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Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients (Review)

Hodson EM, Jones CA, Strippoli GFM, Webster AC, Craig JC

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[Intervention Review]

Immunoglobulins, vaccines or interferon for preventing cytomegalovirus disease in solid organ transplant recipients

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ABSTRACT

Background

Cytomegalovirus (CMV) is the most common virus causing disease and death in solid organ transplant recipients during the first six months post-transplant. Previous systematic reviews have demonstrated the efficacy of antiviral medications used prophylactically or pre-emptively in preventing CMV disease. In this review the efficacy of older agents (immunoglobulins (IgG), anti CMV vaccines and interferon) are examined.

Objectives

To assess the benefits and harms of IgG, anti CMV vaccines or interferon for preventing symptomatic CMV disease in solid organ transplant recipients.

Search methods

We searched the Cochrane Renal Group's Specialised Register, Cochrane Central Register of Controlled Trials (CENTRAL, in *The Cochrane Library*), MEDLINE, EMBASE, reference lists and abstracts from conference proceedings without language restriction.
Date of last search: December 2005

Selection criteria

Randomised and quasi-randomised controlled trials comparing IgG, anti CMV vaccine or interferon with placebo or no treatment, IgG alone or combined with antiviral medications with antiviral medications or IgG alone in recipients of any solid organ transplant.

Data collection and analysis

Two of four authors independently assessed study quality and extracted data from each study. Statistical analyses were performed using the random effects model and results expressed as relative risk (RR) for dichotomous outcomes with 95% confidence intervals (CI).

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Main results

Thirty seven studies (2185 participants) were included in this review. There was no significant difference in the risk for CMV disease (16 studies, 770 patients: RR 0.80, 95% CI 0.61 to 1.05), CMV infection (14 studies, 775 patients: RR 0.94, 95% CI 0.80 to 1.10) or all-cause mortality (8 studies, 502 patients: RR 0.57, 95% CI 0.32 to 1.03) with IgG compared with placebo/no treatment. However IgG significantly reduced the risk of death from CMV disease (6 studies, 346 patients: RR 0.33, 95% CI 0.14 to 0.80). There was no difference in the risk for CMV disease (4 studies, 298 patients: RR 1.17, 95% CI 0.74 to 1.86), CMV infection (4 studies, 298 patients: RR 1.16, 95% CI 0.89 to 1.52) or all-cause mortality (2 studies, 217 patients: RR 0.92, 95% CI 0.37 to 2.29) between antiviral medication combined with IgG and antiviral medication alone. There was no significant difference in the risk of CMV disease with anti CMV vaccine or interferon compared with placebo or no treatment.

Authors' conclusions

Currently there are no indications for IgG in the prophylaxis of CMV disease in recipients of solid organ transplants.

PLAIN LANGUAGE SUMMARY

Prophylaxis with Immunoglobulin G (IgG), anti CMV vaccine or interferon do not significantly reduce CMV disease and CMV-associated mortality in solid organ transplant recipients

Cytomegalovirus (CMV) is the most common virus causing disease and death in solid organ transplant recipients (kidney, heart, liver, lung and pancreas) during the first six months after transplantation. This review looked at the benefits and harms of IgG, anti CMV vaccines and interferon to prevent CMV disease in solid organ transplant recipients. Thirty seven studies (2185 participants) were identified. This review shows that IgG did not reduce the risk of CMV disease or all-cause mortality compared with placebo or no treatment. The combination of IgG with antiviral medications (aciclovir or ganciclovir) were not more effective than antiviral medications alone in reducing the risk of CMV disease or all-cause mortality. Anti CMV vaccines and interferon did not reduce the risk of CMV disease compared with placebo or no treatment. Currently there are no indications for IgG in the prevention of CMV disease in recipients of solid organ transplants.

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BACKGROUND

Cytomegalovirus (CMV) is the most common virus causing disease and death in solid organ transplant recipients during the first six months post-transplant with an overall incidence of 30% to 50% (Fishman 1998; Rubin 2000). Like all herpes viruses, CMV has the propensity to establish lifelong 'latency' infection in the host after the initial infection has resolved. Therefore, solid organ transplant recipients may be infected either by exogenous virus or by reactivation of latent virus if they were CMV positive pre-transplant. Those at highest risk of symptomatic CMV disease are CMV sero-negative patients who receive organs from CMV sero-positive donors, and CMV sero-positive patients on heavily immunosuppressive regimens (Fishman 1998; Rubin 2000).

CMV may manifest as a non-specific illness characterised by fever, mononucleosis, leucopenia and thrombocytopenia, or as a variety of clinical syndromes including pneumonitis, hepatitis, encephalitis and focal gastrointestinal disease. In addition, CMV causes morbidity in organ recipients through indirect effects on their immune response (Rubin 1989), and is associated with increased risk of allograft injury and rejection (Grattan 1989; Keenan 1991), opportunistic infections (Fishman 1995; Hadley 1995; Van den Berg 1996) and late onset malignancies such as EBV-lymphoproliferative disease (Basgoz 1995). For these reasons, many strategies have been proposed to prevent CMV infection and/or prevent systematic CMV disease. Two main strategies to prevent CMV disease have been adopted; prophylaxis of all organ recipients with antiviral medications and/or immunoglobulins (IgG), or 'pre-emptive therapy' or 'targeted therapy' for high-risk groups such as patients receiving antilymphocyte antibody preparations (Rubin 1989). Pre-emptive therapy relies upon monitoring for CMV infection by newly available sensitive techniques such as antigenaemia or polymerase chain reaction (PCR) that allow the diagnosis of CMV infection to be made much earlier than traditional culture methods (Emery 2000).

A systematic review of prophylactic treatment using antiviral medications (aciclovir, ganciclovir, valaciclovir, valganciclovir) versus placebo/no treatment has demonstrated the efficacy of prophylactic therapy to prevent CMV disease (Hodson 2005a; Hodson 2005b). In addition, a second review evaluating pre-emptive therapy at detection of CMV viraemia has demonstrated its efficacy compared with placebo/no treatment on the prevention of CMV disease (Strippoli 2006a; Strippoli 2006b). In this review we examined the benefits and harms of prophylaxis using IgG including hyperimmune CMV IgG, vaccines, interferon compared with placebo/ no specific therapy or other agents in recipients of solid organ transplant on CMV disease, all CMV infection, the incidence of acute rejection, graft loss, opportunistic infections and death. Data on the use of vaccines and interferon in prophylaxis is included in this review for historical interest. However although valganciclovir has largely replaced other therapies for prevention or pre-emptive therapy of CMV disease, some transplant centres continue to use hyperimmune CMV IgG in combination with antiviral medications in solid organ transplant recipients. Previous reviews of IgG therapy, published in 1994 (Glowacki 1994) and 1996 (Wittes 1996), included 12 randomised controlled trials (RCT) using IgG or CMV IgG and of four RCTs using CMV IgG respectively. Both concluded that IgG prophylaxis was more effective than placebo or no specific treatment in preventing CMV disease. In addition we needed to determine whether the addition of CMV IgG to antiviral therapy was more effective than antiviral therapy alone. A previous review published in 1999 included four RCTs and concluded that there was no convincing evidence for an additional benefit of CMV IgG (King 1999). Additional RCTs have now been published necessitating an update of these reviews.

OBJECTIVES

The aim of this review was to assess the benefits and harms of IgG, anti-CMV vaccines or interferon for preventing symptomatic CMV disease in solid organ transplant recipients of all ages, irrespective of CMV sero-status prior to transplantation. The secondary aims were to evaluate the efficacy of these agents in preventing all CMV infection (symptomatic and asymptomatic where CMV is detected only by laboratory investigation) and in decreasing the incidence of acute rejection, graft loss, death (all-cause mortality and mortality due to CMV disease), opportunistic infections and to evaluate the harms of each antiviral medication.

Firstly, the review examined studies of IgG alone with placebo/no treatment. Secondly, it explored comparisons between IgG and other antiviral medications including aciclovir and ganciclovir, IgG and antiviral medications with IgG alone and IgG and antiviral medications with antiviral medications alone. Thirdly, it compared the treatment effect of each regimen between different solid organs and between the different risk groups (i.e. pre-existent CMV sero-status and/or level of immunosuppression). Finally it examined the benefits and harms of anti-CMV vaccine or interferon in comparison with placebo.

METHODS

Criteria for considering studies for this review

Types of studies

All RCTs and quasi-RCTS (RCTs in which allocation to treatment was obtained by alternation, use of alternate medical records, date of birth or other predictable methods) were included.

Types of participants

Participants of all ages, irrespective of CMV sero-status prior to transplantation, who had undergone at least one solid organ transplant (kidney, liver, lung, heart, pancreas) or combined solid organ transplant (heart/lung, kidney/pancreas). Bone marrow and other cellular transplants were excluded.

Types of interventions

Prophylactic interventions included hyperimmune CMV IgG, other IgG, anti-CMV vaccines or interferon. Comparisons were made between:-

1. IgG and placebo/no treatment
2. IgG and antiviral medications
3. IgG combined with antiviral medications and IgG alone
4. IgG combined with antiviral medications and antiviral medications alone
5. Different types of IgG
6. Anti-CMV vaccine and placebo/no treatment
7. Interferon and placebo/no treatment

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Studies of prophylaxis with antiviral medications or of pre-emptive treatment on detection of CMV viraemia were excluded as these are subjects of separate reviews (Hodson 2005b; Strippoli 2006a). Treatment regimens for symptomatic CMV disease were excluded.

Types of outcome measures

The primary outcome measures were the incidence of symptomatic CMV disease and all-cause mortality. Secondary outcomes included the incidence of all CMV infection (symptomatic and asymptomatic), acute rejection, graft loss, death, opportunistic infections, harms (including nephrotoxicity, bone marrow suppression). No data could be obtained on time to CMV disease or emergence of resistant CMV strains. All outcomes were recorded as present/absent.

CMV infection was defined as reported by the investigators of included studies. This was usually the isolation of CMV from a cultured specimen from any site, or positive histopathology or CMV antigen detection in a tissue specimen, or the presence of CMV pp65 antigenaemia, or an elevation in CMV viral load as detected by quantitative PCR (as defined by the investigator). 'Symptomatic CMV disease' was defined by the investigator. This was usually the diagnosis of CMV infection in association with one or more of the following: CMV syndrome (temperature of 38ºC or more with no other documented source in association with one or more of atypical lymphocytosis, leukopenia or thrombocytopenia), pneumonitis, focal gastrointestinal disease, liver function abnormality, or encephalitis. Graft loss was defined as the need for dialysis or further kidney transplantation or re-transplantation for other organs during the follow-up period of the study. Acute rejection was defined as used by the individual authors. This was either biopsy proven or clinical, defined by rise in creatinine levels with respect to kidney transplants or response to rejection treatment.

Search methods for identification of studies

A systematic and comprehensive literature search was carried out to identify eligible RCTs for three systematic reviews of strategies to prevent CMV disease in solid organ transplants. The reviews of "Antiviral medications to prevent cytomegalovirus disease in solid organ transplant recipients" and "Pre-emptive therapy for cytomegalovirus viraemia to prevent cytomegalovirus disease in solid organ transplant recipients" have already been published in *The Cochrane Library* (Hodson 2005b; Strippoli 2006a). Three authors independently searched the following resources without language restriction (see Appendix 1 - *Electronic search strategies* for search terms used).

1. The Cochrane Central Register of Controlled Trials (CENTRAL in *The Cochrane Library* - Issue 1 2004).
2. The Cochrane Renal Group's Specialised Register (December 2005).
3. MEDLINE (1966 to February 2004) using search strategy optimally sensitive search strategies developed for identification of RCTs (Dickersin 1994) combined with MeSH and text words.
4. EMBASE (1980 to February 2004) using search strategy optimally sensitive search strategies developed for identification of RCTs (Lefebvre 1996) combined with MeSH and text words.

The Trials Search Coordinator of the Cochrane Renal Group was contacted to ensure all relevant studies had been identified. Additional studies were also located through article reference lists and proceedings of some scientific meetings, which are routinely searched by the Cochrane Renal Group. These are principally the American Transplant Congresses, the American Society of Nephrology meetings, International Society of Nephrology meetings and European Dialysis and Transplant meetings.

Data collection and analysis

Included and excluded studies

Two authors (EH, CJ) independently screened titles and abstracts retrieved from the searches to identify those studies that meet the inclusion criteria. This process favoured over-selection in order to include all relevant studies. The full article was retrieved if uncertainty existed about eligibility or when the abstract was not available. Any disagreement with article selection was resolved through discussion.

Two of four authors (EH, CJ, GS, AW) independently extracted data from eligible studies. Participant characteristics (number, age, sex, comorbidities), intervention (type of treatment, dose, duration, co-interventions) and primary and secondary outcome measures were recorded. Any discrepancies in data extraction were also be discussed with a third author (JC) and resolved by consensus. In the instances where results of a study were published more than once, the most complete data were extracted from all sources and used in the analysis only once.

Study quality

The quality of studies to be included was assessed independently by 2/4 authors (EH, CJ, GS, AW) without blinding to authorship or journal of publication using the checklist developed for the Cochrane Renal Group (see Quality checklist). Discrepancies were resolved by consensus. The quality items assessed were allocation concealment, blinding of investigators, participants and outcome assessors, intention-to-treat analysis and completeness of follow-up (Hollis 1999; Moher 1998; Schultz 1995).

Quality checklist

Allocation concealment

- Adequate (A): Randomisation method described that would not allow investigator/participant to know or influence intervention group before eligible participant entered in the study
- Unclear (B): Randomisation stated but no information on method used is available
- Inadequate (C): Method of randomisation used (i.e. alternate medical record numbers or unsealed envelopes) or any information in the study that indicated that investigators or participants could influence intervention group

Blinding

- Blinding of investigators: Yes/No/not stated
- Blinding of participants: Yes/No/not stated
- Blinding of outcome assessor: Yes/No/not stated
- Blinding of data analysis: Yes/No/not stated

The above were considered not blinded if the treatment group could be identified in greater than 20% of participants due to side

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effects of treatment or the treatment groups could be identified through different routes or frequency of administration of study medications.

Intention-to-treat analysis

- Yes: Specifically reported by authors that intention-to-treat analysis was undertaken and this was confirmed on study assessment.
- No: Not reported and lack of intention-to-treat analysis confirmed on study assessment. (Patients who were randomised but were not included in the analysis because they did not receive the study intervention, they withdrew from the study or were not included because of protocol violation).
- Not stated: Not reported and could be determined (Studies with 100% follow-up of patients included so that patient exclusion after randomisation cannot be excluded).

Completeness of follow-up

Per cent of participants lost to follow-up or with no data for the primary outcome of effectiveness.

Statistical assessment

Risk ratios (RR) with 95% confidence intervals (CI) for each outcome with the experimental compared to the control intervention were computed. Data were pooled using a random effects model to calculate a summary estimate of effect. Heterogeneity was formally tested using Cochran's Q and I^2 statistics (Higgins 2003). To determine whether there were any differences between study results due to plausible effect modifiers, subgroup analysis were performed, whenever sufficient number of studies were available for analysis. The analysis explored the type of solid organ transplanted, type of intervention and the level of pre-existent risk (CMV positive recipients or CMV negative recipients of CMV positive donors).

RESULTS

Description of studies

From 1167 articles, 203 underwent full text review and 37 studies (50 reports, 2185 participants) were included in this review. The remaining studies were excluded as they were not randomised or included randomised and non randomised patients (75), were review articles (23), were studies of pre-emptive therapy (10), were studies of antiviral medications alone (32) or involved another ineligible intervention (14).

Twenty one studies examined IgG preparations. Most studies were small with only seven studies enrolling more than 50 patients. Twelve studies (704 enrolled patients) compared hyperimmune CMV IgG with placebo (Metselaar 89-Kidney; Snydman 93-Liver) or no treatment (Boland 93-Heart/kid; Greger 85a-Kidney; Greger 85b-Kidney; Grundmann 87-Kidney; Kruger 03-Lung; Mitsioni 87-Kidney; Saliba 89-Liver; Snydman 87-Kidney; Stippel 91-Kidney; Wirnsberger 99-Kid; Yamani 05-Heart). One of these studies included two groups with significantly different immunosuppressive regimens so it has been treated as two studies (Greger 85a-Kidney; Greger 85b-Kidney). One study (Stippel 91-Kidney) had three treatment groups, CMV IgG, IgG and no treatment. Only the data comparing the CMV IgG and no treatment groups were included. The participants of these studies were kidney transplant recipients (8 studies), kidney and heart transplant recipients (1), lung transplant recipients (1), heart transplant recipients (1) and liver transplant recipients (2). Six studies (189 enrolled patients) compared IgG with placebo (Cofer 91-Liver) or no treatment (Kasiske 89-Kidney; McCune 92-Kid/KP; Preiksaitis 82-Heart; Schechner 93-Kidney; Steinmuller 90-Kid). Of these Preiksaitis 82-Heart did not report any outcome data relevant to this review. The participants of these studies were kidney transplant recipients (4 studies), liver transplant recipients (1), heart transplant recipients (1) and kidney and kidney-pancreas transplant recipients (1). Four studies (204 enrolled patients) compared different IgG preparations; three compared CMV IgG with IgG (Fassbinder 86-Kidney; Stippel 91-Kidney; Stratta 94-K/P) and one compared two CMV IgG preparations (Pakkala 92-Kidney).

Nine studies examined regimens of IgG and antiviral medications. Only four studies enrolled more than 50 patients. Four studies (441 enrolled patients) compared ganciclovir (Aguado 95-Heart/GCV; Conti 94-Kidney/GCV; Morales 02-Kid/GCV) or acyclovir (Dunn 94-all/ACV) with IgG. Of these, two studies included kidney transplant recipients, one kidney and heart transplant recipients and one kidney, liver, kidney-pancreas and pancreas transplant recipients. Four studies (294 enrolled patients) compared ganciclovir (Huang 05-Liver/GCV; Johnson 04-L/K/GCV; Rostaing 97-Kid/GCV) or acyclovir (Bailey 93-All/ACV) and IgG with antiviral medication alone. One study had three arms and only the arms receiving oral ganciclovir and CMV IgG plus oral ganciclovir are included in the analysis. One study included kidney transplant recipients, one liver and kidney transplant recipients, one kidney, heart and lung transplant recipients and one liver transplant recipients. One study (56 enrolled children) of liver transplant recipients compared ganciclovir and IgG with IgG alone (King 97-Liver/GCV).

Three studies (400 enrolled patients) compared an anti-CMV vaccine with placebo in kidney transplant recipients (Balfour 84-Kid/vacc; Plotkin 84-Kid/vacc; Plotkin 94-Kid/vacc). All studies enrolled more than 50 patients.

Four studies (207 enrolled patients) compared interferon with placebo in kidney transplant recipients (Cheeseman 79-Kid/IFN; Hirsch 83-Kid/IFN; Kovarik 88-Kid/IFN; Lui 92-Kid/IFN). Only Lui 92-Kid/IFN enrolled more than 50 patients.

Risk of bias in included studies

See Table 1 - *Methodological quality of included studies.*

Allocation concealment

Allocation concealment was adequately reported in six studies (Hirsch 83-Kid/IFN; King 97-Liver/GCV; Plotkin 84-Kid/vacc; Plotkin 94-Kid/vacc; Snydman 87-Kidney; Snydman 93-Liver), inadequate in two (Greger 85a-Kidney; Greger 85b-Kidney; Lui 92-Kid/IFN) and unclear in the remaining studies.

Blinding

In 10 studies there was blinding of participants and investigators (Balfour 84-Kid/vacc; Cofer 91-Liver; Hirsch 83-Kid/IFN; King 97-Liver/GCV; Kovarik 88-Kid/IFN; Lui 92-Kid/IFN; Metselaar 89-Kidney; Plotkin 84-Kid/vacc; Plotkin 94-Kid/vacc; Snydman 93-Liver). Nine studies reported blinding of outcome assessors (Hirsch 83-Kid/IFN; Huang 05-Liver/GCV; King 97-Liver/GCV; Kruger 03-Lung; Plotkin 84-

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Kid/vacc; Plotkin 94-Kid/vacc; Snydman 87-Kidney; Snydman 93-Liver; Steinmuller 90-Kid).

Intention-to-treat

Six studies were considered to have analysed their results on an intention-to-treat basis (Cofer 91-Liver; Conti 94-Kidney/GCV; Kasiske 89-Kidney; Kruger 03-Lung; Morales 02-Kid/GCV; Saliba 89-Liver).

Completeness of follow-up

No study reported that any patient was lost to follow-up but in four studies it was unclear whether all patients completed follow-up (Preiksaitis 82-Heart; Schechner 93-Kidney; Stippel 91-Kidney; Yamani 05-Heart).

Effects of interventions

CMV IgG or IgG with placebo/no treatment (17 studies, 793 analysed patients)

CMV disease and CMV infection in all patients

The results for CMV disease and CMV infection did not differ between studies comparing CMV IgG and placebo/no treatment and IgG and placebo/no treatment so studies have been combined. Overall there was no significant difference in the risk for CMV disease (Analysis 1.1 (16 studies, 770 patients): RR 0.80, 95% CI 0.61 to 1.05) or in the risk for CMV infection (Analysis 1.2 (14 studies, 775 patients): RR 0.94, 95% CI 0.80 to 1.10). For the outcome of CMV disease, the point estimate favoured the use of IgG in nine studies (CMV IgG (6), IgG(3)) while the point estimate favoured the use of placebo/no treatment in seven studies (CMV IgG (5), IgG(2)). There was some heterogeneity among results of this analysis for CMV disease (I^2 = 23.6%) and CMV infection (I^2 = 24.2%). For CMV disease, the heterogeneity of 34.4% among studies comparing CMV IgG with placebo/no treatment could be eliminated by excluding studies which reported larger numbers of patients with CMV disease in the CMV IgG group compared with placebo/no treatment (Greger 85b-Kidney; Kruger 03-Lung). It is not clear why these studies contributed to the heterogeneity. One study involved lung transplant recipients (immunosuppressed with antilymphocyte preparations and cyclosporin), who are known to be at a high risk of CMV pneumonitis (Kruger 03-Lung) while in the other study all patients were receiving antilymphocyte globulin, which increases the risk for CMV disease (Greger 85b-Kidney). However other studies (Grundmann 87-Kidney; Kasiske 89-Kidney; Snydman 93-Liver), in which immunosuppression included antilymphocyte preparations and cyclosporin, found a reduced number of patients with CMV disease during IgG treatment.

Overall study quality was poor with only 2/17 studies reporting adequate allocation, 4/17 reporting blinding of participants and investigators, 5/17 reporting blinding of outcome assessors and 4/17 undertaking an intention-to-treat analysis. Greger 85a-Kidney reported inadequate allocation concealment and Preiksaitis 82-Heart did not include any data on the outcomes of interest.

CMV disease and CMV infection in CMV positive recipients

There was no significant difference in the risk for CMV disease (Analysis 2.1: RR 0.84, 95% CI 0.54 to 1.33; I^2 = 17.5%) or CMV infection (Analysis 2.2: RR 0.94, 95% CI 0.76 to 1.16; I^2 = 30.4%) in CMV positive recipients. For CMV disease in the eight studies with data for this outcome, point estimates favoured the use of IgG in four studies (Grundmann 87-Kidney; McCune 92-Kid/KP; Snydman 93-Liver; Steinmuller 90-Kid) and the use of placebo/no treatment in three studies (Kruger 03-Lung; Schechner 93-Kidney; Wirnsberger 99-Kid) with the final study having an RR of 1.00 (Metselaar 89-Kidney).

CMV negative recipients of CMV positive organs

The risk for CMV disease (Analysis 3.1.1: RR 0.63, 95% CI 0.36 to 1.12; I^2 = 54.2%) and CMV infection (Analysis 3.2.1: RR 0.92, 95% CI 0.63 to 1.34; I^2 = 32.2%) did not differ in CMV negative recipients of CMV positive organs. For CMV disease of six included studies, point estimates favoured the use of IgG in three studies (Saliba 89-Liver; Snydman 87-Kidney; Wirnsberger 99-Kid) and the use of placebo/no treatment in one study (Boland 93-Heart/kid).

Mortality

Only 8/16 studies reported all-cause mortality (Fassbinder 86-Kidney; Greger 85a-Kidney;Greger 85b-Kidney;Grundmann 87-Kidney;Kruger 03-Lung; Schechner 93-Kidney; Snydman 87-Kidney; Snydman 93-Liver) though only four studies contributed to the analysis by reporting any events. There was no significant difference in all-cause mortality between IgG and placebo/no treatment (Analysis 1.3.1: RR 0.58, 95% CI 0.32 to 1.05) although all point estimates favoured the use of IgG.

The outcome of death due to CMV disease was addressed in six studies though only four contributed events to the analysis (Kruger 03-Lung; Metselaar 89-Kidney; Snydman 87-Kidney; Snydman 93-Liver). Two of the four studies had also reported a reduction in CMV disease in patients treated with CMV IgG (Snydman 87-Kidney; Snydman 93-Liver). There was a significant reduction in the risk of death from CMV disease (Analysis 1.4: RR 0.33, 95% CI 0.14 to 0.80).

When mortality due to CMV disease and non-CMV causes was examined in three studies (Kruger 03-Lung; Snydman 87-Kidney; Snydman 93-Liver). IgG therapy resulted in a significant reduction in the risk of death from CMV disease (Analysis 1.5.1: RR 0.37, 95% CI 0.15 to 0.93) but no effect on death from non-CMV causes (Analysis 1.5.2: RR 0.79, 95% CI 0.30 to 2.08).

Other outcomes

There was no significant difference in the risk of acute rejection (Analysis 1.6 (7 studies): RR 0.88, 95% CI 0.66 to 1.16), graft loss (Analysis 1.7 (7 studies): RR 0.73, 95% CI 0.35 to 1.53) or opportunistic infections (Analysis 1.8 (6 studies): RR 0.61, 95% CI 0.28 to 1.32) overall. There was heterogeneity in the risk of acute rejection with one study showing a significant reduction in acute rejection (Snydman 87-Kidney) and the other six studies demonstrating no significant difference in the risk of acute rejection. There was also heterogeneity in the risk of opportunistic infections with two studies showing more infections in the treatment group, three showing fewer infections in the treatment group and one showing no difference.

Adverse effects

Eight studies did not report adverse effects, five reported that no adverse effects occurred and four reported possible adverse effects. Kruger 03-Lung reported one possible event when a patient showed deterioration in mental state the day after the first infusion; the patient recovered but no further CMV IgG was administered. Preiksaitis 82-Heart reported that 2/7 patients developed fevers

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and chills. Snydman 87-Kidney reported 12 reactions in 7 patients over 205 infusions but none required cessation of CMV IgG. Reactions consisted of flushing, anxiety, nausea, breathlessness, cramps and backache. Snydman 93-Liver reported 29 (6.7%) reactions in 436 CMV IgG infusions and 16 (3.8%) in 419 placebo infusions. The types of reaction were not specified except for one patient, who developed haemolysis with CMV IgG and infusion was ceased.

