathology laboratories of Pathology Queensland. ELISA was performed according to the manufacturer’s instructions using the Beckman Coulter Access HAV Ab kit.
Blood specimens (on / near days 0, 1, 3, 7, 28, 50) from a single participant were tested in parallel.

**Data Analysis:** Hepatitis A antibody level for each participant was plotted against time. Geometric mean titre (GMT) and range of hepatitis A antibody concentrations were recorded for each time point according to study group.

Participant parameters (weight, pre-dose antibody concentration, and dose administered) were input into the pharmacokinetic model developed previously and the resultant predicted serum levels of hepatitis A antibodies at each time point were plotted against the individual’s measured results. The dose administered was calculated in international units by multiplying the measured concentration of hepatitis A antibodies in the batch of NHIG used for the trial by the volume administered. The predicted values were recorded for each individual given bioavailability parameters of 50%, 75% and 100%.

**Ethics:**

**Incentive to participate:**

Participants were offered a free hepatitis A vaccination course as an incentive to participate. If they chose to accept this offer, vaccination was typically administered after the final study blood was drawn (at / near day 50) (as hepatitis A vaccine is not a live virus vaccine, no particular time interval between NHIG and vaccination was required to ensure efficacy of the vaccine), and a time was arranged for the second dose after a six-month interval as per the Australian Immunisation Handbook (34). Both vaccinations were given in the Griffith University Clinical Trials Centre by qualified staff. Standard vaccination procedures as per the Australian Immunisation Handbook were followed. After the first seven participants had completed the trial, the incentive was amended to include the choice between an AU$100 eftpos gift card or the course of vaccinations. The participants whose results are presented here enrolled prior to this modification to the protocol.

**Consent:**

Informed consent was obtained from each participant and recorded on a consent form. The NHIG consumer product information which includes potential side effects was given to each participant in hard copy. Going forward, the terms and conditions of the gift card is also provided to potential participants.

**Communication of screening blood results:**
Participants were advised of their screening blood results by phone.

If abnormal results were found on full blood count, the person was advised to see their general practitioner for follow up. They were asked if they would like a letter and the blood test result to be forwarded to their general practitioner to facilitate this. If measles and rubella serology did not demonstrate immunity, the person was advised to see their vaccine service provider for a free MMR vaccination. Again a letter was provided to facilitate if the person desired. Those immune to hepatitis A did not need further follow up. If the person was eligible for the trial based on their screening blood results, a time for their day 0 visit was arranged.

NHIG administration and adverse event reporting:

NHIG was administered at the Griffith University Clinical Trials Unit (CTU) with resuscitation equipment including adrenaline on hand. Participants remained under observation at the Unit for 20 minutes after NHIG administration.

Participants were questioned about any adverse events potentially related to NHIG administration when they returned for blood sampling on / near days 1, 3 and 7. The following potential adverse events were specifically recorded in addition to any other events volunteered by the participant: local tenderness, erythema, muscle stiffness, pyrexia, malaise, drowsiness, urticaria, local swelling, headache, nausea, dizziness.

Had an anaphylactic reaction to NHIG eventuated, this would have been reported immediately following management of the event to the HREC, and also reported as an adverse event to the TGA. De-identified copies of the data collection form for visits on / near days 1, 3 and 7 were forwarded to Manager, Research Ethics, Griffith University where the answers to any of the adverse event questions were ‘yes’.

Adverse event management:

The guidelines of the National Immunisation Handbook were followed regarding adverse events (34). Severe anaphylactic reactions usually have a rapid onset, thus participants remained in the CTU for 20 minutes after NHIG injection. The CTU has resuscitation equipment and this was on hand during and after NHIG administration. Rapid IM administration of adrenaline is the cornerstone of the treatment of anaphylaxis. The following instructions for management of anaphylaxis from the Immunisation Handbook (34) would have been followed should it have eventuated:

- If the patient is unconscious, lie him / her on the left side and position to keep the airway clear.
• If the patient is conscious, lie him / her supine in ‘head-down and feet-up’ position (unless this results in breathing difficulties).

• If there are any respiratory and / or cardiovascular symptoms or signs of anaphylaxis, give 0.5mL of 1:1000 adrenaline by IM injection into the anterolateral thigh. Adrenaline is not required for generalised non-anaphylactic reactions (such as skin rash or angioedema). If in doubt, IM adrenaline should be given. No serious or permanent harm is likely to occur from mistakenly administering adrenaline to an individual who is not experiencing anaphylaxis.

• Call for assistance. Never leave the patient alone.

• If oxygen is available, administer by facemask at a high flow rate.

• If there is no improvement in the patient’s condition within 5 minutes, repeat doses of adrenaline every 5 minutes until improvement occurs.

• Check breathing; if absent, commence basic life support or appropriate cardiopulmonary resuscitation (CPR), as per the Australian Resuscitation Council guideline (available at www.resus.org.au/guidelines).

• In all cases, transfer the person to hospital for further observation and treatment.

• Complete full documentation of the event, including the time and dose(s) of adrenaline given.

Local tenderness, erythema, muscle stiffness, local swelling, headache, nausea, malaise and dizziness are usually short lived and don’t require any specific therapy. The participant was reassured where these occurred. If tenderness, erythema, muscle stiffness, local swelling or headache were still present on day 1, the participant was advised they may use a cold compress and / or paracetamol to ease the symptom/s. If these symptoms had been prolonged (ie still present and not improving by day 3), the participant would have been referred to their general practitioner for further investigation and an adverse event form would have been completed and forwarded to the TGA. In the event of urticaria, this may indicate likelihood of more severe allergic reaction should NHIG be administered in the future. Had this occurred, it would have been communicated to the participant and the participant offered a letter to advise their general practitioner of the adverse event, so this is considered should NHIG be required in the future. The participant would also have been informed that urticaria is
usually self-limited and may be assisted by the use of oral antihistamines. Any prolonged urticaria would have initiated referral for further investigation to the participant's general practitioner.

**Blood sample collection and testing:**

Phlebotomy was conducted by trained staff at the Griffith University Clinical Trials Centre. Specimen handling and transport was in accordance with industry standards.

Experienced laboratory personnel adhering to recommended workplace health and safety standards undertook testing of serum samples.

**Data management:**

Hard copy participant data was identified. This was kept in a locked filing cabinet for the duration of the study and will be kept for seven years after the conclusion of the study and then destroyed by shredding.

The hard copy information was transcribed into 2 electronic datasets. Data stored on the password secured study database was identified by study ID number and included date of birth, age, sex, weight, height, regular medications, study group, NHIG dose, quantitative hepatitis A results and adverse events. Identifying information such as name, phone number, email address and address was recorded in a separate password secured database for the purposes of contact with those potential participants who proceeded to the screening blood tests and reminders to participants of their appointments for phlebotomy. The de-identified electronic data will be stored for 7 years as per university protocol. The identified electronic information will be deleted at the end of the study.

Identified serum samples will be retained until the completion of the study and then destroyed.

No participating individual will be identified in any published work.

**Trial Registration:**

This trial was and is registered on ANZCTR [http://www.anzctr.org.au](http://www.anzctr.org.au)

Trial Registration number: ACTRN12617001567314
5.3.3 Results of validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A: a randomised controlled clinical trial

As at 1 January 2019, 164 potential participants had been contacted by email (Figure 3). Ninety-nine of these were existing volunteers on the Clinical Trials Unit register at the start of recruitment. Of the forty-six people in total who responded to the communication, 18 were ineligible, 21 declined to participate, and seven participants were recruited and completed the trial. Of those who were ineligible for the trial, the most common reason was existing hepatitis A immunity (n=10), followed by underweight (n=4). Other reasons included travel plans requiring hepatitis A vaccination and being already enrolled in another trial.

Figure 3. Consort flow diagram for the trial: Validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A
Two completed participants were in the test dose group and five were in the usual care group. Three of these participants were female and four were male. Participants' weights ranged from 60.9kg to 131.8kg.

Figures 4 and 5 display the measured serum concentrations of hepatitis A antibodies for each participant.

Table 4 contains the GMT and range of titres by study group for each of the time points of measurement.

Figure 4. Serum concentrations of hepatitis A antibodies for Test Dose group participants
Figure 5. Serum concentrations of hepatitis A antibodies for Usual Care group participants

Table 4. Geometric mean titre (GMT) of hepatitis A antibodies in the serum of trial participants

<table>
<thead>
<tr>
<th>Day</th>
<th>Test dose (0.025 mL/kg NHIG) (n=2)</th>
<th>Usual care (2 mL NHIG) (n=5)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>GMT Values</td>
<td>GMT Range</td>
</tr>
<tr>
<td>0</td>
<td>6.5 6, 7.1</td>
<td>5.7 3.5-12</td>
</tr>
<tr>
<td>1</td>
<td>22.0 18.3, 26.4</td>
<td>22.4 11.9-30.2</td>
</tr>
<tr>
<td>3</td>
<td>34.3 33.7, 34.9</td>
<td>34.4 23.1-49.1</td>
</tr>
<tr>
<td>7</td>
<td>28.9 27.5, 30.3</td>
<td>30.1 20.5-45.8</td>
</tr>
<tr>
<td>28</td>
<td>19.2 16.2, 22.7</td>
<td>19.8 14.3-28.6</td>
</tr>
<tr>
<td>50</td>
<td>12.4 11.3, 13.6</td>
<td>16.5 10.3-26</td>
</tr>
</tbody>
</table>

The concentration of hepatitis A antibodies in the batch of NHIG used in the trial was 135I U/mL (personal communication, Joe Bertolini, Research and Development Manager, CSL Behring Australia). Participants in the test dose group therefore received 3.375 IU/kg. Participants in the usual care group received 2 mLs of NHIG, which equated to between 2.05 and 4.43 IU/kg. There seemed to be a general trend of increasing serum hepatitis A antibody concentration at day 50 with dose administered per kilogram (Table 5), although participant 5’s result was a notable anomaly. This
participant’s day 0 titre was the highest of the cohort at 12 IU/mL. The next highest day 0 titre was that of participant 2 at 7.1 IU/mL.

Table 5. Serum hepatitis A antibody concentrations at day 50 and dose of disease-specific antibodies administered for each trial participant.

<table>
<thead>
<tr>
<th>Participant</th>
<th>Dose of hepatitis A antibodies administered (IU/kg)</th>
<th>Serum hepatitis A antibodies at day 50 after NHIG administration (mIU/mL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3</td>
<td>2.05</td>
<td>10.3</td>
</tr>
<tr>
<td>4</td>
<td>2.35</td>
<td>14.2</td>
</tr>
<tr>
<td>5</td>
<td>2.8</td>
<td>20.9</td>
</tr>
<tr>
<td>7</td>
<td>3.37</td>
<td>15.6</td>
</tr>
<tr>
<td>1</td>
<td>3.38</td>
<td>11.3</td>
</tr>
<tr>
<td>2</td>
<td>3.38</td>
<td>13.6</td>
</tr>
<tr>
<td>6</td>
<td>4.43</td>
<td>26.0</td>
</tr>
</tbody>
</table>

One participant who weighed 131.8 kg had a serum concentration under the target threshold of 11 mIU/mL at day 50 post NHIG administration. This participant’s serum concentration of hepatitis A antibodies at day 50 was 10.3 mIU/mL. All other participants had measured serum hepatitis A antibody concentrations above the immunity threshold at day 50.

When individual participants’ measured values and the values predicted for that person from the pharmacokinetic model were visually compared, the measured values were typically closest to the predicted values at 50% NHIG bioavailability (Figures 6 and 7). It was not possible to statistically compare the measured and predicted values given the small number of trial participants to date.
Figure 6. Predicted pharmacokinetics compared to measured serum concentrations of Hepatitis A antibodies for participants in the test dose group (0.025 mL/kg NHIG)
Figure 7. Predicted pharmacokinetics compared to measured serum concentrations of Hepatitis A antibodies for participants in the usual care group (2 mL NHIG)
5.3.4 Discussion of validating the minimum effective dose of disease-specific antibodies for preventing hepatitis A

The clinical trial results for seven participants seem consistent with the pharmacokinetic model outputs. It is noteworthy that while the volume given to participants in the test dose group was based on the modelled results using a bioavailability of 75%, the measured results are more consistent with model predictions at a bioavailability of 50%. Only one participant's measured results approximated the predicted values at 75% bioavailability more consistently than those at 50% bioavailability (Participant 4).

