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Intravenous immunoglobulin for suspected or proven infection in neonates (Review)

Ohlsson A, Lacy JB

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TABLE OF CONTENTS

[Intervention Review]

Intravenous immunoglobulin for suspected or proven infection in neonates

Arne Ohlsson[1a], Janet B Lacy[2]

[1]Departments of Paediatrics, Obstetrics and Gynaecology and Institute of Health Policy, Management and Evaluation, University of Toronto, Toronto, Canada. [2]Scarborough, Canada

[a]Deceased

Contact: Colleen Ovelman, Cochrane Neonatal, University of Vermont College of Medicine, c/o Vermont Oxford Network, 33 Kilburn Street, Burlington, Vermont, 05401, USA. colleen.ovelman@uvm.edu.

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ABSTRACT

Background

Neonates are at higher risk of infection due to immuno-incompetence. Maternal transport of immunoglobulins to the fetus mainly occurs after 32 weeks' gestation, and endogenous synthesis begins several months after birth. Administration of intravenous immunoglobulin (IVIG) provides immunoglobulin G (IgG) that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody-dependent cytotoxicity and improve neutrophilic chemo-luminescence. Theoretically, infectious morbidity and mortality could be reduced by the administration of IVIG.

Objectives

To assess the effects of IVIG on mortality and morbidity caused by suspected or proven infection at study entry in neonates. To assess in a subgroup analysis the effects of IgM-enriched IVIG on mortality from suspected infection.

Search methods

For this update, MEDLINE, EMBASE, *The Cochrane Library*, CINAHL, trial registries, Web of Science, reference lists of identified studies, meta-analyses and personal files were searched in 2013. No language restrictions were applied.

Selection criteria

Randomised or quasi-randomised controlled trials involving newborn infants (< 28 days old); IVIG for treatment of suspected or proven bacterial or fungal infection compared with placebo or no intervention; and where one of the following outcomes was reported, mortality, length of hospital stay or psychomotor development at follow-up.

Data collection and analysis

Statistical analyses included typical risk ratio (RR), risk difference (RD), weighted mean difference (WMD), number needed to treat for an additional beneficial outcome (NNTB) or an additional harmful outcome (NNTH), all with 95% confidence intervals (CIs), and the I^2 statistic to examine for statistical heterogeneity.

Main results

The updated search identified one published study that was previously ongoing. A total of 9 studies evaluating 3973 infants were included in this review. Mortality during hospital stay in infants with clinically suspected infection was not significantly different after IVIG treatment (9 studies (n = 2527); typical RR 0.95, 95% CI 0.80 to 1.13; typical RD -0.01, 95% CI - 0.04 to 0.02; I^2 = 23% for RR and 29% for RD). Death

or major disability at 2 years corrected age was not significantly different in infants with suspected infection after IVIG treatment (1 study (n = 1985); RR 0.98, 95% CI 0.88 to 1.09; RD -0.01, 95% CI -0.05 to 0.03). Mortality during hospital stay was not significantly different after IVIG treatment in infants with proven infection at trial entry (1 trial (n = 1446); RR 0.95, 95% CI 0.74 to 1.21; RD -0.01, 95% CI -0.04 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with proven infection at trial entry (1 trial (n = 1393); RR 1.03, 95% CI 0.91 to 1.18; RD 0.01, 95% CI -0.04 to 0.06). Mortality during hospital stay in infants with clinically suspected or proven infection at trial entry was not significantly different after IVIG treatment (1 study (n = 3493); RR 1.00, 95% CI 0.86 to 1.16; RD 0.00, 95% CI - 0.02 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with suspected or proven infection at trial entry (1 study (n = 3493); RR 1.00, 95% CI 0.92 to 1.09; RD -0.00, 95% CI -0.03 to 0.03). Length of hospital stay was not reduced for infants with suspected or proven infection at trial entry (1 study (n = 3493); mean difference (MD) 0.00 days, 95% CI -0.61 to 0.61). No significant difference in mortality during hospital stay after administration of IgM-enriched IVIG for suspected infection at trial entry was reported in 4 studies (n = 266) (typical RR 0.68, 95% CI 0.39 to 1.20; RD -0.06, 95% CI -0.14 to 0.02; I^2 = 17% for RR and 53% for RD).

Authors' conclusions

The undisputable results of the INIS trial, which enrolled 3493 infants, and our meta-analyses (n = 3973) showed no reduction in mortality during hospital stay, or death or major disability at two years of age in infants with suspected or proven infection. Although based on a small sample size (n = 266), this update provides additional evidence that IgM-enriched IVIG does not significantly reduce mortality during hospital stay in infants with suspected infection. Routine administration of IVIG or IgM-enriched IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended. No further research is recommended.

PLAIN LANGUAGE SUMMARY

Intravenous immunoglobulin for suspected or proven infection in neonates

Background

Infants may acquire infection while in the womb or in the hospital after birth, especially if they require intensive care. Such infections may cause serious illness or death. Maternal transport of immunoglobulins (substances in the blood that can fight infection) to the fetus mainly occurs after 32 weeks' gestation, and infants do not begin to produce their own immunoglobulins until several months after birth. Theoretically, the adverse effects of infection could be reduced by the administration of intravenous immunoglobulin.

Our review question

In newborn infants with suspected or proven infections**,** does the injection of immunoglobulin into the veins reduce death or illness?

What the studies showed

In addition to many small studies**,** a very large trial that enrolled 3493 infants has been published. It is clear from the available studies that intravenous immunoglobulin administration does not prevent death or illness during hospital stay, and death or major disability at two years of age.

Overall

The use of intravenous immunoglobulin to treat suspected or proven infection in neonates is not recommended. No further research is recommended.

BACKGROUND

Congenital and nosocomial bacterial and fungal infections continue to be a significant cause of neonatal morbidity and mortality. In a cohort of 7861 very low birth weight (VLBW) neonates admitted during a 32-month period (1991 to 1993) to the 12 National Institute of Child Health and Human Development (NICHD) Network centres, blood culture proven early-onset (occurring within 72 hours of birth) sepsis occurred in 1.9% of infants (Stoll 1996a). In contrast to the low incidence of proven early-onset sepsis, almost 50% of infants in the cohort were considered to have clinical sepsis and were treated with antibiotics for longer than five days. Neonates with early-onset sepsis were more likely to have later co-morbidities or complications (severe intraventricular haemorrhage, patent ductus arteriosus, and prolonged assisted ventilation). Decreasing gestational age was associated with increased rates of infection; and 26% of VLBW infants with early-onset sepsis died. However, only 4% of the 950 deaths that occurred in the first 72 hours of life were attributed to infection. For infants who survived to discharge, early-onset sepsis was associated with a statistically significant longer hospital stay (86 versus 69 days; $P < 0.02$). From the same 12 centres, a 25% incidence of late-onset infection has been reported in a cohort of 6911 VLBW infants who survived beyond 3 days of life (Stoll 1996b). Neonates in whom late-onset sepsis developed were significantly more likely to die than those who were not infected (17% versus 7%; $P < 0.0001$).

Maternal transport of immunoglobulins to the fetus occurs mainly after 32 weeks' gestation, and endogenous synthesis does not begin until about 24 weeks after birth. Therefore, infants born at term and especially premature infants are at high risk for morbidity and mortality from infections acquired in utero, as well as from exposure to infectious sources in neonatal intensive care units (Baker 1990). The rationale for treating neonatal infection with intravenous immunoglobulin (IVIG) is based on evidence that administration of IVIG provides immunoglobulin G (IgG) that can bind to cell surface receptors, provide opsonic activity, activate complement, promote antibody-dependent cytotoxicity and improve neutrophilic chemo-luminescence (Baley 1988).

Prophylactic administration of IVIG to prevent nosocomial infection has been studied in > 5000 neonates enrolled in randomised controlled trials (RCTs) (Ohlsson 2010a). The results of these meta-analyses show a statistically significant reduction in sepsis (risk difference (RD) -2.8%; number needed to treat to benefit (NNTB) 36) and any serious infection (typical RD -3.2%; NNTB 31) but no reduction in mortality from infection (Ohlsson 2010a).

The effectiveness of IVIG as an adjunct to standard treatment with antibiotics in reducing mortality from suspected infection has been less well studied. In clinical practice, the number of infants with suspected infection considerably outweighs the number of infants eventually proven to have systemic infection. To study the effectiveness of IVIG in reducing mortality and morbidity from infection in the clinical setting, neonates with suspected infection should be entered and randomly assigned into such trials and outcomes should be reported on an 'intention-to-treat basis". Baley 1992 presented a systematic review based on three studies (Haque 1988; Sidiropoulos 1981; Weisman 1992a) that evaluated the effect on mortality of administration of IVIG to neonates with suspected sepsis. However, the study by Weisman (Weisman 1992a) included only infants with subsequently proven infection. Although the meta-analysis showed a statistically significant typical risk difference (RD) for mortality of -14.5% (95% confidence interval (CI) -4.5 to -24.5), the authors stressed that the analysis must be viewed with caution as only a small number of infants had been studied (173 neonates were included in their review). Lacy 1995 excluded the study by Sidiropoulos (1986) in a meta-analysis as the original study published in German (Sidiropoulos 1981) indicated that it was a quasi-randomised trial (a group of 82 newborns with suspected infection were treated with antibiotics alone or with antibiotics and immunoglobulin on an alternating basis). The authors of the meta-analysis concluded that no statistically significant reduction in mortality was noted following IVIG administration for the treatment of neonatal infection. In another meta-analysis, Jenson 1997 included the same three studies as were included by Baley 1992 but concluded that IVIG administration is "of unequivocal benefit in preventing death when administered therapeutically for early-onset neonatal sepsis". In a subsequent publication, these authors concluded, "The additional benefit of decreasing the risk of acute mortality indicates that the inclusion of IVIG should be considered a part of the routine therapy of neonatal sepsis" (Jenson 1998). In a meta-analysis of five studies of IVIG to treat neonatal sepsis, Haque 1997 concluded that IVIG treatment results in a significant reduction in mortality (typical odds ratio (OR) 0.32, 95% CI 0.21 to 0.48). Two of the included studies lacked a randomised control group (Friedman 1990; Haque 1995). A Cochrane review (Alejandria 2001) conducted after publication of the first version of our Cochrane review (Ohlsson 1998b) included all age groups. The authors found a reduction in overall mortality in participants of all ages who received polyclonal IVIG. In a subgroup analysis in neonates (4 studies, 191 infants) no statistically significant reduction in all-cause mortality was reported (typical risk ratio (RR) 0.60, 95% CI 0.31 to 1.14). The analyses by Alejandria (Alejandria 2001) included fewer studies than were included in the previous version of our systematic review in *The Cochrane Library* (Ohlsson 1998b).