Comparisons of different IgG preparations (4 studies, 204 analysed patients)

In direct comparison studies of different IgG preparations, there was no significant difference in the risk of CMV disease between CMV IgG and IgG or between different CMV IgG preparations (Analysis 4.1 (2 studies): RR 1.67, 95% CI 0.72 to 3.86) but patient numbers were small (48 patients). There was also no difference in the risk of CMV infection between CMV IgG and IgG (Analysis 4.2 (3 studies): RR 1.07, 95% CI 0.73 to 1.58). No study reported on adverse effects. None of the studies reported adequate allocation concealment, blinding of investigators, participants or outcome assessors or undertook an intention-to-treat analysis.

Comparisons of antiviral medications alone with IgG alone (4 studies, 392 analysed patients)

CMV disease and CMV infection

Four studies (Aguado 95-Heart/GCV; Conti 94-Kidney/GCV; Dunn 94-all/ACV; Morales 02-Kid/GCV) compared antiviral medications (ganciclovir for 14 to 21 days (3 studies), acyclovir for 3 months (1 study)) with IgG alone given for 1 to 12 weeks. There was a significant reduction in the risk of CMV disease in all studies with antiviral medication alone (ganciclovir or acyclovir) compared with IgG alone (Analysis 5.1.1 (4 studies, 392 patients): RR 0.68, 95% CI 0.48 to 0.98). The point estimates for both CMV positive recipients and CMV negative recipients of CMV positive organs were similar to that for all patients and the 95% CIs overlapped indicating no difference in these groups compared with the meta-analysis of all patients. The summary estimate of effect was dominated by the effects of Dunn 94-all/ACV, which compared 12 weeks of aciclovir with three doses of IgG given over one week and removal of this study resulted in a non-significant difference between antiviral medications and IgG. Antiviral medications seemed to benefit liver (Analysis 5.1.5: RR 0.43, 95% CI 0.17 to 1.08) and heart transplant recipients (Analysis 5.1.6: RR 0.16, 95% CI 0.02 to 1.15) rather than kidney transplant recipients (Analysis 5.1.4: RR 1.26, 95% CI 0.75 to 2.12) though patient and event numbers were small, the differences were not significant and the summary estimate for the meta-analysis of kidney transplant recipients was dominated by Dunn 94-all/ACV. There appeared to be no difference in the risk for CMV syndrome (Analysis 5.2.1: RR 0.96, 95% CI 0.38 to 2.47) or CMV invasive disease (Analysis 5.3.1: RR 0.48, 95% CI 0.08 to 3.03) but small numbers of patients and events resulted in considerable imprecision in the summary estimates as shown by wide confidence intervals. CMV infection (Analysis 5.4.1: RR 0.87, 95% CI 0.66 to 1.14) was only examined in Aguado 95-Heart/GCV and no significant difference was detected. Study quality was poor with no study reporting adequate allocation concealment or blinding of participants, investigators or outcome assessors. Conti 94-Kidney/GCV and Morales 02-Kid/GCV undertook an intention-to-treat analysis.

Mortality

All-cause mortality was only estimable in 2/4 studies (Aguado 95-Heart/GCV;Dunn 94-all/ACV). There was no significant difference in all-cause mortality between antiviral medications and IgG (Analysis 5.5.1: RR 0.70, 95% CI 0.37 to 1.33). No deaths due to CMV disease were reported (Analysis 5.6).

Other outcomes

There were no significant difference in the risks of acute rejection (Analysis 5.7.1: RR 0.82, 95% CI 0.66 to 1.03) between antiviral medications and IgG. In CMV positive recipients graft loss (Analysis 5.8.1: RR 0.83, 95% CI 0.16 to 4.26) did not differ between treatments. Opportunistic infections (Analysis 5.9.1: RR 0.94, 95% CI 0.15 to 5.84) were only reported in one study of CMV positive heart transplant recipients (Aguado 95-Heart/GCV) and no difference was detected.

Adverse effects

Two studies did not report on adverse effects. Aguado 95-Heart/GCV reported one patient with leucopenia and two with elevated creatinine among 16 patients treated with ganciclovir and none in IgG treated patients. Conti 94-Kidney/GCV reported one patient each with leucopenia, hepatic dysfunction and neurological dysfunction with ganciclovir and none in IgG treated patients.

Antiviral medication and IgG compared with antiviral medication alone (4 studies, 298 analysed patients)

CMV disease and CMV infection

Four studies (Bailey 93-All/ACV; Huang 05-Liver/GCV; Johnson 04-L/K/GCV; Rostaing 97-Kid/GCV) compared antiviral medications (acyclovir for 3 months (2 studies), ganciclovir for 3 months (2 studies)) and IgG (given for 10 to 12 weeks) with antiviral medication alone. There was no difference in the risk for CMV disease (Analysis 6.1.1 (4 studies, 298 patients): RR 1.17, 95% CI 0.74 to 1.86), CMV syndrome (Analysis 6.2.1 (2 studies, 215 patients): RR 1.17, 95% CI 0.55 to 2.52), CMV invasive disease (Analysis 6.3.1 (2 studies, 215 patients): RR 1.31, 95% CI 0.43 to 3.99) or CMV infection (Analysis 6.4.1 (4 studies, 298 patients): RR 1.16, 95% CI 0.89 to 1.52) between antiviral medication combined with IgG and antiviral medication alone. Study quality was poor with no study reporting adequate allocation concealment, blinding of participants and investigators or an intention to treat analysis. Huang 05-Liver/GCV reported blinding of outcome assessors.

Mortality

Two studies (Johnson 04-L/K/GCV; Rostaing 97-Kid/GCV) reported on all-cause mortality. There was no significant difference in the risk of death (Analysis 6.5.1: RR 0.92, 95% CI 0.37 to 2.29) between antiviral medications with IgG and antiviral medications alone. One study reported no deaths due to CMV disease (Rostaing 97-Kid/GCV).

Other outcomes

There was no significant difference in the risk for acute rejection (Analysis 6.7.1 (2 studies): RR 0.71, 95% CI 0.44 to 1.13), graft loss (Analysis 6.8.1 (2 studies): RR 1.39, 95% CI 0.32 to 6.04) or opportunistic infections (Analysis 6.9.1(1 study): RR 0.94, 95% CI 0.40 to 2.21).

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Adverse effects

Three of the four studies did not report on adverse effects. Rostaing 97-Kid/GCV reported no adverse effects.

Antiviral medication and IgG compared with IgG alone (1 study, 56 analysed patients)

CMV disease and CMV infection

In CMV negative recipients of CMV positive liver transplants (King 97-Liver/GCV) (ganciclovir for 4 weeks with IgG for 16 weeks versus IgG alone) there was no significant difference at six months in the risk for CMV disease (Analysis 7.1.1: RR 0.67, 95% CI 0.24 to 1.85), CMV syndrome (Analysis 7.2.1: RR 0.93, 95% CI 0.06 to 14.16), CMV invasive disease (Analysis 7.3.1: RR 0.62, 95% CI 0.20 to 1.96) or CMV infection (Analysis 7.4.1: RR 1.35, 95% CI 0.77 to 2.37). However all seven patients treated with IgG alone who developed CMV disease, did so within 8 weeks of transplant while only 2/5 treated with ganciclovir and IgG did so within 8 weeks of transplant. This study reported adequate allocation concealment and blinding of outcome assessors.

Mortality

There was no significant difference in the risk of all-cause mortality (Analysis 7.5.1: RR 1.40, 95% CI 0.44 to 4.42) or death due to CMV disease (Analysis 7.6.1: RR 2.80, 95% CI 0.12 to 65.93) but the number of events were small resulting in imprecision of the results.

Other outcomes

There was no significant difference in the risk of acute rejection (Analysis 7.7.1: RR 0.84, 95% CI 0.60 to 1.17).

Adverse effects

Leucopenia was seen in one patient treated with ganciclovir and IgG compared with seven treated with IgG alone (Analysis 7.8.1: RR 0.13, 95% CI 0.02 to 1.01). The risk of thrombocytopenia did not differ between groups (Analysis 7.8.2: RR 1.01, 95% CI 0.87 to 1.16).

Anti-CMV vaccine compared with placebo (3 studies, 472 analysed patients)

CMV disease and CMV infection

There was no significant difference in the risk of CMV disease in all patients (Analysis 8.1.1: RR 0.79, 95% CI 0.56 to 1.10), CMV positive recipients (Analysis 8.1.2: RR 0.61, 95% CI 0.33 to 1.13), CMV negative recipients of CMV positive organs (Analysis 8.1.3: RR 0.77, 95% CI 0.53 to 1.12) and CMV negative recipients of CMV negative organs (Analysis 8.1.4: RR 1.03, 95% CI 0.15 to 6.92) between anti-CMV vaccine and placebo. However serious CMV disease was significantly less common in vaccine treated CMV negative recipients of CMV positive organs (Analysis 8.2.2: RR 0.12, 95% CI 0.04 to 0.39). There was no significant difference in the risk of CMV infection in all patients (Analysis 8.3.1: RR 0.95, 95% CI 0.69 to 1.30), CMV positive recipients (Analysis 8.3.2: RR 0.86, 95% CI 0.71 to 1.05), all CMV negative recipients (Analysis 8.3.3: RR 1.13, 95% CI 0.86 to 1.49), CMV negative recipients of CMV positive organs (Analysis 8.3.4: RR 1.15, 95% CI 0.92 to 1.43) and CMV negative recipients of CMV negative organs (Analysis 8.3.5: RR 1.03, 95% CI 0.32 to 3.26). Two studies (Plotkin 84-Kid/vacc; Plotkin 94-Kid/vacc) reported adequate allocation concealment and blinding and only Balfour 84-Kid/vacc) reported blinding of investigators and participants.

Acute rejection

The risk of acute rejection did not differ significantly between vaccine and placebo (Analysis 8.4.1: RR 0.93, 95% CI 0.71 to 1.23) for the one study reporting this outcome (Plotkin 84-Kid/vacc).

Adverse effects

All adverse effects were more common in vaccine treated patients compared with placebo (Analysis 8.5.1: RR 6.94, 95% CI 3.59 to 13.49). In particular fever (Analysis 8.5.2: RR 6.46, 95% CI 1.95 to 21.43) and local reactions (Analysis 8.5.3: RR 11.20, 95% CI 4.62 to 27.17) were reported more commonly in vaccine treated patients.

Interferon compared with placebo (4 studies, 173 analysed patients)

CMV disease and CMV infection

There was no significant difference in the risk of CMV disease (Analysis 9.1: RR 0.60, 95% CI 0.33 to 1.12) between interferon and placebo. CMV viraemia was reduced significantly with interferon (Analysis 9.2.1: RR 0.67, 95% CI 0.47 to 0.93). Hirsch 83-Kid/IFN reported adequate allocation concealment and blinding and Lui 92-Kid/IFN reported blinding of outcome assessors.

Other outcomes

There was no significant difference in the risk of all-cause mortality (Analysis 9.3.1: RR 1.66, 95% CI 0.68 to 4.09), acute rejection (Analysis 9.4.1: RR 1.55, 95% CI 1.00 to 2.39), graft loss (Analysis 9.5.1: RR 1.80, 95% CI 0.81 to 4.01) and viral (Analysis 9.6.1: RR 0.63, 95% CI 0.06 to 6.34) bacterial (Analysis 9.6.2: RR 0.42, 95% CI 0.05 to 3.66) and other (Analysis 9.6.3: RR 0.22, 95% CI 0.01 to 4.30) opportunistic infections. Acute rejection and opportunistic infections were only reported in one study for each outcome.

Adverse effects

Adverse effects were reported in 2/4 studies (Cheeseman 79-Kid/IFN; Hirsch 83-Kid/IFN). Leucopenia and thrombocytopenia occurred slightly but not significantly more frequently with interferon (Analysis 9.7.1: RR 2.16, 95% CI 0.80 to 5.84).

DISCUSSION

Thirty seven studies were identified and included in this systematic review. Seventeen studies compared CMV IgG or IgG with placebo or no specific therapy, four studies compared different types of IgG, nine studies compared various combinations of IgG and antiviral medications and seven studies examined vaccines or interferon. Overall study quality was poor particularly in the 30 studies involving IgG with only three studies reporting adequate allocation concealment, four blinding of investigators and participants, six blinding of outcome assessors and six an intention-to-treat analysis. Inadequate study quality can result in overestimation of benefit (Schultz 1995).

Hyperimmune CMV IgG and IgG have been widely used as prophylaxis against CMV disease in solid organ transplant recipients following the publications of two large studies, which demonstrated a benefit of CMV IgG in reducing CMV disease in kidney (Snydman 87-Kidney) and liver transplants (Snydman 93-Liver). This systematic review identified 17 studies which compared hyperimmune CMV IgG or IgG with placebo or no specific treatment in 793 of the 893 enrolled patients. Although the amount of anti-

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CMV antibody present in IgG preparations can be expected to vary and be less than the amount in CMV IgG preparations, no difference between the efficacy of IgG and CMV IgG could be detected so studies were combined. Overall no benefit of IgG as prophylaxis to prevent CMV disease or CMV infection could be demonstrated. However a small but clinically important benefit of IgG against CMV disease cannot be completely excluded as the summary RR of 0.80 favoured IgG though the 95% CI (0.61 to 1.05) just crossed the line of no effect. In addition, for the outcome of CMV disease, there was heterogeneity among studies with point estimates favouring IgG in nine studies and favouring placebo in seven. The heterogeneity could be related to differences in immunosuppression used, the higher risk of CMV disease in lung transplant recipients as well as to differences in study quality and design including definitions of CMV infection and disease and duration of follow-up. The significant reduction in death from CMV disease raises the possibility that CMV IgG reduced the severity of CMV disease. However only 8/17 studies (492 patients) provided data on all-cause mortality and only 4/17 (279 patients) of these contributed data to the meta-analysis. In addition only 6/17 studies provided data on death from CMV disease and only 4/17 (283 patients) contributed data to the meta-analysis. Three of these 4 studies (244 patients) provided data on deaths due to both CMV disease and other causes. Thus the apparent positive effect of IgG on death from CMV disease may have resulted from outcome reporting bias. There was no significant benefit of IgG on acute rejection, graft loss or opportunistic infections overall. Opportunistic infections appeared to be less frequent in CMV IgG treated patients but there was significant heterogeneity between studies. Adverse effects appeared uncommon and limited to mild reactions which did not require discontinuation of IgG. However adverse effects were not reported in 12 studies comparing IgG with placebo or no specific treatment or comparing two IgG preparations.

Only four studies (392 patients) have examined the relative efficacies of antiviral medications (aciclovir, ganciclovir) and IgG and the meta-analysis demonstrated a benefit of antiviral medications. However the meta-analysis is dominated by a single large study (Dunn 94-all/ACV) in which IgG was only administered for one week rather than the more usual period of three months. When this study is excluded, the meta-analysis of the remaining three studies showed no significant difference in the risk of CMV disease. However studies in this meta-analysis only enrolled 126 patients so the small numbers of patients and events resulted in wide confidence intervals indicating imprecision in the results. Thus further studies would be required to determine the relative efficacy of IgG and antiviral medications. However such studies are unlikely to be carried out since the use of IgG has now been largely replaced by antiviral medications based on efficacy (Hodson 2005a; Hodson 2005b) with reduced CMV disease, CMV infection, all-cause mortality and opportunistic infections as well as cost and ease of administration.

There are few data on the relative efficacies of IgG and antiviral medications and antiviral medications given alone in preventing CMV disease. Only four studies (298 patients) have addressed this question. No significant differences in the risk of CMV disease, CMV infection or all-cause mortality were demonstrated suggesting that there is no benefit of administering IgG together with an antiviral medication. However the small patient numbers resulted in wide 95% CIs indicating substantial imprecision for estimates of the effect size for all outcomes. For example for the outcome of CMV disease, the wide 95% CI (0.74 to 1.86) make it plausible that the combination of an antiviral medication and IgG could reduce the risk of CMV disease by 25% or almost double the risk compared with an antiviral medication alone. In addition existing studies have provided few data on the value of combination therapy in high risk patients such as CMV negative recipients of CMV positive organs (Fishman 1998; Rubin 2000) and patients on antilymphocyte preparations (Fishman 1998; Rubin 2000). There are extensive data from studies comparing the antiviral medications (aciclovir, ganciclovir and valaciclovir) with placebo/no treatment to show that prophylaxis with these antiviral medications reduces the risk for CMV disease by 60% (19 studies, 1981 patients: RR 0.42, 95% CI 0.34 to 0.52) and all-cause mortality by 40% (17 studies, 1838 patients: RR 0.63, 95% CI 0.43 to 0.92) (Hodson 2005a; Hodson 2005b). Based on the data available it is unlikely that IgG and antiviral medications together will significantly improve the efficacy of prophylaxis compared with antiviral medications alone. In addition IgG is expensive and is a blood product, which has to be given intravenously over an extended period.

A single small study (King 97-Liver/GCV) compared IgG and ganciclovir with IgG alone and found no significant difference in CMV disease or all-cause mortality. Since ganciclovir was only administered for four weeks, it is possible that the short duration of administration of the antiviral medication compared with 16 weeks of IgG could have influenced the results.

Adverse effects in studies comparing antiviral agents and IgG were generally seen in the antiviral medication treatment group but were only reported in 4/9 studies.

In the 1980s anti-CMV vaccines were developed and tested in well designed RCTs. However no benefit could be demonstrated in the reduction of CMV disease though fewer patients developed severe CMV disease and adverse effects were significantly more common in vaccine treated patients. Similarly interferon was tested in RCTs; no benefit was demonstrated and adverse effects were slightly but not significantly more common in interferon treated patients.

AUTHORS' CONCLUSIONS

Implications for practice

- Hyperimmune CMV IgG or IgG do not significantly reduce the risk for CMV disease, CMV infection and all-cause mortality compared with placebo/no treatment.
- There is no evidence for increased efficacy to prevent CMV disease using a combination of IgG and antiviral medications compared with antiviral medications alone.
- Currently there is no indication for CMV IgG or IgG in the prophylaxis of CMV disease in recipients of solid organ transplants in view of the demonstrated efficacy of antiviral medications (valganciclovir, ganciclovir, aciclovir, valaciclovir) on reducing CMV disease, CMV infection, all-cause and CMV related mortality and opportunistic infections (Hodson 2005a; Hodson 2005b).

Implications for research

- Since antiviral medications are very effective in reducing CMV disease in solid organ transplant recipients and the addition of IgG is unlikely to improve efficacy, it is unlikely that large studies will be carried out to test the relative efficacies of

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valganciclovir (the most commonly used antiviral medication) alone and in combination with IgG. Such a study is only likely to be considered if failure of prophylaxis with a single antiviral medication becomes a major clinical problem.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aguado 95-Heart/GCV

Methods	Country: Spain Setting/Design: Tertiary institution/parallel groups Time frame: January 1991 to December 1992 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Heart transplant recipients Age > 18 years Recipient: CMV +ve Donor: CMV +ve or -ve Patients receiving OKT-3 GANCICLOVIR GROUP Number: 18 (2 excluded from analysis) Age: 50 years (27-62) Sex (M/F): 15/1 CMV IgG GROUP Number: 17 (2 excluded from analysis) Age: 51.5 years (30-64) Sex (M/F): 15/0 EXCLUSIONS: Other viral agents in previous 7 days, WBC < 1500/mm^3, platelets < 50,000/mm^3, creatinine >2.5 mg/dL
Interventions	GANCICLOVIR GROUP Ganciclovir 5 mg/kg IV twice daily for 14 days Started within 48 hours of transplant Dose reduced with renal dysfunction CMV IgG GROUP CMV IgG 100 mg/kg/dose First dose within 24 hours of transplant and at weeks 2, 4, 6, 8, 10 post-transplant CO-INTERVENTIONS Cyclosporin, ALG, azathioprine, steroids
Outcomes	STUDY OUTCOMES

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Aguado 95-Heart/GCV *(Continued)*

	1. CMV disease: CMV infection, fever, leucopenia, thrombocytopenia, hepatitis (CMV inclusion bodies, immunofluorescence), pneumonitis (confirmed on biopsy, BAL), enteritis (biopsy) 2. CMV syndrome: CMV infection, fever, leucopenia, thrombocytopenia 3. Tissue invasive CMV disease: CMV infection, hepatitis, pneumonitis, enteritis 4. CMV infection (asymptomatic and symptomatic): Isolation of virus from blood, urine, throat by conventional culture or shell vial culture. Cultures at 0, 15, 30, 60, 90, 180 and 360 days. 5. Acute rejection: (definition NS) 6. Death 7. Opportunistic infections 8. Adverse effects: Number requiring dose reduction for elevated creatinine or leucopenia
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Two patients from each group because of death in first week post-transplant STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Bailey 93-All/ACV

Methods	Country: USA Setting/Design: Tertiary institution/parallel groups Time frame: 26 December 1989 to 5 July 1991 Randomisation method: Computer generated randomisation scheme Blinding - Participants: No - Investigators: No - Outcome assessors: No - Data analysis: No Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Solid organ transplant (heart, lung, kidney) Recipient: CMV -ve Donor: CMV +ve Age > 17 years ACYCLOVIR/IgG GROUP Number: 10 Age: 31 years (24-50) Sex (M/F): 6/4 ACYCLOVIR GROUP Number: 11 Age: 36 years (18-51) Sex (M/F): 6/5 EXCLUSIONS: NS
Interventions	ACYCLOVIR/IgG GROUP Acyclovir 800 mg four times daily orally for 12 weeks

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Bailey 93-All/ACV *(Continued)*

	Started < 7 hours post-transplant Dose reduction for reduced renal function IgG 300 mg/kg/dose IV. First dose within 3 days post-transplant, doses at 2, 4, 6, 8, 10 weeks ACYCLOVIR GROUP Acyclovir 800 mg four times daily orally for 12 weeks. Started < 7 hours post transplant. Dose reduction for reduced renal function. CO-INTERVENTIONS Cyclosporin, ALG for induction in lung transplants and cadaveric kidney transplants, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, leucopenia, hepatitis, enteritis, pneumonitis (virus isolated on biopsy, BAL) 2. CMV syndrome: CMV infection, leucopenia 3. Tissue invasive CMV disease: CMV infection, hepatitis, enteritis, pneumonitis (virus isolated on biopsy, BAL) 4. CMV infection (asymptomatic and symptomatic): culture of blood or increase in CMV antibody titre by 4-fold. Screened at transplant, discharge, twice monthly for 3 months, at 6 months
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Balfour 84-Kid/vacc

Methods	Country: USA Setting/Design: Single tertiary institution/parallel Time frame: 15 January 1979 to 1 March 1983 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months post-transplant Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Renal transplant recipients > 11 years VACCINE GROUP Number: 83 Age: 34.5 years (mean) Sex (M/F): 59/24 PLACEBO GROUP Number: 91 Age: 36.5 years (mean)

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Balfour 84-Kid/vacc *(Continued)*

	Sex (M/F): 64/27 EXCLUSIONS: NS
Interventions	VACCINE GROUP Towne live attenuated CMV vaccine 1 mL (6,600 plaques/mL) IM single dose given a median of 4.3 months pre-transplant PLACEBO GROUP Placebo of sterile buffered cell culture medium 1 mL IM single dose given a median of 4.6 months pre-transplant CO-INTERVENTIONS ALG, azathioprine and steroids to September 1980 From September 1980, patients randomised to either above or cyclosporin and prednisone (18 in treatment group and 19 in control group received cyclosporin)
Outcomes	STUDY OUTCOMES 1. CMV disease overall and for CMV serostatus; CMV infection, fever, leucopenia, thrombocytopenia, pneumonitis, hepatitis, renal dysfunction, encephalitis 2. Severity of CMV disease: score 1-3 (mild), 4-6 (moderate), > 6 severe 2. CMV infection (asymptomatic and symptomatic) disease overall and for CMV serostatus; positive culture (blood, urine) or seroconversion or 4-fold rise in CFT or immunofluorescence (IF) antibody titre 3. Immunogenicity: Increase in IF titre 4. Adverse reactions (total, local, fever)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 79 patients excluded from each group from efficacy analysis as not yet transplanted 32 excluded from treatment group and 30 from control group from analysis of adverse effects because of insufficient follow-up STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Boland 93-Heart/kid

Methods	Country: Netherlands Setting/Design: Single tertiary institution/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: 3 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Heart and kidney transplant recipients Recipient: CMV -ve

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Boland 93-Heart/kid *(Continued)*

	Donor: CMV +ve IgG GROUP Number: 14 (3 heart, 11 kidney) Age: 49 years (45-56) (heart); 35 years (12-62) (kidney) Sex (M/F): 10M/4F NO TREATMENT GROUP Number: 14 (Heart 3, kidney 11) Age: 44 years (33-54) (heart); 32 years (5-65) (kidney) Sex (M/F): 7M/7F EXCLUSIONS Recipient CMV +ve Donor CMV -ve/recipient CMV -ve
Interventions	IgG GROUP CMV IgG (Cytotect) 1 ml/kg/dose (100 mg protein/mL) at 1, 2, 3, 5, 7 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, fever, leucopenia, hepatitis, pneumonitis, renal dysfunction 2. CMV infection (asymptomatic and symptomatic): CMV antigenaemia or culture (shell vial or conventional), screened at weekly from weeks 2-7, then every 2nd week to 3 months 3. Acute rejection: Definition not stated
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cheeseman 79-Kid/IFN

Methods	Country: USA Setting/Design: Single tertiary centre/parallel groups Time frame: January 1976 to April 1978 Randomisation method: NS Blinding - Participants: No: Placebo controlled but side effects of leucopenia and thrombocytopenia much more common in experimental than control group - Investigators: No: Placebo controlled but side effects of leucopenia and thrombocytopenia much more common in experimental than control group - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: Minimum of 8 months Loss to follow-up: 0%

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Cheeseman 79-Kid/IFN *(Continued)*

Participants	INCLUSION CRITERIA Kidney transplant recipients INTERFERON GROUP Number: 21 Age: NS Sex (M/F): NS PLACEBO GROUP Number: 20 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	INTERFERON GROUP Interferon 3 x 10(7) units IM on day of transplant, day 1 and twice weekly for 15 doses PLACEBO GROUP 0.5% albumin in same volume IM on same days for 15 doses CO-INTERVENTIONS Prednisone, azathioprine, antilymphocyte antibody (50%)
Outcomes	STUDY OUTCOMES 1. CMV disease: Rising CMV antibody, fever, leucopenia, hepatitis, pneumonitis 2. CMV virus excretion: Positive culture of urine or throat 3. CMV viraemia: Rising CMV antibody by CFT or indirect haemagglutination 4. Death 5. Graft loss 6. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Four excluded from analysis (2 died, 2 did not receive medication) STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Cofer 91-Liver

Methods	Country: USA Setting/Design: Single tertiary centre/parallel groups Time frame: 7 September 1988 to 21 May 1989 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 3 months Loss to follow-up: 0%

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Cofer 91-Liver *(Continued)*