The observation that participants measured values approximated the predicted values at 50% bioavailability is reinforced by the fact that test dose participants received 3.375 IU/kg hepatitis A antibodies, and the optimal dose according to the model at 50% bioavailability was 3.6 IU/kg. Recent guidance from the Centers for Disease Control in the United States suggests a similar optimal dose of at least 3.21 IU/kg (178, 179).

Participants in the usual care group received a range of doses per kilogram of hepatitis A antibodies and the serum concentration results for this group at day 50 were quite diverse (between 10.3 and 26 mIU/mL), with an overall trend for larger serum concentrations with larger doses. This seems to support an influence of weight on the results, although small numbers preclude a statistical examination of the role of weight in this group. The anomaly of participant 5’s results in this respect may be due to a comparatively higher day 0 hepatitis A antibody concentration, at least in part.

Despite the modelling results that suggested people over 85 kg may not receive an adequate dose when 2 mL NHIG is administered, all participants (bar one who weighed in excess of 130kg) achieved the target serum threshold at day 50. The dose of NHIG given to the participant who failed to meet the threshold concentration of hepatitis A antibodies at day 50 was 2.05 IU/kg. The calculation of the weight at which current recommended dosing may not be sufficient was based on 100 IU/mL hepatitis A antibodies in NHIG, which equates to 2.35 IU/kg at 85 kg. While in this study, the participant who received 2.35 IU/kg did achieve the target serum concentration at day 50, this participant’s measured results were those that most closely approximated the model’s predictions at 75% bioavailability, while other participants measured results were best predicted at 50% bioavailability.

This highlights a limitation of the current study, that of small numbers of participants, and thus considerable data variability which may occur simply due to chance. The
quantitative hepatitis A antibody assay used could also be a source of variability. However, upon validation testing, the coefficient of variance at a mean of 69.9 IU/mL hepatitis A antibodies was 3.47% and linear correlation exceeded an $R^2$ of 0.95. Ideally, with further measured data, the current clinical trial will allow pooled participant information to be analysed to refine the parameters of the pharmacokinetic model where necessary, thus optimising the accuracy and precision of its predictive ability.

At this point, it seems likely that the optimal dose of hepatitis A antibodies is somewhere between 2.35 and 3.6 IU/kg. As international guidelines suggest an optimal dose of at least 3.21 IU/kg (178, 179), and current measured results seem to approximate model predictions at 50% bioavailability, it seems reasonable to conclude that the model result of 3.6 IU/kg is the optimal dose until further trial results are able to refine this. However, given the mechanics of policy change, and that all participants administered a dose of 2.35 IU/kg or more exceeded the a priori set protective threshold for serum hepatitis A antibodies at day 50, it is suggested that awaiting the remaining clinical trial results prior to recommending any change to national public health guidelines for hepatitis A would be wise. Should a contact of hepatitis A requiring NHIG weigh more than 85 kg (the weight at which the dose of hepatitis A antibodies may be less than 2.35 IU/kg if given 2 mL NHIG), it seems reasonable on balance to provide an increased dose for that individual whilst awaiting further evidence.

Further, the current clinical trial and modelling results for hepatitis A post-exposure prophylaxis do not seem to suggest any refinement at this point to the recommendations made in the previously published study estimating the optimal NHIG doses for measles and rubella post-exposure prophylaxis (173), where conclusions were based on the results of modelling at 50% bioavailability.

Concluding that the measured clinical values are consistent with the pharmacokinetic model results under the 50% bioavailability assumption, this study contributed to thesis objective 3: to estimate the minimum effective doses of disease-specific antibodies when injected to prevent each disease. With completion of this thesis objective, the evidence obtained during the program of research thus far was able to be synthesised to make recommendations for changes to passive immunisation practice in Australia in the next section of this Chapter.
5.4 Recommendations for changes to current public health passive immunisation practice

With thesis objectives 1-3 completed as described in Chapters 2 through 5, the results from the program of research thus far were synthesised to make recommendations for public health passive immunisation practice in Australia.

The systematic reviews undertaken to examine the effectiveness of passive immunisation for post-exposure prophylaxis of measles and rubella, and the pre-existing published reviews of post-exposure prophylaxis for preventing hepatitis A, suggested this intervention is effective for preventing these diseases when administered within the appropriate timeframe to non-immune contacts but were unable to identify the optimal doses of NHIG to effect these results. By utilising information on the concentrations of disease-specific antibodies in NHIG, including measured anti-measles and anti-rubella concentrations, pharmacokinetic modelling was able to estimate the minimum effective doses required for post-exposure prevention. The following recommended changes to public health passive immunisation practice in Australia consider the results of the preceding Chapters as well as knowledge of the clinical environment in Australia:

- For measles control: Remove the maximum intramuscular volume of NHIG recommended for measles contacts and replace the current dose with one equivalent to 25.5 IU/kg. For Australian NHIG, this is 0.5 mL/kg. As this equates to 40 mL of NHIG for an 80 kg individual, which is clinically impractical and likely to be distressing for the person, it is further recommended to consider altering Australian guidelines to include the option of intravenous IG dosing where calculated doses are large. Because intravenous dosing will likely require administration in a hospital setting, it is further recommended that consideration be given to altering Australian measles control guidelines to recommend passive immunisation as post-exposure prophylaxis only for those who are non-immune and most vulnerable to measles complications. This includes infants, pregnant women and people with immunosuppression. Under this scenario, other non-immune close contacts would be offered MMR vaccination irrespective of time since exposure.

- For rubella control: Change the guidelines regarding passive immunisation for non-immune pregnant women to recommend passive immunisation within five days of first exposure followed by serial serology to enable identification of asymptomatic disease. Decrease the current recommended dose of 20 mL
NHIG for post-exposure prophylaxis of non-immune pregnant women to 0.5 mL NHIG for a woman up to 160 kg and 1 mL for those in excess of this weight.

- For hepatitis A control: No change is routinely recommended to the current volume of 2 mL for adults weighing greater than 50 kg pending further results from the ongoing pharmacokinetic clinical trial and subsequent possible refinement of the pharmacokinetic model. For contacts requiring NHIG who weigh more than 85 kg, individual clinical assessment may indicate an increased dose is warranted. In this case, the suggested dose is 3.6 IU/kg, or 0.036 mL/kg.

Implementation of these recommendations would impact on healthcare spending in Australia and the decision to adopt the recommendations must therefore include consideration of the likely budgetary impact. To assess the likely budgetary impact, an understanding of the current use of NHIG for public health passive immunisation is first required. The study in the following Chapter provides this understanding.
Chapter 6  Use of NHIG in Queensland and Australia

Statement of contribution to co-authored published paper

This chapter includes a co-authored published paper. The bibliographic details of the co-authored published paper, including all authors, are:


My contribution to the published paper involved:

Conceptualising the paper, leading the ethics and governance application and management processes, collecting the data from public health units, managing all data used in the study, analysing the data, drafting the manuscript and finalising the manuscript with my co-authors.

(Signed)
Dr Megan Young

(Countersigned)
Corresponding author of published paper: Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
To enable calculations of the cost implications of the recommended changes to practice made at the conclusion of Chapter 5, an understanding of current usage patterns of NHIG is required. The following study collected data on the use of NHIG from public health units around Queensland and from the National Blood Authority to baseline NHIG use for public health purposes between 2004 and 2016.
Original Article

The use of normal human immunoglobulin (NHIG) for public health purposes in Queensland 2004-2014 and Australia 2014-2016

Megan K Young, Allan W Cripps and Graeme R Nimmo

Abstract

Objective

To describe the use of normal human immunoglobulin (NHIG) recommended for public health purposes in Queensland and Australia.

Methods

Queensland public health unit (PHU) data on notified cases of measles, rubella and hepatitis A from 2004 to 2014 were examined; particularly regarding the number of contacts offered NHIG and the volume recommended per contact.

The National Blood Authority (NBA) provided unidentified data from NHIG order form inception (June 2014) through December 2016. Queensland orders were compared to PHU data where the data timeframes overlapped.

Results

NHIG usage varied by condition. For hepatitis A, usage declined after the introduction of vaccination for contacts in 2010. Usage fluctuated across the study period for measles and was not recommended for rubella. Average volumes per contact for hepatitis A and measles were 1.6mL and 11.9mL respectively based on PHU data.

PHU data approximated NBA data on NHIG usage for hepatitis A and rubella contacts. Calculated volumes of NHIG per measles contact were also similar, but PHU data underestimated the number of measles contacts for whom NHIG was ordered.

Discussion

This study is the first to document the use of NHIG for public health purposes in Australia. Results will be valuable for national blood sufficiency planning and cost effectiveness studies in the event of alterations to NHIG dosage recommendations.

Keywords: communicable diseases, normal human immunoglobulin, passive immunisation, measles, rubella, hepatitis A
Introduction

Australian blood donations are used to manufacture a number of different blood products including intravenous, subcutaneous and intramuscular preparations of polyvalent immunoglobulins. These immunoglobulin products are costly to produce and in high demand in Australia. The National Blood Authority regulates the usage of these products under the National Blood Arrangements, with the aim of ensuring an efficient, effective and ethically distributed national supply. To ensure this aim is met, clinical guidelines for immunoglobulin use should be evidence-based with respect to both effectiveness and efficiency.

While intravenous and subcutaneous immunoglobulin products are typically used for treatment of immunodeficiency, intramuscular immunoglobulin (also known as normal human immunoglobulin (NHIG)) is recommended to certain contacts of measles, rubella and hepatitis A cases as part of the public health response to these diseases. The definition of what constitutes contact with each of these diseases differs and is set out in national and state guidelines. Public health staff use these guidelines to counsel contacts about post-exposure prophylaxis, including the requirement, if any, for exclusion or restriction should prophylaxis be refused.

Recent systematic reviews have confirmed the effectiveness of passive immunisation for preventing measles, rubella and hepatitis A among contacts. The reviews did not identify any safety concerns associated with administration of immunoglobulin post-exposure, with no serious intervention-related adverse events reported in included studies. Notably, the reviews were unable to determine the doses of disease-specific antibodies required to effect the recorded preventive results. There is evidence that the effectiveness of passive immunisation is related to disease-specific antibody dose.

The recommended doses of NHIG for contacts of these diseases in Australia have remained unchanged for many years. For measles, the recommended dose is 0.2mL/kg to a maximum of 15mLs for immunocompetent individuals. For rubella, the recommended dose is 20mL. For hepatitis A, the recommended dose is 0.5mL for those less than 25kg, 1mL for those 25-50kg, and 2mL for those over 50kg.

Other countries have increased the recommended dose of NHIG for post-exposure passive immunisation against measles within the last decade in response to concerns about declining antibody levels in their blood products. NHIG in Australia is produced according to the requirements of the European pharmacopeia (personal communication Darryl Maher, CSL Behring, Australia). Thus, hepatitis A antibody concentration in NHIG is standardised to ≥100IU/mL, but measles and rubella antibody concentrations do not require standardisation and are not routinely measured. These latter disease-specific antibody concentrations depend on the respective concentrations of these antibodies in the pooled donated blood used to manufacture NHIG. This may change over time. Measles and rubella antibody levels in Australian NHIG have only recently been published.

If, in light of this new information, Australia were to alter the recommended post-exposure doses of NHIG, current usage data would enable an understanding of the potential budgetary impact of this policy change. Such usage data would also be valuable for informing the management of the national blood supply. This study aimed to describe the use of NHIG recommended for public health purposes in Queensland and Australia over the last decade and thus estimate the average number of contacts per case of disease who were recommended NHIG over time, and the average volume of NHIG recommended for these contacts.

Methods

Ethical approval was granted by Griffith University Human Research Ethics Committee (MED/64/14/HREC) and The Prince Charles...
Hospital Human Research Ethics Committee (HREC/15/QPCH/71) upon approval of data access under the Public Health Act 2005.