This review updates our existing Cochrane review, 'Intravenous immunoglobulin for suspected or subsequently proven infection in neonates', published in 1998 (Ohlsson 1998b). It was updated in 2001 (Ohlsson 2001), 2004 (Ohlsson 2004), 2007 when no new trials were identified, 2010 when one new trial was identified (Ohlsson 2010) and in July 2013 when the large INIS trial (INIS 2011) was included (Ohlsson 2013).

OBJECTIVES

Primary objectives:

- to assess the effects of IVIG on mortality and morbidity caused by suspected infection at study entry in neonates;
- to assess the effects of IVIG on mortality and morbidity caused by proven infection at study entry in neonates;
- to assess the effects of IVIG on mortality and morbidity caused by suspected or proven infection at study entry in neonates; and
- to assess in a subgroup analysis the effects of IgM-enriched IVIG on mortality from suspected infection.

For the 2013 update and this update, we excluded the comparison and related outcomes for 'IVIG versus placebo or no intervention for subsequently proven infection'. As was stated in a previous update of the review, "such estimates are meaningless as the clinician is

unaware, at the point of starting treatment for suspected infection, whether the infant will have proven sepsis or not".

In a deviation from the protocol for the 2013 update, we included a study that enrolled infants with suspected or proven serious infection at the time of randomisation (INIS 2011). For that and this update, we performed a subgroup analysis for mortality in studies that used IgM-enriched IVIG for treatment of suspected infection. Suspected infection was defined as clinical symptoms and signs consistent with infection without isolation of a causative organism. Proven infection was defined as clinical symptoms and signs consistent with infection in association with isolation at autopsy of a causative organism (bacteria or fungi) from a blood culture, cerebrospinal fluid culture, urine culture (urine obtained by suprapubic tap) or a normally sterile site (for example liver, spleen, meninges, lung).

METHODS

Criteria for considering studies for this review

Types of studies

Studies in which neonates were randomly assigned to receive IVIG or either a placebo or no intervention to prevent mortality and morbidity from suspected or proven serious infection during an initial hospital stay were included, as were studies that reported on mortality, length of hospital stay, side effects, long-term psychomotor development or growth following IVIG treatment for serious infection.

Types of participants

Newborn (< 28 days of age) infants with suspected or proven serious infection.

Types of interventions

IVIG (polyvalent or IgM-enriched) to treat suspected or proven bacterial or fungal infection versus control (placebo or no treatment). Species-specific immunoglobulins (such as for *Staphylococcus aureus* or *Staphylococcus epidermidis*) were not included, as they are reviewed separately by others within The Cochrane Collaboration (Shah 2009).

Types of outcome measures

Primary outcome

- Mortality from any cause during initial hospital stay

Secondary outcomes

- Length of hospital stay
- Long-term psychomotor development at 18 months corrected age or at a later age
- Growth at 18 months corrected age or at a later age
- Death at 18 months corrected age or at a later age
- Death or major disability at 18 months corrected age or later
- Increased number of infections during childhood
- Side effects (not predetermined but as reported by authors)

Search methods for identification of studies

Electronic searches

The search strategy used to identify studies was based on the guidelines of the Cochrane Neonatal Review Group.

The search was initiated by a review of personal files. Reference lists of identified studies and subsequently retrieved articles were scanned for additional references. MEDLINE was searched from 1966 to September 2003. EMBASE (Excerpta Medica online) was searched from 1980 to September 2003. *The Cochrane Library* (Issue 3, 2003) was searched. The following keywords were used: immunoglobulin and infant-newborn, and random allocation, or controlled trial, or randomised controlled trial (RCT). No language restrictions were applied. Ms Elizabeth Uleryk developed and applied an extensive search strategy (available upon request) for MEDLINE and EMBASE in February 2001 and September 2003.

For the 2010 update, the same search strategy was applied for all databases in December of 2009. Progress details on the ongoing International Neonatal Imunotherapy Study (INIS) were obtained from the trial website (http://www.npeu.ox.ac.uk/inis) and by communication with the principal investigator, Dr Peter Brocklehurst, in February 2010.

For the 2013 update, Ms Yolanda Brosseau conducted searches of CINAHL, *The Cochrane Library*, PubMed, EMBASE, clinicaltrials.gov and controlledtrials.com on 13 February 2013. On the same day, abstracts from the Pediatric Academic Societies Annual Meetings (www.abstracts2view.com/pas) from 2002 to 2012 were searched, as was Web of Science using the first published trial as the starting point (Sidiropoulos 1981). The Pediatric Academic Societies Annual Meetings website was searched on 6 May 2013 for abstracts published in 2013 (www.abstracts2view.com/pas).

For the 2015 update, Ms Colleen Ovelman conducted searches of CINAHL, *The Cochrane Library*, PubMed, EMBASE, clinicaltrials.gov and controlledtrials.com on 9 January 2015. On the same day, abstracts from the Pediatric Academic Societies Annual Meetings (www.abstracts2view.com/pas) from 2010 to 2014 were searched by one of us (AO), as was Web of Science using the first published trial as the starting point (Sidiropoulos 1981).

Searching other resources

Reference lists of identified trials and systematic reviews were searched for potential trials for inclusion.

Data collection and analysis

Selection of studies

The criteria used in the selection of studies for inclusion in this overview were:

- design, randomised or quasi-randomised controlled trials in which treatment with IVIG was compared with a control group that received a placebo or no intervention;
- population, newborns (< 28 days of age);
- intervention, IVIG to treat suspected or proven serious infection;
- collection of the outcomes of mortality during initial hospital stay or length of hospital stay, or both, as reported. Data for side effects and other morbidities were noted when reported by the authors;

- inclusion of one study that enrolled infants with suspected or proven serious infection (INIS 2011). The authors provided us with unpublished data for two subgroups of infants, infants with suspected infection at trial entry and infants with proven infection at trial entry;
- exclusion of comparison and related outcomes for 'IVIG versus placebo or no intervention for subsequently proven infection'. As was stated in the previous update of the review, "such estimates are meaningless, as the clinician is unaware, at the point of starting treatment for suspected infection, whether the infant will have proven sepsis or not";
- a subgroup analysis for mortality performed in studies that used IgM-enriched IVIG for treatment of suspected infection.

Printouts of the titles (and abstracts when available) in MEDLINE, EMBASE, CINAHL and *The Cochrane Library* were reviewed by the two review authors. Any article that either person felt might meet the inclusion criteria noted above, or that either person felt should have its reference list searched, was retrieved. No systematic attempt was made to locate unpublished studies.

Data extraction and management

All identified trials are listed in the tables: Characteristics of included studies, Characteristics of excluded studies or Characteristics of ongoing studies.

The two review authors independently abstracted information on each study, and AO checked for any discrepancies and pooled the results. Data abstracted included whether the study involved prophylaxis or treatment, number of participants enrolled, number of participants enrolled but later excluded, time period and geographical location of the study, baseline characteristics of participants, inclusion and exclusion criteria, preparation and dosing regimen for IVIG and placebo, and length of follow-up. Information on outcomes (mortality and morbidities, length of hospital stay, long-term follow-up, side effects) was abstracted. This update was conducted by both review authors (AO, JBL).

Assessment of risk of bias in included studies

An assessment of the quality of the included studies (excluding abstracts) was performed independently by JBL and AO using criteria developed by the Cochrane Neonatal Review Group. These criteria include blinding of randomisation, blinding of intervention, complete follow-up and blinding of outcome measurement. For each criterion, there were three possibilities: yes, can't tell, and no. The assignment was not done with the assessors blinded to author, institution, journal of publication or results, as both assessors were familiar with most of the studies and the typographical layout of the journals and would have knowledge of these even when blinded. In addition, the results sections of articles often include methodological information. After independent scoring, the two assessors discussed the ratings for each study, and any discrepancies were resolved. For the 2010 update, the risk of bias tables were completed by one review author (AO). For the 2013 and 2015 updates, both review authors (AO, JBL) completed the Risk of bias in included studies table.

The following headings and associated questions (based on the questions in the Risk of bias in included studies table) were evaluated by the two review authors and were entered into the Risk of bias in included studies table.

Selection bias (random sequence generation and allocation concealment)

Adequate sequence generation?

For each included study, we categorised the risk of selection bias as:

- low risk—adequate (any truly random process, e.g. random number table, computer random number generator);
- high risk—inadequate (any non-random process, e.g. odd or even date of birth, hospital or clinic record number); or
- unclear risk—no or unclear information provided.

Allocation concealment?

For each included study, we categorised the risk of bias regarding allocation concealment as:

- low risk—adequate (e.g. telephone or central randomisation, consecutively numbered sealed opaque envelopes);
- high risk—inadequate (open random allocation, unsealed or non-opaque envelopes, alternation, date of birth); or
- unclear risk—no or unclear information provided.

Blinding?