Participants	INCLUSION CRITERIA First liver transplant IgG GROUP Number: 25 Age: 47.7 years Sex (M/F): 9/16 PLACEBO GROUP Number: 25 Age: 41.5 years Sex (M/F): 8/17 EXCLUSIONS: NS
Interventions	IgG GROUP IgG (6% solution) 500 mg/kg/dose on days 1, 7, 14, 21, 28, 42, 56, 70, 84 (9 doses) PLACEBO GROUP Placebo (6% albumin) on days 1, 7, 14, 21, 28, 42, 56, 70, 84 (9 doses) CO-INTERVENTIONS Cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, hepatitis (biopsy), pneumonitis, enteritis 2. CMV infection (asymptomatic and symptomatic): Cultures of blood, urine, throat; screening day 7, 14, 21, 42, 56, 84 3. Acute rejection (not defined) 4. Opportunistic infections (pneumonia)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: Not reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Conti 94-Kidney/GCV

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: March 1990 to April 1992 Randomisation method: Not stated Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients (46 cadaveric, 5 living donor)

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Conti 94-Kidney/GCV *(Continued)*

	Recipient: CMV -ve Donor: CMV +ve GANCICLOVIR GROUP Number: 24 Age: 34 years (mean) Sex (M/F): 18M/6F IgG GROUP Number: 27 Age: 36 years (mean) Sex (M/F): 17M/10F EXCLUSIONS: Recipient CMV +ve Donor CMV -ve/recipient CMV -ve
Interventions	GANCICLOVIR GROUP Ganciclovir 2.5 mg/kg/d on days 1-21 & during OKT-3 treatment for steroid resistant rejection Dose reduction for renal dysfunction IgG GROUP IgG 500 mg/kg/dose within 48 hours of transplant and 1 week then 250 mg/kg/dose at 2, 3, 4, 5, 6 weeks CO-INTERVENTIONS Cyclosporin, ALG for induction or rejection, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection (culture of blood or urine, +ve CMV IgM or 4-fold rise in CMV IgG titre), fever, leucopenia, hepatitis, enteritis, pneumonitis (tissue invasion on biopsy, BAL) 2. CMV syndrome: CMV infection, fever, leucopenia < 4000/mm^3 3. Tissue invasive CMV disease: CMV infection, hepatitis, hepatitis, enteritis, pneumonitis 4. Acute rejection (definition NS) 5. Death 6. Graft loss 7. Adverse events: leucopenia, thrombocytopenia, liver dysfunction, tremors
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: Not reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Dunn 94-all/ACV

Methods	Country: USA Setting/Design: Single tertiary institution Time frame: 23 May 1990 to 28 February 1993 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS

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Dunn 94-all/ACV *(Continued)*

	- Data analysis: NS Intention-to-treat: No Follow-up period: 12-18 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Solid organ transplant (kidney, kidney-pancreas, kidney-liver, liver, pancreas Antilymphocyte antibody used for induction or rejection All donor and recipient CMV serological combinations ACYCLOVIR GROUP Number: 157 (24 excluded after randomisation from analysis) Age: 42.85 ± 0.84 (SE) years Sex (M/F): 76/57 IgG/GANCICLOVIR GROUP Number: 154 (21 excluded from analysis after randomisation) Age: 42.77 ± 0.85 (SE) years Sex (M/F): 74/59 EXCLUSIONS No antilymphocyte antibody induction
Interventions	ACYCLOVIR GROUP 800 mg four times daily orally or 400 mg four times a day IV for 12 weeks (induction) or 6 weeks (rejection) IgG/GANCICLOVIR GROUP IgG or Minnesota CMV IgG 100 mg/kg/dose on days 1, 4, 7 Ganciclovir 5 mg/kg twice daily IV for 7 days CO-INTERVENTIONS Cyclosporin or tacrolimus, azathioprine, steroids, ALG
Outcomes	STUDY OUTCOMES 1. CMV disease overall and for serostatus: CMV infection, fever, leucopenia, hepatitis, enteritis, pneumonitis (conventional or shell vial culture of blood/tissue, 4-fold increase in anti CMV antibody or seroconversion) 2. CMV disease according to organ transplanted 3. Acute rejection 4. Death
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 24 from acyclovir group, 21 from IgG/ganciclovir group STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Fassbinder 86-Kidney

Methods	Country: Germany Setting/Design: Single tertiary institution/parallel groups Time frame: 1984 onwards

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Fassbinder 86-Kidney *(Continued)*

	Randomisation method: NS Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: More than 3 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients CMV IgG GROUP Number: 42 Age: NS Sex (M/F): NS IgG GROUP Number: 34 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	CMV IgG GROUP CMV IgG (Cytotect) 10 g/dose (5000 IU) IV pre-transplant Peri-operative blood transfusions on days 18, 38, 58, 78 IgG GROUP IgG 10 g/dose IV pre transplant Peri-operative blood transfusions on days 18, 38, 58, 78 CO-INTERVENTIONS Azathioprine, prednisone
Outcomes	STUDY OUTCOMES 1. CMV infection overall and recipient CMV +ve (seroconversion or 4-fold increase in CMV titre) 2. Severity score for CMV disease in recipient CMV +ve and recipient CMV -ve 3. All-cause mortality
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Greger 85a-Kidney

Methods	Country: Germany Setting/Design: Single tertiary centre/parallel groups Time frame: December 1982 to January 1985 Randomisation method: NS Blinding

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Greger 85a-Kidney *(Continued)*

	- Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients on cyclosporin immunosuppression IgG GROUP Number: 12 Age: 37.6 ± 13.6 (SD) years in cyclosporin treated Sex (M/F): 6/6 NO TREATMENT GROUP Number: 12 Age: 46.4 ± 7.6 (SD) years in cyclosporin treated group; 44.9 ± 12.3 (SD) years in ALG treated group Sex (M/F): 7/5 EXCLUSIONS Patients treated with anti-lymphocyte globulin
Interventions	IgG GROUP CMV IgG 0.1 g/kg/dose pre-op and day 1 then every 3 weeks for 6 months NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, prednisone (50%) or ALG, azathioprine and prednisone in 50%
Outcomes	STUDY OUTCOMES 1. CMV disease overall and in donor CMV +ve/recipient CMV -ve: CMV infection, fever, leucopenia, hepatitis, encephalitis, renal dysfunction 2. CMV infection (asymptomatic and symptomatic): Seroconversion or 4-fold rise in CMV CFT titres 3. Graft loss 4. All-cause mortality
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: Not reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Greger 85b-Kidney

Methods	Country: Germany Setting/Design: Single tertiary centre/parallel groups Time frame: December 1982 to January 1985 Randomisation method: NS Blinding - Participants: No

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Greger 85b-Kidney *(Continued)*

	- Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Immunosuppression with ALG IgG GROUP Number: 12 Age: 41.3 ± 12.3 (SD) years Sex (M/F): 7/5 NO TREATMENT GROUP Number: 12 (1 excluded from analysis) Age: 44.9 ± 12.3 (SD) years Sex (M/F): 5/7 EXCLUSIONS Patients treated with cyclosporin
Interventions	IgG GROUP CMV IgG 0.1 g/kg/dose pre-op, day 1 and then every 3 weeks for 6 months NO TREATMENT GROUP No treatment CO-INTERVENTIONS ALG, azathioprine, prednisone
Outcomes	STUDY OUTCOMES 1. CMV disease overall and in donor CMV +ve/recipient CMV -ve: CMV infection, fever, leucopenia, hepatitis, encephalitis, renal dysfunction 2. CMV infection (asymptomatic and symptomatic): Seroconversion or 4-fold rise in CMV antibody titres on complement fixation test 3. Graft loss 4. All-cause mortality
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION One patient died and excluded from analysis STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

Grundmann 87-Kidney

Methods	Country: Germany Setting/Design: Single tertiary institution/parallel groups Time frame: December 1983 to December 1985 Randomisation method: NS

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Grundmann 87-Kidney *(Continued)*

	Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: Average 22 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV +ve or -ve Donor: serology not available IgG GROUP Number: 50 Age: 38.8 ± 10.25 (SD) years Sex: Ratio 2.8:1 (M:F) NO TREATMENT GROUP Number: 50 Age: 38.96 ± 11.81 (SD) years Sex: 1.94:1 (M:F) EXCLUSIONS: NS
Interventions	IgG GROUP CMV IgG 2 mL/kg/dose IV after surgery and days 1, 21, 42, 84, 105 NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, ALG, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, fever, leucopenia, hepatitis, renal dysfunction 2. CMV infection (asymptomatic and symptomatic): CMV IgM titre > 1:10, 4-fold increase in CMV - CFT titre 3. Death 4. Opportunistic infections 5. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Eight excluded after randomisation STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Hirsch 83-Kid/IFN

Methods	Country: USA Setting/Design: Single tertiary centre

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Hirsch 83-Kid/IFN *(Continued)*

	Time frame: Febuary 1980 to January 1982 Randomisation method: Random number table Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: Yes Intention-to-treat: No Follow-up period: 10 months or more Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient :CMV antibody positive INTERFERON GROUP Number: 20 Age: 44.2 ± 2.9 (SEM) years Sex (M/F): 9/11 PLACEBO GROUP Number: 22 Age: 40.1 ± 3.4 (SEM) years Sex (M/F): 14/8 EXCLUSIONS Recipient CMV negative
Interventions	INTERFERON GROUP Interferon 3 x 10(7) units IM 3/wk for 6 weeks then 2/wk for 8 weeks PLACEBO GROUP Human serum albumin IM in same volume and same dose regimen CO-INTERVENTIONS Prednisone, azathioprine, antilymphocyte globulin in 19
Outcomes	STUDY OUTCOMES 1. CMV disease: Rising CMV antibody titre, fever, leucopenia, atypical lymphocytes, organ dysfunction 2. CMV virus excretion: Urine, blood, throat cultures 3. CMV viraemia: Rising antibody titre by CFT or indirect immunofluorescence 4. Death 5. Opportunistic infections 6. Graft loss 7. Adverse effects
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Six excluded from analysis as received < 10 doses STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

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Huang 05-Liver/GCV

Methods	Country: USA Setting/Design: Tertiary institution/parallel groups Time frame: April 1999 to August 2002 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients INTRAVENOUS GANCICLOVIR GROUP Number: 30 Age: NS Sex (M/F): NS ORAL GANCICLOVIR GROUP Number: 30 Age: NS Sex (M/F): NS CMV IgG + ORAL GANCICLOVIR GROUP Number: 30 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	INTRAVENOUS GANCICLOVIR GROUP 5 mg/kg ganciclovir IV for 14 days within 5 days of transplant ORAL GANCICLOVIR GROUP 15 mg/kg ganciclovir orally three times daily for 90 days given within 5 days of transplant CMV IgG + ORAL GANCICLOVIR GROUP 150 mg/kg of CMV IgG within 48 hours of transplant and on weeks 2, 4, 6, 8, 12 15 mg/kg ganciclovir orally three times daily for 90 days given within 5 days of transplant CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV infection (CMV antigenaemia and/or CMV DNA) 2. CMV infection in D+/R- patients 3. CMV symptomatic disease
Notes	Ninety consecutive patients enrolled and all followed for one year EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement

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Huang 05-Liver/GCV *(Continued)*

Allocation concealment?	Unclear risk	B - Unclear

Johnson 04-L/K/GCV

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: September 1997 to October 2002 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: Unclear Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA Liver or kidney transplant All donor and recipient CMV serological combinations CMV IgG/GANCICLOVIR GROUP Number: 95 Age: 50.59 ± 1.15 (SEM) years Sex (M/F): 54/41 GANCICLOVIR GROUP Number: 99 Age: 43.9 ± 1.25 (SEM) years Sex (M/F): 59/50 EXCLUSIONS: NS
Interventions	CMV IgG/GANCICLOVIR GROUP CMV IgG 150 mg/kg/dose IV within 48 hours of transplant - Liver transplant 150 mg/kg/dose at weeks 2, 4, 6, 8 and then 100 mg/kg/dose at 12 weeks - Kidney transplant 100 mg/kg/dose at weeks 2, 4, 6, 8 and then 50 mg/kg/dose at 12 weeks Ganciclovir 1000 mg three times daily orally for 3 months GANCICLOVIR GROUP Ganciclovir 1000 mg three times daily orally for 3 months CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV disease (definition not provided) 2. CMV syndrome 3. Tissue invasive CMV disease 4. CMV infection (asymptomatic and symptomatic) (definition not provided) 5. Acute rejection 6. Death 7. Opportunistic infections 8. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Six patients unaccounted for STOP OR END POINT/S: None reported

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Johnson 04-L/K/GCV *(Continued)*

ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kasiske 89-Kidney

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: 1 September 1987 to 5 April 1988 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients IgG GROUP Number: 15 Age: 47.4 ± 14.6 (SD) years Sex (M/F): 9/6 NO TREATMENT GROUP Number: 13 Age: 42.2 ± 17.8 (SD) years Sex (M/F): 5/8 EXCLUSIONS: NS
Interventions	IgG GROUP IgG 500 mg/kg/dose IV weekly for 12 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, ALG, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, leucopenia, hepatitis, enteritis, pneumonitis, encephalitis (positive culture or CMV antigenaemia) 2. CMV infection (asymptomatic and symptomatic): 4-fold rise in CMV CFT titre 3. Opportunistic infections (bacterial, herpetic) 4. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

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Kasiske 89-Kidney *(Continued)*

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

King 97-Liver/GCV

Methods	Country: USA/Canada Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: January 1991 to December 1994 Randomisation method: Block randomisation with stratification for centres Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: Unclear Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Children < 18 years receiving liver transplants Recipient: CMV -ve Donor: CMV +ve GANCICLOVIR/IgG GROUP Number: 29 Age: 65 months (3-197) Sex (M/F): 14/15 IgG GROUP Number: 27 Age: 75 months (7-191) Sex (M/F): 16/11 EXCLUSIONS: NS
Interventions	GANCICLOVIR/IgG GROUP Ganciclovir 5 mg/kg/d IV for 30 days Dose reduced for leucopenia IgG 1000 mg/kg within 72 hrs, 500 mg/kg/dose weekly to week 8 and every 2nd week to week 16 IgG GROUP Saline infusion as placebo IgG 1000 mg/kg within 72 hrs, 500 mg/kg/dose weekly to week 8 and every 2nd week to week 16 CO-INTERVENTIONS Acyclovir to treat herpes simplex or varicella Immunosuppression induction according to centre
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, fever, neutropenia, hepatitis, pneumonitis 2. CMV syndrome: CMV infection, fever, neutropenia 3. Tissue invasive CMV disease: CMV infection, hepatitis (clinical or biopsy), pneumonitis (clinical, radiograph, biopsy, BAL) 4. CMV infection (asymptomatic and symptomatic): Positive shell vial culture or PCR for CMV DNA. Screened wkly to 8 weeks, 2 weekly to 16 weeks, week 24

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King 97-Liver/GCV *(Continued)*

	5. Acute rejection (biopsy proven) 6. Death 7. Opportunistic infections (bacterial, fungal) 8. Adverse events: leucopenia, thrombocytopenia
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Six excluded after randomisation STOP OR END POINT/S Enrolment stopped because by January 1995, physicians preferred antiviral medications ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Kovarik 88-Kid/IFN

Methods	Country: Austria Setting/Design: Single tertiary centre/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients INTERFERON GROUP Number: 28 (21 analysed) Age: 37.1 ± 10.7 (SD) years Sex (M/F): 12/9 (analysed group) PLACEBO GROUP Number: 22 (19 analysed) Age: 38.3 ± 12.5 (SD) years Sex (M/F): 10/9 (analysed group) EXCLUSIONS: WBC < 2000/mm^3 pre-transplant
Interventions	INTERFERON GROUP Interferon 2 x 10(7) units IM daily x 1 month, 3/wk x 1 month, 2/wk x 1 month, 1/wk to 6 months PLACEBO GROUP Diluent given in same volume and at same intervals CO-INTERVENTIONS Cyclosporin, prednisone
Outcomes	STUDY OUTCOMES

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Kovarik 88-Kid/IFN *(Continued)*

	1. CMV disease: CMV infection, leucopenia, fever, hepatitis, pneumonitis 2. CMV infection (asymptomatic and symptomatic): Seroconversion or rise in antibody titre by CFT 3. Opportunistic infections (herpes, bacterial) 4. Graft loss (total and irreversible rejection)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Seven excluded from interferon group for surgical complications (3), low WBC (2), fever (1), non compliance (1). 3 were excluded from placebo group for surgical complications (1), non compliance (2) Six other patients excluded from efficacy study as lost graft before completing 6 months treatment STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Kruger 03-Lung

Methods	Country: USA Setting/Design: single tertiary institution/parallel groups Time frame: April 1998 to July 2000 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: Yes Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Unilateral or bilateral lung transplant recipient Recipient: CMV +ve IgG GROUP Number: 22 Age: 51.9 ± 10.3 (SD) years Sex (M/F): 11/11 NO TREATMENT GROUP Number: 22 Age: 50.5 ± 11.8 (SD) years Sex (M/F): 11/11 EXCLUSIONS Age < 18 years, reaction to CMV IgG or ganciclovir, on IgG for other reasons, pregnant
Interventions	IgG GROUP 150 mg/kg/dose IV within 72 hours and weeks 2, 4, 6, 8 100 mg/kg/dose IV at 12 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS

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Kruger 03-Lung *(Continued)*

	Cyclosporin, ALG, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, pneumonitis, hepatitis, enteritis, encephalitis 2. CMV infection (asymptomatic and symptomatic) and time to infection: Positive CMV culture (conventional or shell vial); surveillance weekly for 12 weeks, 6 months, 12 months); surveillance bronchoscopies (monthly for 3 months, 6 months, 12 months) 3. Acute rejection (biopsy proven) 4. Death overall and from CMV disease 5. Opportunistic infections (bacterial, fungal) 6. Adverse effects (neurological)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Lui 92-Kid/IFN

Methods	Country: UK Setting/Design: Single tertiary centre/parallel groups Time frame: 1 January 1986 to 1 June 1989 Randomisation method: Stratified randomisation list Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients INTERFERON GROUP Number: 37 (32 analysed) Age: 38 ± 2 (SEM) years (analysed group) Sex (M/F): 22/10 (analysed group) PLACEBO GROUP Number: 37 (36 analysed) Age: 41 ± 2 (SEM) years (analysed group) Sex (M/F): 18/18 (analysed group) EXCLUSIONS Hepatocellular dysfunction, neurological disease
Interventions	INTERFERON GROUP Interferon 3 x 10(7) units SC x 3 doses/wk for 6 weeks, 2 doses/wk for 8 weeks PLACEBO GROUP Glycine buffered saline in same quantity SC at same dose times

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Lui 92-Kid/IFN *(Continued)*

	CO-INTERVENTIONS Prednisone, cyclosporin
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV isolation from any site, fever, leucopenia, thrombocytopenia, hepatitis, enteritis, pneumonitis 2. CMV virus excretion: Blood/urine/throat by conventional or shell vial cultures 3. Number with 2 or more episodes of acute rejection 4. Death 5. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Six excluded from analysis but reasons not stated STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	High risk	C - Inadequate

McCune 92-Kid/KP

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: March 1990 to August 1990 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney or kidney-pancreas transplant recipient Recipient: CMV +ve IgG GROUP Number: 14 (1 excluded from analysis) Age: 38 ± 10 (SD) years Sex (M/F): 5/8 NO TREATMENT GROUP Number: 16 Age: 41 ± 10 (SD) years Sex (M/F): 6/10 EXCLUSIONS: NS
Interventions	IgG GROUP IgG 500 mg/kg/dose IV within 72 hours of transplant, then 250 mg/kg/dose IV on weeks 1, 2, 4, 6 NO TREATMENT GROUP

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McCune 92-Kid/KP *(Continued)*

	No treatment CO-INTERVENTIONS ALG, cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection (4-fold rise in IgG or 2-fold in IgM or positive culture), fever, leucopenia, hepatitis, enteritis, pneumonitis, renal dysfunction 2. CMV syndrome: CMV infection, fever, leucopenia 3. Tissue invasive CMV disease: CMV infection, hepatitis, enteritis, pneumonitis, renal dysfunction 4. Acute rejection 5. Death from CMV disease 6. Graft loss 7. Adverse effects (none reported)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION One patient excluded post randomisation STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Metselaar 89-Kidney

Methods	Country: Netherlands Setting/Design: Single tertiary institution/parallel groups Time frame: July 1985 to October 1987 Randomisation method: NS Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 3 months after start of treatment Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Biopsy proven rejection requiring ALG IgG GROUP Number: 20 (1 subsequently excluded from analysis) Age: 36 (17-67) years Sex (M/F): 13/7 PLACEBO GROUP Number: 20 Age: 35 (16-55) years Sex (M/F): 12/8 EXCLUSIONS: NS

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Metselaar 89-Kidney *(Continued)*

Interventions	IgG GROUP CMV IgG 100 mg/kg/dose IV on first day of ATG, days 7, 14, 35, 77 PLACEBO GROUP Albumin 100 mg/kg IV on first day of ATG, days 7, 14, 35, 77 CO-INTERVENTIONS Cyclosporin, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease and according to serostatus: CMV infection, fever, leucopenia < 3000/mm^3, thrombocytopenia < 100,000/mm^3, abnormal liver function tests, enteritis (biopsy), pneumonitis (biopsy), encephalitis 2. CMV infection and according to serostatus: +ve CMV blood culture (conventional or shell vial); screened before each infusion 3. Deaths due to CMV disease
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Mitsioni 87-Kidney

Methods	Country: France Setting/Design: Single tertiary centre/parallel groups Time frame: June 1986 to June 1987 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: 3 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Children receiving kidney transplants (cadaveric 27, living donor 1) IgG GROUP Number: 13 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 15 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	IMMUNOGLOBULIN GROUP

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Mitsioni 87-Kidney *(Continued)*

	CMV IgG 250 mg/kg IV before and on days 15, 30 and 45 post-transplant NO TREATMENT GROUP No treatment CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV antibodies, fever, raised transaminases, leucopenia, low platelets 2. CMV infection: Development of CMV IgG or IgM antibodies 3. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Morales 02-Kid/GCV

Methods	Country: Spain Setting/Design: Single tertiary institution/parallel groups Time frame: January 1997 to December 19999 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 9 to 45 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients receiving ALG for induction Recipient: CMV +ve Donor: CMV +ve or -ve GANCICLOVIR GROUP Number: 22 Age: 48.2 ± 10.8 (SD) years Sex (M/F): Uncertain IgG GROUP Number: 22 Age: 46 ± 12 years Sex (M/F): Uncertain EXCLUSIONS Donor CMV +ve; recipient CMV -ve
Interventions	GANCICLOVIR GROUP Ganciclovir 6 mg/kg IV twice daily while on antilymphocyte globulin CMV IgG GROUP

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Morales 02-Kid/GCV *(Continued)*

	CMV IgG 1 mg/kg/dose days 0, 7, 14, 21, 45, 60, 75, 90 post-transplant (dose may be reported incorrectly) CO-INTERVENTIONS Cyclosporin or tacrolimus, ALG, mycophenolate mofetil, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: Viraemia (positive CMV antigen, culture), fever > 38, leucopenia < 3500/mm^3, platelets < 90,000/mm^3, atypical lymphocytes, hepatitis, enteritis, pneumonitis 2. CMV syndrome: Viraemia, fever > 38, leucopenia < 3500/mm^3, platelets < 90,000/mm^3, atypical lymphocytes 3. Tissue invasive CMV disease: Viraemia, hepatitis, enteritis, pneumonitis 4. Acute rejection 5. Death 6. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None STOP OR END POINT/S: None ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Pakkala 92-Kidney

Methods	Country: Finland Setting/Design: Single tertiary institution/parallel groups Time frame: December 1988 to December 1989 Randomisation method: NS Blinding - Participants: Unclear - Investigators: Unclear - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV -ve Donor: CMV +ve IgG 1 GROUP Number: 15 Age: NS Sex (M/F): NS IgG 2 GROUP Number: 15 Age: NS Sex (M/F): NS EXCLUSIONS Recipients CMV +ve

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Pakkala 92-Kidney *(Continued)*

Interventions	IgG 1 GROUP CMV IgG (Cytotect) 150 mg/kg IV on day 1 100 mg/kg/dose IV on days 14 and 28 50 mg/kg/dose IV on days 42, 56, 84, 112 IgG 2 GROUP CMV IgG (Anti CMV FRC) 150 mg/kg IV on day 1 100 mg/kg/dose IV on days 14, 28 50 mg/kg/dose IV on days 42, 56, 84, 112 CO-INTERVENTIONS Cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: Viraemia (+ve shell vial culture), fever, leucopenia, thrombocytopenia, hepatitis, pneumonitis 2. Acute rejection: definition not stated 3. Death 4. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Plotkin 84-Kid/vacc

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: February 1979 to February 1989 Randomisation method: Random number tables Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: Unclear Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients VACCINE GROUP Number: 124 (67 were CMV donor +ve/recipient -ve) Age: 31.2 ± 9.6 (SD) years (CMV donor +ve/recipient -ve group) Sex (M/F): 21/15 (CMV donor +ve/recipient -ve) PLACEBO GROUP Number: 113 Age: 32.2 ± 9.6 (SD) years (CMV donor +ve/recipient -ve group) Sex (M/F): 21/15 (CMV donor +ve/recipient -ve group)

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Plotkin 84-Kid/vacc *(Continued)*

	EXCLUSIONS Pregnancy, allergy to vaccine vehicle, inability to determine donor CMV status
Interventions	VACCINE GROUP Towne live attenuated CMV vaccine 1 mL (3000-7000 pfu) IM single dose given 8 weeks before entry to transplant list PLACEBO GROUP Placebo lyophilised medium 1 mL IM single dose given 8 weeks before entry to transplant list CO-INTERVENTIONS Azathioprine and steroids or cyclosporin and steroids ± azathioprine
Outcomes	STUDY OUTCOMES 1. CMV disease overall and according to serostatus: CMV infection, fever, leucopenia, thrombocytopenia, enteritis, pneumonitis, hepatitis, renal dysfunction 2. Severity of CMV disease score: Severe > 6 3. CMV infection overall and according to serostatus: positive CMV culture (blood, urine, throat) or seroconversion or 4-fold increase in CFT antibody. Screened every 2 weeks to 6 months. 4. Acute rejection in donor CMV +ve/recipient -ve 5. Adverse reactions
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 473 patients randomised, 162 excluded as not transplanted and 74 excluded because donor CMV status unknown STOP OR END POINT/S: Not reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Plotkin 94-Kid/vacc

Methods	Country: USA/UK Setting/Design: Multicentre tertiary institutions Time frame: February 1986 to March 1990 Randomisation method: Random number tables Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV -ve Donor: CMV +ve VACCINE GROUP Number: 37 Age: NS

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Plotkin 94-Kid/vacc *(Continued)*

	Sex (M/F): NS PLACEBO GROUP Number: 24 Age: NS Sex (M/F): NS EXCLUSIONS Recipient CMV +ve, donor CMV -ve/recipient CMV -ve
Interventions	VACCINE GROUP 5000 pfu IM single dose given pre-transplant PLACEBO GROUP Placebo (saline diluent) IM single dose CO-INTERVENTIONS ALG (one centre only), cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: Positive viral culture (conventional or shell vial from blood, urine) or seroconversion or rise in CFT antibody, fever and organ symptoms 2. Severe CMV disease (disease score > 6)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 177 enrolled, 89 vaccine and 89 placebo but only 68/177 received CMV +ve organs. 7 excluded from analysis because of early surgical loss or follow up > 6 months STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Preiksaitis 82-Heart