Queensland Public Health Unit Data

Paper and electronic public health records held in public health units on notified cases of measles, rubella and hepatitis A in Queensland were interrogated. Unidentified data were collected into a purpose built database. Fields collected for each notified case included: public health unit name, case notification date, disease notified (hepatitis A, measles, rubella), number of contacts, number of susceptible contacts, and number of contacts recommended NHIG. Susceptible contacts were those who were offered post-exposure prophylaxis (either vaccine or NHIG) and/or who were noted to be susceptible on the public health unit record. Public health unit staff use susceptibility definitions of contacts as per national and state guidelines.

Fields collected for each contact recommended NHIG included: age at case notification date, weight, immunocompromised (yes/no), and volume of NHIG recommended.

Analyses were undertaken separately for measles, rubella and hepatitis A. The median number of contacts, susceptible contacts and contacts offered NHIG per case for the entirety of the available data period was calculated. Descriptive analysis examined the proportion of contacts recommended NHIG according to age group. The average volume (and range) in millilitres of NHIG recommended per contact was calculated. Where possible, missing data were then imputed and calculations of average volume (and range) of NHIG recommended per contact were repeated. The total number of contacts recommended NHIG and the average number of contacts recommended NHIG per case was graphed against time.

National Blood Authority Data

Unidentified data collected on NHIG order forms was supplied by CSL Behring, Australia under approval from the National Blood Authority. The current system of ordering NHIG for post-exposure prophylaxis purposes was implemented in June 2014. The following fields from the current order form were requested for the time period June 2014 through December 2016 inclusive: state/territory, date ordered, total volume NHIG required (mL), and number of patients being treated.

Analyses were undertaken separately for measles, rubella and hepatitis A. The total volume of NHIG ordered over the time period was calculated and examined by state/territory and over time. The volume of NHIG for each order was divided by the number of patients being treated by that order to calculate the average volume per contact for the order. The range of the average volumes per contact across orders was recorded. Where the number of patients was not recorded, the maximum volume recommended for the condition according to national guidelines was used to impute the number of contacts for the order. The average volume of NHIG ordered per contact overall was calculated. The total volume of NHIG ordered in Queensland from June to December 2014 was compared to the data collected from public health unit records for the same time period.

Results

Queensland Public Health Unit Data

Hepatitis A

Four hundred and sixty one cases were notified over the study period, the majority (31%) in the Brisbane area. The total number of contacts identified was 3,951. Fifty-two cases did not have any identified contacts within Australia. The largest number of contacts recorded for a case was 766. There were several other cases over the study period where large numbers of contacts were identified. Child care attendance and food handling were the most common situations resulting in large numbers of contacts. The median number of contacts per notified case of hepatitis A was 3.
Of 3,851 contacts, 3,091 (79%) were identified as being susceptible to hepatitis A. The median number of susceptible contacts per case was 3 (range 0-765). The median number of contacts per case recommended NHIG was zero (range 0-31). A total of 878 contacts were recommended NHIG over the study period, with 94% of these being contacts of cases notified between 2004 and 2009 inclusive (Figure 1). The average number of contacts recommended NHIG per notified case of hepatitis A noticeably declined after 2008 from 4 in that year to less than one from 2011 to 2014 (Figure 1).

Twelve contacts recommended NHIG refused, leaving 866 for whom NHIG was ordered. The volume of NHIG recommended for individual contacts was frequently not recorded. Of the 866 for whom NHIG was ordered, the volume recommended was recorded for 66 contacts. The average volume for these 66 contacts was 1.3mL (range 0.15-2.2mL).

As current recommendations for the volume of NHIG are based on weight categories, the amount ordered was subsequently assumed to be consistent with these recommendations where the individual’s weight was available. Where weight was also not recorded, adults were assumed to weigh more than 50kg and hence receive 2mL of NHIG, and children were assumed to be of average weight for their age and receive the volume recommended for that weight. Hence, boys aged 7 to 12 years and girls aged 8 to 14 years were assumed to be ordered 1mL.

On this basis, it was estimated that 19% of contacts (n=164) ordered NHIG were less than 25kg, 10% (n=84) were 25-50kg, and 67% (n=583) were 50kg.

Figure 1. Number of contacts of hepatitis A cases and average number of contacts per case of hepatitis A recommended normal human immunoglobulin post-exposure prophylaxis by year in Queensland, Australia.
were more than 50kg. Contacts for whom age and weight details were not recorded (n=35) were omitted from calculations of the average volume of NHIG per contact. The average volume of NHIG recommended for 831 contacts was 1.6mL (range 0.15-2.2mL).

Twenty-five of 866 contacts for whom NHIG was ordered did not have any age details recorded, 25 were identified as children but numerical age was not recorded, and 224 were identified as adults but numerical age was not recorded. Of the remainder (n=592), the majority (54%) were aged less than 20 years (Table 1).

Seven of 866 contacts ordered NHIG were identified as being immunocompromised.

Measles

Two hundred and eighteen cases were notified over the study period. Forty percent of cases were notified in the Brisbane area, a further 20% on the Sunshine Coast and a further 12% on the Gold Coast. The number of recorded contacts totalled 15,767 and ranged from none to 1,363, with a median of 18 contacts per case. Removing the influence of a single institutional outbreak where contacts of subsequent cases were the same as for the initial cases and thus not recounted, resulted in a median of 24 contacts per case.

Of 15,767 contacts, 2,359 (15%) were identified as being susceptible to measles. The median number of susceptible contacts per case was 3 (range 0-322). This was unaltered by removing the cases from the institutional outbreak. The median number of contacts per case recommended NHIG was zero (range 0-45). Again, this was unaltered by removing cases from the institutional outbreak. A total of 579 contacts were recommended NHIG over the study period, with 85% of these being contacts of cases notified between 2010 and 2014 inclusive. The average number of contacts recommended NHIG per case fluctuated, with no apparent trend over time (Figure 2).

Thirty-six contacts recommended NHIG refused, leaving 543 for whom NHIG was ordered. The volume of NHIG recommended for individual contacts was recorded for only 55 contacts. The average volume recommended for these contacts was 11.0mL (range 1-15mL). Twenty-one contacts without recommended volume of NHIG recorded had details of weight recorded, which enabled calculation of the

Table 1. Age group of contacts of Hepatitis A cases who received normal human immunoglobulin post-exposure prophylaxis in Queensland, 2004-2014

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>Proportion of Total Contacts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td>192</td>
<td>22</td>
</tr>
<tr>
<td>10-19</td>
<td>126</td>
<td>15</td>
</tr>
<tr>
<td>20-29</td>
<td>99</td>
<td>11</td>
</tr>
<tr>
<td>30-39</td>
<td>71</td>
<td>8</td>
</tr>
<tr>
<td>40-49</td>
<td>44</td>
<td>5</td>
</tr>
<tr>
<td>50-59</td>
<td>31</td>
<td>4</td>
</tr>
<tr>
<td>60-69</td>
<td>20</td>
<td>2</td>
</tr>
<tr>
<td>70+</td>
<td>9</td>
<td>1</td>
</tr>
<tr>
<td>Child – no numerical age given</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Adult – no numerical age given</td>
<td>224</td>
<td>26</td>
</tr>
<tr>
<td>Age data missing</td>
<td>25</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>866</td>
<td>100</td>
</tr>
</tbody>
</table>
Figure 2. Number of contacts of measles cases and average number of contacts per case of measles recommended normal human immunoglobulin post-exposure prophylaxis by year in Queensland, Australia

Eighteen of 543 contacts ordered NHIG were identified as being immunocompromised. All were adults. Thirty-four of 543 contacts ordered NHIG were identified as being pregnant.

Rubella

Seventy-two cases were notified over the study period, the majority (64%) in the Brisbane area. The total number of contacts recorded was 2,088, however, 1,900 of these were recorded against one case as the estimated number of contacts for that case, and these contacts were not identified individually. The records for 14 of 72 cases did not have details about the number of contacts. For the remaining 58 cases, the median number of contacts per case was one.

Sufficient detail about the susceptibility of identified contacts was available for 40 of 57 cases. Among the 168 contacts of these 40 cases, 34 (20%) were recorded as susceptible to rubella. Three of these contacts were pregnant at the...
time of exposure. One was 37 weeks pregnant and advised to receive vaccination after delivery, one of unknown gestation was also advised to receive vaccination after delivery, and the third was 11 weeks pregnant without record of vaccination and was advised to undergo serology testing. The remaining susceptible contacts were also recommended vaccination. There was no record of NHIG being recommended for any contact of a rubella case.

National Blood Authority Data

Hepatitis A

Thirty-one orders for NHIG were identified as being for the purpose of hepatitis A prophylaxis over the period June 2014 through December 2016 inclusive. A total of 119.25mL was requested. The state of Victoria ordered the most NHIG during this time period at 95.25mL, followed by New South Wales at 10mL, Queensland at 8mL, South Australia at 4mL, and Western Australia at 2mL. Tasmania, the Australian Capital Territory, and the Northern Territory did not order any NHIG for contacts of hepatitis A during this time.

The volume ordered nationally each 6 months over the period of available data is shown in Figure 3. The average volume of NHIG ordered per contact during the available data period was 1.78mL (range 0.25 – 5mL).

From June to December 2014, Queensland placed 2 orders for NHIG for hepatitis A post-exposure prophylaxis totalling 1.5mL to treat 3 contacts. Public health unit data for the same time period included 3 contacts who were recommended NHIG totalling 2mL.

Measles

One hundred and twenty-six orders for NHIG were identified as being for the purpose of measles prophylaxis over the period June 2014 through December 2016 inclusive. A total of 6,679.1mL was requested. The state of Victoria ordered the most NHIG during this time period at 3,009.8mL, followed by Queensland at 2,802.7mL, Western Australia at 410mL, New South Wales at 369.6mL, Northern Territory at 50mL, South Australia at 32mL and Tasmania at 5mL. The Australian Capital Territory did not order any NHIG for contacts of measles during this time.

Table 2. Age group of contacts of measles cases who received normal human immunoglobulin post-exposure prophylaxis in Queensland, 2004-2014

<table>
<thead>
<tr>
<th>Age group</th>
<th>Number</th>
<th>Proportion of Total Contacts (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;10 years</td>
<td>87</td>
<td>16</td>
</tr>
<tr>
<td>10-19</td>
<td>31</td>
<td>6</td>
</tr>
<tr>
<td>20-29</td>
<td>84</td>
<td>15</td>
</tr>
<tr>
<td>30-39</td>
<td>158</td>
<td>29</td>
</tr>
<tr>
<td>40-49</td>
<td>101</td>
<td>19</td>
</tr>
<tr>
<td>50-59</td>
<td>6</td>
<td>1</td>
</tr>
<tr>
<td>60-69</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>Child – no numerical age given</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Adult – no numerical age given</td>
<td>54</td>
<td>10</td>
</tr>
<tr>
<td>Age data missing</td>
<td>16</td>
<td>3</td>
</tr>
<tr>
<td>Total</td>
<td>543</td>
<td>100</td>
</tr>
</tbody>
</table>
The volume ordered nationally each 6 months over the time period of available data is shown in Figure 3. The average volume of NHIG ordered per contact was 11.6mL (range 1.8 – 27mL).

From June to December 2014, Queensland placed 24 orders for NHIG for measles post-exposure prophylaxis totalling 2,470.2mL to treat 170 contacts. Public health unit data for the same time period included 84 contacts recommended NHIG totalling 960.4mL.

Rubella

No orders for NHIG were identified as being for the purpose of rubella prophylaxis during the time period of available data.

Discussion

The use of NHIG recommended for public health purposes in Queensland and Australia over the last decade varied by notifiable condition. NHIG usage declined substantially as a prevention measure for hepatitis A in Queensland after 2010, corresponding to a change in the national guideline to recommend vaccination for post-exposure prophylaxis for most contacts. The average number of contacts recommended NHIG per case of hepatitis A between 2011 and 2014 was less than one. Contacts were on average recommended a volume of 1.6mL. NHIG usage for measles post-exposure prophylaxis fluctuated across the study period. The average number of contacts recommended NHIG per case of measles varied between zero and 1.75. The factor most likely to contribute to this is the number of notified cases each year. For example, 2014 stands out as the peak year for NHIG consumption for measles contacts in this study and corresponds to an annual number of notifications in Queensland that was 3 times the preceding 5 year average. On average, measles contacts were recommended a volume of 11.9mL of NHIG. There was no evidence that NHIG has been recommended for the post-exposure prophylaxis of rubella in Queensland (or Australia) during the study period.
The volumes of NHIG ordered for post-exposure prophylaxis of measles and hepatitis A between 2014 and 2016 varied across the country. Again, the factor most likely to influence usage according to condition by state is the number of notified cases, although population differences in the proportion of contacts who are susceptible may also impact. Overall the average volume of NHIG ordered per contact was 11.6mL for hepatitis A and 11.6mL for measles.