Performance bias

For each included study, we categorised the methods used to blind study personnel from knowledge of which intervention a participant received (as our study population consisted of neonates, all would be blinded to the study intervention) as:

- low risk—adequate for personnel (a placebo that could not be distinguished from the active drug was used in the control group);
- high risk—inadequate, personnel aware of group assignment; or
- unclear risk—no or unclear information provided.

Detection bias

For each included study, we categorised the methods used to blind outcomes assessors from knowledge of which intervention a participant received (as our study population consisted of neonates, all would be blinded to the study intervention). Blinding was assessed separately for different outcomes or classes of outcomes. We categorised the methods used with regard to detection bias as:

- low risk—adequate, follow-up was performed with assessors blinded to group;
- high risk—inadequate, assessors at follow-up were aware of group assignment; or
- unclear risk—no or unclear information provided.

Incomplete data addressed?

Attrition bias

For each included study and for each outcome, we described completeness of data including attrition and exclusions from the analysis. We noted whether attrition and exclusions were reported, as well as the numbers included in the analysis at each stage (compared with the total number of randomised participants), reasons for attrition or exclusion, and whether missing data were

balanced across groups or were related to outcomes. Where sufficient information was reported or supplied by the trial authors, we would re-include missing data in the analyses. We categorised methods used with respect to the risk attrition bias as:

- low risk—adequate (≤ 10% missing data);
- high risk—inadequate (> 10% missing data); or
- unclear risk—no or unclear information provided.

Free of selective reporting?

Reporting bias

For each included study, we described how we investigated the risk of selective outcome reporting bias and what we found. We assessed these methods as:

- low risk—adequate (where it is clear that all of the study's pre-specified outcomes and all expected outcomes of interest to the review have been reported);
- high risk—inadequate (where not all of the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest were reported incompletely and so could not be used; study failed to include results of a key outcome that would have been expected to have been reported); or
- unclear risk—no or unclear information provided (the study protocol was not available).

Free of other bias?

Other bias

For each included study, we described any important concerns that we had about other possible sources of bias (for example whether there was a potential source of bias related to the specific study design, whether the trial was stopped early because of some data-dependent process). We assessed whether each study was free of other problems that could put it at risk of bias as:

- low risk—no concerns of other bias raised;
- high risk—concerns raised about multiple looks at the data with results made known to the investigators, difference in number of participants enrolled in abstract and in final publications of the paper;
- unclear—concerns raised about potential sources of bias that could not be verified by contacting the authors.

Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias according to the criteria given in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). We assessed the likely magnitude and direction of the bias, and whether we considered it likely to impact the findings. We explored the impact of the level of bias by undertaking sensitivity analyses (see Sensitivity analysis).

For the original review, independent quality assessments were conducted by two review authors (JBL, AO) who were not blinded to the authors, institution or journal of publication. The current update in 2015 was conducted by both review authors (AO, JBL).

Measures of treatment effect

The statistical package RevMan 5.3 (RevMan 2014), provided by The Cochrane Collaboration, was used (Higgins 2011). Typical risk ratio (RR) and risk difference (RD) with 95% confidence intervals (CIs) using the fixed-effect model were reported for dichotomous data and weighted mean difference (WMD) for continuous data. If a statistically significant reduction in the RD had been found, the number needed to treat to benefit (NNTB) would have been calculated. If a statistically significant increase in the RD had been found, the number needed to treat to harm (NNTH) would have been calculated. For previous updates, the RD and the NNTB were not calculated for the subset of participants who entered the trials with suspected sepsis, and who were subsequently proven to have sepsis. Such estimates are meaningless as the clinician is unaware at the point of starting treatment whether or not the infant will have proven sepsis. This comparison for a subset of participants was excluded for both the 2013 and this update.

Unit of analysis issues

In all studies, the individual infant was the unit of analysis.

Dealing with missing data

Additional information was requested from authors of published studies, and we received seven replies as of January 2015.

Assessment of heterogeneity

Heterogeneity tests including the I^2 statistic were performed to assess the appropriateness of pooling the data (Higgins 2003). We used the following criteria to describe the percentages of heterogeneity: < 25% no heterogeneity, 25% to 49% low heterogeneity, 50% to 74% moderate heterogeneity, and ≥ 75% high heterogeneity. Statistically significant heterogeneity was noted and reported.

Assessment of reporting biases

We conducted a funnel plot for the primary outcome: IVIG versus placebo or no intervention for suspected infection at trial entry (Comparison 1), mortality from any cause (Outcome 1.1).

Data synthesis

Meta-analysis was performed using Review Manager software (RevMan 2014) supplied by The Cochrane Collaboration. For estimates of typical RR and RD values, we used the Mantel-Haenszel method. For measured quantities, we used the inverse variance method. All meta-analyses were done using the fixed-effect model. If means and standard deviations were not reported, we estimated these from the median, range and size of the sample as reported by Hozo and coworkers (Hozo 2005).

Subgroup analysis and investigation of heterogeneity

In the 2013 and the 2015 updates, we performed one separate analysis for the primary outcome of 'mortality from any cause during initial hospitalisation' (Analysis 4.1) for studies that reported they had used IgM-enriched IVIG for suspected infection at trial entry.

Sensitivity analysis

No sensitivity analyses were performed.

RESULTS

Description of studies

Details of the included studies are provided in the table Characteristics of included studies. Eight studies (Ahmed 2006; Christensen 1991; Erdem 1993; Haque 1988; INIS 2011; Samatha 1997; Shenoi 1999; Sidiropoulos 1981) met the inclusion criteria. One previously ongoing study was published in 2014 (Akdag 2014).

Five studies were excluded (see the table Characteristics of excluded studies).

Included studies

Ahmed 2006 randomly assigned 60 neonates with suspected infection to receive IVIG or placebo. Outcomes for all infants were reported. Blood cultures were positive in 76.7% (23 infants) in the IVIG group and 73.3% (22 infants) in the control group. Results were reported as an intention-to-treat analysis with later proven cases of sepsis combined with suspected cases of sepsis.

Akdag 2014 randomly assigned 204 infants with suspected sepsis to receive IgM-enriched IVIG, pentoxifylline, IgM-enriched IVIG and pentoxifylline, or normal saline (placebo). In the IgM-enriched IVIG group 23 of 51 infants had positive blood cultures and in the placebo group 19 of 51 infants had positive blood cultures. Outcomes were reported on all enrolled infants. We included in our analysis only infants in the IgM-enriched IVIG group and the placebo group (51 infants in each group).

Christensen 1991 randomly assigned 24 infants with suspected sepsis to receive IVIG or placebo. Two infants were excluded from the analysis, and the authors did not state in which group(s) these infants belonged. Fifteen participants (six of the 11 IVIG recipients and 9 of the 11 placebo recipients) had bacteria recovered from their blood or trachea, or identified by bacterial antigen detection.

Erdem 1993 enrolled 44 infants with suspected sepsis. Twenty were randomly chosen to receive IgM-enriched IVIG, and 24 were controls. Fifteen infants in each group had blood culture proven sepsis, and the remaining infants were classified as having suspected but not proven infection. Outcomes for all randomly assigned infants were reported. Through correspondence, the authors indicated that allocation was performed on an 'alternating basis'.

Haque 1988 randomly assigned 60 infants with suspected infection to either antibiotics alone or antibiotics with IgM-enriched IVIG. Forty-four infants had proven infection, and 16 had suspected but not proven infection. Outcomes were reported on all infants. All deaths in the study population were reported (information provided by the author).

INIS 2011 (new inclusion) randomly assigned 3493 infants with suspected or proven infection. All randomly assigned infants were accounted for. In contrast to all other studies, this study enrolled infants with both proven infection and suspected infection and, in the original publication, outcomes were reported for a combination of these two groups. The authors provided us with unpublished data for the outcomes: death at two years corrected age, death in hospital, and death or major disability at two years (corrected age) for the two separate groups; infants with suspected infection at trial entry, and Infants with proven infection at trial entry.

Samatha 1997 assigned 60 neonates, who satisfied the criteria for possible sepsis, by picking up lots to receive standard treatment or standard treatment plus IgM-enriched IVIG. Outcomes were reported on all infants.

Shenoi 1999 allocated 58 newborns with suspected sepsis to IVIG treatment or placebo. Seven neonates who qualified but did not receive either IVIG or placebo were taken into a separate control group, and one infant who received only one dose of IVIG was excluded from the analysis. Twenty infants were confirmed as having a positive blood culture, whereas in 30 infants bacteraemia was not confirmed. Outcomes were reported for these 50 randomly assigned participants. On request, the author reported that a random table was used to assign the randomisation sequence, and that sealed envelopes were used to allocate the neonates to treatment or control groups. A non-identical placebo was used in the control group.

Sidiropoulos 1981 allocated (alternating basis) 82 newborns with suspected sepsis to IVIG treatment or no IVIG treatment. Thirty-five of the neonates were confirmed as having sepsis, whereas in 47 infants bacteraemia was not confirmed. Outcomes were reported for all 82 randomly assigned participants.

Different IVIG preparations, amounts and dosing schedules were used: 500 mg/kg for three consecutive days of Octagam (Ahmed 2006); a single dose of 750 mg/kg of Gamimmune-N (Christensen 1991); 5 mL/kg/day of Pentaglobin for three days (Erdem 1993; Samatha 1997); 250 mg/kg IV over 4 hours, daily for three consecutive days (Akdag 2014); 5 mL/kg/day of Pentaglobin for four days (Haque 1988); a daily dose of 0.5 to 1 g for six days of Immunoglobulin SRK (Sidiropoulos 1981); 1 g/kg of Sandoglobulin on three consecutive days (Shenoi 1999); and two infusions of polyvalent IgG immune globulin (at a dose of 500 mg/kg body weight) (in Europe and Argentina the IVIG was produced by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service; in Australia and New Zealand the IVIG preparation was Intragam P) (INIS 2011).