Methods	Country: USA Setting/Design: Multicentre/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: NS Loss to follow-up: No data
Participants	INCLUSION CRITERIA Heart transplant recipients Recipient CMV +ve or -ve randomised separately IgG GROUP Number: 7 Age: NS

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Preiksaitis 82-Heart *(Continued)*

	Sex (M/F): NS NO TREATMENT GROUP Number: 6 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	IgG GROUP IgG 5% (CMV titre of 1:30,000) 20 mL/kg/dose IV at 24 hours, weekly to 10 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. Adverse events (fluid overload, worsening of control of diabetes mellitus, serum sickness reaction) 2. No other outcomes reported
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Rostaing 97-Kid/GCV

Methods	Country: France Setting/Design: Single tertiary institution/parallel groups Time frame: February 1992 to July 1994 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 1 year Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV -ve Donor: CMV +ve ACYCLOVIR/IgG GROUP Number: 14 (4 excluded from analysis) Age: NS Sex (M/F): NS ACYCLOVIR GROUP Number: 14 (1 excluded from analysis) Age: NS

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Rostaing 97-Kid/GCV *(Continued)*

	Sex (M/F): NS EXCLUSIONS Recipient CMV +ve
Interventions	ACYCLOVIR/IgG GROUP Acyclovir 6 mg/kg/d IV for 4 days and then 800 mg orally, four times daily for 3 months. Dose reduction for renal dysfunction CMV IgG 7.5 g/dose IV on days 1, 8, 15, 30, 45, 60, 75, 90 ACYCLOVIR GROUP Acyclovir 6 mg/kg/d IV for 4 days and then 800 mg orally four times daily for 3 months. Dose reduction for renal dysfunction CO-INTERVENTIONS ATG, cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, fever, leucopenia, thrombocytopenia, pneumonitis, nephritis 2. CMV infection (asymptomatic and symptomatic): Culture of blood/urine. Screened at 8,15, 22, 30 days, then every 2 weeks to day 90 3. Acute rejection (not defined) 4. Death 5. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Five recipients excluded from analysis: CMV +ve (3), died before day 10 (2) STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Saliba 89-Liver

Methods	Country: France Setting/Design: Single tertiary institution/parallel groups Time frame: January 1987 to June 1988 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Yes Follow-up period: 2 to 18 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Liver transplant recipients Recipient: CMV -ve Donor: CMV +ve or -ve IgG GROUP

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Saliba 89-Liver *(Continued)*

	Number: 22 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 12 Age: NS Sex (M/F): NS EXCLUSIONS Recipient CMV +ve
Interventions	IgG GROUP CMV IgG 250 mg/kg/dose IV on day of transplant, 125 mg/kg/dose every 10 days to 3 months NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection (CMV culture of blood, urine and seroconversion), fever, leucopenia, thrombocytopenia, hepatitis, enteritis (biopsy), pneumonitis (biopsy, BAL) 2. CMV syndrome: CMV infection, fever, leucopenia, thrombocytopenia 3. Tissue invasive CMV disease: CMV infection, hepatitis, enteritis, pneumonitis
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Schechner 93-Kidney

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: NS - Investigators: NS - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: NS Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV +ve ALG for rejection IgG GROUP

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Schechner 93-Kidney *(Continued)*

	Number: 14 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 20 Age: NS Sex (M/F): NS EXCLUSIONS Other immunosuppressive agents not stated
Interventions	IgG GROUP IgG 400 mg/kg IV on days 0, 21, 42 NO TREATMENT GROUP No treatment CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV disease: Positive viral culture, elevated IgG titre, fever, leucopenia, enteritis, pneumonitis 2. Death
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Snydman 87-Kidney

Methods	Country: USA Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: October 1982 to January 1986 Randomisation method: Central randomisation using randomisation lists Blinding - Participants: No - Investigators: No - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients Recipient: CMV -ve Donor: CMV +ve IgG GROUP Number: 24 Age: 31 ± 13.1 (SD) years Sex (M/F): 12/12

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Snydman 87-Kidney *(Continued)*

	NO TREATMENT GROUP Number: 35 Age: 30.9 ± 14.7 (SD) years Sex (M/F): 23/12 EXCLUSIONS Donor/Recipients CMV +ve/+ve, -ve/-ve
Interventions	IgG GROUP CMV IgG IV 150 mg/kg within 72 hours 100 mg/kg/dose at 2, 4 weeks 50 mg/kg/dose at 6, 8, 12, 16 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, azathioprine and steroids according to centre. Two IgG treated and 8 no treatment patients given ATG
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection (positive culture), fever, leucopenia, thrombocytopenia, elevated transaminases,pneumonitis, retinitis, encephalitis 2. CMV syndrome: Fever, leucopenia, thrombocytopenia, elevated transaminases 3. Tissue invasive CMV disease: Pneumonitis, retinitis, encephalitis 4. CMV infection: Viraemia, viral isolation from any site, seroconversion 5. Acute rejection (not defined) 6. Death 7. Opportunistic infections 8. Graft loss 9. Adverse reactions (systemic symptoms)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 99 enrolled, 40 excluded after randomisation STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Snydman 93-Liver

Methods	Country: USA Setting/Design: Multicentre tertiary institutions/parallel groups Time frame: December 1987 to June 1990 Randomisation method: Block randomisation Blinding - Participants: Yes - Investigators: Yes - Outcome assessors: Yes - Data analysis: NS Intention-to-treat: No Follow-up period: 12 months Loss to follow-up: 0%

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Snydman 93-Liver *(Continued)*

Participants	INCLUSION CRITERIA Liver transplant recipients of all ages and all CMV serostatus IgG GROUP Number: 73 (69 included in analysis) Age: 40.5 ± 17.3 (SD) years Sex (M/F): 39/30 PLACEBO GROUP Number: 73 (72 included in analysis) Age: 37.9 ± 19.4 (SD) years Sex (M/F): 49/23 EXCLUSIONS: NS
Interventions	IgG GROUP 150 mg/kg IV within 72 hours and 2, 4, 6, 8 weeks 100 mg/kg at 12, 16 weeks PLACEBO GROUP 1% serum albumin packaged and given as in treatment group CO-INTERVENTIONS Cyclosporin, azathioprine and steroids 35% received ATG (OKT-3) as part of study
Outcomes	STUDY OUTCOMES 1. CMV disease overall and for CMV serostatus: CMV infection, fever > 3 days, leucopenia < 4000/mm^3, atypical lymphocytes > 5%, platelets < 100,000, hepatitis, pneumonitis (clinical and biopsy/BAL) 2. CMV infection (asymptomatic and symptomatic): Positive CMV culture (conventional and shell vial) from any site. Screened blood, urine, throat swab wkly for 2 months, monthly to 6 months 3. CMV syndrome: Leucopenia < 4000/mm^3, atypical lymphocytes > 5%, platelets < 100,000 4. Tissue invasive CMV disease: Hepatitis, pneumonitis (clinical and biopsy/BAL), 2 organs involved 5. Deaths overall and from CMV disease 6. Opportunistic infections 7. Adverse reactions
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION Five excluded after randomisation: death (4), refusal to take part (1) STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Low risk	A - Adequate

Steinmuller 90-Kid

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No

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Steinmuller 90-Kid *(Continued)*

	- Outcome assessors: Yes - Data analysis: NS Intention-to-treat: NS Follow-up period: Unclear Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney transplant recipients CMV +ve; ALG induction or for rejection IgG GROUP Number: 16 Age: 44 years (mean) Sex (M/F): 9/7 NO TREATMENT GROUP Number: 18 Age: 43 years (mean) Sex (M/F): 13/5 EXCLUSIONS Recipient CMV -ve
Interventions	IgG GROUP IgG 500 mg/kg/dose IV at time of ALG, 2, 4 weeks 250 mg/kg/dose 6, 8 weeks NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: Positive CMV culture, fever, leucopenia < 4000/mm^3, hepatitis, pneumonitis, retinitis 2. CMV syndrome: Fever, leucopenia < 4000/mm^3 3. Tissue invasive CMV disease: Hepatitis, pneumonitis, retinitis 4. CMV infection (asymptomatic and symptomatic): Positive CMV culture (blood, urine, pharyngeal) 5. Acute rejection (not defined) 6. Death from CMV disease 7. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stippel 91-Kidney

Methods	Country: Germany Setting/Design: Single tertiary institution/parallel groups Time frame: NS Randomisation method: NS

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Stippel 91-Kidney *(Continued)*

	Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: NS Follow-up period: Unclear Loss to follow-up: Unclear
Participants	INCLUSION CRITERIA Kidney transplant recipients IgG 1 GROUP Number: 40 Age: NS Sex (M/F): NS IgG 2 GROUP Number: 40 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 40 Age: NS Sex (M/F): NS EXCLUSIONS: NS
Interventions	IgG 1 GROUP CMV IgG 2 mL/kg/dose IV Number of doses: NS IgG 2 GROUP IgG 15 g/dose IV Number of doses: NS NO TREATMENT GROUP No treatment CO-INTERVENTIONS ALG, cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV infection (asymptomatic and symptomatic) definition: NS
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

Stratta 94-K/P

Methods	Country: USA

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Stratta 94-K/P *(Continued)*

	Setting/Design: Single tertiary institution Time frame: December 1990 to February 1992 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: 6 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA Kidney/pancreas transplant recipients Recipient CMV +ve IgG 1 GROUP Number: 9 Age: 35.4 ± 2 (SEM) years Sex (M/F): 5M/4F IgG 2 GROUP Number: 9 Age: 34.9 ± 2 (SEM) years Sex (M/F): 5M/4F EXCLUSIONS: NS
Interventions	IgG 1 GROUP CMV IgG 150 mg/kg/dose IV at 2-3 days 100 mg/kg/dose at 2, 4, 6, 8 weeks Ganciclovir 2.5 mg/kg IV twice daily for 14 days Acyclovir 800 mg orally 4 times daily for 3 months IgG 2 GROUP IgG 500 mg/kg/dose IV at 2-3 days and 2 ,4, 6, 8 weeks Ganciclovir 2.5 mg/kg IV twice daily for 14 days Acyclovir 800 mg orally 4 times daily for 3 months CO-INTERVENTIONS ATG, cyclosporin, azathioprine, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease: CMV infection, fever, hepatitis, enteritis, pneumonitis (histology/viral culture) 2. CMV infection (asymptomatic and symptomatic): Positive culture (conventional, shell vial), seroconversion or 4-fold rise in IgG. Weekly surveillance 3. Acute rejection (not defined) 4. Death 5. Opportunistic infections (non-viral, viral non-CMV) 6. Graft loss
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: None reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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Wirnsberger 99-Kid

Methods	Country: Austria Setting/Design: Single tertiary institution/parallel groups Time frame: September 1992 to March 1995 Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: No Follow-up period: Mean 45 months Loss to follow-up: 0%
Participants	INCLUSION CRITERIA First kidney transplant IgG GROUP Number: 38 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 36 Age: NS Sex (M/F): NS EXCLUSIONS Retransplants, ALG for induction, CMV antigen +ve at transplant
Interventions	IgG GROUP CMV IgG (Cytotect) 2 mL/kg/dose IV pre-transplant, 1, 2, 4, 18, 32, 46, 60, 74, 88 days NO TREATMENT GROUP No treatment CO-INTERVENTIONS Cyclosporin, steroids
Outcomes	STUDY OUTCOMES 1. CMV disease overall and according to CMV serostatus (CMV infection, fever, leucopenia, thrombocytopenia, enteritis, pneumonitis, encephalitis) 2. CMV infection (asymptomatic and symptomatic); CMV antigenaemia and/or IgG or IgM seroconversion 3. Acute rejection (biopsy proven)
Notes	EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION 83 randomised, 8 excluded because of graft loss STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

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Yamani 05-Heart

Methods	Country: USA Setting/Design: Single tertiary institution/parallel groups Time frame: NS Randomisation method: NS Blinding - Participants: No - Investigators: No - Outcome assessors: NS - Data analysis: NS Intention-to-treat: Unclear Follow-up period: NS Loss to follow-up: NS
Participants	INCLUSION CRITERIA Heart transplant recipients developing moderate hypogammaglobulinaemia (IgG: 350-500 mg/dL) randomised at 105 ± 63 days post-transplant IgG GROUP Number: 13 Age: NS Sex (M/F): NS NO TREATMENT GROUP Number: 10 Age: NS Sex (M/F): NS EXCLUSIONS Patients with normal gammaglobulin levels
Interventions	IgG GROUP CMV IgG Dosage regimen: NS PLACEBO GROUP Type and dosage regimen: NS CO-INTERVENTIONS: NS
Outcomes	STUDY OUTCOMES 1. CMV infection: definition NS
Notes	56 patients developed hypogammaglobulinaemia but 33 declined randomisation EXCLUSIONS POST RANDOMISATION BUT PRE-INTERVENTION: Non reported STOP OR END POINT/S: None reported ADDITIONAL DATA REQUESTED FROM AUTHORS: None

Risk of bias

Bias	Authors' judgement	Support for judgement
Allocation concealment?	Unclear risk	B - Unclear

ATG = antibody treatment with antilymphocyte globulin, antithymocyte globulin or OKT3; BAL = specimens obtained from bronchopulmonary lavage; CFT = complement fixation test; CMV = cytomegalovirus; IgG = Immunoglobulin G; NS = not stated; pfu = plague forming units

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Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Fehir 1989	Non randomised kidney transplant patients included in the control group
Stratta 1992	Non randomised patients included in prophylaxis group

DATA AND ANALYSES

Comparison 1. IgG versus placebo/no treatment (all patients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	16	770	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.61, 1.05]
1.1 CMV IgG	11	595	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.55, 1.13]
1.2 IgG	5	175	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.54, 1.28]
2 CMV infection	15	775	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.80, 1.10]
2.1 CMV IgG	12	664	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.80, 1.19]
2.2 IgG	3	111	Risk Ratio (M-H, Random, 95% CI)	0.81 [0.61, 1.07]
3 All-cause mortality	8	502	Risk Ratio (M-H, Random, 95% CI)	0.57 [0.32, 1.03]
3.1 CMV IgG	7	468	Risk Ratio (M-H, Random, 95% CI)	0.58 [0.32, 1.05]
3.2 IgG	1	34	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.02, 10.69]
4 Death due to CMV disease	6	346	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.80]
4.1 CMV IgG	4	283	Risk Ratio (M-H, Random, 95% CI)	0.33 [0.14, 0.80]
4.2 IgG	2	63	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Mortality due to CMV disease and non-CMV causes	3	488	Risk Ratio (M-H, Random, 95% CI)	0.56 [0.29, 1.07]
5.1 Death due to CMV disease	3	244	Risk Ratio (M-H, Random, 95% CI)	0.37 [0.15, 0.93]
5.2 Death due to non CMV causes	3	244	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.30, 2.08]
6 Acute rejection	7	318	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.66, 1.16]
6.1 CMV IgG	4	205	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.51, 1.40]

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Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.2 IgG	3	113	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.49, 1.27]
7 Graft loss	7	297	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.35, 1.53]
7.1 CMV IgG	5	235	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.31, 1.73]
7.2 IgG	2	62	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.18, 3.05]
8 Opportunistic infections	6	422	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.28, 1.32]
8.1 CMV IgG	4	344	Risk Ratio (M-H, Random, 95% CI)	0.39 [0.19, 0.79]
8.2 IgG	2	78	Risk Ratio (M-H, Random, 95% CI)	1.56 [0.62, 3.92]

Analysis 1.1. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 1 CMV disease.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.1.1 CMV IgG					
Boland 93-Heart/kid	3/14	2/14		2.51%	1.5[0.29,7.65]
Greger 85a-Kidney	0/12	2/12		0.82%	0.2[0.01,3.77]
Greger 85b-Kidney	7/12	4/12		6.47%	1.75[0.69,4.44]
Grundmann 87-Kidney	5/50	11/50		5.97%	0.45[0.17,1.21]
Kruger 03-Lung	11/22	8/22		9.86%	1.38[0.69,2.75]
Metselaar 89-Kidney	7/19	6/20		6.93%	1.23[0.5,2.99]
Mitsioni 87-Kidney	4/13	4/15		4.49%	1.15[0.36,3.72]
Saliba 89-Liver	5/22	6/12		6.22%	0.45[0.17,1.18]
Snydman 87-Kidney	5/24	21/35		7.76%	0.35[0.15,0.79]
Snydman 93-Liver	13/69	22/72		11.74%	0.62[0.34,1.12]
Wirnsberger 99-Kid	5/38	6/36		5%	0.79[0.26,2.36]
Subtotal (95% CI)	**295**	**300**		**67.77%**	**0.79[0.55,1.13]**
Total events: 65 (IgG), 92 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.12; Chi^2=15.24, df=10(P=0.12); I^2=34.37%					
Test for overall effect: Z=1.29(P=0.2)					
1.1.2 IgG					
Cofer 91-Liver	8/25	5/25		6.08%	1.6[0.61,4.22]
Kasiske 89-Kidney	8/15	10/13		12.73%	0.69[0.4,1.21]
McCune 92-Kid/KP	3/13	5/16		4.12%	0.74[0.22,2.53]
Schechner 93-Kidney	5/14	6/20		6.08%	1.19[0.45,3.14]
Steinmuller 90-Kid	2/16	7/18		3.21%	0.32[0.08,1.33]
Subtotal (95% CI)	**83**	**92**		**32.23%**	**0.83[0.54,1.28]**
Total events: 26 (IgG), 33 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.03; Chi^2=4.45, df=4(P=0.35); I^2=10.05%					
Test for overall effect: Z=0.83(P=0.4)					
Total (95% CI)	**378**	**392**		**100%**	**0.8[0.61,1.05]**
			IgG 0.01 0.1 1 10 100 Placebo/no treatment		

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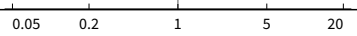
Study or subgroup	IgG	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Total events: 91 (IgG), 125 (Placebo/no treatment)					
Heterogeneity: Tau²=0.07; Chi²=19.64, df=15(P=0.19); I²=23.62%					
Test for overall effect: Z=1.58(P=0.11)					
Test for subgroup differences: Not applicable					

Analysis 1.2. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 2 CMV infection.

Study or subgroup	IgG	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.2.1 CMV IgG					
Boland 93-Heart/kid	7/14	7/14		3.91%	1[0.48,2.1]
Greger 85a-Kidney	4/12	3/12		1.47%	1.33[0.38,4.72]
Greger 85b-Kidney	8/12	4/12		2.8%	2[0.82,4.89]
Grundmann 87-Kidney	32/50	31/50		14.31%	1.03[0.76,1.39]
Kruger 03-Lung	16/22	13/22		9.19%	1.23[0.8,1.9]
Metselaar 89-Kidney	15/19	11/20		8.42%	1.44[0.91,2.27]
Mitsioni 87-Kidney	4/13	5/15		1.96%	0.92[0.31,2.73]
Snydman 87-Kidney	13/24	20/35		8.23%	0.95[0.59,1.51]
Snydman 93-Liver	39/69	44/72		15.52%	0.92[0.7,1.22]
Stippel 91-Kidney	11/40	19/40		5.59%	0.58[0.32,1.05]
Wirnsberger 99-Kid	8/38	15/36		4.04%	0.51[0.24,1.05]
Yamani 05-Heart	2/13	6/10		1.26%	0.26[0.07,1.01]
Subtotal (95% CI)	**326**	**338**		**76.72%**	**0.97[0.8,1.19]**
Total events: 159 (IgG), 178 (Placebo/no treatment)					
Heterogeneity: Tau²=0.04; Chi²=17.08, df=11(P=0.11); I²=35.6%					
Test for overall effect: Z=0.26(P=0.8)					
1.2.2 IgG					
Cofer 91-Liver	11/25	14/25		6.2%	0.79[0.45,1.38]
Kasiske 89-Kidney	10/14	11/13		10.05%	0.84[0.56,1.26]
Steinmuller 90-Kid	9/16	13/18		7.04%	0.78[0.46,1.31]
Subtotal (95% CI)	**55**	**56**		**23.28%**	**0.81[0.61,1.07]**
Total events: 30 (IgG), 38 (Placebo/no treatment)					
Heterogeneity: Tau²=0; Chi²=0.08, df=2(P=0.96); I²=0%					
Test for overall effect: Z=1.48(P=0.14)					
Total (95% CI)	**381**	**394**		**100%**	**0.94[0.8,1.1]**
Total events: 189 (IgG), 216 (Placebo/no treatment)					
Heterogeneity: Tau²=0.02; Chi²=18.48, df=14(P=0.19); I²=24.23%					
Test for overall effect: Z=0.81(P=0.42)					
Test for subgroup differences: Not applicable					



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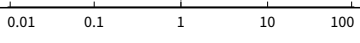
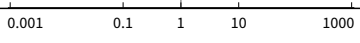
Analysis 1.3. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 3 All-cause mortality.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.3.1 CMV IgG					
Fassbinder 86-Kidney	0/42	0/34			Not estimable
Greger 85a-Kidney	0/12	0/12			Not estimable
Greger 85b-Kidney	0/12	0/12			Not estimable
Grundmann 87-Kidney	0/50	0/50			Not estimable
Kruger 03-Lung	2/22	4/22		13.47%	0.5[0.1,2.45]
Snydman 87-Kidney	1/24	5/35		7.86%	0.29[0.04,2.34]
Snydman 93-Liver	11/69	18/72		75.19%	0.64[0.33,1.25]
Subtotal (95% CI)	**231**	**237**		**96.52%**	**0.58[0.32,1.05]**
Total events: 14 (IgG), 27 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.54, df=2(P=0.76); I^2=0%					
Test for overall effect: Z=1.81(P=0.07)					
1.3.2 IgG					
Schechner 93-Kidney	0/14	1/20		3.48%	0.47[0.02,10.69]
Subtotal (95% CI)	**14**	**20**		**3.48%**	**0.47[0.02,10.69]**
Total events: 0 (IgG), 1 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.48(P=0.63)					
Total (95% CI)	**245**	**257**		**100%**	**0.57[0.32,1.03]**
Total events: 14 (IgG), 28 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.56, df=3(P=0.91); I^2=0%					
Test for overall effect: Z=1.86(P=0.06)					
Test for subgroup differences: Not applicable					



Analysis 1.4. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 4 Death due to CMV disease.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.4.1 CMV IgG					
Kruger 03-Lung	0/22	1/22		7.86%	0.33[0.01,7.76]
Metselaar 89-Kidney	0/19	4/20		9.55%	0.12[0.01,2.03]
Snydman 87-Kidney	1/24	3/35		16.06%	0.49[0.05,4.4]
Snydman 93-Liver	4/69	12/72		66.53%	0.35[0.12,1.03]
Subtotal (95% CI)	**134**	**149**		**100%**	**0.33[0.14,0.8]**
Total events: 5 (IgG), 20 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=3(P=0.88); I^2=0%					
Test for overall effect: Z=2.46(P=0.01)					
1.4.2 IgG					
McCune 92-Kid/KP	0/13	0/16			Not estimable
Steinmuller 90-Kid	0/16	0/18			Not estimable
Subtotal (95% CI)	**29**	**34**			**Not estimable**
Total events: 0 (IgG), 0 (Placebo/no treatment)					



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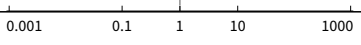
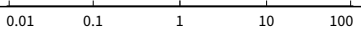
Study or subgroup	IgG	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
Total (95% CI)	**163**	**183**		**100%**	**0.33[0.14,0.8]**
Total events: 5 (IgG), 20 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.65, df=3(P=0.88); I^2=0%					
Test for overall effect: Z=2.46(P=0.01)					
Test for subgroup differences: Not applicable					



Analysis 1.5. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 5 Mortality due to CMV disease and non-CMV causes.