Across the period of study, a considerable proportion of identified contacts of Queensland cases of measles were deemed susceptible (15%), though this figure is consistent with the latest national serosurvey results that indicated 19.2% of the Australian population aged between one and 49 years are either seronegative or have an equivocal result for measles immunity.35 Within this group, susceptibility would have been assumed for some contacts in accordance with national guidelines4 due to a lack of documented measles vaccination or immunity, while others would have identified that they were unimmunised and or been seronegative to measles. The proportion of contacts in each of these categories is unknown, but it is likely that a lack of documentation of immunisation resulted in some contacts who were already immune to measles receiving post-exposure prophylaxis. The recent implementation of a national whole of life immunisation register should reduce this occurrence in the future.

Queensland public health unit data approximated National Blood Authority data on NHIG usage for the post-exposure prophylaxis of hepatitis A and rubella. Calculated volumes of NHIG per measles case were also similar across these data sources, but the number of Queensland measles cases who were ordered NHIG between June and December 2014 was double that recorded in Queensland public health unit records. This is likely to be due to limitations of public health unit data management capacity during measles outbreaks and that contacts resulting from hospital or primary health care exposures were likely to have been followed up directly by the relevant clinical facility.

This discrepancy in the number of measles contacts offered NHIG highlights a limitation of the public health unit data. Because only contacts identified to public health are recorded, the calculated numbers of contacts per case are susceptible contacts per case and contacts per case recommended NHIG are likely to be underestimates. However, it is reassuring that during a measles outbreak year (2014) the number of contacts per case recommended NHIG according to National Blood Authority data (4.59) was within the range estimated by public health unit data across the study period (Figure 2: 0–4.79).

A further limitation of this study was the amount of missing data, mostly regarding recommended volumes of NHIG. To redress this issue, missing data was imputed where possible. It is reassuring that the volumes of NHIG per contact calculated after imputing data were very similar to those using only complete data.

To our knowledge, this is the first study documenting the use of NHIG for the public health management of communicable diseases in Australia or elsewhere. It provides detailed baseline information to allow future comparisons within Australia and internationally.

The results are therefore beneficial to national blood sufficiency planning. Prior to the introduction of the national NHIG order form, public health unit data were the only collated records of the public health indications for NHIG used in Australia. By demonstrating approximation between the recommendations of public health professionals for the requirement for prophylaxis with NHIG and the orders placed for this blood product, this study provides a valid historical comparison for future analyses of NHIG usage utilising the national NHIG order form.

The results will also be valuable for future cost effectiveness studies. Cost effectiveness studies require information on utilisation of an inter-
vention to allow cost comparison to an alternative. In the event alterations to the nationally recommended NHIG dosages, or other policy change concerning passive immunisation for the prevention of hepatitis A, measles or rubella are considered, this study will facilitate more reliable budgetary impact estimates.

Acknowledgements

We gratefully acknowledge the support provided by the following public health units in the conduct of this research:

Tropical Public Health Service (Cairns)
Townsville
Mackay
Central Queensland
Wide Bay
Sunshine Coast
Metro North
Metro South
Darling Downs
West Moreton
Gold Coast

We wish to thank CSL Behring (Australia) Pty Ltd, and particularly Laetitia Orlandini, for supply of the unidentified national NHIG order data.

Authors

Dr Megan K Young1,2

Corresponding author: School of Medicine, Griffith University, Gold Coast Campus, 58 Parklands Dr, Southport QLD 4215
email: megan.young@griffith.edu.au
ph 07 5678 0624

Prof Allan W Cripps1
email: allan.cripps@griffith.edu.au

Prof Graeme R Nimmo1,3
email: graeme.nimmo@health.qld.gov.au

1. School of Medicine and Menzies Health Institute Queensland, Griffith University

2. Metro North Public Health Unit, Metro North Hospital and Health Service

3. Pathology Queensland, Queensland Health

References


By documenting NHIG use for the public health control of measles, rubella and hepatitis A, this study contributed to thesis objective 4: to identify the quantity of NHIG used for the public health management of communicable diseases in Queensland and Australia over the past decade. This study completed the information required to enable assessment of the budgetary impact of the recommended changes to public health passive immunisation practice made at the conclusion of Chapter 5.
Statement of contribution to Chapter 7

My contribution to this chapter involved:

Researching the most appropriate economic study design for this circumstance, conceptualising the study, drafting the study protocol, finalising the study protocol with input from Associate Professor Louise Gordon (Health Economist, QIMR), collecting the data, conducting the data analyses, interpreting the analyses, drafting the chapter and finalising the chapter with editorial input from my primary supervisor and Associate Professor Louise Gordon.

(Signed)
Dr Megan Young

(Countersigned)
Supervisor: Prof Allan Cripps
Changes to public health passive immunisation practice in Australia were recommended at the conclusion of Chapter 5. Regarding the use of NHIG, no change to the population for whom passive immunisation is used was recommended for the control of hepatitis A. Consideration of an increased dose for individuals who weigh greater than 85kg was suggested. For rubella, there was no change to the population recommended NHIG post-exposure, but an increase to the length of time since exposure where NHIG is recommended was suggested. The new recommendations included a decrease in the dose required for rubella post-exposure prophylaxis. For measles, the new recommendations included decreasing the population who would currently be offered passive immunisation overall, decreasing the population who would be offered passive immunisation with NHIG, increasing the dose of NHIG required and increasing the indications for intravenous immunoglobulin to include post-exposure prophylaxis of measles. These recommendations would also result in a concurrent increase in the use of measles vaccine post-exposure.

Inherent with these recommendations is a change to the costs of the public health management of notified cases. There are a number of methodologies that might be used to assess these cost implications.

Economic evaluations, such as cost-benefit analyses and cost-utility analyses, provide information on the costs compared to benefits of an intervention over alternative/s and allow judgement of the efficiency of interventions and therefore their prioritisation (184). The public health management of measles, rubella and hepatitis A, including post-exposure prophylaxis for contacts of these conditions, is already prioritised as noted in national guidelines, and the recommendations of Chapter 5 continue to implement post-exposure prophylaxis for contacts. The recommendations have taken the existing evidence of effectiveness into account and propose to maintain or improve disease control compared to current guidelines, so it is the cost of implementation that remains the pertinent question.

A cost analysis may be used to compare the cost of current passive immunisation practice to practice under the recommendations of Chapter 5 for a typical case (184). However, this comparison does not take into account disease incidence and therefore the overall budgetary impact of implementing the recommendations.

Budget impact analysis forecasts the short and medium-term effects on expenditure resulting from an alteration to the mix of health services used in a region (185). A change to the mix of services used may occur because a new service or intervention is introduced, because an existing service or intervention is no longer available, or
because of a change to the recommendations or regulations around an existing service or intervention. The latter is particularly applicable in the case of implementation of the recommendations of Chapter 5, and as budget impact analysis compares the current mix of services (the base case) to the proposed mix of services (the comparison case) for a given region and thus takes into account the volume of the service/s required, it is a suitable methodology to complete thesis objective 5: to identify the cost implications of any changes to practice recommended in light of fulfilment of objectives 1-4.

The budget impact analysis of the recommendations made in Chapter 5 are presented here. The study is presented in the format of an unpublished paper.

7.1 Introduction of budget impact analysis

Normal human immunoglobulin, injected intramuscularly (NHIG), for non-immune contacts post-exposure is recommended in Australian national guidelines as part of the public health disease control strategies for measles, rubella and hepatitis A (10, 11, 34). Systematic review evidence supports the efficacy of passive immunisation used in this way and suggests a dose response relationship but does not indicate the minimum doses of disease-specific antibodies required (147, 164, 186).

More recently, pharmacokinetic modelling studies have proposed minimum effective doses of disease-specific antibodies and Australian NHIG for the post-exposure prevention of these diseases (one study unpublished at this time) (173). The model predictions were supported by the interim results of a clinical pharmacokinetic trial (unpublished at this time).

The proposed minimum effective doses of NHIG, if adopted, would require some changes to public health passive immunisation practice. For measles and rubella control, recommended changes are as per Young et al (173). Briefly, it is recommended that passive immunisation as post-exposure prophylaxis for measles be offered only to infants, immunosuppressed individuals and pregnant women, with remaining non-immune close contacts being offered vaccination irrespective of the time since exposure; that IVIG replace NHIG as the product of choice for passive immunisation for measles where calculated doses of NHIG are large; and that where NHIG is used for measles prophylaxis, it be administered at a volume of 0.5 mL/kg. For rubella, it is recommended that a dose of 0.5 mL NHIG be offered to non-immune pregnant women weighing <161 kg within five days of exposure and that for women weighing 161 kg or more, a dose of 1 mL be administered. For adults who weigh more
than 50 kg and require post-exposure passive immunisation against hepatitis A, it is recommended to continue providing 2 mL NHIG in most instances. However, for contacts requiring NHIG who weigh more than 85 kg, individual clinical assessment may indicate an increased dose is warranted. In this case, the suggested dose is 0.036 mL/kg.

As with all health care system funding decisions, the adoption of these recommendations requires consideration of the opportunity costs. To facilitate such appropriate consideration, costing information is needed. In particular, the results of a budget impact analysis would be valuable in this instance where the interventions are already deemed to be cost-effective, but an alteration to the current service is sought. Budget impact analysis forecasts the short and medium-term effects on expenditure resulting from an alteration to the mix of health services used in a region (185).

This budget impact analysis estimates the costs to government of implementing the above recommendations in Australia over a three-year horizon compared to current practice.

7.2 Methods of budget impact analysis

Budget impact analysis followed the methods recommended in Sullivan et al (187) and Mauskopf et al (185).

The setting for the analysis was Australia, with a government perspective (State and National government) and excluded supplier or other third-party costs. The time horizon was set at three years to reflect typical Australian government election cycles. Future costs were not discounted.

The eligible population considered was contacts of measles, rubella and hepatitis A as per Table 6. Base case utilisation of NHIG was as per national NHIG order data (188) and comparison case commenced with these same historical contact numbers. As the size of the eligible population will fluctuate with the incidence of disease over time, sensitivity analyses included upper and lower estimates of the number of eligible contacts based on the average number of contacts offered NHIG per case (188) multiplied by the total number of cases nationally (as recorded on the National Notifiable Diseases Surveillance System (NNDSS)) in the trough and the peak years since the turn of the century (189). As no rubella contacts were offered NHIG during the time of the study detailed in Young et al (188), the maximum and minimum number
of notifications of congenital rubella syndrome as per NNDSS between 2000 and 2018 were used to estimate passive immunisation utilisation for rubella in the comparison case.