Risk of bias in included studies

For details see the Risk of bias in included studies table and Figure 1 and Figure 2. Most included studies (Ahmed 2006; Christensen 1991; Erdem 1993; Haque 1988; Samatha 1997; Shenoi 1999; Sidiropoulos 1981) were of small size (24 to 82 infants were enrolled). The currently included study by Akdag 2014 was of small sample size too and enrolled 102 infants to receive either IgM-enriched IVIG or placebo. In the 2013 update, one large study that included infants with proven and suspected infection at trial entry was included (INIS 2011). This study enrolled 3493 infants. In only three studies was a sample size calculation reported as part of the study design (Akdag 2014; INIS 2011; Shenoi 1999).

Figure 1. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

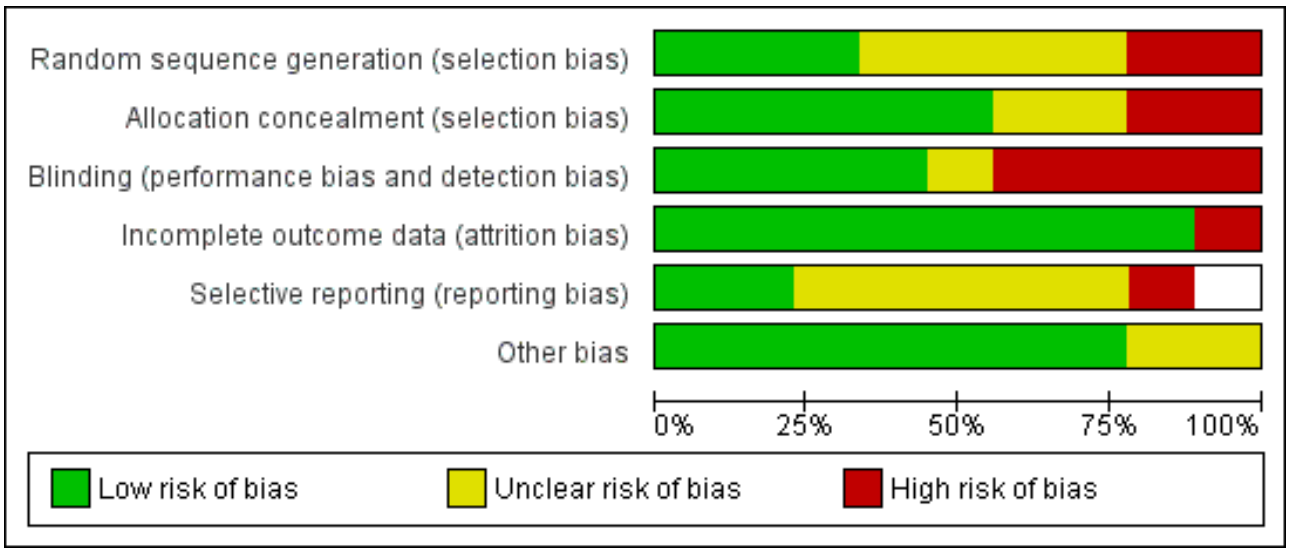
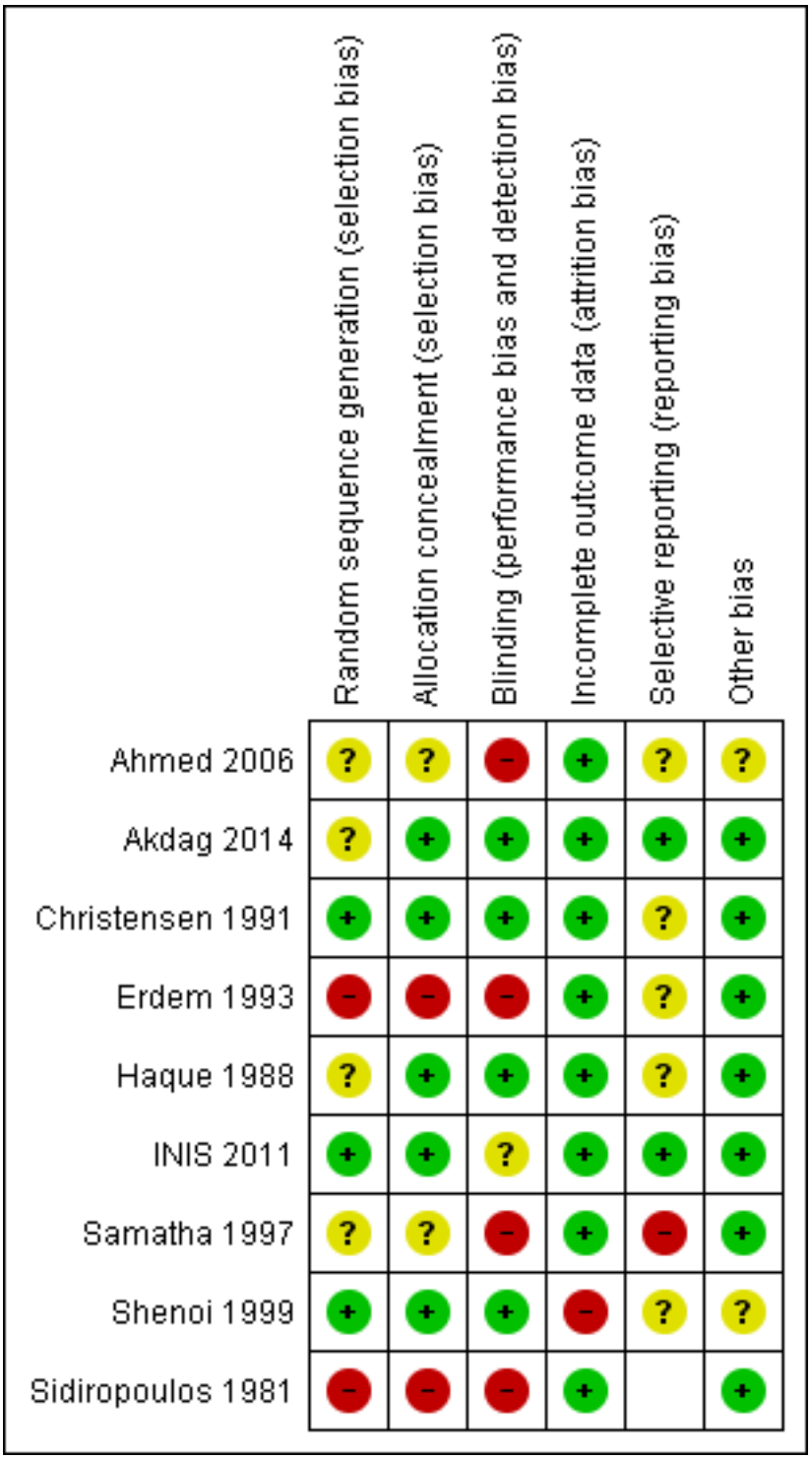


Figure 2. Risk of bias summary: review authors' judgements about each risk of bias item for each included study.



The eight small studies were performed in six countries (Bangladesh, India (n = 2), Saudi Arabia, Switzerland, Turkey (n = 2) and the US). The level of intensive care offered to these neonates was poorly described and was likely to have varied. The large INIS 2011 study was conducted in 113 hospitals in nine countries (including Argentina, Australia, New Zealand and several countries in Europe).

In all but one study, infants were enrolled because of suspected infection. It is our interpretation that randomisation and initiation of treatment occurred at this stage. In the INIS study (INIS 2011) infants were enrolled with either suspected infection or proven infection at the time of initiation of treatment. Seven of the studies (Ahmed 2006; Akdag 2014; Erdem 1993; Haque 1988; INIS 2011; Samatha 1997; Sidiropoulos 1981) reported on outcomes as per intention to treat. Christensen (Christensen 1991) did not report on

the allocation of two infants who were excluded from the study (one infant died). In the study by Shenoi (Shenoi 1999), 58 newborns with suspected sepsis were allocated to IVIG treatment or placebo. Seven neonates who qualified but did not receive either IVIG or placebo were taken into a separate control group, and one infant who received only one dose of IVIG was excluded from the analysis.

Allocation

Blinding of randomisation was certain in five studies (Akdag 2014; Christensen 1991; Haque 1988; INIS 2011 Shenoi 1999). For the INIS study (INIS 2011), the assignment sequence was generated by the National Perinatal Epidemiology Unit in Oxford, UK, with balance within random block sizes of 2 and 8.

Information on blinding of randomisation was lacking for two studies (Ahmed 2006; Samatha 1997). In the studies by Sidiropoulos 1981 and Erdem 1993 allocation to the IVIG or control group was done on an alternating basis.

Blinding

Four studies used a placebo to blind the intervention and the outcome measurement (Akdag 2014; Christensen 1991; Haque 1988; INIS 2011). In the INIS study (INIS 2011) in Europe and Argentina, neonatal staff opened the next sequentially numbered study pack, which was stored in the neonatal unit and contained all materials necessary to administer a course of the study drug. In Australia and New Zealand, the hospital pharmacy was contacted and the next assignment was taken from a randomisation list generated by the National Health and Medical Research Council Clinical Trials Centre in Sydney. One study (Shenoi 1999) used a placebo that was not prepared by the pharmaceutical company providing the IVIG but was prepared by the investigators after random allocation to the placebo group. Four studies (Ahmed 2006; Erdem 1993; Samatha 1997; Sidiropoulos 1981) did not use a placebo.

Incomplete outcome data

It is uncertain whether reported deaths represented total mortality from all causes in all studies. Ahmed (Ahmed 2006) defined the mortality outcome as those infants who died in hospital as the result of sepsis, prematurity or its complications. Haque (Haque 1988) stated that the deaths were the result of sepsis, but some reported deaths occurred in neonates with suspected sepsis. Haque has confirmed that all deaths in the study population were reported (personal communication, 1998). In the other studies, it was assumed that all deaths during the initial hospitalisation were accounted for. Ahmed (Ahmed 2006) defined hospital stay as the time needed to heal from the problem or its associated complications until discharge.