Study or subgroup	IgG	Placebo/no treatment	Risk Ratio	Weight	Risk Ratio
	n/N	n/N	M-H, Random, 95% CI		M-H, Random, 95% CI
1.5.1 Death due to CMV disease					
Kruger 03-Lung	0/22	1/22		4.18%	0.33[0.01,7.76]
Snydman 87-Kidney	1/24	3/35		8.54%	0.49[0.05,4.4]
Snydman 93-Liver	4/69	12/72		35.37%	0.35[0.12,1.03]
Subtotal (95% CI)	**115**	**129**		**48.09%**	**0.37[0.15,0.93]**
Total events: 5 (IgG), 16 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.08, df=2(P=0.96); I^2=0%					
Test for overall effect: Z=2.11(P=0.03)					
1.5.2 Death due to non CMV causes					
Kruger 03-Lung	1/22	3/22		8.68%	0.33[0.04,2.96]
Snydman 87-Kidney	0/24	3/35		4.86%	0.21[0.01,3.81]
Snydman 93-Liver	7/69	6/72		38.37%	1.22[0.43,3.44]
Subtotal (95% CI)	**115**	**129**		**51.91%**	**0.79[0.3,2.08]**
Total events: 8 (IgG), 12 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.06; Chi^2=2.13, df=2(P=0.35); I^2=5.93%					
Test for overall effect: Z=0.47(P=0.63)					
Total (95% CI)	**230**	**258**		**100%**	**0.56[0.29,1.07]**
Total events: 13 (IgG), 28 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=3.71, df=5(P=0.59); I^2=0%					
Test for overall effect: Z=1.76(P=0.08)					
Test for subgroup differences: Not applicable					



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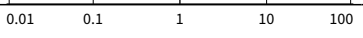
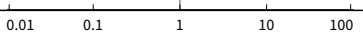
Analysis 1.6. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 6 Acute rejection.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.6.1 CMV IgG					
Boland 93-Heart/kid	5/14	6/14		8.78%	0.83[0.33,2.11]
Kruger 03-Lung	13/22	11/22		24.45%	1.18[0.69,2.04]
Snydman 87-Kidney	3/24	16/35		6.08%	0.27[0.09,0.84]
Wirnsberger 99-Kid	17/38	16/36		27.72%	1.01[0.61,1.67]
Subtotal (95% CI)	**98**	**107**		**67.04%**	**0.84[0.51,1.4]**
Total events: 38 (IgG), 49 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.13; Chi^2=6.06, df=3(P=0.11); I^2=50.53%					
Test for overall effect: Z=0.65(P=0.51)					
1.6.2 IgG					
Cofer 91-Liver	9/25	11/25		15.8%	0.82[0.41,1.62]
McCune 92-Kid/KP	5/13	8/16		10.54%	0.77[0.33,1.79]
Steinmuller 90-Kid	4/16	6/18		6.62%	0.75[0.26,2.19]
Subtotal (95% CI)	**54**	**59**		**32.96%**	**0.79[0.49,1.27]**
Total events: 18 (IgG), 25 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=2(P=0.99); I^2=0%					
Test for overall effect: Z=0.98(P=0.33)					
Total (95% CI)	**152**	**166**		**100%**	**0.88[0.66,1.16]**
Total events: 56 (IgG), 74 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.01; Chi^2=6.23, df=6(P=0.4); I^2=3.67%					
Test for overall effect: Z=0.92(P=0.36)					
Test for subgroup differences: Not applicable					



Analysis 1.7. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 7 Graft loss.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
1.7.1 CMV IgG					
Greger 85a-Kidney	0/12	0/12			Not estimable
Greger 85b-Kidney	2/12	1/12		10.66%	2[0.21,19.23]
Grundmann 87-Kidney	1/50	0/50		5.41%	3[0.13,71.92]
Mitsioni 87-Kidney	0/13	2/15		6.27%	0.23[0.01,4.37]
Snydman 87-Kidney	4/24	10/35		50.79%	0.58[0.21,1.64]
Subtotal (95% CI)	**111**	**124**		**73.13%**	**0.73[0.31,1.73]**
Total events: 7 (IgG), 13 (Placebo/no treatment)					
Heterogeneity: Tau^2=0; Chi^2=2.3, df=3(P=0.51); I^2=0%					
Test for overall effect: Z=0.72(P=0.47)					
1.7.2 IgG					
Kasiske 89-Kidney	2/15	2/13		16.59%	0.87[0.14,5.32]
Steinmuller 90-Kid	1/16	2/18		10.28%	0.56[0.06,5.63]
Subtotal (95% CI)	**31**	**31**		**26.87%**	**0.73[0.18,3.05]**
Total events: 3 (IgG), 4 (Placebo/no treatment)					



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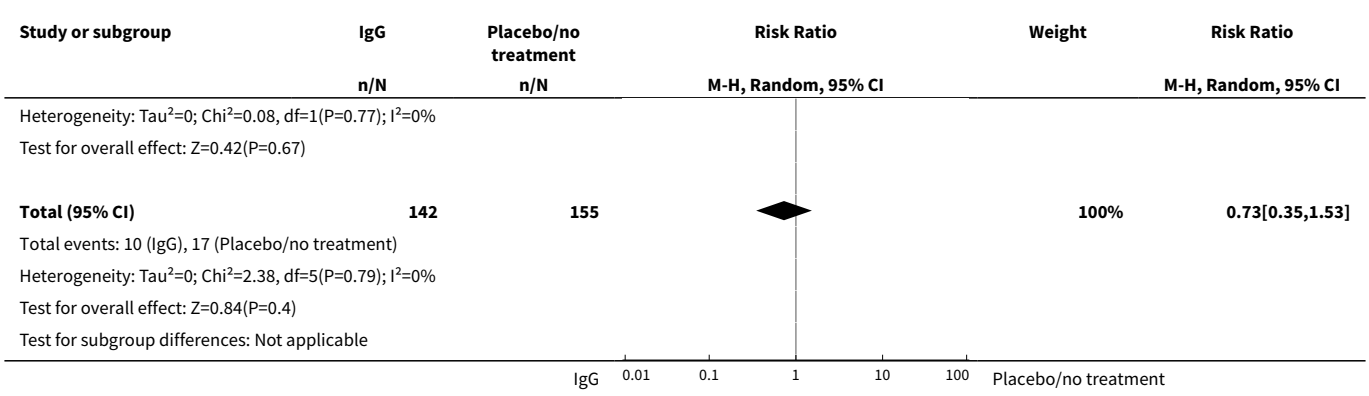
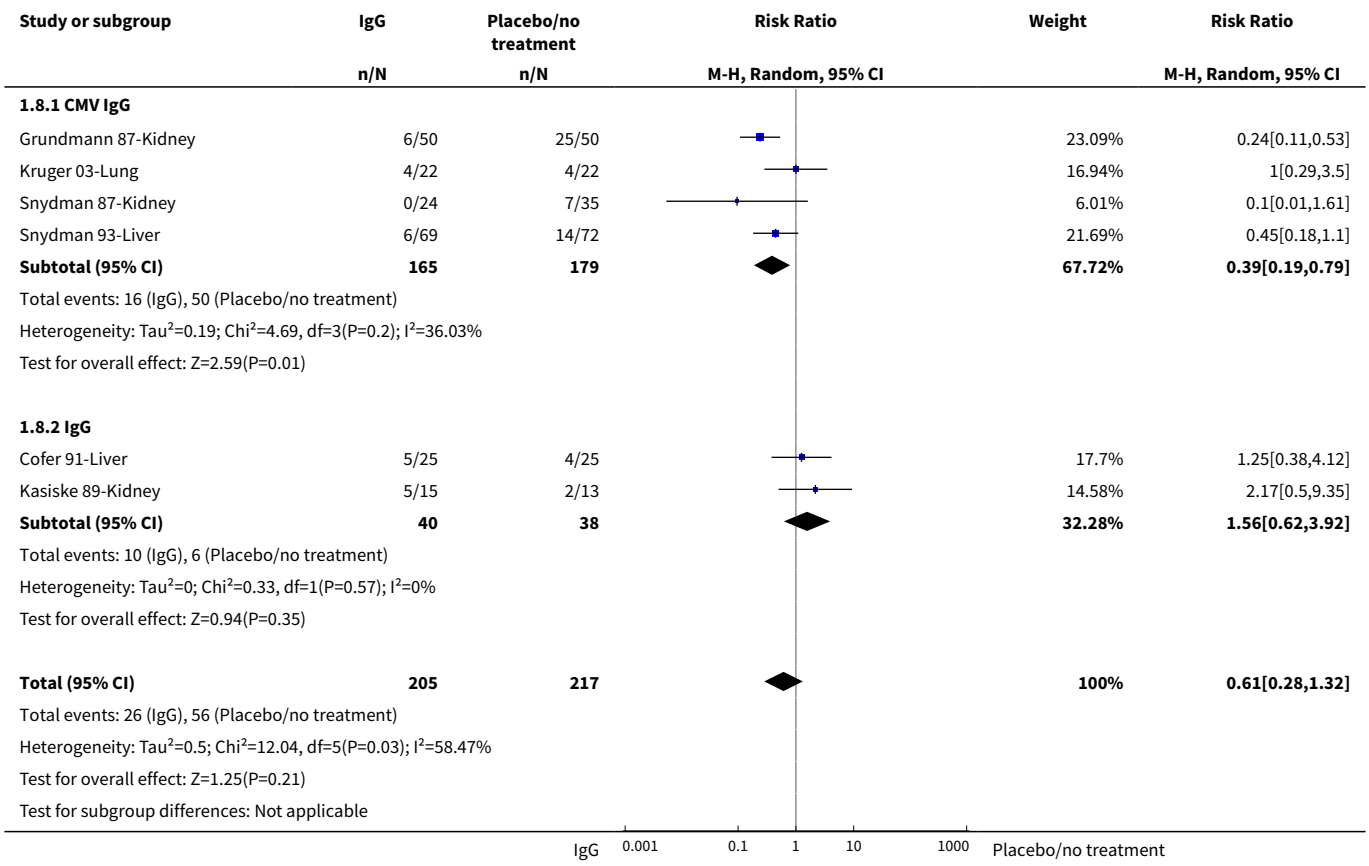


Analysis 1.8. Comparison 1 IgG versus placebo/no treatment (all patients), Outcome 8 Opportunistic infections.



Comparison 2. IgG versus placebo/no treatment (CMV positive recipients)

Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CMV disease	8	334	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.54, 1.33]

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Outcome or sub-group title	No. of studies	No. of partici-pants	Statistical method	Effect size
1.1 CMV IgG	5	237	Risk Ratio (M-H, Random, 95% CI)	0.88 [0.45, 1.71]
1.2 IgG	3	97	Risk Ratio (M-H, Random, 95% CI)	0.75 [0.36, 1.56]
2 CMV infection	5	243	Risk Ratio (M-H, Random, 95% CI)	0.94 [0.76, 1.16]
2.1 CMV IgG	4	209	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.76, 1.23]
2.2 IgG	1	34	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.46, 1.31]

Analysis 2.1. Comparison 2 IgG versus placebo/no treatment (CMV positive recipients), Outcome 1 CMV disease.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
2.1.1 CMV IgG					
Grundmann 87-Kidney	3/34	6/35		10.42%	0.51[0.14,1.89]
Kruger 03-Lung	11/22	8/22		26.96%	1.38[0.69,2.75]
Metselaar 89-Kidney	3/11	3/11		9.63%	1[0.26,3.91]
Snydman 93-Liver	3/31	8/28		11.58%	0.34[0.1,1.15]
Wirnsberger 99-Kid	3/21	1/22		4.1%	3.14[0.35,27.88]
Subtotal (95% CI)	**119**	**118**		**62.69%**	**0.88[0.45,1.71]**
Total events: 23 (IgG), 26 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.18; Chi^2=5.94, df=4(P=0.2); I^2=32.65%					
Test for overall effect: Z=0.38(P=0.71)					
2.1.2 IgG					
McCune 92-Kid/KP	3/13	5/16		11.49%	0.74[0.22,2.53]
Schechner 93-Kidney	5/14	6/20		16.83%	1.19[0.45,3.14]
Steinmuller 90-Kid	2/16	7/18		8.98%	0.32[0.08,1.33]
Subtotal (95% CI)	**43**	**54**		**37.31%**	**0.75[0.36,1.56]**
Total events: 10 (IgG), 18 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.06; Chi^2=2.3, df=2(P=0.32); I^2=12.94%					
Test for overall effect: Z=0.76(P=0.45)					
Total (95% CI)	**162**	**172**		**100%**	**0.84[0.54,1.33]**
Total events: 33 (IgG), 44 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.07; Chi^2=8.48, df=7(P=0.29); I^2=17.46%					
Test for overall effect: Z=0.73(P=0.47)					
Test for subgroup differences: Not applicable					

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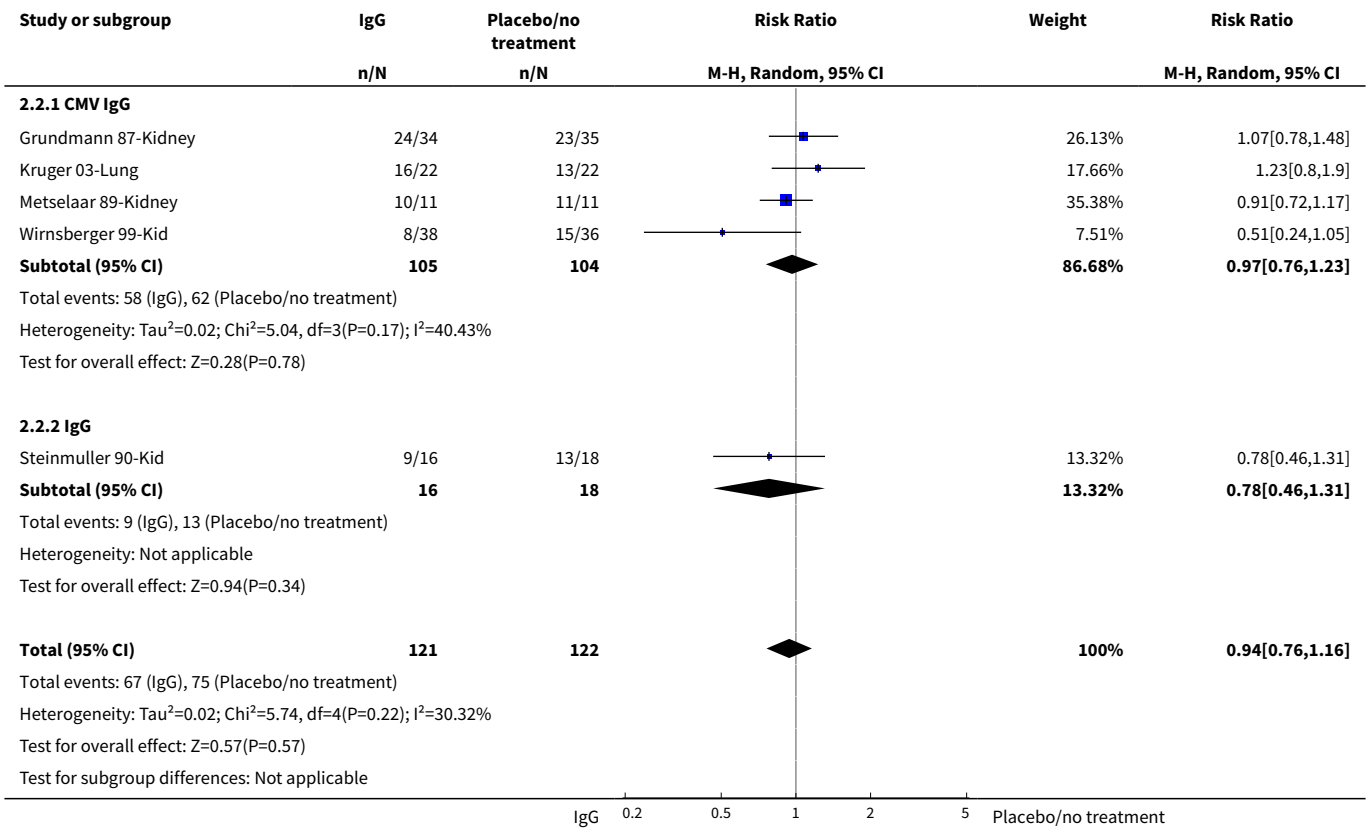
Analysis 2.2. Comparison 2 IgG versus placebo/no treatment (CMV positive recipients), Outcome 2 CMV infection.



Comparison 3. Immunoglobulins versus placebo/no treatment (CMV negative recipients of CMV positive donors)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CMV disease	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 CMV IgG	6	176	Risk Ratio (M-H, Random, 95% CI)	0.63 [0.36, 1.12]
1.2 IgG	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 CMV infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV IgG	4	170	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.63, 1.34]
2.2 IgG	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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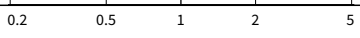
Analysis 3.1. Comparison 3 Immunoglobulins versus placebo/no treatment (CMV negative recipients of CMV positive donors), Outcome 1 CMV disease.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.1.1 CMV IgG					
Boland 93-Heart/kid	3/14	2/14		9%	1.5[0.29,7.65]
Metselaar 89-Kidney	4/5	3/4		22.06%	1.07[0.52,2.18]
Saliba 89-Liver	4/15	6/7		18.5%	0.31[0.13,0.76]
Snydman 87-Kidney	5/24	21/35		19.79%	0.35[0.15,0.79]
Snydman 93-Liver	10/19	10/19		24.52%	1[0.55,1.83]
Wirnsberger 99-Kid	1/11	3/9		6.13%	0.27[0.03,2.19]
Subtotal (95% CI)	**88**	**88**		**100%**	**0.63[0.36,1.12]**
Total events: 27 (IgG), 45 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.25; Chi^2=10.91, df=5(P=0.05); I^2=54.15%					
Test for overall effect: Z=1.56(P=0.12)					
3.1.2 IgG					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IgG), 0 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					

Analysis 3.2. Comparison 3 Immunoglobulins versus placebo/no treatment (CMV negative recipients of CMV positive donors), Outcome 2 CMV infection.

Study or subgroup	IgG n/N	Placebo/no treatment n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
3.2.1 CMV IgG					
Boland 93-Heart/kid	7/14	7/14		19.48%	1[0.48,2.1]
Metselaar 89-Kidney	5/5	3/4		24.97%	1.31[0.7,2.44]
Snydman 87-Kidney	13/24	20/35		35.51%	0.95[0.59,1.51]
Wirnsberger 99-Kid	8/38	15/36		20.04%	0.51[0.24,1.05]
Subtotal (95% CI)	**81**	**89**		**100%**	**0.92[0.63,1.34]**
Total events: 33 (IgG), 45 (Placebo/no treatment)					
Heterogeneity: Tau^2=0.05; Chi^2=4.42, df=3(P=0.22); I^2=32.17%					
Test for overall effect: Z=0.46(P=0.65)					
3.2.2 IgG					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (IgG), 0 (Placebo/no treatment)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



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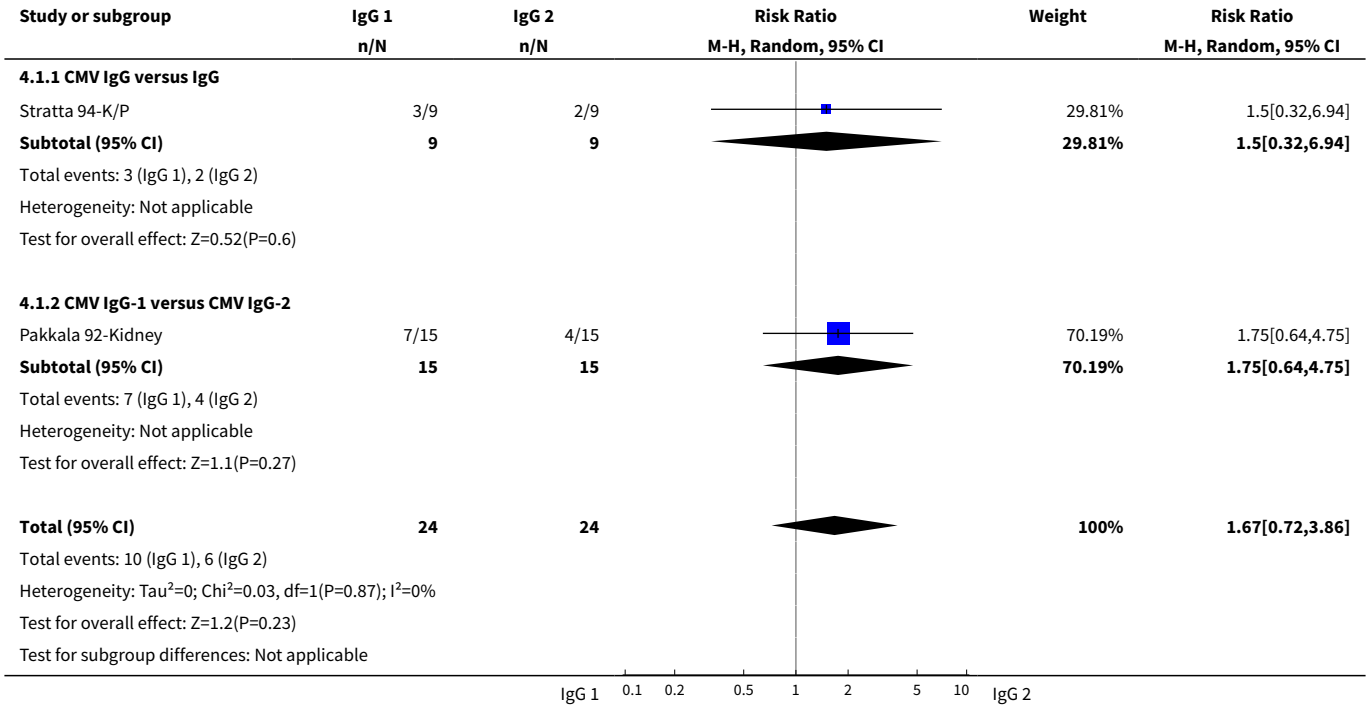
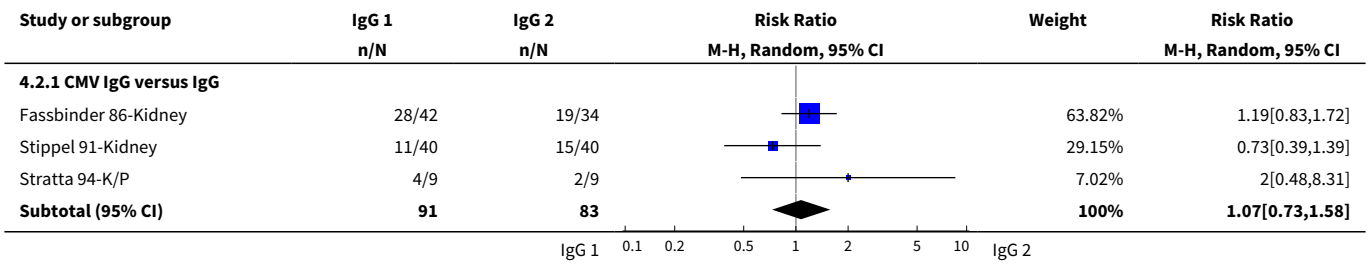
Comparison 4. Comparisons between different immunoglobulins

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	2	48	Risk Ratio (M-H, Random, 95% CI)	1.67 [0.72, 3.86]
1.1 CMV IgG versus IgG	1	18	Risk Ratio (M-H, Random, 95% CI)	1.5 [0.32, 6.94]
1.2 CMV IgG-1 versus CMV IgG-2	1	30	Risk Ratio (M-H, Random, 95% CI)	1.75 [0.64, 4.75]
2 CMV infection	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV IgG versus IgG	3	174	Risk Ratio (M-H, Random, 95% CI)	1.07 [0.73, 1.58]

Analysis 4.1. Comparison 4 Comparisons between different immunoglobulins, Outcome 1 CMV disease.



Analysis 4.2. Comparison 4 Comparisons between different immunoglobulins, Outcome 2 CMV infection.



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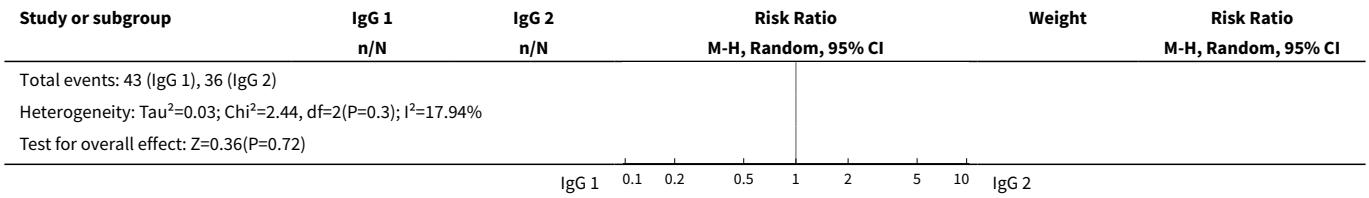

Comparison 5. Antiviral medication alone versus IgG alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All patients	4	392	Risk Ratio (M-H, Random, 95% CI)	0.68 [0.48, 0.98]
1.2 CMV positive recipients	3	221	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.34, 1.31]
1.3 CMV negative recipients of CMV positive organs	2	114	Risk Ratio (M-H, Random, 95% CI)	0.59 [0.33, 1.08]
1.4 Kidney transplant recipients	3	238	Risk Ratio (M-H, Random, 95% CI)	1.26 [0.75, 2.12]
1.5 Liver transplant recipients	1	26	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.17, 1.08]
1.6 Heart transplant recipients	1	31	Risk Ratio (M-H, Random, 95% CI)	0.16 [0.02, 1.15]
2 CMV syndrome	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All patients	3	126	Risk Ratio (M-H, Random, 95% CI)	0.96 [0.38, 2.47]
3 CMV tissue invasive disease	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All patients	3	126	Risk Ratio (M-H, Random, 95% CI)	0.48 [0.08, 3.03]
4 CMV infection in CMV positive heart transplant recipients	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 All-cause mortality	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
5.1 All patients	4	392	Risk Ratio (M-H, Random, 95% CI)	0.70 [0.37, 1.33]
5.2 CMV positive recipients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.05, 4.65]
5.3 CMV negative recipients of CMV positive organs	1	51	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.4 Kidney transplant recipients	2	95	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.5 Heart transplant recipients	1	31	Risk Ratio (M-H, Random, 95% CI)	0.47 [0.05, 4.65]
6 Death due to CMV disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All patients	4	392	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Acute rejection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 All patients	4	392	Risk Ratio (M-H, Random, 95% CI)	0.82 [0.66, 1.03]
7.2 CMV positive recipients	2	75	Risk Ratio (M-H, Random, 95% CI)	0.91 [0.54, 1.53]
7.3 CMV recipients of CMV positive organs	1	51	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.38, 1.36]
8 Graft loss in CMV positive recipients	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 All patients	2	95	Risk Ratio (M-H, Random, 95% CI)	0.83 [0.16, 4.26]
9 Opportunistic infections in CMV positive heart transplant recipients	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
10 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
10.1 Leucopenia	2	82	Risk Ratio (M-H, Random, 95% CI)	2.82 [0.12, 64.39]
10.2 Increase in creatinine	1	31	Risk Ratio (M-H, Random, 95% CI)	4.71 [0.24, 90.69]

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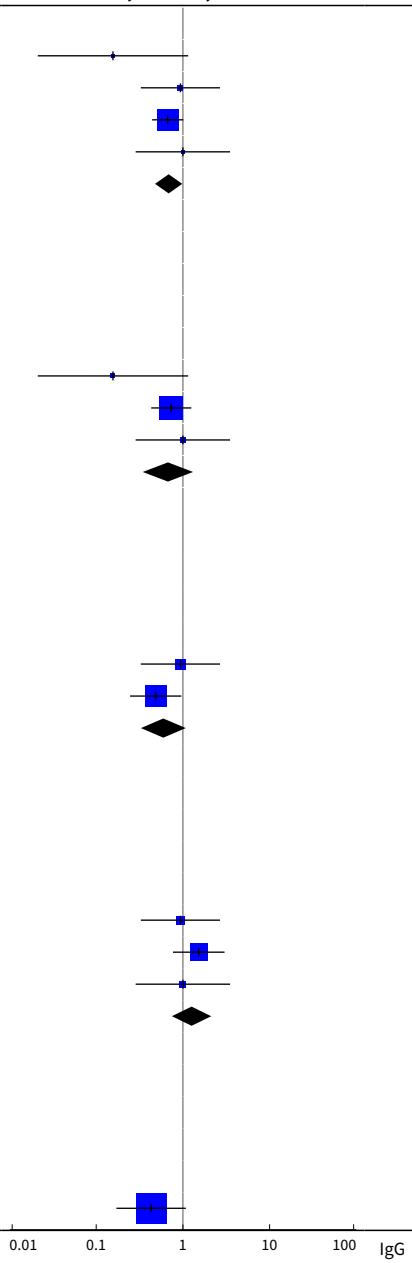
Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
10.3 Liver dysfunction	1	51	Risk Ratio (M-H, Random, 95% CI)	3.36 [0.14, 78.79]
10.4 Neurological dysfunction	1	51	Risk Ratio (M-H, Random, 95% CI)	3.36 [0.14, 78.79]

Analysis 5.1. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 1 CMV disease.