Table 6. Eligible populations for passive immunisation under base case and comparison case budget impact analysis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Contacts eligible for NHIG current guidelines (Base case)</th>
<th>Contacts eligible for NHIG under new recommendations (Comparison case)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>Non-immune pregnant women within 3 days of exposure</td>
<td>Non-immune pregnant women within 5 days of exposure</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>Contact groups:</td>
<td>Contact groups:</td>
</tr>
<tr>
<td></td>
<td>• immediate family, household members and sexual partners, including people who stayed and shared their primary bathroom facilities with the case</td>
<td>• immediate family, household members and sexual partners, including people who stayed and shared their primary bathroom facilities with the case</td>
</tr>
<tr>
<td></td>
<td>• persons who consumed food not subjected to further cooking that was prepared by the case</td>
<td>• persons who consumed food not subjected to further cooking that was prepared by the case</td>
</tr>
<tr>
<td></td>
<td>• If the case is a food handler, other food handlers in the same establishment</td>
<td>• If the case is a food handler, other food handlers in the same establishment</td>
</tr>
<tr>
<td></td>
<td>• if the case is in nappies, persons who provided direct care to the case</td>
<td>• if the case is in nappies, persons who provided direct care to the case</td>
</tr>
<tr>
<td></td>
<td>• If the case attends child care or preschool, other children and adults in the same classroom or care group.</td>
<td>• If the case attends child care or preschool, other children and adults in the same classroom or care group.</td>
</tr>
<tr>
<td></td>
<td>Recommended NHIG if within 2 weeks of last exposure to an infectious case and:</td>
<td>Recommended NHIG if within 2 weeks of last exposure to an infectious case and:</td>
</tr>
<tr>
<td></td>
<td>Infants aged &lt;12 months; immunosuppressed; chronic liver</td>
<td>Infants aged &lt;12 months; immunosuppressed; chronic liver</td>
</tr>
</tbody>
</table>
disease; those for whom vaccine is contraindicated

<table>
<thead>
<tr>
<th>Measles</th>
<th>NHIG should usually be reserved for contacts at higher risk of disease or severity of disease such as:</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>• Susceptible household contacts (between 3 and 6 days of first exposure to the case)</td>
</tr>
<tr>
<td></td>
<td>• Immunocompromised individuals (within 6 days of first exposure to the case)</td>
</tr>
<tr>
<td></td>
<td>• Pregnant women who cannot provide evidence of either immunisation or immunity (within 6 days of first exposure to the case)</td>
</tr>
<tr>
<td></td>
<td>• Infants too young to be vaccinated and who are not likely to be protected by maternal antibodies (i.e. infants born to susceptible mothers; those aged 6–8 months; and those aged 9–11 months if not timely for MMR). (within 6 days of first exposure to the case)</td>
</tr>
</tbody>
</table>

NHIG may also be considered for use in school children exposed to a confirmed case, and may be used sparingly in exposed susceptible healthcare workers in situations where their exclusion from the workplace would affect service delivery significantly. (between 3 and 6 days of first exposure to the case)

NHIG should usually be reserved for contacts at higher risk of disease or severity of disease such as:

- Immunocompromised individuals (within 7 days of first exposure to the case)
- Pregnant women who cannot provide evidence of either immunisation or immunity (within 7 days of first exposure to the case)
- Infants too young to be vaccinated and who are not likely to be protected by maternal antibodies (i.e. infants born to susceptible mothers; those aged 6–8 months; and those aged 9–11 months if not timely for MMR). (within 7 days of first exposure to the case)

However, where volumes of NHIG exceed 15 mL (patients above 30 kg in weight) or are deemed 'large', IVIG should be used instead.

Unit costs were obtained from published information and are detailed in Table 7. The base case treatment mix was as per published Australian national public health guidelines (10, 11, 34). The comparison treatment mix was as per the recommendations of Young et al (173) and summarised in the introduction here. Base case and comparison treatment mixes are detailed in Table 8.
Table 7. Unit costs related to utilising passive immunisation for the control of measles, rubella and hepatitis A in Australia

<table>
<thead>
<tr>
<th>Item</th>
<th>Cost (AU$)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td>Plasma to CSL</td>
<td>394.45 per kg</td>
<td>National Blood Authority Product List (190)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Fresh product prices at 1 July 2018</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Australian Red Cross Blood Service Fact Sheet (191)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Plasma donation is maximum 800mL</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Australian Red Cross Blood Service Fact Sheet (192)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Number of plasma donations to make IG products</td>
</tr>
<tr>
<td>NHIG 2 mL</td>
<td>31.65</td>
<td>National Blood Authority Product List (190)</td>
</tr>
<tr>
<td>NHIG 5 mL</td>
<td>51.89</td>
<td>Plasma and recombinant product prices at 1 Jan 2019</td>
</tr>
<tr>
<td>IVIG</td>
<td>3 g/50 mL 175.48</td>
<td>National Blood Authority Product List (190)</td>
</tr>
<tr>
<td></td>
<td>2.5 g/25 mL 146.23</td>
<td>Queensland Health Wage rates – Nursing Stream (193)</td>
</tr>
<tr>
<td></td>
<td>10 g/100 mL 584.93</td>
<td>Nursing wage rates as at 1 April 2018,</td>
</tr>
<tr>
<td></td>
<td>20 g/200 mL 1169.66</td>
<td>Highest band for grade 6 nurse:</td>
</tr>
<tr>
<td></td>
<td>n/a</td>
<td>CSL is responsible for transport costs (pers comms S. Johnson, Senior Manager Supply Chain and Logistics, CSL Behring Logistics, 4 February 2018)</td>
</tr>
<tr>
<td>Public health unit follow up of contact</td>
<td>NG6 wage/hr 51.01</td>
<td>Flego et al 2013 (194)</td>
</tr>
<tr>
<td></td>
<td>PHU time per contact</td>
<td>Queensland Health Wage rates – Nursing Stream (193)</td>
</tr>
<tr>
<td></td>
<td>38 mts</td>
<td>Nursing wage rates as at 1 April 2018,</td>
</tr>
<tr>
<td></td>
<td>= 32.31</td>
<td>Flego et al 2013 (194)</td>
</tr>
<tr>
<td>Administrative costs for Public health unit per contact</td>
<td>1.11 (2011 AU$)</td>
<td>Flego et al 2013 (194)</td>
</tr>
<tr>
<td></td>
<td>= 1.27 (2018 AU$)</td>
<td>Reserve Bank of Australia inflation calculator (195)</td>
</tr>
<tr>
<td>GP consultation</td>
<td>Item 23 - Level B 37.60</td>
<td>Medicare Benefits Schedule Category 1 (196)</td>
</tr>
<tr>
<td>MBS item for transfusion (13706)</td>
<td>83.35</td>
<td>Medicare Benefits Schedule Category 3 (197)</td>
</tr>
<tr>
<td>*MMR vaccine</td>
<td>25.69</td>
<td>Private vaccine purchase price (198)</td>
</tr>
</tbody>
</table>

*While not passive immunisation, measles-mumps-rubella vaccine (MMR) is included here as a cost relevant to the recommended change in public health passive immunisation practice for the control of measles.
Table 8. Treatment mixes for passive immunisation under base case and comparison case budget impact analysis

<table>
<thead>
<tr>
<th>Disease</th>
<th>Current treatment mix for non-immune contacts (Base case)</th>
<th>Treatment mix under new recommendations (Comparison case)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rubella</td>
<td>NHIG 20 mL</td>
<td>NHIG 0.5 mL up to contact weight of 160 kg</td>
</tr>
<tr>
<td></td>
<td></td>
<td>NHIG 1 mL if contact weight over 160 kg</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>NHIG 0.5 mL if &lt;25 kg</td>
<td>NHIG 0.5 mL if &lt;25 kg</td>
</tr>
<tr>
<td></td>
<td>NHIG 1 mL if 25-50 kg</td>
<td>NHIG 1 mL if 25-50 kg</td>
</tr>
<tr>
<td></td>
<td>NHIG 2 mL if &gt;50 kg</td>
<td>NHIG 2 mL if &gt;50 kg</td>
</tr>
<tr>
<td></td>
<td>For - Infants aged &lt;12 months; immunosuppressed; chronic</td>
<td>NHIG 0.036 mL/kg if &gt;85 kg</td>
</tr>
<tr>
<td></td>
<td>liver disease; those for whom vaccine is contraindicated.</td>
<td>For - Infants aged &lt;12 months; immunosuppressed; chronic</td>
</tr>
<tr>
<td></td>
<td>All others in contact groups recommended vaccine.</td>
<td>liver disease; those for whom vaccine is contraindicated.</td>
</tr>
<tr>
<td></td>
<td></td>
<td>All others in contact groups recommended vaccine.</td>
</tr>
<tr>
<td>Measles</td>
<td>NHIG 0.2 mL/kg to max 15 mL for</td>
<td>NHIG 0.5 mL/kg for</td>
</tr>
<tr>
<td></td>
<td>• Susceptible household contacts (between 3 and 6 days of</td>
<td>• Immunocompromised individuals (within 7 days of first</td>
</tr>
<tr>
<td></td>
<td>first exposure to the case)</td>
<td>exposure to the case)</td>
</tr>
<tr>
<td></td>
<td>• Pregnant women who cannot provide evidence of either</td>
<td>• Pregnant women who cannot provide evidence of either</td>
</tr>
<tr>
<td></td>
<td>immunity or immunity (within 6 days of first exposure to</td>
<td>immunisation or immunity (within 7 days of first exposure</td>
</tr>
<tr>
<td></td>
<td>the case)</td>
<td>to the case)</td>
</tr>
<tr>
<td></td>
<td>• Infants too young to be vaccinated and who are not likely</td>
<td>• Infants too young to be vaccinated and who are not likely</td>
</tr>
<tr>
<td></td>
<td>to be protected by maternal antibodies (i.e. infants</td>
<td>to be protected by maternal antibodies (i.e. infants</td>
</tr>
<tr>
<td></td>
<td></td>
<td>born to susceptible mothers; those aged 6-8 months;</td>
</tr>
<tr>
<td></td>
<td></td>
<td>and those aged 9–11</td>
</tr>
</tbody>
</table>
born to susceptible mothers; those aged 6-8 months; and those aged 9–11 months if not timely for MMR). (within 6 days of first exposure to the case)

NHIG may also be considered for use in school children exposed to a confirmed case, and may be used sparingly in exposed susceptible healthcare workers in situations where their exclusion from the workplace would affect service delivery significantly. (between 3 and 6 days of first exposure to the case)

NHIG 0.5 mL / kg for

• Immunocompromised individuals (within 6 days of first exposure to the case)

Vaccine for other non-immune contacts unless contraindicated.

However, where volumes of NHIG exceed 15 mL (patients above 30 kg in weight) or volume deemed ‘large’, IVIG should be used instead.

Vaccine for all other non-immune contacts unless contraindicated.

A cost calculator approach was applied using Microsoft Excel to develop a static model with results presented annually for each year of the time horizon. Specifically, the following steps were followed:

a. The size of the population receiving treatment in each scenario annually was calculated

b. The costs associated with NHIG use (and IVIG use and MMR use for measles) in each scenario on a per person basis was calculated
c. a was multiplied by b (and adjusted for the proportion receiving NHIG vs IVIG vs MMR for the measles comparison case)

d. Comparison case dollar value was subtracted from the base case dollar value for the budget impact per year

e. Budget impact per year was multiplied by three to give total predicted budget impact over the time horizon considered.

The following assumptions were made when calculating costs:

- 1 mL of plasma weighs 1 g.
- Three 5 mL vials of NHIG are required per measles contact under the base case. This is based on the average NHIG order for measles as per Young et al (188) of 11.6 mL per contact, but is also consistent with the maximum volume required per contact under the base case.
- Twenty-five percent of hepatitis A contacts will require a 5 mL vial of NHIG to allow administration of 0.036 mL/kg for those weighing more than 85 kg and 75% of contacts will require a 2 mL vial of NHIG under the comparison case. This is based on the ‘worst-case scenario’ considering that between 2011 and 2014, 3-4 contacts were recommended NHIG for post-exposure prophylaxis for hepatitis A in Queensland, and typically only one of these was an adult.
- In the comparison case, measles contacts no longer recommended passive immunisation are recommended MMR vaccination and the proportions of contacts recommended NHIG, IVIG and MMR are equivalent to the proportions of those Queensland contacts offered NHIG between 2004 and 2014 (188) in the following categories respectively: infants; the combination of pregnant women and immunocompromised contacts; and the remainder of contacts.
- The amount of IVIG required by pregnant women and immunocompromised contacts in the measles comparison case is one 200 mL vial (with a sensitivity analysis of two 200 mL vials). This is based on preliminary pharmacokinetic modelling data that suggest an optimal dose of 13 IU/kg, the measured minimum dose of measles-specific antibodies in IVIG in Australia of 6 IU/mL (199), and the average weight of Queensland measles contacts (2004-2014) where this was recorded, which equated to 75.6 kg ((188) data not shown in the publication). The sensitivity analysis uses the maximum recorded contact weight of 160 kg.
• For infants who require NHIG in the measles comparison case, the amount of NHIG required is a 5 mL vial. This is based on Australian growth charts (200) that indicate the average infant aged 1 – 11 months weighs greater than 4 kg and less than 10 kg.