Selective reporting

The study protocol was available for only two studies (Akdag 2014; INIS 2011). No deviation from the protocol was noted for these studies. For the other studies, we cannot judge whether or not deviations from the study protocol occurred.

Other potential sources of bias

Methodological weaknesses identified in several of these studies included the lack of a sample size calculation (in general, very small cohorts were recruited), uncertainty about concealment of randomisation and how randomisation was undertaken, lack of a placebo, not ascertained that assessors of outcomes were blinded to group allocation and outcomes not reported as per intention to treat.

Effects of interventions

One new trial was identified in this update (Akdag 2014) to give a total of nine trials (Ahmed 2006; Akdag 2014; Christensen 1991; Erdem 1993; Haque 1988; INIS 2011; Samatha 1997; Shenoi 1999; Sidiropoulos 1981) that have evaluated the effects of IVIG on important outcomes. Five studies were excluded as they reported only on the outcomes for infants who were proven to be infected after randomisation (Chen 1996; Gökalp 1994; Haque 1995; Mancilla-R 1992; Weisman 1992). One study identified for this update was not a randomised controlled trial (Salihoglu 2013).

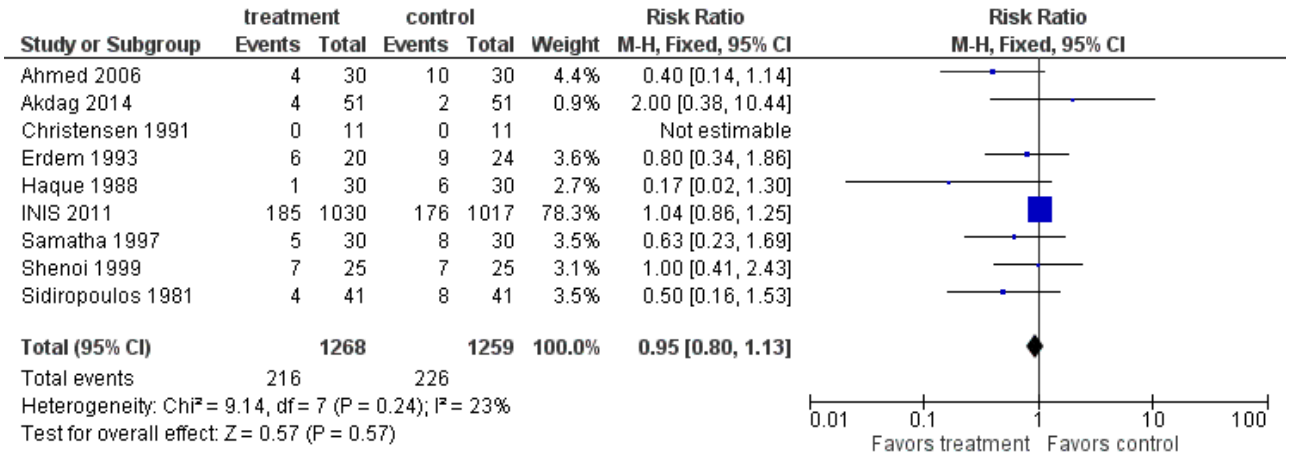
IVIG versus placebo or no intervention for suspected infection at trial entry (Comparison 1)

The following outcomes were reported for infants with suspected infection at trial entry.

Mortality from any cause (Outcome 1.1)

(Figure 3)

Figure 3. Forest plot of comparison: 1 IVIG versus placebo or no intervention for suspected infection, outcome: 1.1 Mortality from any cause.



Nine studies (n = 2527 infants) reported on the outcome of mortality from any cause in participants with clinically suspected infection at trial entry. The results showed no statistically significant difference in mortality (typical RR 0.95, 95% CI 0.80 to 1.13; typical RD -0.01, 95% CI -0.04 to 0.02). Low heterogeneity was noted for this outcome: I^2 = 23% for RR and 29% for RD.

Length of hospital stay (Outcome 1.2)

Three studies enrolling 170 infants reported on this outcome. A statistically significant reduction in length of hospital stay was noted (mean difference (MD) -4.08 days, 95% CI -6.47 to -1.69; I^2 = 33%, low).

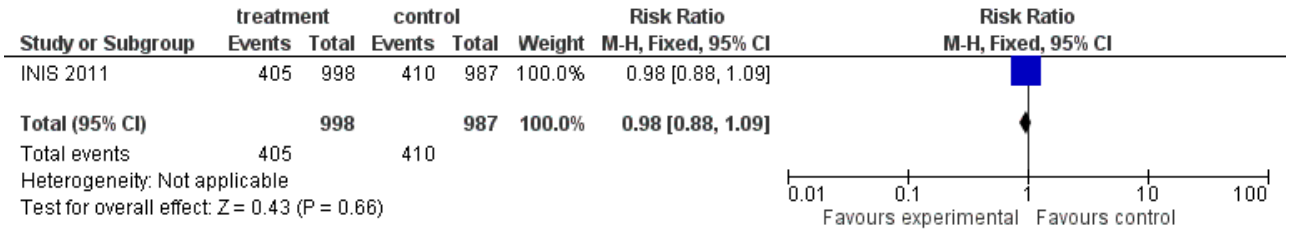
Death at two years corrected age (Outcome 1.3)

One study (INIS 2011) (n = 2047 infants) reported on this outcome. No significant difference was noted between groups (RR 1.03, 95% CI 0.86 to 1.24; RD 0.01, 95% CI -0.03 to 0.04). Tests for heterogeneity were not applicable.

Death or major disability at two years corrected age (Outcome 1.4)

(Figure 4)

Figure 4. Forest plot of comparison: 1 IVIG versus placebo or no intervention for suspected infection at trial entry, outcome: 1.4 Death or major disability at 2 years corrected age.



One study (INIS 2011) (n = 1985 infants) reported on this outcome. No significant difference was noted between the groups (RR 0.98, 95% CI 0.88 to 1.09; RD -0.01, 95% CI - 0.05 to 0.03). Tests for heterogeneity were not applicable.

IVIG versus placebo or no intervention for proven infection at trial entry (Comparison 2)

Mortality from any cause during hospital stay (Outcome 2.1)

One study (INIS 2011) (n = 1446 infants) reported on mortality from any cause during hospital stay. No significant difference between groups was noted for this outcome (RR 0.95, 95% CI 0.74 to 1.21; RD -0.01, 95% CI -0.04 to 0.03). Tests for heterogeneity were not applicable.

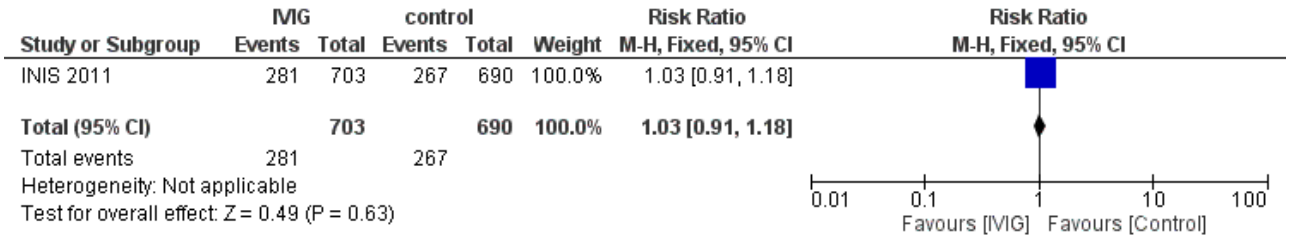
Death at two years corrected age (Outcome 2.2)

One study (INIS 2011) (n = 1446 infants) reported on death at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 1.04, 95% CI 0.83 to 1.31; RD 0.01, 95% CI -0.03 to 0.05). Tests for heterogeneity were not applicable.

Death or major disability at two years corrected age (Outcome 2.3)

(Figure 5)

Figure 5. Forest plot of comparison: 2 IVIG versus placebo or no intervention for proven infection at trial entry, outcome: 2.3 Death or major disability at 2 years corrected age.



One study (INIS 2011) (n = 1393 infants) reported on death or major disability at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 1.03, 95% CI 0.91 to 1.18; RD 0.01, 95% CI -0.04 to 0.06). Tests for heterogeneity were not applicable.

IVIG versus placebo for suspected or proven infection at trial entry (Comparison 3)

The following outcomes were reported for infants with suspected or proven infection at trial entry.

Mortality from any cause (Outcome 3.1)

One study (INIS 2011) (n = 3493 infants) reported on mortality from any cause during the initial hospital stay. No significant difference between groups was noted (RR 1.00, 95% CI 0.86 to 1.16; RD 0.00, 95% CI -0.02 to 0.03). Tests for heterogeneity were not applicable.

Use of supplemental oxygen on day 28 (Outcome 3.2)

One study (INIS 2011) (n = 2785 infants) reported on the use of supplemental oxygen on day 28. No significant difference between groups was noted for this outcome (RR 0.98, 95% CI 0.92 to 1.04; RD -0.01, 95% CI -0.05 to 0.02). Tests for heterogeneity were not applicable.

Major cerebral abnormality (Outcome 3.3)

One study (INIS 2011) (n = 3493) reported on major cerebral abnormality. No significant difference between groups was noted for this outcome (RR 1.15, 95% CI 0.96 to 1.37; RD 0.02, 95% CI -0.00 to 0.04). Tests for heterogeneity were not applicable.

Necrotizing enterocolitis (new episode) (Outcome 3.4)

One study (INIS 2011) (n = 3493) reported on necrotizing enterocolitis (new episode). No significant difference between groups was noted for this outcome (RR 1.08, 95% CI 0.85 to 1.38; RD 0.01, 95% CI -0.01 to 0.02). Tests for heterogeneity not applicable.