Study or subgroup	GCV or ACV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.1.1 All patients					
Aguado 95-Heart/GCV	1/16	6/15		5.1%	0.16[0.02,1.15]
Conti 94-Kidney/GCV	5/24	6/27		16.8%	0.94[0.33,2.68]
Dunn 94-all/ACV	28/133	42/133		65.83%	0.67[0.44,1.01]
Morales 02-Kid/GCV	4/22	4/22		12.26%	1[0.29,3.5]
Subtotal (95% CI)	**195**	**197**		**100%**	**0.68[0.48,0.98]**
Total events: 38 (GCV or ACV), 58 (IgG)					
Heterogeneity: Tau²=0; Chi²=2.85, df=3(P=0.42); I²=0%					
Test for overall effect: Z=2.05(P=0.04)					
5.1.2 CMV positive recipients					
Aguado 95-Heart/GCV	1/16	6/15		7.71%	0.16[0.02,1.15]
Dunn 94-all/ACV	18/77	22/69		73.77%	0.73[0.43,1.25]
Morales 02-Kid/GCV	4/22	4/22		18.52%	1[0.29,3.5]
Subtotal (95% CI)	**115**	**106**		**100%**	**0.67[0.34,1.31]**
Total events: 23 (GCV or ACV), 32 (IgG)					
Heterogeneity: Tau²=0.1; Chi²=2.58, df=2(P=0.28); I²=22.46%					
Test for overall effect: Z=1.16(P=0.24)					
5.1.3 CMV negative recipients of CMV positive organs					
Conti 94-Kidney/GCV	5/24	6/27		32.76%	0.94[0.33,2.68]
Dunn 94-all/ACV	8/31	17/32		67.24%	0.49[0.25,0.96]
Subtotal (95% CI)	**55**	**59**		**100%**	**0.59[0.33,1.08]**
Total events: 13 (GCV or ACV), 23 (IgG)					
Heterogeneity: Tau²=0.01; Chi²=1.06, df=1(P=0.3); I²=5.86%					
Test for overall effect: Z=1.71(P=0.09)					
5.1.4 Kidney transplant recipients					
Conti 94-Kidney/GCV	5/24	6/27		26.57%	0.94[0.33,2.68]
Dunn 94-all/ACV	17/72	11/71		54.04%	1.52[0.77,3.02]
Morales 02-Kid/GCV	4/22	4/22		19.39%	1[0.29,3.5]
Subtotal (95% CI)	**118**	**120**		**100%**	**1.26[0.75,2.12]**
Total events: 26 (GCV or ACV), 21 (IgG)					
Heterogeneity: Tau²=0; Chi²=0.73, df=2(P=0.69); I²=0%					
Test for overall effect: Z=0.86(P=0.39)					
5.1.5 Liver transplant recipients					
Dunn 94-all/ACV	4/14	8/12		100%	0.43[0.17,1.08]



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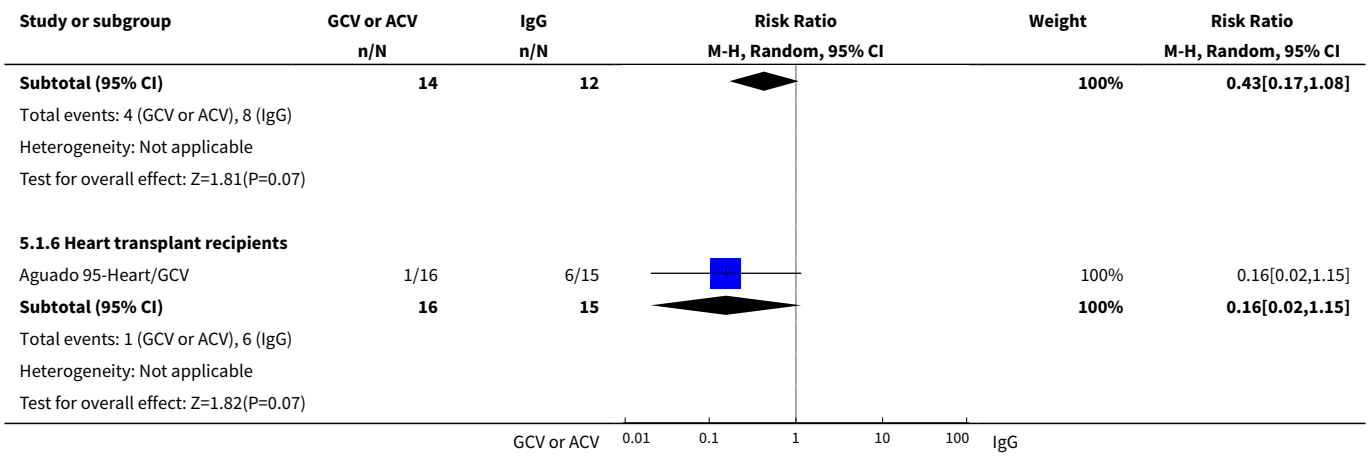
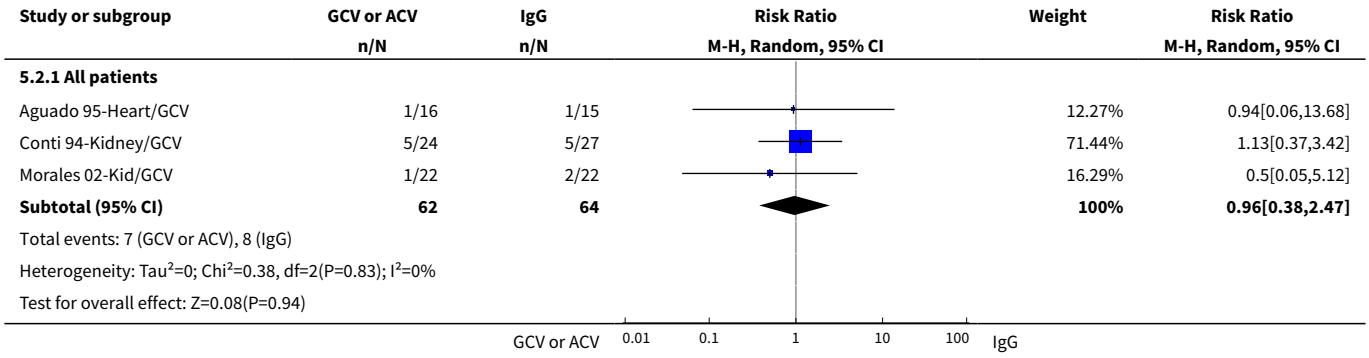
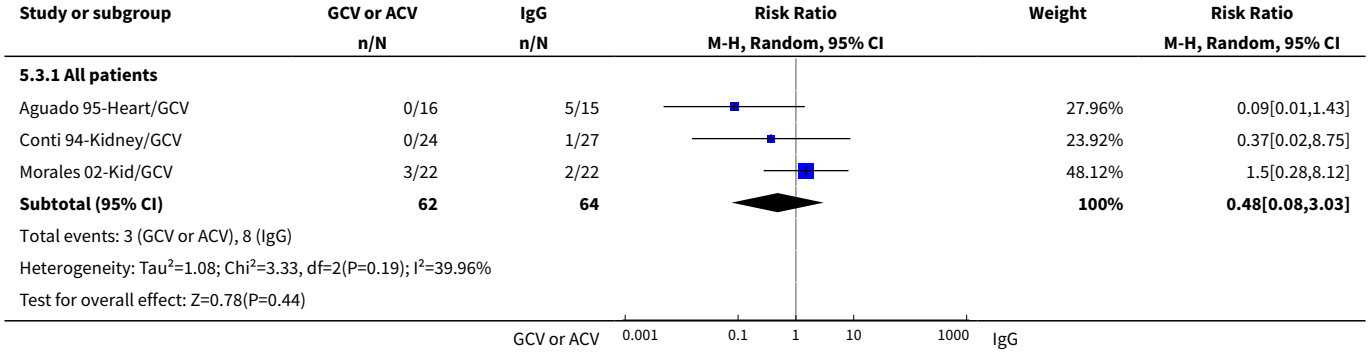


Analysis 5.2. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 2 CMV syndrome.



Analysis 5.3. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 3 CMV tissue invasive disease.



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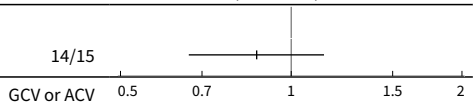
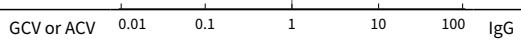
Analysis 5.4. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 4 CMV infection in CMV positive heart transplant recipients.

Study or subgroup	GCV or ACV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
5.4.1 All patients				
Aguado 95-Heart/GCV	13/16	14/15		0.87[0.66,1.14]



Analysis 5.5. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 5 All-cause mortality.

Study or subgroup	GCV or ACV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.5.1 All patients					
Aguado 95-Heart/GCV	1/16	2/15		7.89%	0.47[0.05,4.65]
Conti 94-Kidney/GCV	0/24	0/27			Not estimable
Dunn 94-all/ACV	13/133	18/133		92.11%	0.72[0.37,1.41]
Morales 02-Kid/GCV	0/22	0/22			Not estimable
Subtotal (95% CI)	**195**	**197**		**100%**	**0.7[0.37,1.33]**
Total events: 14 (GCV or ACV), 20 (IgG)					
Heterogeneity: Tau^2=0; Chi^2=0.13, df=1(P=0.72); I^2=0%					
Test for overall effect: Z=1.09(P=0.27)					
5.5.2 CMV positive recipients					
Aguado 95-Heart/GCV	1/16	2/15		100%	0.47[0.05,4.65]
Morales 02-Kid/GCV	0/22	0/22			Not estimable
Subtotal (95% CI)	**38**	**37**		**100%**	**0.47[0.05,4.65]**
Total events: 1 (GCV or ACV), 2 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					
5.5.3 CMV negative recipients of CMV positive organs					
Conti 94-Kidney/GCV	0/24	0/27			Not estimable
Subtotal (95% CI)	**24**	**27**			**Not estimable**
Total events: 0 (GCV or ACV), 0 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.5.4 Kidney transplant recipients					
Conti 94-Kidney/GCV	0/24	0/27			Not estimable
Morales 02-Kid/GCV	0/22	0/22			Not estimable
Subtotal (95% CI)	**46**	**49**			**Not estimable**
Total events: 0 (GCV or ACV), 0 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					
5.5.5 Heart transplant recipients					
Aguado 95-Heart/GCV	1/16	2/15		100%	0.47[0.05,4.65]
Subtotal (95% CI)	**16**	**15**		**100%**	**0.47[0.05,4.65]**
Total events: 1 (GCV or ACV), 2 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.65(P=0.52)					



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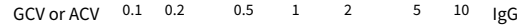
Analysis 5.6. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 6 Death due to CMV disease.

Study or subgroup	GCV or ACV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.6.1 All patients					
Aguado 95-Heart/GCV	0/16	0/15			Not estimable
Conti 94-Kidney/GCV	0/24	0/27			Not estimable
Dunn 94-all/ACV	0/133	0/133			Not estimable
Morales 02-Kid/GCV	0/22	0/22			Not estimable
Subtotal (95% CI)	**195**	**197**			**Not estimable**
Total events: 0 (GCV or ACV), 0 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Not applicable					



Analysis 5.7. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 7 Acute rejection.

Study or subgroup	GCV or ACV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
5.7.1 All patients					
Aguado 95-Heart/GCV	9/16	9/15		13.84%	0.94[0.52,1.7]
Conti 94-Kidney/GCV	9/24	14/27		12.4%	0.72[0.38,1.36]
Dunn 94-all/ACV	54/133	66/133		69.1%	0.82[0.63,1.07]
Morales 02-Kid/GCV	5/22	6/22		4.67%	0.83[0.3,2.33]
Subtotal (95% CI)	**195**	**197**		**100%**	**0.82[0.66,1.03]**
Total events: 77 (GCV or ACV), 95 (IgG)					
Heterogeneity: Tau^2=0; Chi^2=0.35, df=3(P=0.95); I^2=0%					
Test for overall effect: Z=1.73(P=0.08)					
5.7.2 CMV positive recipients					
Aguado 95-Heart/GCV	9/16	9/15		74.77%	0.94[0.52,1.7]
Morales 02-Kid/GCV	5/22	6/22		25.23%	0.83[0.3,2.33]
Subtotal (95% CI)	**38**	**37**		**100%**	**0.91[0.54,1.53]**
Total events: 14 (GCV or ACV), 15 (IgG)					
Heterogeneity: Tau^2=0; Chi^2=0.04, df=1(P=0.84); I^2=0%					
Test for overall effect: Z=0.36(P=0.72)					
5.7.3 CMV recipients of CMV positive organs					
Conti 94-Kidney/GCV	9/24	14/27		100%	0.72[0.38,1.36]
Subtotal (95% CI)	**24**	**27**		**100%**	**0.72[0.38,1.36]**
Total events: 9 (GCV or ACV), 14 (IgG)					
Heterogeneity: Not applicable					
Test for overall effect: Z=1.01(P=0.31)					

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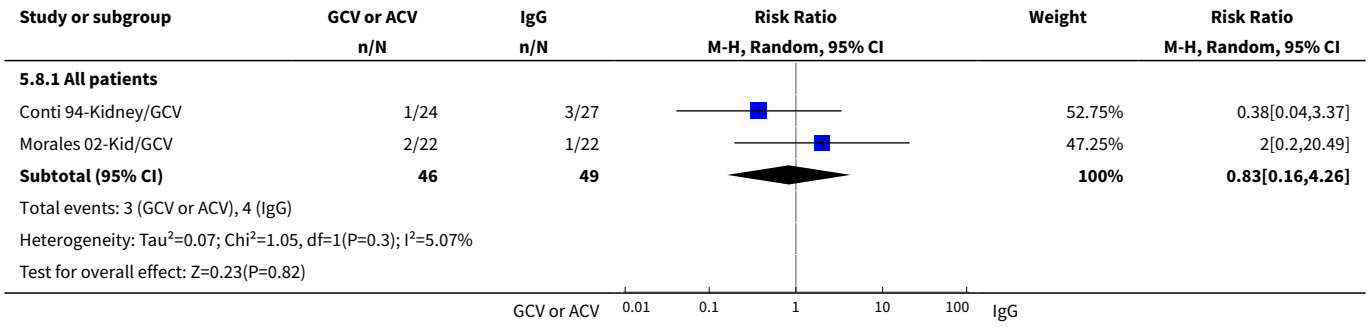
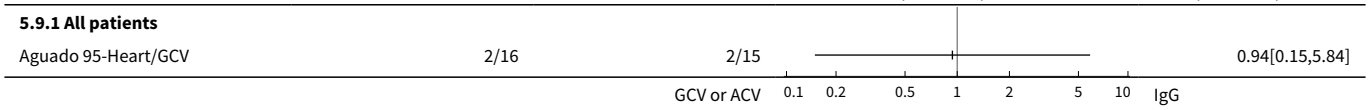
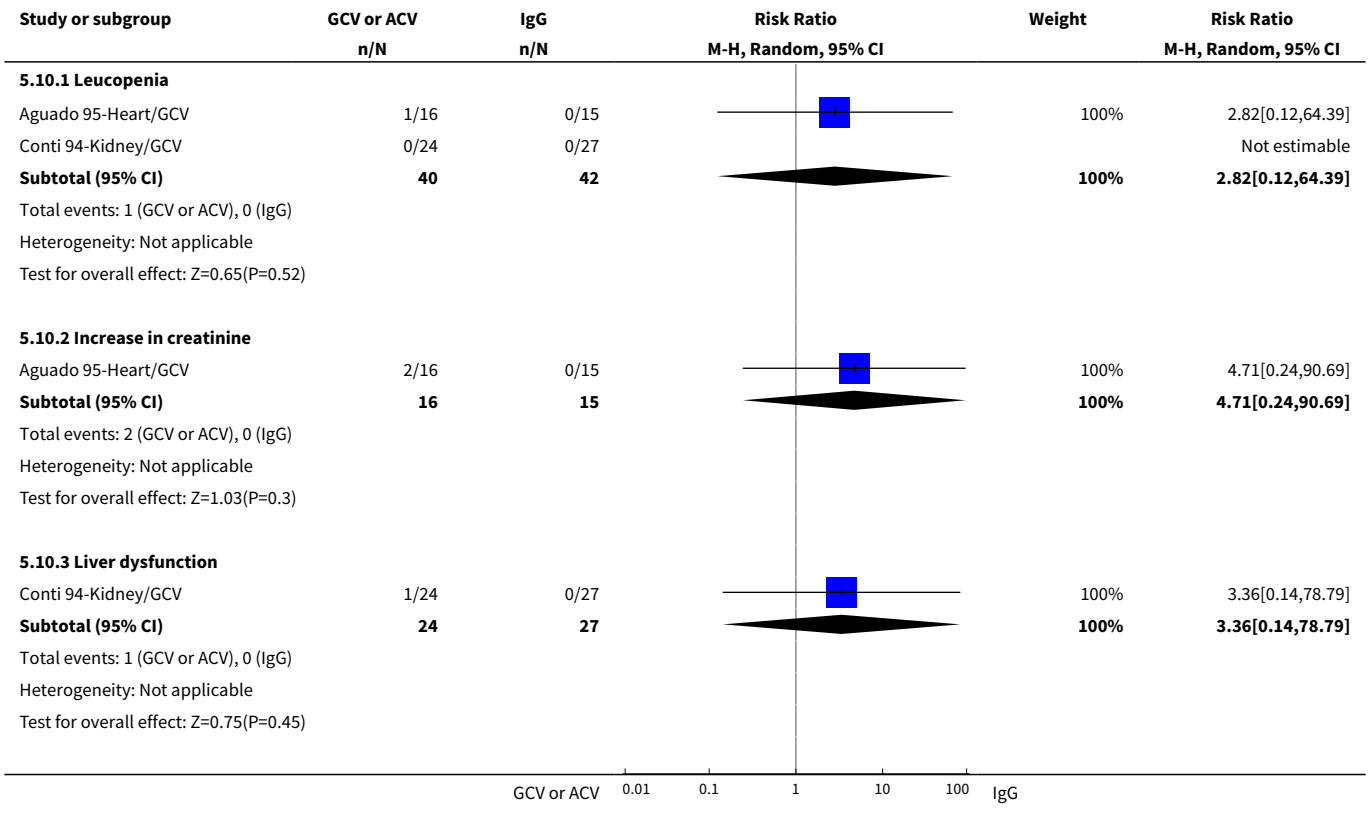
Analysis 5.8. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 8 Graft loss in CMV positive recipients.



Analysis 5.9. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 9 Opportunistic infections in CMV positive heart transplant recipients.



Analysis 5.10. Comparison 5 Antiviral medication alone versus IgG alone, Outcome 10 Adverse effects.



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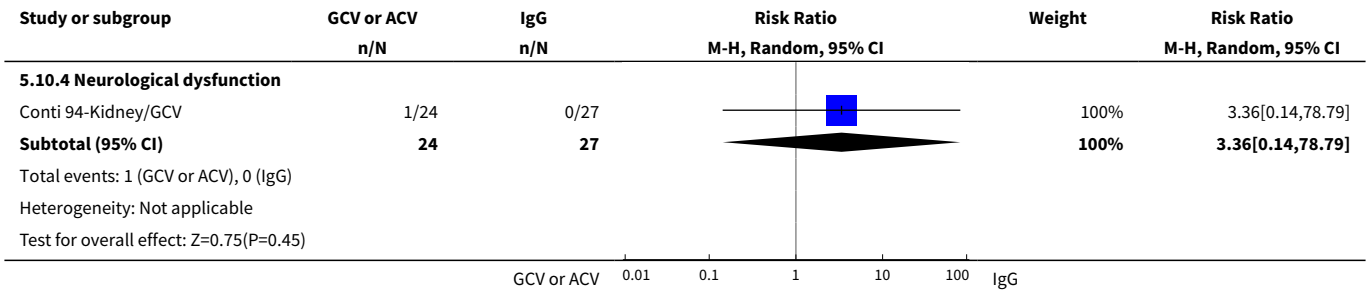

Comparison 6. Antiviral medication plus IgG versus antiviral medication alone

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All patients	4	298	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.74, 1.86]
1.2 CMV negative recipients of CMV positive organs	2	44	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.70, 1.94]
1.3 Kidney transplant recipients	1	23	Risk Ratio (M-H, Random, 95% CI)	0.65 [0.15, 2.87]
2 CMV syndrome	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All patients	2	215	Risk Ratio (M-H, Random, 95% CI)	1.17 [0.55, 2.52]
3 CMV tissue invasive disease	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All patients	2	215	Risk Ratio (M-H, Random, 95% CI)	1.31 [0.43, 3.99]
4 CMV infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
4.1 All patients	4	298	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.89, 1.52]
4.2 CMV negative recipients of CMV positive organs	2	44	Risk Ratio (M-H, Random, 95% CI)	1.16 [0.87, 1.56]
4.3 Kidney transplant recipients	1	23	Risk Ratio (M-H, Random, 95% CI)	0.93 [0.42, 2.06]
5 All-cause mortality	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only

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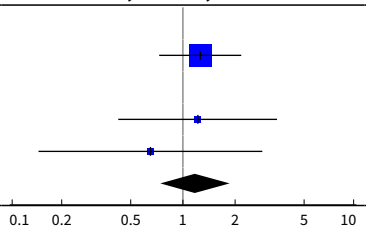
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5.1 All patients	2	217	Risk Ratio (M-H, Random, 95% CI)	0.92 [0.37, 2.29]
5.2 CMV negative recipients of CMV positive organs	1	23	Risk Ratio (M-H, Random, 95% CI)	3.82 [0.17, 84.90]
5.3 Kidney transplant recipients	1	23	Risk Ratio (M-H, Random, 95% CI)	3.82 [0.17, 84.90]
6 Death due to CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
6.1 All patients	1	23	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Acute rejection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 All patients	2	217	Risk Ratio (M-H, Random, 95% CI)	0.71 [0.44, 1.13]
7.2 CMV negative recipients of CMV positive organs	1	23	Risk Ratio (M-H, Random, 95% CI)	0.43 [0.16, 1.19]
8 Graft loss	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
8.1 All patients	2	217	Risk Ratio (M-H, Random, 95% CI)	1.39 [0.32, 6.04]
8.2 CMV negative recipients of CMV positive organs	1	23	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
9 Opportunistic infections	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
9.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 6.1. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 1 CMV disease.

Study or subgroup	GCV/ACV + IgG n/N	GCV or ACV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.1.1 All patients					
Bailey 93-All/ACV	8/10	7/11		71.4%	1.26[0.73,2.17]
Huang 05-Liver/GCV	0/30	0/30			Not estimable
Johnson 04-L/K/GCV	7/95	6/99		19.02%	1.22[0.42,3.49]
Rostaing 97-Kid/GCV	2/10	4/13		9.59%	0.65[0.15,2.87]
Subtotal (95% CI)	**145**	**153**		**100%**	**1.17[0.74,1.86]**



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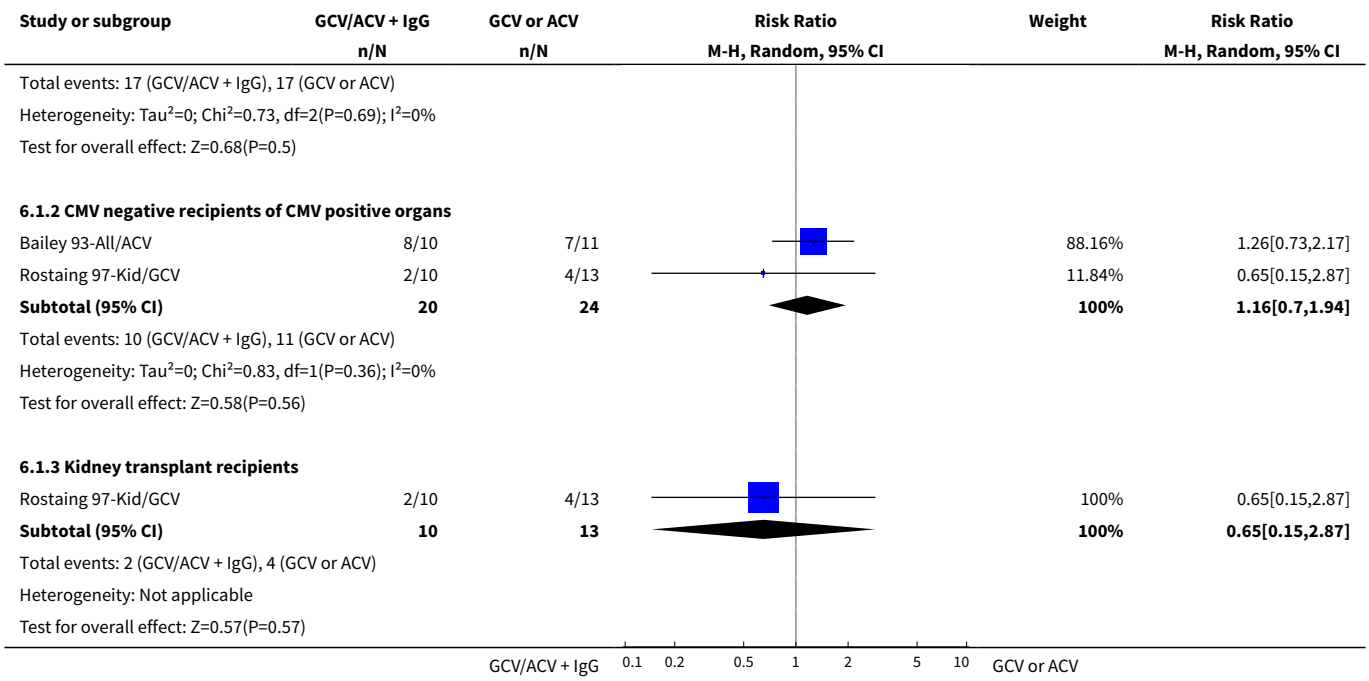
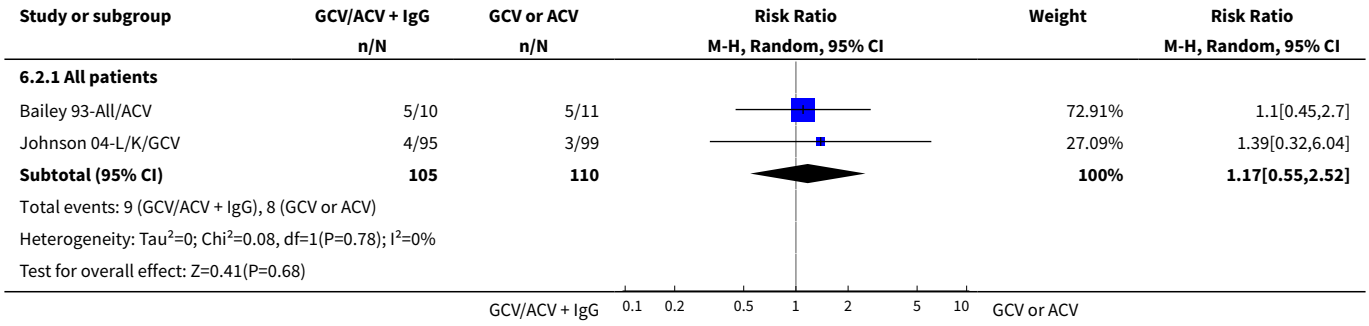
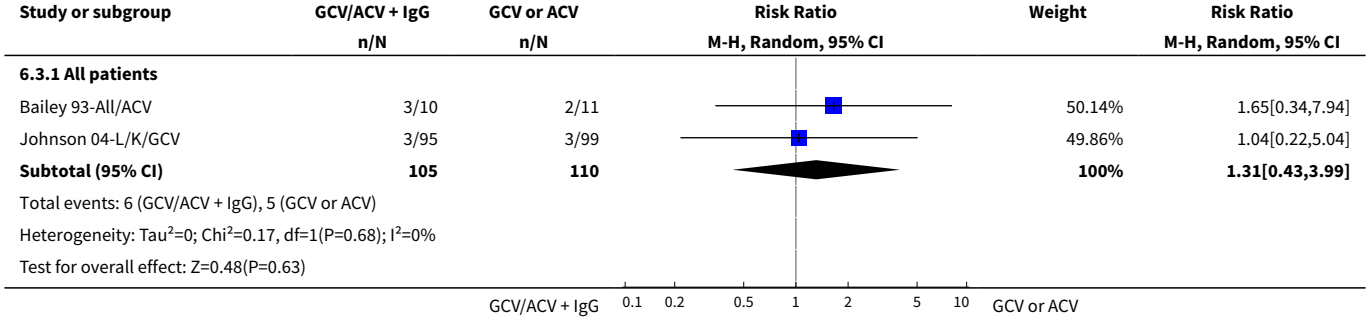


Analysis 6.2. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 2 CMV syndrome.