• For measles contacts under the comparison case who require MMR, their usual vaccine service provider has sufficient stock on hand and is able to replace this in their usual monthly order, so no extra transportation costs will be incurred.

7.3 Results of budget impact analysis

Compared to base case and with the same eligible population, the comparison case was cost saving for measles in the order of AU$120 000 over three years (Table 9). When the IVIG volume required per measles contact was doubled, the comparison case cost around AU$22 000 over three years with the same eligible population as the base case. Suggested changes in practice for hepatitis A contacts requiring passive immunisation was predicted to cost AU$1 500 over three years, while no cost would continue to be incurred in the absence of an eligible population for rubella post-exposure passive immunisation.

Under trough year estimates, savings would be realised for both measles (irrespective of the IVIG volume required per contact) and hepatitis A (Table 9). Under peak year estimates, recommended changes in passive immunisation practice for measles would be the most expensive at approximately AU$500 000 over three years (or AU$1.038 million if 400 mL IVIG is required per immunocompromised or pregnant contact). The cost of alterations to passive immunisation practice for hepatitis A and rubella would be modest at approximately AU$22 000 and AU$1 300 respectively over three years.
Table 9. Annual cost estimates (2018 AU$) for comparison case compared to base case for historical, trough and peak year numbers of contacts

<table>
<thead>
<tr>
<th></th>
<th>Historical eligible population</th>
<th>Trough year estimate</th>
<th>Peak year estimate</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>AU$</td>
<td>Number of contacts</td>
<td>AU$</td>
</tr>
<tr>
<td>Hepatitis A</td>
<td>500.76</td>
<td>26</td>
<td>-1738.68</td>
</tr>
<tr>
<td>Measles (200mL IVIG required)</td>
<td>-40 563.44</td>
<td>222</td>
<td>-105 205.41</td>
</tr>
<tr>
<td>Measles (400mL IVIG required)</td>
<td>7 401.97</td>
<td>222</td>
<td>-99 803.90</td>
</tr>
<tr>
<td>Rubella</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

7.4 Discussion of budget impact analysis

The recommendations for changes to Australian passive immunisation practice for the control of measles, hepatitis A and rubella would result in minimal budgetary impact even if notified cases of these diseases were at their highest rate since the turn of the century. Under these conditions, the most extreme comparison case for measles was estimated to cost less than AU$350 000 per year. When notified case numbers are the same or fewer than historical estimates, the recommendations were either approximately equal in cost to the base case, or cost saving.

Currently, no head to head evidence of the effectiveness of the new recommendations compared to the current guidelines exists. Mauskopf et al (185: p92) suggest disease-related costs should only be included in a budget impact analysis if supporting evidence of the effect of the change to the treatment mix is robust, hence disease-related costs have not been included in this study. Acknowledging this limitation, it is notable that the comparison case treatment mixes for each condition are expected to be either equi-effective or more effective than the base case. Under this assumption, the results would represent the ‘worst-case’ costing scenario.

Other assumptions were also made when calculating base case and comparison case costs. These are detailed in the methods. With the exception of omitting MMR
transportation costs, these other assumptions were also likely to over-estimate the budgetary impact. Practical experience supports MMR availability at general practice surgeries, so the odd instance where extra transport costs may be incurred is unlikely to add significantly to the estimated budgetary impact.

A detailed search of the literature did not reveal any published budget impact analyses of proposed changes to post-exposure prophylaxis for the control of communicable diseases. As the first such study in this field, the results presented here offer important information for decision-makers when considering whether or not to implement the proposed changes to public health passive immunisation practice in Australia.
8.1 Summary

A detailed examination of the effectiveness and efficiency of passive immunisation for the public health management of measles, rubella and hepatitis A was prompted by discrepancies between Australian state and national guidelines and those of other high-income countries. Several evidence gaps were noted as possible contributors to the discrepancies. The studies presented in the Chapters of this thesis aimed to fill these identified gaps and provide evidence-based recommendations for changes, where required, to Australian passive immunisation post-exposure practices.

Systematic reviews (Chapters 2 and 3) provided a critical discourse of the existing evidence of effectiveness for the prevention of measles and rubella and congenital rubella syndrome with post-exposure passive immunisation, finding moderate quality evidence of the effectiveness of the intervention for preventing measles, moderate quality evidence of the efficacy of the intervention for preventing rubella and insufficient evidence of effectiveness for preventing congenital rubella syndrome. These reviews were published in the Cochrane Database of Systematic Reviews as the first reviews of these topics.

These reviews, and an existing Cochrane review on the effectiveness of passive immunisation for preventing hepatitis A, were not able to ascertain the minimum effective doses of disease-specific antibodies required for post-exposure prophylaxis, and so a number of collaborative studies strove towards this goal. Collaborations with CSL Behring Australia Pty Ltd resulted in the first published concentrations of measles and rubella antibodies in Australian blood products that may be used for post-exposure prophylaxis (Chapter 4). These results, as well as the understanding of immunoglobulin manufacturing processes that was gained via the collaboration, were invaluable in the pharmacokinetic modelling studies that ultimately proposed minimum effective doses of normal human immunoglobulin (NHIG) for preventing measles, rubella and hepatitis A post-exposure (Chapter 5). These are 0.5 ml/kg for measles prevention, 0.5-1 mL for rubella prevention and 0.036 ml/kg for hepatitis A prevention.

An ongoing pharmacokinetic clinical trial took the first steps towards validating and/or optimising the model predictions. The completed trial will be one of only two studies that report on serum concentrations of quantitative hepatitis A antibodies out to an incubation period after injection of NHIG. Interim trial results supported the proposed
minimum effective doses of NHIG for preventing these diseases post-exposure (Chapter 5).

Having established the minimum effective doses of Australian NHIG required for post-exposure prophylaxis, and finding existing clinical trial data consistent with these model predictions, recommendations for changes to Australian passive immunisation post-exposure prophylaxis practice were made. These considered the structure and functions of the Australian health system as well as the new information gained from the aforementioned studies. The recommendations included changes to:

- The subpopulations offered NHIG for preventing measles post-exposure
- The timeframe for offering NHIG for preventing congenital rubella syndrome post-exposure, and
- The dosages of NHIG used for preventing measles, rubella and hepatitis A post-exposure.

The final studies of this thesis worked to understand the cost implications of the changes recommended, as every change comes at an opportunity cost in a resource scarce system. Data on the use of passive immunisation for post-exposure prophylaxis for these diseases existed only in individual public health unit databases prior to 2014, so data collection at each public health unit around Queensland gave the first and most comprehensive understanding of how often this intervention is used for each disease. Comparing this with data retrieved from the newly implemented national NHIG ordering system in 2014 and finding approximation of results meant the study is able to serve as a valid historical record for future analyses of NHIG usage (Chapter 6).

This record of NHIG usage was also invaluable in estimating the budget impact of the recommendations for public health practice change. Budget impact analysis (Chapter 7) demonstrated that the recommended changes to passive immunisation post-exposure practice in Australia are likely to have minimal budgetary impact and may in fact be cost saving. In a ‘worst-case’ scenario, with peak numbers of cases of each of rubella, hepatitis A and measles in the same year, the budgetary impact of all the recommended changes was estimated at just under AU$354 000 as an annual expense.

While each study in the preceding Chapters has its own limitations, and these are detailed in the discussion on each, the thesis as a whole is geared towards a conservative approach to passive immunisation post-exposure prophylaxis, choosing to err on the side of caution regarding the proposed minimum effective doses of NHIG.
and therefore the recommendations for practice change, and the resulting budgetary impact. In effect, this may mean that the true minimum effective doses and the budget impact are somewhat less than is proposed. However, given the serious complications of the diseases on point, and that passive immunisation (particularly in the given recommendations) is directed at those most vulnerable to these complications, over-estimating the required doses of NHIG seems preferable to under-estimation.

8.2 Conclusion

This comprehensive program of research on the effectiveness and efficiency of passive immunisation for the public health management of measles, rubella and hepatitis A has the potential to change public health practice in Australia. Recommended changes to the doses of NHIG administered to contacts of each disease, the duration since exposure when a non-immune pregnant woman should be offered NHIG, and the subpopulations of contacts of measles offered passive immunisation may improve the effectiveness of this intervention and either minimally impact on government health spending or be cost saving.

Going forward, a number of the studies contained herein provide valid benchmarks for future research or quality audits, including the first published concentrations of measles and rubella antibodies in Australian NHIG and IVIG, and the first published Australian usage of NHIG for post-exposure prophylaxis.

At a global level, the systematic reviews of effectiveness of passive immunisation for preventing measles and rubella and congenital rubella syndrome post-exposure, and also the published pharmacokinetic model, have application for countries revising their own public health guidelines.
References


96. World Health Organization Department of Measurement and Health Information. Mortality and Burden of Disease Estimates for WHO Member States in 2004 [Excel file]. WHO;


159. European Pharmacopoeia. 7th ed. Strasbourg, France: European Department for the Quality of Medicines, Council of Europe; 2008.
172. European Pharmacopoeia. 8th ed. Strasbourg, France: European Department for the Quality of Medicines, Council of Europe; 2014.


Appendix 1 Statements of Ethical Clearance

Human research ethics committee approval letters for randomised controlled trial (Chapter 5)

9/8/2017

Griffith University - Staff Mail - Full Research Ethics Clearance 2017/645 (provisional to full approval)

Megan Young <megan.young@griffith.edu.au>

Full Research Ethics Clearance 2017/645 (provisional to full approval)

1 message

rims@griffith.edu.au <rims@griffith.edu.au> 8 September 2017 at 08:08
To: g.nimmo@griffith.edu.au, megan.young@griffith.edu.au, Allan.Cripps@griffith.edu.au
Cc: research-ethics@griffith.edu.au, rick.williams@griffith.edu.au

GRiffTH UNIVERsITy HUMAN RESEARCH ETHICS REVIEW

Dear Prof Allan Cripps

I write further to the additional information provided in relation to the provisional approval granted to your application for ethical clearance for your project "Validating the optimal dose of normal immunoglobulin for protection against hepatitis A" (GU Ref No: 2017/645).

This is to confirm that this response has addressed the comments and concerns of the HREC.

The ethics reviewers resolved to grant your application a clearance status of "Fully Approved".

Consequently, you are authorised to immediately commence this research on this basis.

Regards

Mr Rick Williams
Manager Research Ethics and Integrity
Office for Research Ethics
Bray Centre, Nathan Campus
Griffith University
Tel: +61 (0)7 373 54375
Email: Rick.Williams@Griffith.edu.au
30 October 2017

Dr Megan Young
Lecturer, Population Health
School of Medicine
Griffith University

Dear Dr Young,

Reference number: 2017#29
Project title: Validating the optimal dose of normal immunoglobulin for protection against hepatitis A

Thank you for submitting the above research project to the Australian Red Cross Blood Service Human Research Ethics Committee for ethical review. The submission was received on 13 October 2017. Your project has been assigned the reference: 2017#29. This number must be quoted in all correspondence to this HREC.

Your project was considered by the Chair on behalf of the Blood Service Human Research Ethics Committee. I am pleased to advise that the Blood Service HREC has granted ethical approval of this submission, for an initial period of three years, from 30 October 2017 to 30 October 2020 subject to the following conditions being met:

- The Principal Investigator will immediately report anything that might warrant review of ethical approval of the project.
- The Principal Investigator will notify the Blood Service HREC of any event that requires a modification to the protocol or other project documents and submit any required amendments in accordance with the instructions provided by the HREC.
- The Principal Investigator will report to the Blood Service HREC annually and notify the HREC when the project is completed.
- The Principal Investigator will notify the Blood Service HREC of any plan to extend the duration of the project past the approval period listed above and will submit any associated required documentation.

Should you require any further information, please contact the Secretary, Human Research Ethics Committee on 02 9234 2368 or at ethics@redcrossblood.org.au.

Yours faithfully,

Larissa Aldridge
Human Research Ethics Committee Secretary,
Research and Development
Australian Red Cross Blood Service
Human research ethics committee approval letters for usage of NHIG study (Chapter 6)

3 March 2016

Dr Megan Young
School of Medicine
Griffith University
Meadowbrook Qld 4131

Dear Dr Young


I am pleased to advise that The Prince Charles Hospital Human Research Ethics Committee reviewed the amendments submitted and upon recommendation, the Chair has granted approval for the following:


This information will be tabled at the HREC meeting on 24 March 2016 for noting.