Duration of hospital stay (Outcome 3.5)

One study (INIS 2011) (n = 3493) reported on hospital stay (days). No significant difference between groups was noted for this outcome (MD 0.00, 95% CI -0.61 to 0.61). Tests for heterogeneity were not applicable.

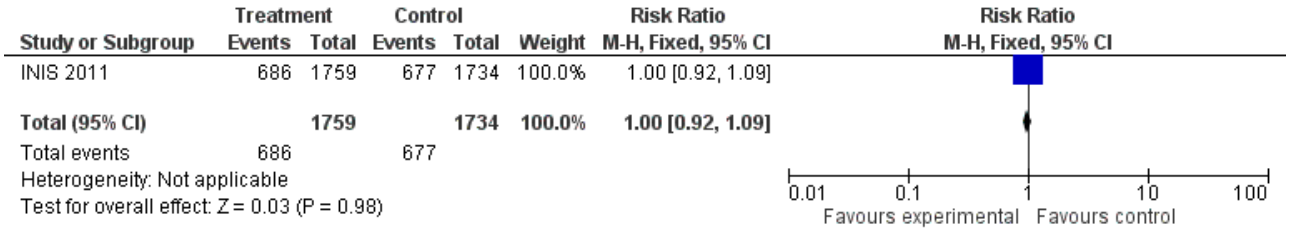
Death at two years corrected age (Outcome 3.6)

One study (INIS 2011) (n = 3493 infants) reported on death at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 1.04, 95% CI 0.90 to 1.20; RD 0.01, 95% CI -0.02 to 0.03). Tests for heterogeneity were not applicable.

Death or major disability at two years corrected age (Outcome 3.7)

(Figure 6)

Figure 6. Forest plot of comparison: 3 IVIG versus placebo for suspected or proven infection at trial entry, outcome: 3.7 Death or major disability at 2 years corrected age.



One study (INIS 2011) (n = 3493 infants) reported on death or major disability at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 1.00, 95% CI 0.92 to 1.09; RD -0.00, 95% CI -0.03 to 0.03). Tests for heterogeneity were not applicable.

Non-major disability at two years corrected age (Outcome 3.8)

One study (INIS 2011) (n = 2865 infants) reported on non-major disability at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 1.01, 95% CI 0.91 to 1.13; RD 0.00, 95% CI -0.03 to 0.04). Tests for heterogeneity were not applicable.

Major disability at two years corrected age (Outcome 3.9)

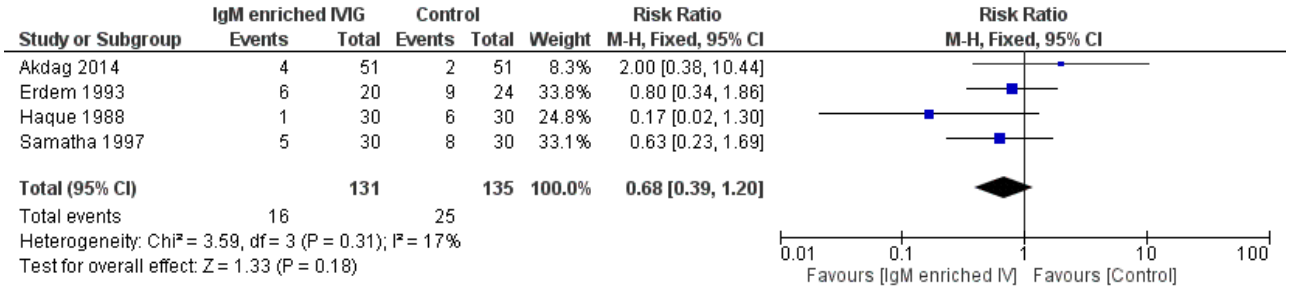
One study (INIS 2011) (n = 2865 infants) reported on major disability at 2 years corrected age. No significant difference between groups was noted for this outcome (RR 0.97, 95% CI 0.86 to 1.10; RD -0.01, 95% CI -0.04 to 0.03). Tests for heterogeneity were not applicable.

IgM-enriched IVIG versus placebo for suspected infection at trial entry (Comparison 4)

Mortality from any cause during hospital stay (Outcome 4.1)

(Figure 7)

Figure 7. Forest plot of comparison: 4 IgM-enriched IVIG for suspected infection at trial entry, outcome: 4.1 Mortality from any cause during initial hospitalisation.



Four studies (n = 266 infants) reported on this outcome. No significant difference between groups was noted for this outcome (typical RR 0.68, 95% CI 0.39 to 1.20; RD -0.06, 95% CI -0.14 to 0.02). No heterogeneity was observed for this outcome for RR (I^2 = 17%), but heterogeneity was moderate for RD (I^2 = 53%).

Serum IgG levels

An increase in serum IgG levels was noted in the studies that measured the levels (Ahmed 2006; Chen 1996; Christensen 1991; Haque 1988; Sidiropoulos 1981).

Adverse effects

Five studies reported on possible side effects (Christensen 1991; INIS 2011; Samatha 1997; Shenoi 1999; Sidiropoulos 1981). No adverse effects were noted in four studies (Christensen 1991; Samatha 1997; Shenoi 1999; Sidiropoulos 1981). The INIS study (INIS 2011) reported 22 adverse events: 12 in the group receiving IVIG (including 2 deaths) and 10 in the placebo group (including 4 deaths).

DISCUSSION

Summary of main results

The updated search in January 2015 identified one published study (Akdag 2014) that was ongoing in the previous update. The study included 102 infants of which 51 were randomised to IgM-enriched IVIG and 51 to normal saline.

For the update in 2013, we identified one new published study (INIS 2011) with a very large sample size (n = 3493 infants) and one ongoing study. We made several changes from our previous reviews; studies that reported only on infants diagnosed with proven infection after randomisation were excluded. As was stated in the previous update of the review, "such estimates are meaningless, as the clinician is unaware, at the point of starting treatment for suspected infection, whether the infant will have proven sepsis or not". In the 2013 update, we reported on the outcomes of infants with suspected infection, as well as infants with proven infection, at trial entry. In a subgroup analysis, we reported on in-hospital mortality among infants treated with IgM-enriched IVIG for suspected infection. After the findings from the large, high-quality INIS trial (INIS 2011) were incorporated, the results became unequivocal. For suspected or proven infection (or a combination of the two) intravenous immunoglobulin, in addition to antibiotics, did not confer any advantage with regard to mortality while in hospital, death at two years corrected age, or death or major disability at two years corrected age. For suspected or proven infection at trial entry, no significant difference was evident for the outcomes of use of supplemental oxygen on day 28, major cerebral abnormality, necrotizing enterocolitis, or duration of hospital stay. Intravenous immunoglobulin enriched with IgM did not seem to confer any advantage.

A total of nine studies evaluating 3973 infants were included in this update of the review.

Mortality during hospital stay in infants with clinically suspected infection was not significantly different after IVIG treatment (9 studies (n = 2527); typical RR 0.95, 95% CI 0.80 to 1.13; typical RD -0.01, 95% CI - 0.04 to 0.02; I^2 = 23% for RR and 29% for RD). Death or major disability at 2 years corrected age was not significantly different in infants with suspected infection after IVIG treatment (1 study (n = 1985); RR 0.98, 95% CI 0.88 to 1.09; RD -0.01, 95% CI -0.05 to 0.03). Mortality during hospital stay was not significantly different after IVIG treatment in infants with proven infection at trial entry (1 study (n =1446); RR 0.95, 95% CI 0.74 to 1.21; RD -0.01, 95% CI -0.04 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with proven infection at trial entry (1 trial (n = 1393); RR 1.03, 95% CI 0.91 to 1.18; RD 0.01, 95% CI -0.04 to 0.06). Mortality during hospital stay in infants with clinically suspected or proven infection at trial entry was not significantly different after IVIG treatment (1 study (n = 3493); RR 1.00, 95% CI 0.86 to 1.16; RD 0.00, 95% CI -0.02 to 0.03). Death or major disability at 2 years corrected age was not significantly different after IVIG treatment in infants with suspected or proven infection at trial entry (1 study (n = 3493); RR 1.00, 95% CI 0.92 to 1.09; RD -0.00, 95% CI -0.03 to 0.03). Three studies enrolling 170 infants with suspected infection reported on length of hospital stay. A statistically significant reduction in length of hospital stay was noted (MD -4.08 days, 95% CI -6.47 to -1.69; I^2 = 33%, low). Length of hospital stay was not reduced for infants with

suspected and proven infection at trial entry (1 study (n = 3493); mean difference (MD) 0.00 days, 95% CI -0.61 to 0.61).

No significant difference in mortality during hospital stay after administration of IgM-enriched IVIG for suspected infection at trial entry was reported in 4 studies (n = 266); typical RR 0.68, 95% CI 0.39 to 1.20; RD -0.06, 95% CI -0.14 to 0.02; I^2 = 17% for RR and 53% for RD).

Overall completeness and applicability of evidence

The large INIS 2011 study was conducted in 113 hospitals in nine countries (including Argentina, Australia, New Zealand and several countries in Europe) and enrolled 3493 infants with suspected or proven infection at trial entry. It was a high-quality trial and because of its size carried a high weight in all analyses in which it was included.

Eight small studies (enrolment included between 24 and 102 infants) were performed in six countries (Bangladesh, India (n = 2), Saudi Arabia, Switzerland, Turkey (n = 2) and the US). The level of intensive care offered to these neonates was poorly described and is likely to have varied. The evidence from the meta-analyses of IVIG for suspected or proven infection in neonates clearly indicates that IVIG does not reduce mortality or other important outcomes and should not be used. Although the sample size for the meta-analysis of IgM-enriched IVIG is small, there is no indication that its use would significantly reduce mortality in infants with suspected infection.