Analysis 6.3. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 3 CMV tissue invasive disease.



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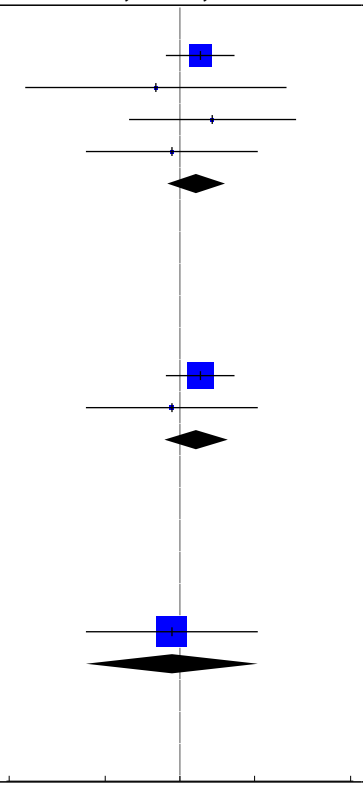
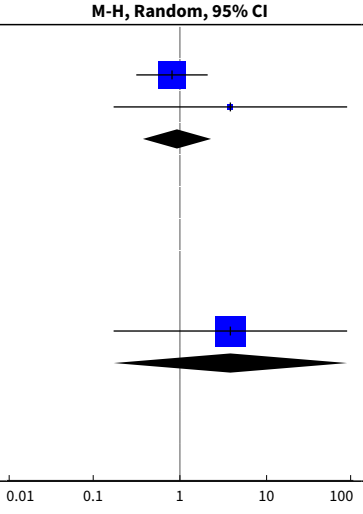
Analysis 6.4. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 4 CMV infection.

Study or subgroup	GCV/ACV + IgG n/N	GCV or ACV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.4.1 All patients					
Bailey 93-All/ACV	10/10	9/11		71.7%	1.21[0.88,1.66]
Huang 05-Liver/GCV	4/30	5/30		4.91%	0.8[0.24,2.69]
Johnson 04-L/K/GCV	13/95	10/99		12.05%	1.35[0.62,2.94]
Rostaing 97-Kid/GCV	5/10	7/13		11.35%	0.93[0.42,2.06]
Subtotal (95% CI)	**145**	**153**		**100%**	**1.16[0.89,1.52]**
Total events: 32 (GCV/ACV + IgG), 31 (GCV or ACV)					
Heterogeneity: Tau²=0; Chi²=0.91, df=3(P=0.82); I²=0%					
Test for overall effect: Z=1.1(P=0.27)					
6.4.2 CMV negative recipients of CMV positive organs					
Bailey 93-All/ACV	10/10	9/11		86.34%	1.21[0.88,1.66]
Rostaing 97-Kid/GCV	5/10	7/13		13.66%	0.93[0.42,2.06]
Subtotal (95% CI)	**20**	**24**		**100%**	**1.16[0.87,1.56]**
Total events: 15 (GCV/ACV + IgG), 16 (GCV or ACV)					
Heterogeneity: Tau²=0; Chi²=0.52, df=1(P=0.47); I²=0%					
Test for overall effect: Z=1.01(P=0.31)					
6.4.3 Kidney transplant recipients					
Rostaing 97-Kid/GCV	5/10	7/13		100%	0.93[0.42,2.06]
Subtotal (95% CI)	**10**	**13**		**100%**	**0.93[0.42,2.06]**
Total events: 5 (GCV/ACV + IgG), 7 (GCV or ACV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.18(P=0.86)					



Analysis 6.5. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 5 All-cause mortality.

Study or subgroup	GCV/ACV + IgG n/N	GCV or ACV n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
6.5.1 All patients					
Johnson 04-L/K/GCV	7/95	9/99		91.48%	0.81[0.31,2.09]
Rostaing 97-Kid/GCV	1/10	0/13		8.52%	3.82[0.17,84.9]
Subtotal (95% CI)	**105**	**112**		**100%**	**0.92[0.37,2.29]**
Total events: 8 (GCV/ACV + IgG), 9 (GCV or ACV)					
Heterogeneity: Tau²=0; Chi²=0.88, df=1(P=0.35); I²=0%					
Test for overall effect: Z=0.17(P=0.87)					
6.5.2 CMV negative recipients of CMV positive organs					
Rostaing 97-Kid/GCV	1/10	0/13		100%	3.82[0.17,84.9]
Subtotal (95% CI)	**10**	**13**		**100%**	**3.82[0.17,84.9]**
Total events: 1 (GCV/ACV + IgG), 0 (GCV or ACV)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.85(P=0.4)					



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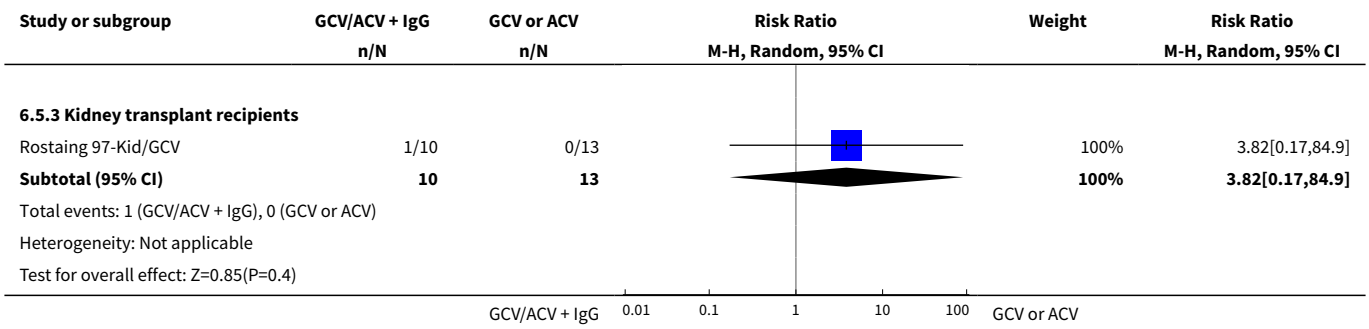
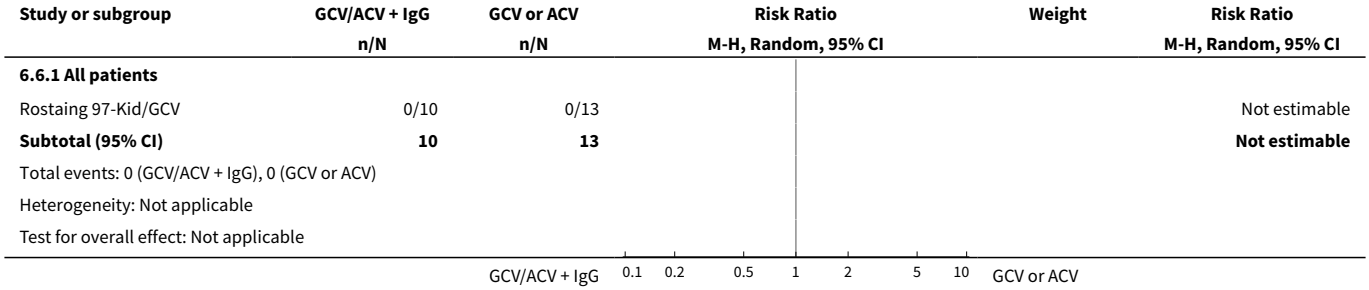
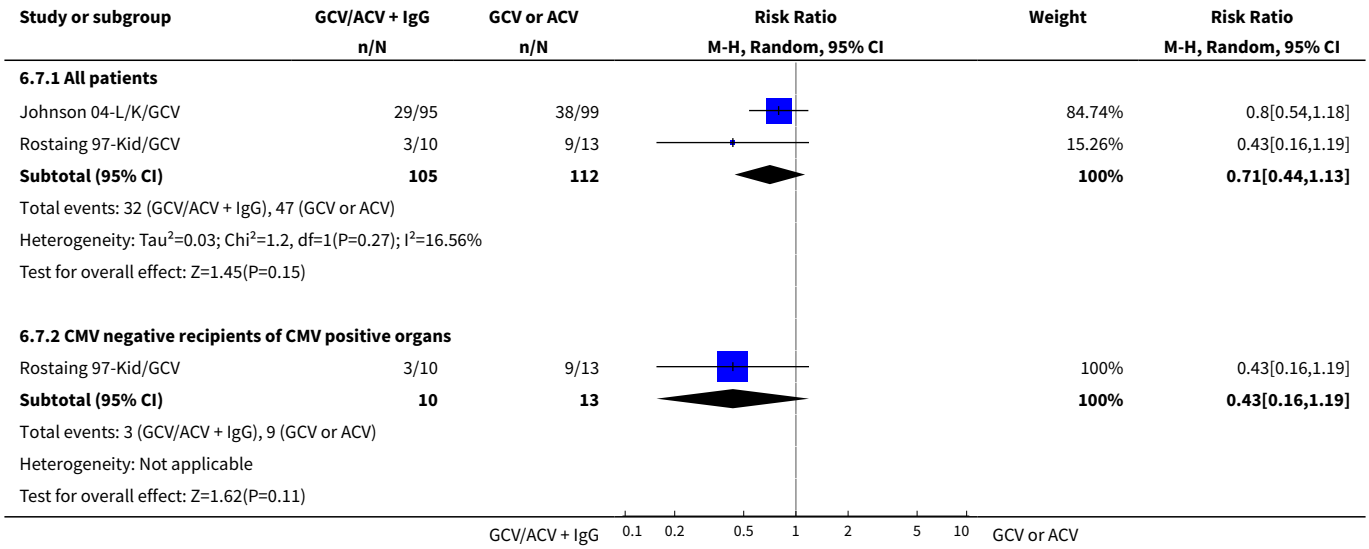


Analysis 6.6. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 6 Death due to CMV disease.



Analysis 6.7. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 7 Acute rejection.



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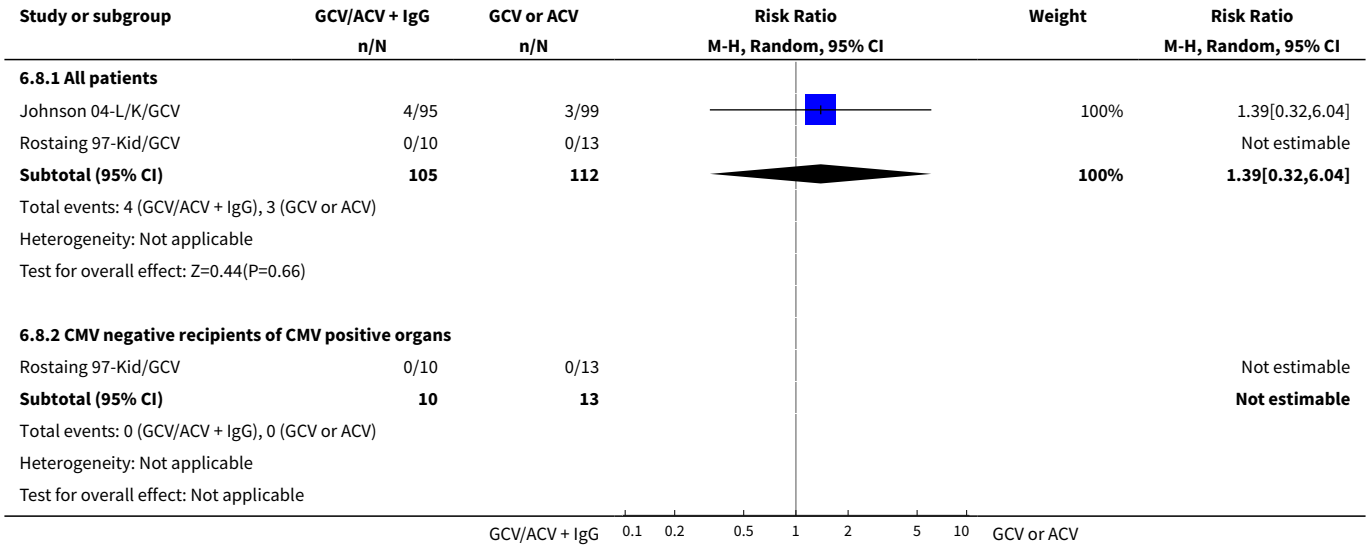
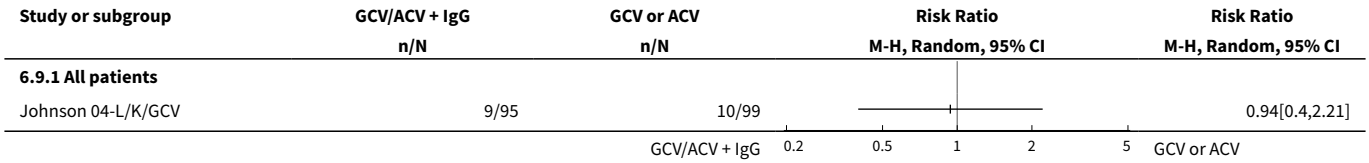
Analysis 6.8. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 8 Graft loss.



Analysis 6.9. Comparison 6 Antiviral medication plus IgG versus antiviral medication alone, Outcome 9 Opportunistic infections.



Comparison 7. Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors)

Outcome or subgroup title	No. of studies	No. of partici-pants	Statistical method	Effect size
1 CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
1.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2 CMV syndrome	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
2.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 CMV tissue invasive disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
3.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
4 CMV infection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

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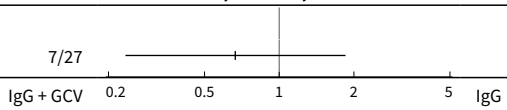
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
5 All-cause mortality	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6 Death due to CMV disease	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
7.1 All patients	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
8.1 Leucopenia <1000 neutrophils	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
8.2 Thrombocytopenia (<20,000)	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

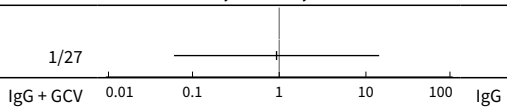
Analysis 7.1. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 1 CMV disease.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.1.1 All patients				
King 97-Liver/GCV	5/29	7/27		0.67[0.24,1.85]



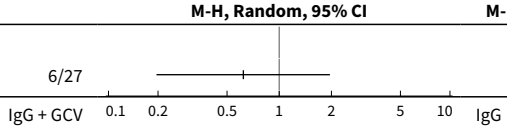
Analysis 7.2. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 2 CMV syndrome.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.2.1 All patients				
King 97-Liver/GCV	1/29	1/27		0.93[0.06,14.16]



Analysis 7.3. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 3 CMV tissue invasive disease.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.3.1 All patients				
King 97-Liver/GCV	4/29	6/27		0.62[0.2,1.96]



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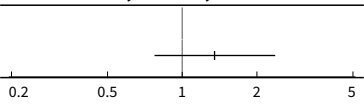
Analysis 7.4. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 4 CMV infection.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.4.1 All patients				
King 97-Liver/GCV	16/29	11/27		1.35[0.77,2.37]



Analysis 7.5. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 5 All-cause mortality.

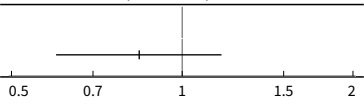
Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.5.1 All patients				
King 97-Liver/GCV	6/29	4/27		1.4[0.44,4.42]

Analysis 7.6. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 6 Death due to CMV disease.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.6.1 All patients				
King 97-Liver/GCV	1/29	0/27		2.8[0.12,65.93]

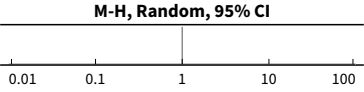
Analysis 7.7. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 7 Acute rejection.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.7.1 All patients				
King 97-Liver/GCV	19/29	21/27		0.84[0.6,1.17]



Analysis 7.8. Comparison 7 Antiviral medication plus IgG versus IgG alone (CMV negative recipients of CMV positive liver donors), Outcome 8 Adverse effects.

Study or subgroup	IgG + GCV n/N	IgG n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
7.8.1 Leucopenia <1000 neutrophils				



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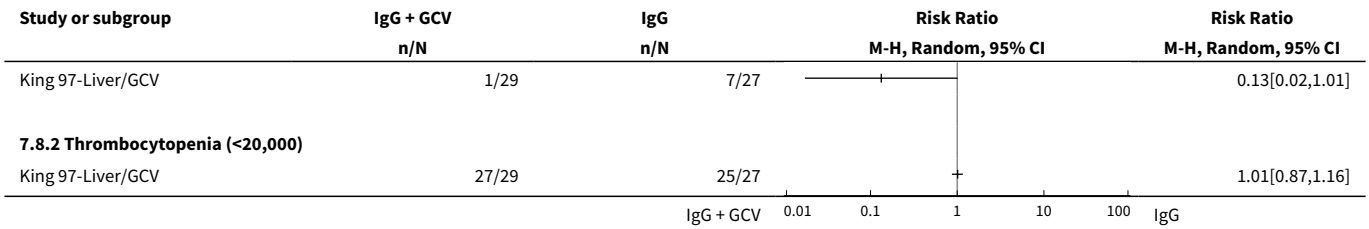

Comparison 8. CMV vaccine versus placebo (all patients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All patients	3	472	Risk Ratio (M-H, Random, 95% CI)	0.79 [0.56, 1.10]
1.2 Recipient CMV positive	2	180	Risk Ratio (M-H, Random, 95% CI)	0.61 [0.33, 1.13]
1.3 Donor CMV positive/recipient CMV negative	3	151	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.53, 1.12]
1.4 Donor CMV negative/recipient CMV negative	1	77	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.15, 6.92]
2 CMV disease (severity score > 6)	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 All patients	1	174	Risk Ratio (M-H, Random, 95% CI)	0.27 [0.06, 1.25]
2.2 Donor CMV positive/recipient CMV negative	3	151	Risk Ratio (M-H, Random, 95% CI)	0.12 [0.04, 0.39]
3 CMV infection	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All patients	2	417	Risk Ratio (M-H, Random, 95% CI)	0.95 [0.69, 1.30]
3.2 All CMV positive recipients	2	180	Risk Ratio (M-H, Random, 95% CI)	0.86 [0.71, 1.05]
3.3 All CMV negative recipients	2	231	Risk Ratio (M-H, Random, 95% CI)	1.13 [0.86, 1.49]
3.4 Donor CMV positive/recipient CMV negative	1	67	Risk Ratio (M-H, Random, 95% CI)	1.15 [0.92, 1.43]
3.5 Donor CMV negative/recipients CMV negative	1	77	Risk Ratio (M-H, Random, 95% CI)	1.03 [0.32, 3.26]

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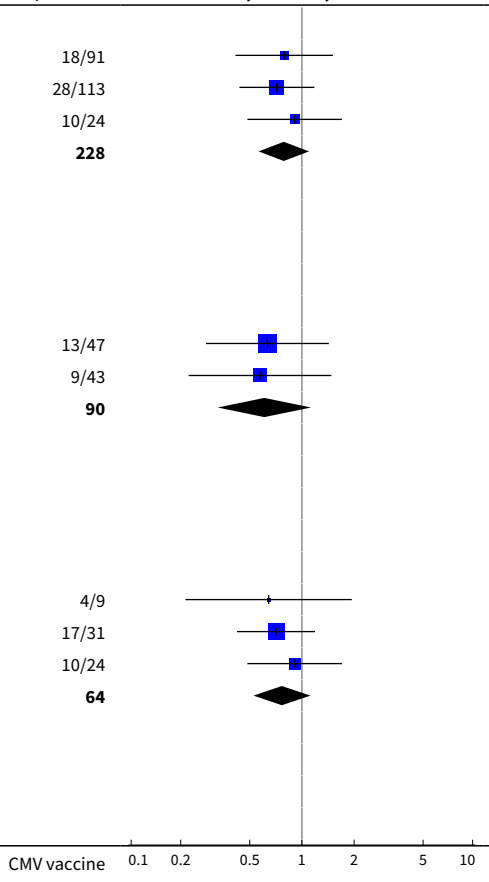
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4 Acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Donor CMV positive/recipient CMV negative	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Adverse effects	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
5.1 All reactions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.2 Fever	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5.3 Local reactions	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

Analysis 8.1. Comparison 8 CMV vaccine versus placebo (all patients), Outcome 1 CMV disease.

Study or subgroup	CMV vaccine n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
8.1.1 All patients					
Balfour 84-Kid/vacc	13/83	18/91		26.54%	0.79[0.41,1.51]
Plotkin 84-Kid/vacc	22/124	28/113		45.2%	0.72[0.44,1.18]
Plotkin 94-Kid/vacc	14/37	10/24		28.27%	0.91[0.48,1.7]
Subtotal (95% CI)	**244**	**228**		**100%**	**0.79[0.56,1.1]**
Total events: 49 (CMV vaccine), 56 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.34, df=2(P=0.84); I^2=0%					
Test for overall effect: Z=1.41(P=0.16)					
8.1.2 Recipient CMV positive					
Balfour 84-Kid/vacc	7/40	13/47		57.48%	0.63[0.28,1.43]
Plotkin 84-Kid/vacc	6/50	9/43		42.52%	0.57[0.22,1.48]
Subtotal (95% CI)	**90**	**90**		**100%**	**0.61[0.33,1.13]**
Total events: 13 (CMV vaccine), 22 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.02, df=1(P=0.88); I^2=0%					
Test for overall effect: Z=1.58(P=0.11)					
8.1.3 Donor CMV positive/recipient CMV negative					
Balfour 84-Kid/vacc	4/14	4/9		11.61%	0.64[0.21,1.94]
Plotkin 84-Kid/vacc	14/36	17/31		52.5%	0.71[0.42,1.19]
Plotkin 94-Kid/vacc	14/37	10/24		35.88%	0.91[0.48,1.7]
Subtotal (95% CI)	**87**	**64**		**100%**	**0.77[0.53,1.12]**
Total events: 32 (CMV vaccine), 31 (Placebo)					
Heterogeneity: Tau^2=0; Chi^2=0.46, df=2(P=0.79); I^2=0%					
Test for overall effect: Z=1.39(P=0.17)					



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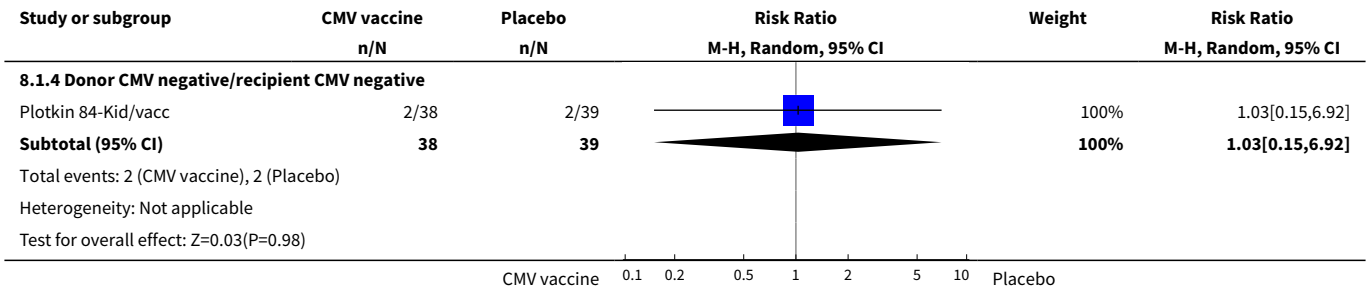
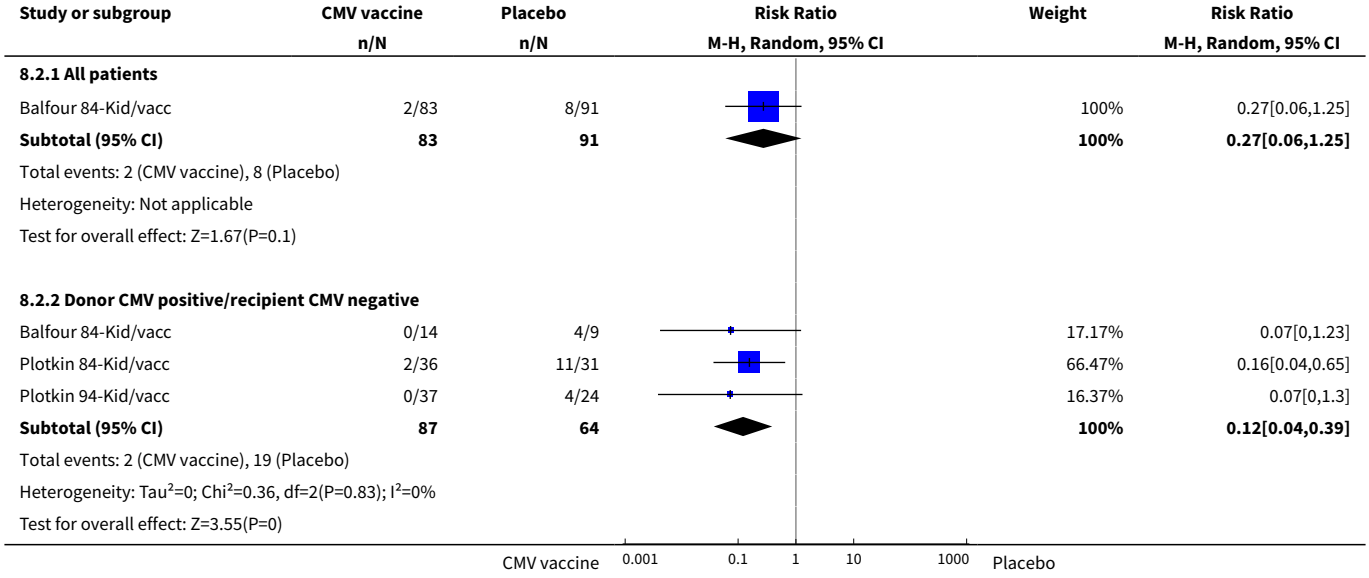
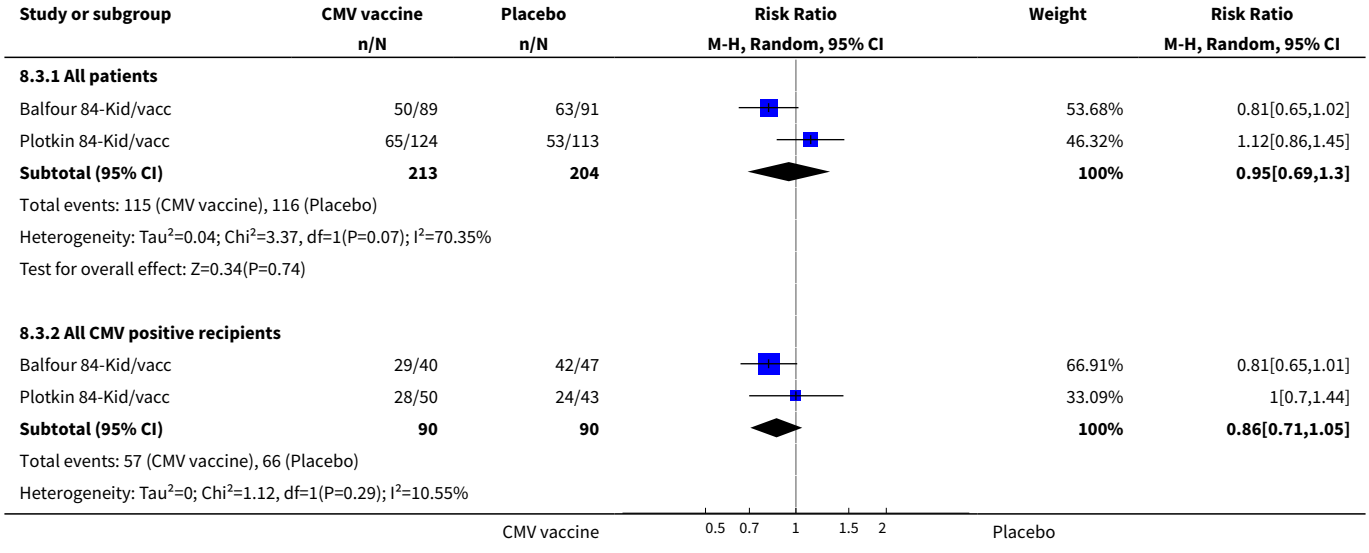


Analysis 8.2. Comparison 8 CMV vaccine versus placebo (all patients), Outcome 2 CMV disease (severity score > 6).