A copy of this approval must be submitted to the relevant Hospital & Health Service Research Governance Officers or Delegated Personnel, along with Site Specific documentation, for CEO or Delegate authorisation for each site.

List of approved Sites:

<table>
<thead>
<tr>
<th>No.</th>
<th>Site</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Cairns and Hinterland Public Health Unit</td>
</tr>
<tr>
<td>2.</td>
<td>Townsville Public Health Unit</td>
</tr>
<tr>
<td>3.</td>
<td>Mackay Public Health Unit</td>
</tr>
<tr>
<td>4.</td>
<td>Central Queensland Public Health Unit</td>
</tr>
<tr>
<td>5.</td>
<td>Wide Bay Public Health Unit</td>
</tr>
<tr>
<td>6.</td>
<td>Sunshine Coast Public Health Unit</td>
</tr>
<tr>
<td>7.</td>
<td>Metro North Public Health Unit</td>
</tr>
<tr>
<td>8.</td>
<td>Metro South Public Health Unit</td>
</tr>
<tr>
<td>9.</td>
<td>Darling Downs Public Health Unit</td>
</tr>
<tr>
<td>10.</td>
<td>West Moreton Public Health Unit</td>
</tr>
<tr>
<td>12.</td>
<td>Gold Coast Public Health Unit</td>
</tr>
</tbody>
</table>

Office
Research, Ethics & Governance Office
The Prince Charles Hospital
Building 14
Rode Road, Chermside Q 4032
(07) 3139 4198

Postal
Building 14
Rode Road, Chermside Q 4032
(07) 3139 4198
This HREC is constituted and operates in accordance with the National Health and Medical Research Council’s (NHMRC) National Statement on Ethical Conduct in Human Research (2007), NHMRC and Universities Australia Australian Code for the Responsible Conduct of Research (2007) and the CPMP/ICH Note for Guidance on Good Clinical Practice.

Please be advised that in the instance of an investigator being a member of the HREC, they are absented from the decision making process relating to that study.

On behalf of the Human Research Ethics Committee, I would like to wish you every success with your research endeavour.

Yours truly,

Anne Carle  
Executive Officer  
Research, Ethics and Governance Unit  
The Prince Charles Hospital
Dear Doctor Young

I write further to the additional information provided in relation to the conditional approval granted to your application for ethical clearance for your project "NR: The use of normal human immunoglobulin for public health purposes in Queensland 2004-2014" (GU Ref No: MED/64/14/HREC).

This is to confirm receipt of the remaining required information, assurances or amendments to this protocol.

Consequently, I reconfirm my earlier advice that you are authorised to immediately commence this research on this basis.

The standard conditions of approval attached to our previous correspondence about this protocol continue to apply.

Regards

Ms Kim Madison
Policy Officer
Office for Research
Bray Centre, Nathan Campus
Griffith University
ph: +61 (0)7 373 58043
fax: +61 (07) 373 57994
email: k.madison@griffith.edu.au
web:

Cc:

Researchers are reminded that the Griffith University Code for the Responsible Conduct of Research provides guidance to researchers in areas such as conflict of interest, authorship, storage of data, & the training of research students.

You can find further information, resources and a link to the University’s Code by visiting http://policies.griffith.edu.au/pdf/Code%20for%20the%20Responsible%20Conduct%20of%20Research.pdf

PRIVILEGED, PRIVATE AND CONFIDENTIAL

This email and any files transmitted with it are intended solely for the use of the addressee(s) and may contain information which is confidential or privileged. If you receive this email and you are not the addressee(s) [or responsible for delivery of the email to the addressee(s)], please disregard the contents of the email,
Appendix 2 Conference presentations of thesis work


Young MK, Cripps AW, Nimmo GR, van Driel ML. *Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome.* Communicable Disease Control Conference 2015, 1-2 June 2015, Brisbane, Australia.

Young MK, Nimmo GR, Cripps AW, Jones MA. *Post-exposure passive immunisation for preventing measles: a systematic review.* International Student Research Forum, 2-4 June 2014, Odense, Denmark.


Appendix 3 Publications and conference presentations related to thesis work

Young MK. The indications and safety of polyvalent immunoglobulin for post-exposure prophylaxis of hepatitis A, rubella and measles. Human Vaccines & Immunotherapeutics, 2019, online 22 May, https://doi.org/10.1080/21645515.2019.1621148 [invited manuscript]


Young MK, Cripps AW. Passive immunisation for the public health control of communicable diseases: Current status in four high-income countries and where to next? Human Vaccines & Immunotherapeutics 2013; 9(9): 1885-1893

Young MK, Cripps AW, Nimmo GR, van Driel ML. Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome [Protocol]. Cochrane Database of Systematic Reviews, 2013, Issue 6; DOI: 10.1002/14651858.CD010586

Appendix 4 Publisher Permissions

This Agreement between Dr. Megan Young ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number 4515631504395
License date Jan 24, 2019
Licensed Content Publisher John Wiley and Sons
Licensed Content Publication Cochrane Database of Systematic Reviews
Licensed Content Title Post-exposure passive immunisation for preventing measles
Licensed Content Author Megan K Young, Graeme R Nimmo, Allan W Cripps, et al
Licensed Content Date Apr 1, 2014
Licensed Content Pages 1
Type of use Dissertation/Thesis
Requestor type Author of this Wiley article
Format Print and electronic
Portion Full article
Will you be translating? No
Title of your thesis / dissertation The use of Normal Human Immunoglobulin (NHIG) in the public health management of communicable diseases: effectiveness and efficiency
Expected completion date Sep 2019
Expected size (number of pages) 200
Requestor Location Dr. Megan Young
Griffith University, Parklands Drive
Southport, Qld 4215
Australia
Attn: Dr. Megan Young
Publisher Tax ID EU826007151
Total 0.00 AUD
Terms and Conditions

TERMS AND CONDITIONS
This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions
The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, and any CONTENT (PDF or image file) purchased as part of your order, is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner. For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.
You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY’s prior written consent.

Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.
• This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

• This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS

Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC-BY) License only; the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License

The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-

Creative Commons Attribution Non-Commercial License

The Creative Commons Attribution Non-Commercial (CC-BY-NC) License permits use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. (see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License

The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations

Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Further details can be found on Wiley Online Library http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015
Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
This Agreement between Dr. Megan Young ("You") and John Wiley and Sons ("John Wiley and Sons") consists of your license details and the terms and conditions provided by John Wiley and Sons and Copyright Clearance Center.

License Number: 4515691238250
License date: Jan 24, 2019
Licensed Content Publisher: John Wiley and Sons
Licensed Content Publication: Cochrane Database of Systematic Reviews
Licensed Content Title: Post-exposure passive immunisation for preventing rubella and congenital rubella syndrome
Licensed Content Author: Megan K Young, Allan W Cripps, Graeme R Nimmo, et al
Licensed Content Date: Sep 9, 2015
Licensed Content Pages: 1
Type of use: Dissertation/Thesis
Requestor type: Author of this Wiley article
Format: Print and electronic
Portion: Full article
Will you be translating?: No
Title of your thesis / dissertation: The use of Normal Human Immunoglobulin (NHIG) in the public health management of communicable diseases: effectiveness and efficiency
Expected completion date: Sep 2019
Expected size (number of pages): 200
Requestor Location: Dr. Megan Young
Griffith University, Parklands Drive
Southport, Qld 4215
Australia
Attn: Dr. Megan Young
Publisher Tax ID: EU826007151
Total: 0.00 AUD

TERMS AND CONDITIONS
This copyrighted material is owned by or exclusively licensed to John Wiley & Sons, Inc. or one of its group companies (each a "Wiley Company") or handled on behalf of a society with which a Wiley Company has exclusive publishing rights in relation to a particular work (collectively "WILEY"). By clicking "accept" in connection with completing this licensing transaction, you agree that the following terms and conditions apply to this transaction (along with the billing and payment terms and conditions established by the Copyright Clearance Center Inc., ("CCC's Billing and Payment terms and conditions"), at the time that you opened your RightsLink account (these are available at any time at http://myaccount.copyright.com).

Terms and Conditions

https://s100.copyright.com/AppDispatchServlet
The materials you have requested permission to reproduce or reuse (the "Wiley Materials") are protected by copyright.

You are hereby granted a personal, non-exclusive, non-sub licensable (on a stand-alone basis), non-transferable, worldwide, limited license to reproduce the Wiley Materials for the purpose specified in the licensing process. This license, and any CONTENT (PDF or image file) purchased as part of your order, is for a one-time use only and limited to any maximum distribution number specified in the license. The first instance of republication or reuse granted by this license must be completed within two years of the date of the grant of this license (although copies prepared before the end date may be distributed thereafter). The Wiley Materials shall not be used in any other manner or for any other purpose, beyond what is granted in the license. Permission is granted subject to an appropriate acknowledgement given to the author, title of the material/book/journal and the publisher. You shall also duplicate the copyright notice that appears in the Wiley publication in your use of the Wiley Material. Permission is also granted on the understanding that nowhere in the text is a previously published source acknowledged for all or part of this Wiley Material. Any third party content is expressly excluded from this permission.

With respect to the Wiley Materials, all rights are reserved. Except as expressly granted by the terms of the license, no part of the Wiley Materials may be copied, modified, adapted (except for minor reformatting required by the new Publication), translated, reproduced, transferred or distributed, in any form or by any means, and no derivative works may be made based on the Wiley Materials without the prior permission of the respective copyright owner. For STM Signatory Publishers clearing permission under the terms of the STM Permissions Guidelines only, the terms of the license are extended to include subsequent editions and for editions in other languages, provided such editions are for the work as a whole in situ and does not involve the separate exploitation of the permitted figures or extracts. You may not alter, remove or suppress in any manner any copyright, trademark or other notices displayed by the Wiley Materials. You may not license, rent, sell, loan, lease, pledge, offer as security, transfer or assign the Wiley Materials on a stand-alone basis, or any of the rights granted to you hereunder to any other person.

The Wiley Materials and all of the intellectual property rights therein shall at all times remain the exclusive property of John Wiley & Sons Inc, the Wiley Companies, or their respective licensors, and your interest therein is only that of having possession of and the right to reproduce the Wiley Materials pursuant to Section 2 herein during the continuance of this Agreement. You agree that you own no right, title or interest in or to the Wiley Materials or any of the intellectual property rights therein. You shall have no rights hereunder other than the license as provided for above in Section 2. No right, license or interest to any trademark, trade name, service mark or other branding ("Marks") of WILEY or its licensors is granted hereunder, and you agree that you shall not assert any such right, license or interest with respect thereto.

NEITHER WILEY NOR ITS LICENSORS MAKES ANY WARRANTY OR REPRESENTATION OF ANY KIND TO YOU OR ANY THIRD PARTY, EXPRESS, IMPLIED OR STATUTORY, WITH RESPECT TO THE MATERIALS OR THE ACCURACY OF ANY INFORMATION CONTAINED IN THE MATERIALS, INCLUDING, WITHOUT LIMITATION, ANY IMPLIED WARRANTY OF MERCHANTABILITY, ACCURACY, SATISFACTORY QUALITY, FITNESS FOR A PARTICULAR PURPOSE, USABILITY INTEGRATION OR NON-INFRINGEMENT AND ALL SUCH WARRANTIES ARE HEREBY EXCLUDED BY WILEY AND ITS LICENSORS AND WAIVED BY YOU.

WILEY shall have the right to terminate this Agreement immediately upon breach of this Agreement by you.
You shall indemnify, defend and hold harmless WILEY, its Licensors and their respective directors, officers, agents and employees, from and against any actual or threatened claims, demands, causes of action or proceedings arising from any breach of this Agreement by you.