It is possible that the various IVIG preparations used by the authors in different geographical locations were not optimally targeted for the bacteria that were commonly isolated. No serious short-term side effects were reported in these studies; a finding that is consistent with a previous meta-analysis of prophylactic IVIG in preterm or low birth weight infants (Ohlsson 2013a).

IVIG preparations with high concentrations of antibodies to bacteria that are commonly isolated from neonates in specific local settings or geographical areas may be more effective in reducing adverse outcomes. However, the use of anti-staphylococcal immunoglobulins to prevent staphylococcal infection in very low birth weight infants has been reviewed and currently is not recommended (Shah 2009).

Quality of the evidence

Methodological weaknesses identified in several of the studies included the lack of a sample size calculation (in general, very small cohorts were recruited), uncertainty about concealment of randomisation and how randomisation was undertaken, lack of a placebo, outcomes where assessors were not ascertained as blinded to group allocation, and outcomes not reported as per intention to treat. The large INIS 2011 trial was of high quality and provided clear evidence that IVIG does not confer any significant benefits regarding death or major disability at two years corrected age in neonates with suspected or proven serious infection. The meta-analyses of all trials support the findings of no impact of IVIG on mortality during hospital stay.

Potential biases in the review process

We are not aware of any potential biases in our review process.

Agreements and disagreements with other studies or reviews

The reviews of Baley and Fanaroff (Baley 1992), Jenson and Pollock (Jenson 1997) and Haque (Haque 1997) included a quasi-randomised study (Sidiropoulos 1981). Our 2001 review (Ohlsson 2001) included five studies (Chen 1996; Erdem 1993; Mancilla-R 1992; Samatha 1997; Shenoi 1999) that were not included in the reviews by Baley and Fanaroff (Baley 1992), Lacy and Ohlsson (Lacy 1995), Jenson and Pollock (Jenson 1997), Haque (Haque 1997) or Jenson and Pollock (Jenson 1998).

Alejandria (Alejandria 2001) included four studies in her analysis of IVIG for treatment of sepsis (Chen 1996; Erdem 1993; Haque 1988; Weisman 1992). In her analysis, studies that reported deaths among neonates with suspected or subsequently proven infection were combined. She excluded the trial by Sidiropoulos 1981 as it was a quasi-randomised trial but included the trial by Erdem 1993, which is now known to be a quasi-randomised trial.

Our updated meta-analyses (Ohlsson 2001; Ohlsson 2004) had increased power, compared with previous reviews, to provide a more precise estimate of the possible advantages of IVIG treatment for neonatal sepsis. The updated review in 2010 reported on an additional 60 infants (Ohlsson 2010). Results then showed a statistically significant reduction in mortality in cases of suspected infection with an NNTB of 10 infants (95% CI 6 to 33) to avoid one death. Because of concerns regarding the quality of the studies we cautioned against the routine use of IVIG.

In the 2013 update of our review (Ohlsson 2013) it was clear that IVIG did not reduce mortality in infants with suspected or proven infection at study entry. Another recent review that used slightly different inclusion criteria reached the same conclusions (Franco 2012). The Cochrane review 'Intravenous immunoglobulin for treating sepsis, severe sepsis and septic shock' was updated in 2013 (Alejandria 2013). They included both adults and newborns but provided separate analyses for the two age groups. They included three trials (Chen 1996; Mancilla-R 1992; Weisman 1992) that we excluded because the authors reported only on the infants with subsequently proven infection, not on infants with suspected or proven infection at the trial entry. For the IgM-enriched IVIG subgroup analysis they included the same trials as we have, except for the trial by Akdag 2014, which was not published at the time of their update in 2013. However, they concluded "Among neonates with sepsis, there is sufficient evidence that standard polyclonal IVIG, as adjunctive therapy, does not reduce mortality based on the inclusion of the large polyclonal IVIG trial on neonates. For IgM-enriched IVIG, the trials on neonates and adults were small and the totality of the evidence is still insufficient to support a robust conclusion of benefit".

AUTHORS' CONCLUSIONS

Implications for practice

The undisputable results of the INIS trial, which enrolled 3493 infants, and our meta-analysis (n = 3973) showed no reduction in mortality during hospital stay, or death or major disability at two years of age in infants with suspected or proven infection. Although based on a small sample size (n = 266), this update provides additional evidence that IgM-enriched IVIG does not significantly reduce mortality during hospital stay in infants with suspected

infection. Routine administration of IVIG or IgM-enriched IVIG to prevent mortality in infants with suspected or proven neonatal infection is not recommended.

Implications for research

No further research is recommended to test currently available IVIG preparations.

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The literature searches in January 2015 were conducted by Ms Colleen Ovelman, Cochrane Neonatal Review GroupTrials Search Co-ordinator, the Cochrane Neonatal Review Group.

Dr Orlando DaSilva translated, from Spanish to English, one of the reports included in this review.
Drs Erdem, Gökalp, Haque, Mancilla-Ramirez and Shenoi provided information on their trials, in addition to what was previously published in journal articles.
Dr Shenoi provided us with the publication by Dr Samantha et al from *Karnataka Paediatric Journal.*
Dr Peter Brocklehurst volunteered information directly related to this topic in 2001, 2003 and 2010, related to the INIS trial, which started to recruit participants in 2001. In May 2012, we obtained unpublished data from Dr Peter Brocklehurst regarding the INIS trial (INIS 2011).

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CHARACTERISTICS OF STUDIES

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

Ahmed 2006

Methods	Randomised, controlled trial (no placebo) I Blinding of randomisation—Can't tell II Blinding of intervention—No III Complete follow-up—Yes IV Blinding of outcome measurement—No
Participants	60 infants with suspected infection June 2000 to November 2001 Single centre, Bangladesh
Interventions	30 preterm infants; mean GA (SD) 30.93 ± 1.96 wk, mean BW (SD) 1.45 ± 0.29; mean (SD) age on admission 9.80 ± 4.13 days, received 500 mg/kg of IVIG (Octagam, Octapharma AG) once daily for three consecutive days 30 preterm infants; mean GA (SD) 30.87 ± 1.80 wk, mean BW (SD) 1.56 ± 0.30; mean (SD) age on admission 10.30 ± 4.06 days, received no placebo
Outcomes	Mortality, length of hospital stay
Notes	

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Insufficent information to permit judgement of 'yes' or 'no'
Allocation concealment (selection bias)	Unclear risk	Insufficent information to permit judgement of 'yes' or 'no'
Blinding (performance bias and detection bias) All outcomes	High risk	The control group did not receive a placebo. Lack of blinding is not likely to influence the reporting of mortality
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all 60 enrolled infants

Ahmed 2006 *(Continued)*

Selective reporting (reporting bias)	Unclear risk	Insufficent information to permit judgement of 'yes' or 'no'
Other bias	Unclear risk	Appears to be free of other biases

Akdag 2014

Methods	Randomised, placebo-controlled trial I Blinding of randomisation—Can't tell II Blinding of intervention—Yes III Complete follow-up—Yes IV Blinding of outcome measurement—Yes
Participants	A total of 204 newborns with suspicion of sepsis August 2009 to October 2010 NICU of Zekai Tahis Burak Maternity Teaching Hospital, Ankara, Turkey
Interventions	51 infants: median (range) GA 30 (24 to 41) weeks, median (range BW 1320 g (620 to 3860) received pentaglobin (IgM-enriched IVIG, 250 mg/kg IV, over 4 hours), daily for three consecutive days 51 infants: median (range) GA 31 (25 to 40) weeks, median (range) BW 1410 g (620 to 4300) received placebo (5 mL/kg of normal saline IV over 4 hours), daily for three consecutive days 51 infants received pentoxifylline and 51 infants received pentoxifylline and IgM-enriched IVIG. These 102 infants were not included in our analyses
Outcomes	Mortality
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	Patients were assigned randomly to treatment groups by using cards in sealed opaque envelopes and sequentially numbered
Blinding (performance bias and detection bias) All outcomes	Low risk	The nurses who were taking care of the infants were blinded to group assignment. The parents and other investigators were blinded to group assignment. Infusion vials were identical. A small slit allowed nurses to watch the level of infusion without seeing the bubbles of the infusion
Incomplete outcome data (attrition bias) All outcomes	Low risk	Outcomes reported for all randomised infants
Selective reporting (reporting bias)	Low risk	This trial was registered at ClinicalTrials.gov 2009; NCT01006499, and there does not appear to be any major deviations from the protocol
Other bias	Low risk	Appears free of other bias

Christensen 1991

Methods	Randomised, placebo-controlled trial I Blinding of randomisation—Yes II Blinding of intervention—Yes III Complete follow-up—Yes IV Blinding of outcome measurement—Yes
Participants	A total of 24 neonates with suspected infection; 15 participants had bacteria recovered from their blood or trachea or identified by bacterial antigen detection. Two were excluded from the study before the infusion: one because of treatment with extracorporeal membrane oxygenation, and the other because of death before the infusion Dates not given Single centre, USA
Interventions	11 neonates: mean GA (SD) 33 ± 4 wk; mean BW (SD) 2.222 ± 0.984 kg; mean age (SD) 1.2 ± 0.4 days received a single dose of 750 mg/kg of IVIG (5% human immunoglobulin in a sterile 10% maltose solution) (Gamimmune-N, Cutter Biological, Miles Inc., Berkeley, California) 11 neonates: mean GA (SD) 31 ± 7 wk; mean BW (SD) 1.725 ± 1.138 kg; mean age (SD) 1.5 ± 0.5 days received human albumin 0.1% in a sterile 10% maltose solution
Outcomes	Mortality from 'suspected sepsis' White blood cell response, serum IgG; mechanical ventilation, intubation, oxygen administration, serum electrolytes, urine output
Notes	Mortality associated with suspected infection could be ascertained from this study Neutropenia resolved in participants receiving IVIG. The ratio of arterial oxygen tension to fraction of inspired oxygen increased in infants receiving IVIG but not after control infusions. No differences were observed in the duration of mechanical ventilation, intubation or oxygen administration. Serum IgG concentrations increased after IVIG infusions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"..neonates were randomly selected, by means of a random number table. In an attempt to provide an equal distribution of smaller infants and larger infants, two randomisation tables were employed". Central allocation was pharmacy controlled
Allocation concealment (selection bias)	Low risk	The IV preparation was dispensed from the hospital pharmacy
Blinding (performance bias and detection bias) All outcomes	Low risk	The IV preparation was dispensed from the hospital pharmacy in identical units so that investigators and caretakers were not aware of which participants received IVIG and which received placebo
Incomplete outcome data (attrition bias) All outcomes	Low risk	A total of 24 neonates were enrolled in the study. Two were excluded from the study before the infusion was given: one because of treatment with extracorporeal membrane oxygenation, and the other because of death before the infusion was given. It is not stated to which group the two excluded infants belonged. No adverse drug reactions were reported. The outcomes reported were mortality from any cause, side effects
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available to us, so we cannot ascertain whether or not there was selective reporting