Analysis 8.3. Comparison 8 CMV vaccine versus placebo (all patients), Outcome 3 CMV infection.



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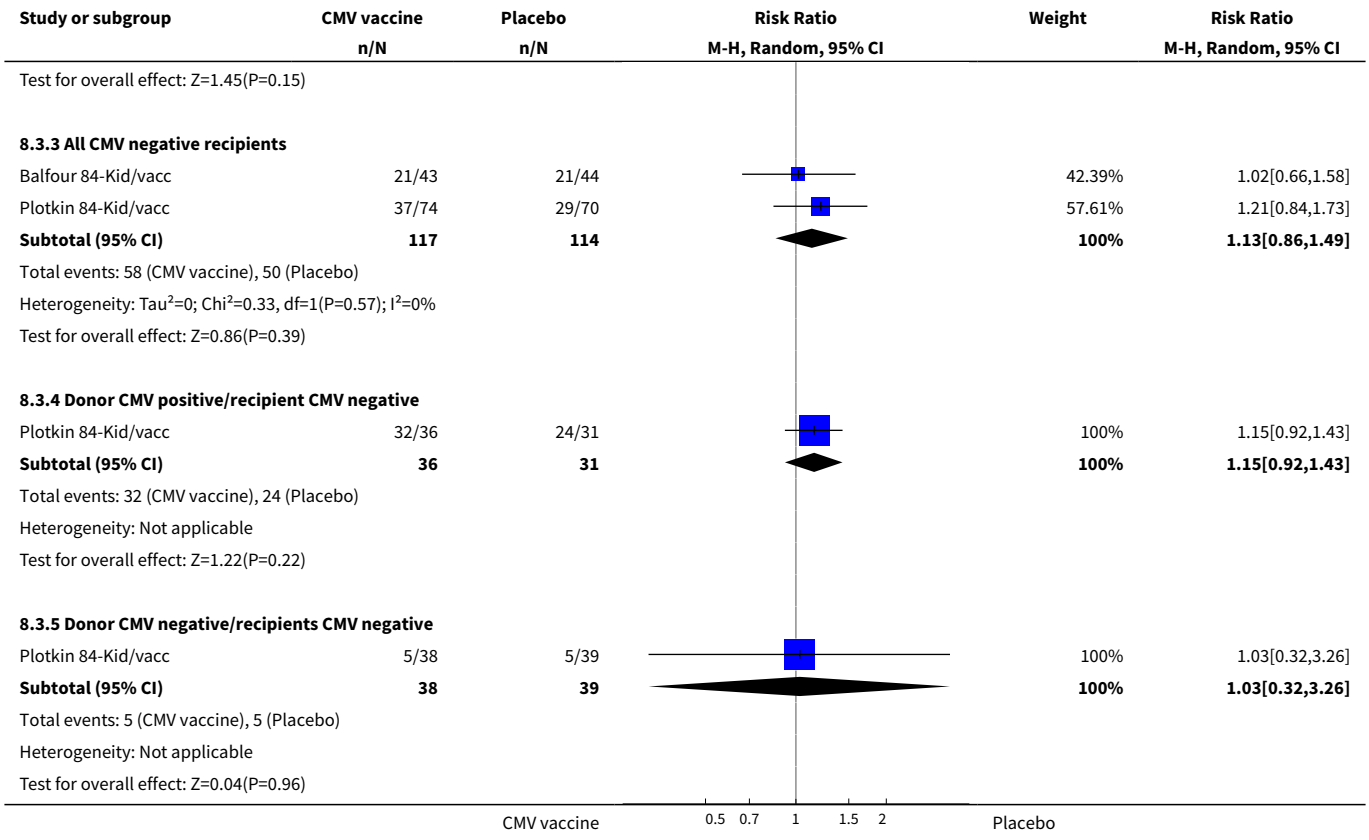
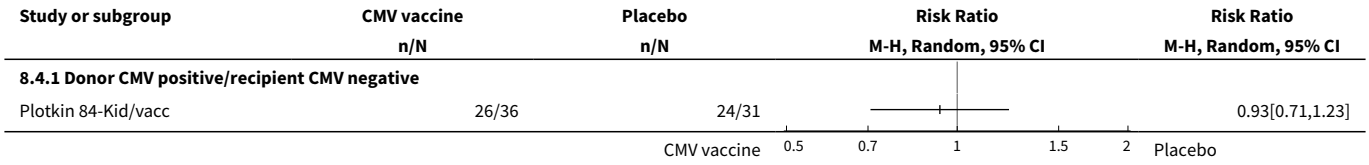
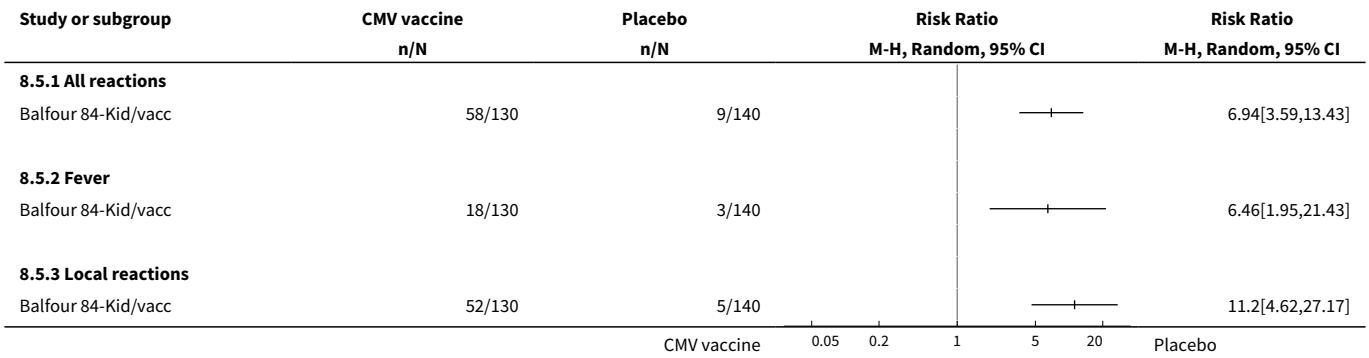


Analysis 8.4. Comparison 8 CMV vaccine versus placebo (all patients), Outcome 4 Acute rejection.



Analysis 8.5. Comparison 8 CMV vaccine versus placebo (all patients), Outcome 5 Adverse effects.



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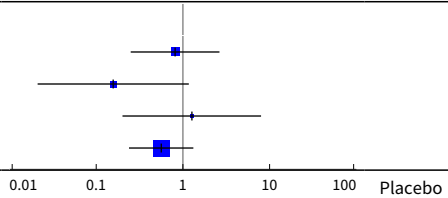
Comparison 9. Interferon versus placebo (all patients)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 CMV disease	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
1.1 All patients	4	173	Risk Ratio (M-H, Random, 95% CI)	0.60 [0.33, 1.12]
2 CMV infection	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 CMV viraemia	3	102	Risk Ratio (M-H, Random, 95% CI)	0.67 [0.47, 0.93]
2.2 CMV virus excretion	2	110	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.58, 1.10]
3 All-cause mortality	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
3.1 All patients	3	151	Risk Ratio (M-H, Random, 95% CI)	1.66 [0.68, 4.09]
4 Acute rejection	1		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
4.1 Patients with 2 or more episodes	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
5 Graft loss	4		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
5.1 All patients	4	205	Risk Ratio (M-H, Random, 95% CI)	1.80 [0.81, 4.01]
5.2 Graft loss due to irreversible rejection	2	108	Risk Ratio (M-H, Random, 95% CI)	3.05 [0.47, 19.89]
6 Opportunistic infections	2		Risk Ratio (M-H, Random, 95% CI)	Totals not selected
6.1 Viral infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.2 Bacterial infection	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
6.3 Other infections	1		Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
7 Adverse effects	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
7.1 Leucopenia and thrombocytopenia	2	83	Risk Ratio (M-H, Random, 95% CI)	2.16 [0.80, 5.84]

Analysis 9.1. Comparison 9 Interferon versus placebo (all patients), Outcome 1 CMV disease.

Study or subgroup	Interferon n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.1.1 All patients					
Cheeseman 79-Kid/IFN	4/16	4/13		27.46%	0.81[0.25,2.64]
Hirsch 83-Kid/IFN	1/20	7/22		9.45%	0.16[0.02,1.17]
Kovarik 88-Kid/IFN	2/15	2/19		11.24%	1.27[0.2,7.97]
Lui 92-Kid/IFN	6/32	12/36		51.85%	0.56[0.24,1.32]



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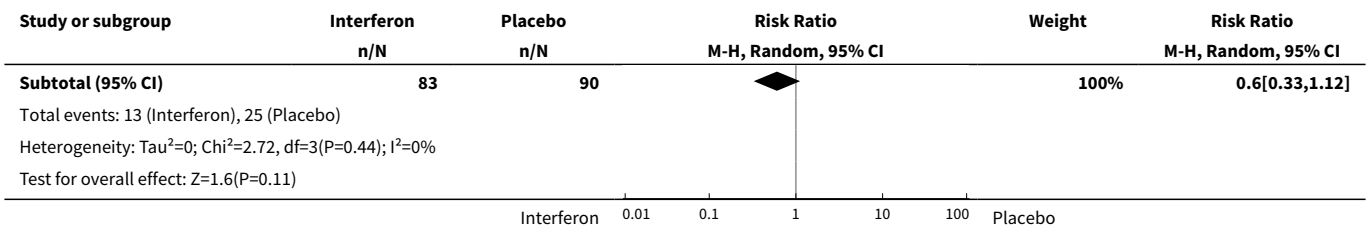
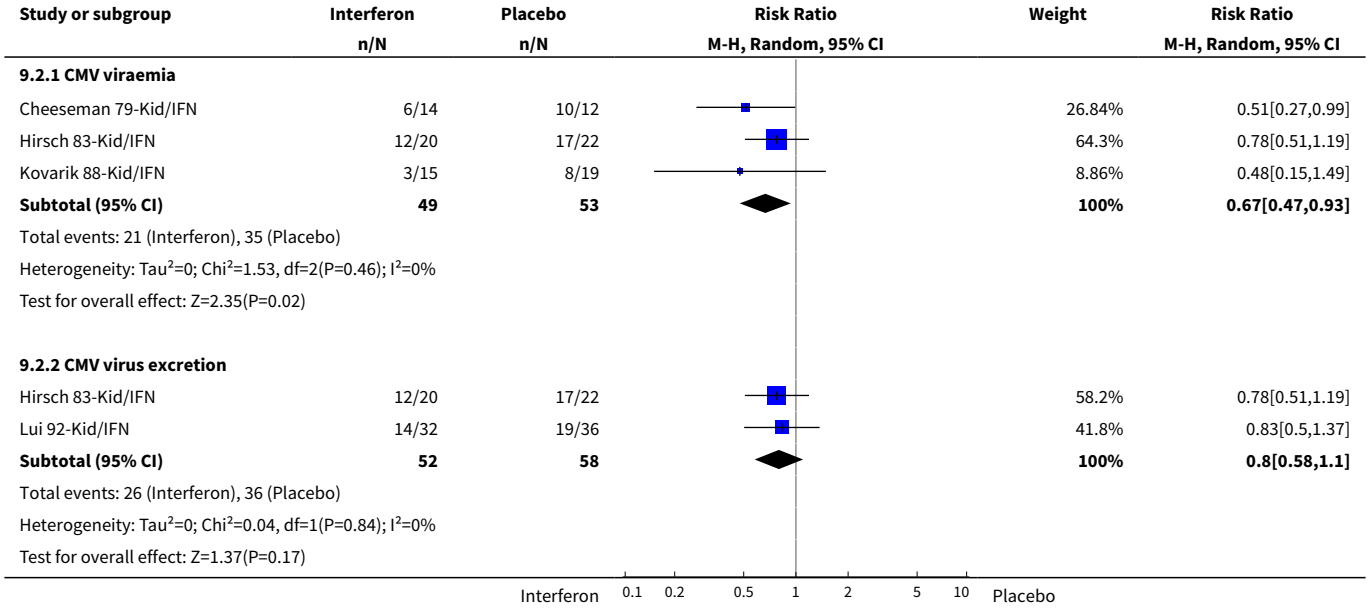
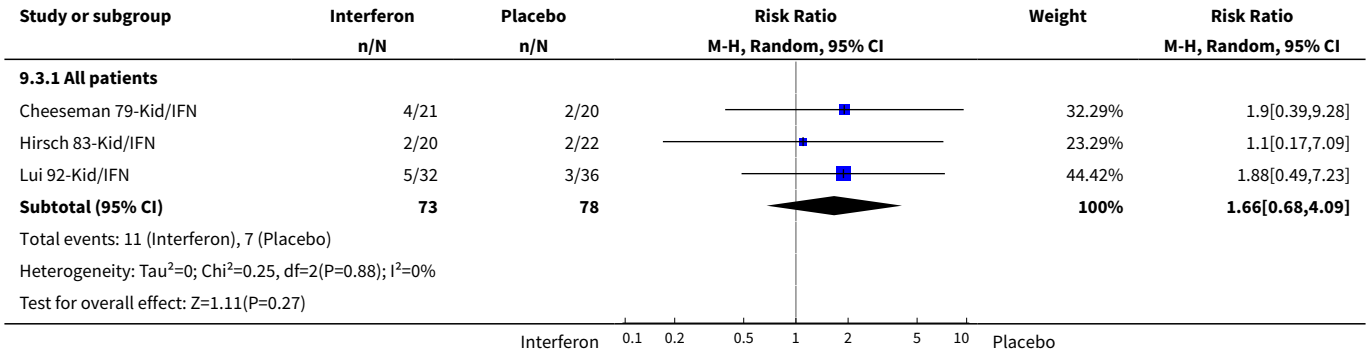


Analysis 9.2. Comparison 9 Interferon versus placebo (all patients), Outcome 2 CMV infection.



Analysis 9.3. Comparison 9 Interferon versus placebo (all patients), Outcome 3 All-cause mortality.



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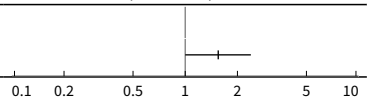
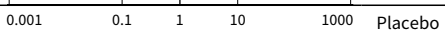
Analysis 9.4. Comparison 9 Interferon versus placebo (all patients), Outcome 4 Acute rejection.

Study or subgroup	Interferon n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.4.1 Patients with 2 or more episodes				
Lui 92-Kid/IFN	22/32	16/36		1.55[1,2.39]



Analysis 9.5. Comparison 9 Interferon versus placebo (all patients), Outcome 5 Graft loss.

Study or subgroup	Interferon n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Weight	Risk Ratio M-H, Random, 95% CI
9.5.1 All patients					
Cheeseman 79-Kid/IFN	7/21	3/20		28.63%	2.22[0.67,7.42]
Hirsch 83-Kid/IFN	1/20	3/22		10.32%	0.37[0.04,3.25]
Kovarik 88-Kid/IFN	9/28	1/22		12.21%	7.07[0.97,51.68]
Lui 92-Kid/IFN	11/36	7/36		48.84%	1.57[0.69,3.59]
Subtotal (95% CI)	**105**	**100**		**100%**	**1.8[0.81,4.01]**
Total events: 28 (Interferon), 14 (Placebo)					
Heterogeneity: Tau^2=0.19; Chi^2=4.14, df=3(P=0.25); I^2=27.47%					
Test for overall effect: Z=1.45(P=0.15)					
9.5.2 Graft loss due to irreversible rejection					
Kovarik 88-Kid/IFN	6/21	0/19		17.63%	11.82[0.71,196.69]
Lui 92-Kid/IFN	6/32	4/36		82.37%	1.69[0.52,5.45]
Subtotal (95% CI)	**53**	**55**		**100%**	**3.05[0.47,19.89]**
Total events: 12 (Interferon), 4 (Placebo)					
Heterogeneity: Tau^2=0.96; Chi^2=1.79, df=1(P=0.18); I^2=44.23%					
Test for overall effect: Z=1.16(P=0.24)					



Analysis 9.6. Comparison 9 Interferon versus placebo (all patients), Outcome 6 Opportunistic infections.

Study or subgroup	Interferon n/N	Placebo n/N	Risk Ratio M-H, Random, 95% CI	Risk Ratio M-H, Random, 95% CI
9.6.1 Viral infection				
Kovarik 88-Kid/IFN	1/15	2/19		0.63[0.06,6.34]
9.6.2 Bacterial infection				
Kovarik 88-Kid/IFN	1/15	3/19		0.42[0.05,3.66]
9.6.3 Other infections				
Hirsch 83-Kid/IFN	0/20	2/22		0.22[0.01,4.3]

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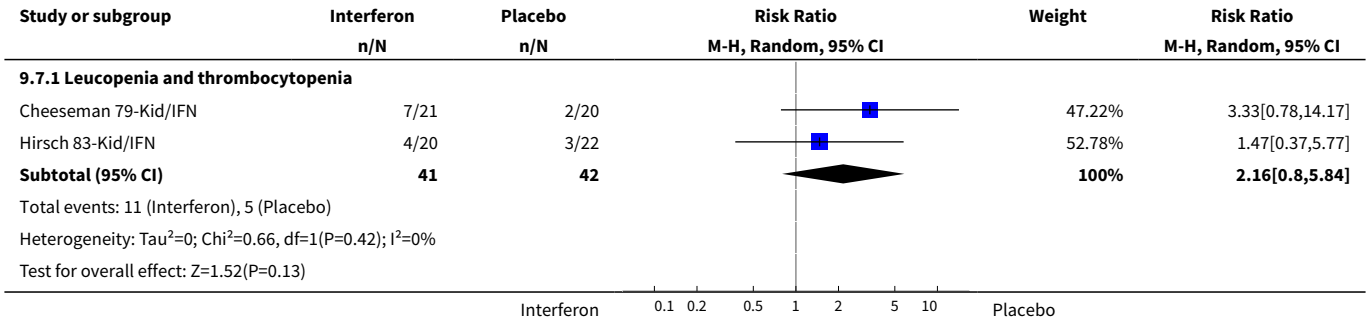
Analysis 9.7. Comparison 9 Interferon versus placebo (all patients), Outcome 7 Adverse effects.



ADDITIONAL TABLES

Table 1. Methodological quality of included studies

Study ID	Allocation concealment	Blinding: participants	Blinding: investigators	Blinding: assessors	Intention-to-treat analysis	Loss to follow-up
Aguado 1995	Unclear	No	No	Not stated	No	0%
Bailey 1993	Unclear	No	No	Not stated	Not stated	0%
Balfour 1984	Unclear	Yes	Yes	No	No	0%
Boland 1993	Unclear	No	No	Not stated	No	0%
Cheeseman 1979	Unclear	No	No	Not stated	No	0%
Cofer 1991	Unclear	Yes	Yes	Not stated	Yes	0%
Conti 1994	Unclear	No	No	Not stated	Yes	0%
Dunn 1994	Unclear	No	No	Not stated	No	0%
Fassbinder 1986	Unclear	Not stated	Not stated	Not stated	Not stated	0%
Greger 1985 a/b	Inadequate	No	No	Not stated	No	0%
Grundmann 1987	Unclear	No	No	Not stated	No	0%
Hirsch 1983	Adequate	Yes	Yes	Yes	No	0%
Huang 2005	Unclear	No	No	Yes	Not stated	0%
Johnson 2004	Unclear	No	No	Not stated	No	0%
Lui 1992	Inadequate	Yes	Yes	Not stated	No	0%
Kasiske 1989	Unclear	No	No	Not stated	Yes	0%

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Table 1. Methodological quality of included studies *(Continued)*

King 1997	Adequate	Yes	Yes	Yes	No	0%
Kovarik 1988	Unclear	Yes	Yes	Not stated	No	0%
Kruger 2003	Unclear	No	No	Yes	Yes	0%
McCune 1992	Unclear	No	No	Not stated	No	0%
Metselaar 1989	Unclear	Yes	Yes	Not stated	No	0%
Mitsioni 1987	Unclear	No	No	Not stated	Not stated	0%
Morales 2002	Unclear	No	No	Not stated	Yes	0%
Pakkala 1992	Unclear	Unclear	Unclear	Not stated	Not stated	0%
Plotkin 1991	Adequate	Yes	Yes	Yes	Not stated	0%
Plotkin 1994	Adequate	Yes	Yes	Yes	No	0%
Preiksaitis 1982	Unclear	No	No	Not stated	Not stated	Unclear
Rostaing 1997	Unclear	No	No	Not stated	No	0%
Saliba 1989	Unclear	No	No	Not stated	Yes	0%
Schechner 1993	Unclear	No	No	Not stated	Not stated	Unclear
Snydman 1987	Adequate	No	No	Yes	No	0%
Snydman 1993	Adequate	Yes	Yes	Yes	No	0%
Steinmuller 1990	Unclear	No	No	Yes	Not stated	0%
Stippel 1991	Unclear	No	No	Not stated	Not stated	Unclear
Stratta 1994	Unclear	No	No	Not stated	No	0%
Wirnsberger 1999	Unclear	No	No	Not stated	No	0%
Yamani 2005	Unclear	No	No	Not stated	Not stated	Unclear

APPENDICES

Appendix 1. Electronic search strategies

Database	Search terms
CENTRAL	#1 MeSH descriptor Cytomegalovirus, this term only in MeSH products #2 MeSH descriptor Cytomegalovirus Infections explode all trees in MeSH products #3 MeSH descriptor Cytomegalovirus Vaccines explode all trees in MeSH products #4 cytomegalovirus* in All Fields in CENTRAL

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(Continued)

	#5 cmv* in All Fields in CENTRAL #6 (#1 OR #2 OR #3 OR #4 OR #5) #7 MeSH descriptor Organ Transplantation explode all trees in MeSH products #8 MeSH descriptor Bone Transplantation, this term only in MeSH products #9 (#7 AND NOT #8) #10 (organ or renal or kidney or heart or lung or liver or pancreas) adj transplant in All Fields in all products #11 (#9 OR #10) #12 (#6 AND #11)
MEDLINE	1. randomized controlled trial.pt. 2. controlled clinical trial.pt. 3. randomized controlled trials/ 4. random allocation/ 5. double blind method/ 6. single blind method/ 7. or/1-6 8. animal/ not (animal/ and human/) 9. 7 not 8 10. clinical trial.pt. 11. exp clinical trials/ 12. (clin$ adj25 trial$).ti,ab. 13. cross-over studies/ 14. (crossover or cross-over or cross over).tw. 15. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. 16. placebos/ 17. placebo$.ti,ab. 18. random$.ti,ab. 19. research design/ 20. or/10-19 21. 20 not 8 22. 21 or 9 23. exp cytomegalovirus/ or exp cytomegalovirus infection/ 24. exp organ transplantation/ 25. 24 not exp bone transplantation/ 26. 23 and 25 27. exp acyclovir/ or exp ganciclovir/ or exp antiviral agents/ 28. ac?clovir.tw./ or ganc?clovir.tw./ or valac?clovir.tw./ or valganc?clovir.tw./ or cidofovir.tw. 29. exp immunoglobulins/ or exp gamma-globulins/ or exp immunoglobulins, intravenous/ or exp immunotherapy/ 30. 27 or 28 or 29 31. 26 and 30 32. 22 and 31
EMBASE	1. exp clinical trial/ 2. evidence based medicine/ 3. outcomes research/ 4. crossover procedure/ 5. double blind procedure/ 6. single blind procedure/ 7. prospective study/ 8. major clinical study/ 9. exp comparative study/ 10. placebo/ 11. "evaluation and follow up"/ 12. follow up 13. randomization/ 14. or/1-13 15. controlled study/ not case control study 16. or/14-15

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(Continued)

17. (clinic$ adj5 trial$).ti,ab.
18. ((single$ or doubl$ or trebl$ or tripl$) adj (blind$ or mask$)).ti,ab.
19. (control$ or prospectiv$ or volunteer$).ti,ab.
20. random$.ti,ab.
21. placebo$.ti,ab.
22. or/17-21
23. 16 or 22
24. limit 23 to human
25. exp cytomegalovirus/ or exp cytomegalovirus infection
26. exp kidney transplantation/ or exp heart transplantation/ or exp lung transplantation/ or exp liver transplantation/ or exp pancreas transplantation
27. 25 and 26
28. exp aciclovir/ or exp ganciclovir/ or exp valaciclovir/ or valganciclovir/ or exp antiviral agents/ or exp immunoglobulin/ or exp immunotherapy
29. ac?clovir.tw./ or ganc?clovir.tw./ or valac?clovir.tw./ or valganc?clovir.tw./ or cidofovir.tw.
30. 28 or 29
31. 27 and 30
32. 24 and 31

WHAT'S NEW

Date	Event	Description
18 March 2010	Amended	Contact details updated.

HISTORY

Protocol first published: Issue 1, 2005
Review first published: Issue 2, 2007

Date	Event	Description
13 May 2009	Amended	Contact details updated.
13 May 2008	Amended	Converted to new review format.

CONTRIBUTIONS OF AUTHORS

Writing of protocol and review - EH, CJ, AW, GS, JC
Screening of titles and abstracts - EH, CJ
Assessment for inclusion - EH. CJ
Quality assessment - EH, CJ, AW, GS
Data extraction - EH, CJ, AW, GS
Data entry into RevMan - EH
Data analysis - EH, CJ, AW, GS, JC
Disagreement resolution - EH, CJ, AW, GS, JC

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INDEX TERMS

Medical Subject Headings (MeSH)

Antiviral Agents [*therapeutic use]; Cytomegalovirus Infections [*prevention & control]; Cytomegalovirus Vaccines [*therapeutic use]; Immunoglobulin G [*therapeutic use]; Interferons [*therapeutic use]; Randomized Controlled Trials as Topic

MeSH check words

Humans

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