IN NO EVENT SHALL WILEY OR ITS LICENSORS BE LIABLE TO YOU OR ANY OTHER PARTY OR ANY OTHER PERSON OR ENTITY FOR ANY SPECIAL, CONSEQUENTIAL, INCIDENTAL, INDIRECT, EXEMPLARY OR PUNITIVE DAMAGES, HOWEVER CAUSED, ARISING OUT OF OR IN CONNECTION WITH THE DOWNLOADING, PROVISIONING, VIEWING OR USE OF THE MATERIALS REGARDLESS OF THE FORM OF ACTION, WHETHER FOR BREACH OF CONTRACT, BREACH OF WARRANTY, TORT, NEGLIGENCE, INFRINGEMENT OR OTHERWISE (INCLUDING, WITHOUT LIMITATION, DAMAGES BASED ON LOSS OF PROFITS, DATA, FILES, USE, BUSINESS OPPORTUNITY OR CLAIMS OF THIRD PARTIES), AND WHETHER OR NOT THE PARTY HAS BEEN ADVISED OF THE POSSIBILITY OF SUCH DAMAGES. THIS LIMITATION SHALL APPLY NOTWITHSTANDING ANY FAILURE OF ESSENTIAL PURPOSE OF ANY LIMITED REMEDY PROVIDED HEREIN.

Should any provision of this Agreement be held by a court of competent jurisdiction to be illegal, invalid, or unenforceable, that provision shall be deemed amended to achieve as nearly as possible the same economic effect as the original provision, and the legality, validity and enforceability of the remaining provisions of this Agreement shall not be affected or impaired thereby.

The failure of either party to enforce any term or condition of this Agreement shall not constitute a waiver of either party's right to enforce each and every term and condition of this Agreement. No breach under this agreement shall be deemed waived or excused by either party unless such waiver or consent is in writing signed by the party granting such waiver or consent. The waiver by or consent of a party to a breach of any provision of this Agreement shall not operate or be construed as a waiver of or consent to any other or subsequent breach by such other party.

This Agreement may not be assigned (including by operation of law or otherwise) by you without WILEY's prior written consent.

Any fee required for this permission shall be non-refundable after thirty (30) days from receipt by the CCC.

These terms and conditions together with CCC's Billing and Payment terms and conditions (which are incorporated herein) form the entire agreement between you and WILEY concerning this licensing transaction and (in the absence of fraud) supersedes all prior agreements and representations of the parties, oral or written. This Agreement may not be amended except in writing signed by both parties. This Agreement shall be binding upon and inure to the benefit of the parties' successors, legal representatives, and authorized assigns.

In the event of any conflict between your obligations established by these terms and conditions and those established by CCC's Billing and Payment terms and conditions, these terms and conditions shall prevail.

WILEY expressly reserves all rights not specifically granted in the combination of (i) the license details provided by you and accepted in the course of this licensing transaction, (ii) these terms and conditions and (iii) CCC's Billing and Payment terms and conditions.
This Agreement will be void if the Type of Use, Format, Circulation, or Requestor Type was misrepresented during the licensing process.

This Agreement shall be governed by and construed in accordance with the laws of the State of New York, USA, without regards to such state's conflict of law rules. Any legal action, suit or proceeding arising out of or relating to these Terms and Conditions or the breach thereof shall be instituted in a court of competent jurisdiction in New York County in the State of New York in the United States of America and each party hereby consents and submits to the personal jurisdiction of such court, waives any objection to venue in such court and consents to service of process by registered or certified mail, return receipt requested, at the last known address of such party.

WILEY OPEN ACCESS TERMS AND CONDITIONS
Wiley Publishes Open Access Articles in fully Open Access Journals and in Subscription journals offering Online Open. Although most of the fully Open Access journals publish open access articles under the terms of the Creative Commons Attribution (CC BY) License only; the subscription journals and a few of the Open Access Journals offer a choice of Creative Commons Licenses. The license type is clearly identified on the article.

The Creative Commons Attribution License
The Creative Commons Attribution License (CC-BY) allows users to copy, distribute and transmit an article, adapt the article and make commercial use of the article. The CC-BY license permits commercial and non-commercial use, distribution and reproduction in any medium, provided the original work is properly cited and is not used for commercial purposes. (see below)

Creative Commons Attribution Non-Commercial License
The Creative Commons Attribution Non-Commercial (CC-BY-NC) License permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Creative Commons Attribution-Non-Commercial-NoDerivs License
The Creative Commons Attribution Non-Commercial-NoDerivs License (CC-BY-NC-ND) permits use, distribution and reproduction in any medium, provided the original work is properly cited, is not used for commercial purposes and no modifications or adaptations are made. (see below)

Use by commercial "for-profit" organizations
Use of Wiley Open Access articles for commercial, promotional, or marketing purposes requires further explicit permission from Wiley and will be subject to a fee. Further details can be found on Wiley Online Library http://olabout.wiley.com/WileyCDA/Section/id-410895.html

Other Terms and Conditions:

v1.10 Last updated September 2015
Questions? customercare@copyright.com or +1-855-239-3415 (toll free in the US) or +1-978-646-2777.
FW: Permissions to include articles in a PhD thesis that has now been examined

Academic UK Non Rightslink <permissionrequest@tandf.co.uk>
Fri 30/12/2019 7:18 PM
To: Megan Young <megan.young@griffith.edu.au>

2 attachments (206 KB)
measles abs in rhig Rightslink® by Copyright Clearance Center.pdf; rubella antibodies in rhig Rightslink® by Copyright Clearance Center.pdf; measles rubella modelling Rightslink® by Copyright Clearance Center.pdf;

20 December 2019

Dear Megan K. Young,


Megan K Young, Shu-Kay Ng, Graeme R Nimmo & Allan W Cripps (2018) The optimal dose of disease-specific antibodies for post-exposure prophylaxis of measles and rubella in Australia: new guidelines recommended, Expert Opinions on Drug Metabolism & Toxicology, 14:7, 663-669, DOI: 10.1080/17425255.2018.1484449

Thank you for your correspondence requesting permission to reproduce your authors accepted manuscript from our Journal in your printed thesis and to be posted in the university's repository – Griffith University.

We will be pleased to grant permission on the sole condition that you acknowledge the original source of publication and insert a reference to the article on the Journals website:  http://www.tandfonline.com

This is the authors accepted manuscript of an article published as the version of record in [JOURNAL TITLE] © [YEAR], republished by permission of Informa UK Limited, trading as Taylor & Francis Group, available online [INCLUDE A LINK TO THE ARTICLE]

This permission does not cover any third party copyrighted work which may appear in the material requested.

Please note that this license does not allow you to post our content on any third party websites or repositories.

This license does not allow the use of the Publishers version/PDF (this is the version of record that is published on the publisher's website) to be posted online.

With best wishes,

Lee-Ann

Lee-Ann Anderson - Senior Permissions & Licensing Executive, Journals
Routledge, Taylor & Francis Group
3 Park Square, Milton Park, Abingdon, Oxon, OX14 4RN, UK.
Permissions Tel: (0)20 7017 7617
Permissions e-mail: permissionsrequest@tandf.co.uk
Direct Tel: +44 (0)20 7017 7932

https://outlook.office.com/mail/doeshtml?version=20141203.02&gposteid=1/5

305
As a valued author do you need any assistance or guidance? Please see our helpful links below

Author’s guide to reusing your own content / Accessing my authored Works

Information Classification: General

From: Megan Young <megan.young@griffith.edu.au>
Sent: 20 December 2019 01:29
To: Academic UK Non Rightslink <permissionrequest@tandf.co.uk>; Academic VIP Requests <AcademicVIPRequests@tandf.co.uk>; US Journal Permissions <USJournalPermissions@taylorandfrancis.com>
Cc: Allan Cripps <Allan.Cripps@griffith.edu.au>
Subject: Fw: Permissions to include articles in a PhD thesis that has now been examined

Hello

I sent the below email to the customer care email address for the Copyright Clearance Center last week, but still have not received a reply. I was wondering if the enquiry needed to go directly to Taylor and Francis instead, so am forwarding here in hopes that you may be able to help please? I am in Australia and so the time difference makes it difficult to phone the Clearance Centre.

I am trying to seek permission to retain the copies of published articles within my completed PhD thesis now that it has been examined. As I understand, The University typically makes the thesis available via the library in electronic form once the degree has been conferred and so it is to be 'published' in this manner.

Thanks for any help you can provide regarding the appropriate process to seek permissions. I have been back to the Clearance Centre website, but there doesn’t seem to be a category of request appropriate to this circumstance other than the "Thesis / dissertation reuse" category that generated the attached interim permissions.

kind regards
Megan

Dr Megan Young
Senior Lecturer, Population Health
School of Medicine
Gold Coast Campus
Griffith University
(Thursdays and Fridays)

megan.young@griffith.edu.au

From: Megan Young <megan.young@griffith.edu.au>
Sent: Thursday, 12 December 2019 4:59 PM
To: customercare@copyright.com <customercare@copyright.com>
Subject: Permissions to include articles in a PhD thesis that has now been examined

Hello

When preparing my PhD thesis for examination, I went onto the website and applied for permission to include some articles published by Taylor and Francis in the thesis. The permissions for these articles are attached.

My thesis has now been examined and is nearly ready for publication with the University Library. I have been back to the website but cannot see how to reapply for permissions to include these articles in the final thesis as is indicated is a requirement on the permissions. Are you able to assist please?

with kind regards
Megan

Dr Megan Young
Senior Lecturer, Population Health
School of Medicine
Gold Coast Campus
Griffith University
(Thursdays and Fridays)
megan.young@griffith.edu.au
Hi Megan,

Re. including a copy of the published article within your PhD thesis document. Since the article is published under Creative Commons licence CC BY-NC-ND, there’s no need for permission from CDI. For more information, please check CC BY-NC-ND licence: https://creativecommons.org/licenses/by-nc-nd/3.0/au/

Kind regards,
Kasra

---

From: Megan Young <megan.young@griffith.edu.au>
Sent: Friday, 22 March 2019 12:48 PM
To: CDI EDITOR <CDI.EDITOR@health.gov.au>
Subject: Re: Publication Notice: Communicable Diseases Intelligence – Vol. 43 – 15/03/2019 [SEC=OFFICIAL]

Thanks Kasra!

Dr Megan Young
Senior Lecturer, Population Health
School of Medicine
Gold Coast Campus
Griffith University
(Thursdays and Fridays)
megan.young@griffith.edu.au

---

From: CDI EDITOR <CDI.EDITOR@health.gov.au>
Sent: Friday, 22 March 2019 10:16 AM
To: Megan Young; CDI EDITOR
Subject: RE: Publication Notice: Communicable Diseases Intelligence – Vol. 43 – 15/03/2019 [SEC=OFFICIAL]

Hi Megan,

Thanks for the email. About the permission you mentioned, I’ll check with my editor today and get back to you asap.
By the way, I’ve created your article’s entry in PubMed:


Please note your article has the following DOI that is recommended to use where referencing:

https://doi.org/10.33321/cdi.2019.43.9

Kind regards,
Kasra

---

From: Megan Young <megan.young@griffith.edu.au>
Sent: Friday, 22 March 2019 11:01 AM
To: CDI EDITOR <CDI.EDITOR@health.gov.au>
Subject: Re: Publication Notice: Communicable Diseases Intelligence – Vol. 43 – 15/03/2019 [SEC=OFFICIAL]

Hi Kasra
Thanks very much!
I have had a look and the Word version looks to have retained the style as per the pdf.

May I ask please for permission to include a copy of the published article within my PhD thesis document?
Please let me know if you need any further information to facilitate this.
with kind regards
Megan

Dr Megan Young
Senior Lecturer, Population Health
School of Medicine
Gold Coast Campus
Griffith University
(Thursdays and Fridays)
megan.young@griffith.edu.au

---

From: CDI EDITOR <CDI.EDITOR@health.gov.au>
Sent: Friday, 15 March 2019 1:11 PM
To: CDI EDITOR
Cc: TOMS, Cindy; Wright, Phil; TRAPANI, Leroy
Subject: Publication Notice: Communicable Diseases Intelligence – Vol. 43 – 15/03/2019 [SEC=OFFICIAL]

Dear valued CDI contributor,

Your article is published on CDI website in the following location:

Australian Government agencies are required to make information and services are provided in a non-discriminatory accessible manner. To ensure this, the CDI team recreates a verbatim copy of any article they publish into accessible Microsoft Word format.

I would appreciate it if you could check your article’s Word copy for possible style errors that might have occurred during the conversion process.