Christensen 1991 *(Continued)*

Other bias	Low risk	The study appears to be free of other sources of bias

Erdem 1993

Methods	Quasi-randomised controlled trial I Blinding of randomisation—No II Blinding of intervention—No III Complete follow up—Yes IV Blinding of outcome measurement—No
Participants	A total of 44 preterm infants (GA 31 to 37 weeks) with suspected sepsis (Tollner's Sepsis Scoring System) After randomisation, 16 infants in the control group and 15 in the IVIG group had proven infection Dates not given Single centre, Turkey
Interventions	20 infants (mean GA (SD) 34.4 ± 1.9 wk, mean BW (SD) 2085 ± 352 g) with suspected infection received 5 mL/kg/day of IgM-enriched IVIG (Pentaglobin, Biotest Pharma, Frankfurt, Germany), consisting of IgM 6 mg, IgA 6 mg and IgG 38 mg/mL daily for three days All infants received antibiotic therapy and fresh frozen plasma or whole blood transfusion, or both 24 infants (mean GA (SD) 34.9 ± 1.7 wk, mean BW (SD) 2050 ± 369 g) with suspected sepsis received no placebo
Outcomes	Mortality for cases with suspected sepsis at study entry
Notes	This is a quasi-randomised trial—"alternating basis". Mortality associated with suspected infection could be ascertained from this study. No other outcomes were reported There was no mention of adverse reactions

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Allocation of participants on "alternating basis" (information provided by the author on request)
Allocation concealment (selection bias)	High risk	Allocation of participants on "alternating basis" (information provided by the author on request)
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding, but the outcome measured, mortality from any cause, is not likely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	No missing outcome data. The outcome measured was mortality from any cause
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'yes' or 'no'
Other bias	Low risk	The study appears to be free of other sources of bias

Haque 1988

Methods	Randomised, placebo-controlled trial I Blinding of randomisation—Yes II Blinding of intervention—Yes III Complete follow-up—Yes IV Blinding of outcome measurement—Yes
Participants	A total of 60 preterm infants (GA 28 to 37 weeks) with suspected sepsis Sepsis was defined as clinical features of sepsis, abnormal white cell indices and a positive blood or cerebrospinal fluid culture; 23 infants in the control group and 21 in the IVIG group had subsequently proven sepsis Dates not given (6-month period) Single centre, Saudi Arabia
Interventions	30 infants (mean GA (SD) 33.4 wk, mean BW (SD) 1.32 kg) with suspected sepsis received 5 mL/kg/day of IgM-enriched IVIG (Pentaglobin, Biotest Pharma, Frankfurt, Germany). Immunoglobulin therapy was administered over 2 hours per day for four days 30 infants (mean GA (SD) 35 wk, mean BW (SD) 1.48 kg) with suspected sepsis received 5 mL/kg/day of 10% dextrose for four days
Outcomes	Mortality Serum immunoglobulin concentrations
Notes	Mortality associated with suspected infection could be ascertained from this study Adverse reactions were not reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	No information provided
Allocation concealment (selection bias)	Low risk	"Whenever sepsis was suspected for the first time in a preterm infant, a sealed envelope was drawn, and the infant was allocated to receive either supportive and antibiotic therapy (control group) or supportive and antibiotic therapy .. plus IgM-enriched IVIG"
Blinding (performance bias and detection bias) All outcomes	Low risk	Blinding of key personnel was ensured
Incomplete outcome data (attrition bias) All outcomes	Low risk	The outcomes measured were mortality from any cause, side effects. No missing outcome data. All deaths in the study population were reported (information provided by the principal investigator). No major side effects of the therapy were reported
Selective reporting (reporting bias)	Unclear risk	The protocol for the study was not available to us, so we cannot ascertain whether or not there was selective reporting
Other bias	Low risk	The study appears to be free from other sources of bias

INIS 2011

Methods	Randomised, placebo-controlled trial I Blinding of randomisation—Yes II Blinding of intervention—Yes

INIS 2011 *(Continued)*

	III Complete follow-up — Yes IV Blinding of outcome measurement — Yes
Participants	A total of 3493 infants with birth weight < 1500 g; evidence of infection in blood culture, cerebrospinal fluid, or usually sterile body fluid; or need for respiratory support through an endotracheal tube Study period: October 2001 through September 2007 Infants were recruited from 9 countries: the UK, Australia, Argentina, New Zealand, Serbia, Greece, Denmark, Belgium and Ireland
Interventions	1759 infants were assigned to receive an IV infusion of immune globulin at a dose of 500 mg (10 mL) per kg of body weight, repeated after 48 hours. In Europe and Argentina, IVIG was produced by the Protein Fractionation Centre of the Scottish National Blood Transfusion Service. In Australlia and New Zealand, the IVIG preparation was Intragam P (CSL) 1734 infants were assigned to receive placebo, an identical volume as the active drug, initially and after 48 hours
Outcomes	Primary outcome: the rate of death or major disability at the age of 2 years, with adjustment for gestational age (major disability was assessed by means of questionnaires sent to the child's parents and healthcare professionals). Major disability was defined according to pre-specified criteria in the following domains: neuromotor function, seizures, auditory function, communication, visual function, cognitive function and other physical disability (described in the protocol) (INIS 2008) Secondary short-term outcomes: mortality before hospital discharge, chronic lung disease (defined as oxygen dependency 28 days after birth), major cerebral abnormality, relevant positive culture after trial entry (and causative organisms), pneumonia and necrotizing enterocolitis; length of hospital stay Secondary long-term outcomes at 2 years with adjustment for gestational age were rates of death and major and non-major disability
Notes	This study enrolled infants with proven infection or suspected infection and, in the original publication, the outcomes are reported for a combination of these two groups. The authors provided us with unpublished data for the outcomes of death at 2 years corrected age, death in hospital, and death or major disability at 2 years (corrected age) for the two groups of infants with suspected infection at trial entry and infants with proven infection at trial entry

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	The assignment sequence was generated by the National Perinatal Epidemiology Unit in Oxford, United Kingdom, with balance within random block sizes of 2 and 8
Allocation concealment (selection bias)	Low risk	In Europe and Argentina, neonatal staff opened the next sequentially numbered study pack, which was stored in the neonatal unit and contained all materials necessary to administer a course of the study drug. In Australia and New Zealand, the hospital pharmacy was contacted, and the next assignment was taken from a randomisation list generated by the National Health and Medical Research Council Clinical Trials Centre in Sydney
Blinding (performance bias and detection bias) All outcomes	Unclear risk	In Europe and Argentina, placebo was 0.2% albumin solution in normal saline. IVIG and placebo infusions looked identical, were colourless, and frothed on agitation. In Australia and New Zealand, the pharmacy made up the IVIG or placebo solution (normal saline). Syringes and tubing were masked with yellow tape. Staff in Europe and Argentina would have been blinded to the intervention, but in Australia and New Zealand it is possible that healthcare providers could have detected whether IVIG or placebo was given as the solutions would have behaved differently (no froth on agitation for normal saline).

INIS 2011 *(Continued)*

		(Most healthcare providers would push a small amount of fluid from a syringe before infusing its content to the infant.) The outcome of mortality is unlikely to have been affected by the lack of blinding of staff in Australia and New Zealand
Incomplete outcome data (attrition bias) All outcomes	Low risk	All enrolled infants were accounted for
Selective reporting (reporting bias)	Low risk	The protocol for the study was published, and there does not seem to have been any deviation (INIS 2008)
Other bias	Low risk	Appears free of other bias

Samatha 1997

Methods	Randomised controlled trial (no placebo) I. Blinding of randomisation — Can't tell II. Blinding of intervention — No III. Complete follow-up — Yes IV. Blinding of outcome measurement — No
Participants	A total of 60 neonates with suspected sepsis were enrolled; 44 were born preterm and 51 were LBW Single centre, India January 1993 to December 1993
Interventions	30 neonates (26/30 preterm and 27/30 LBW) received 5 mL/kg/day of IgM-enriched IVIG (Pentaglobin) for 3 days 30 (18/30 preterm, 24/30 LBW) neonates received antibiotics only
Outcomes	Mortality from any cause Mortality from sepsis Length of hospital stay
Notes	Mortality from any cause and mortality from sepsis and hospital stay could be ascertained from this study. No adverse effects were noted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	Insufficient information to make judgement of 'yes' or 'no'
Allocation concealment (selection bias)	Unclear risk	The method of concealment is not described
Blinding (performance bias and detection bias) All outcomes	High risk	No blinding, but the outcome of mortality from any cause is unlikely to be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	Low risk	Complete for mortality. Insufficient reporting on attrition to permit judgement on the outcome of length of hospital stay

Samatha 1997 *(Continued)*

Selective reporting (reporting bias)	High risk	The outcome 'length of hospital stay' is reported incompletely, so that it cannot be entered in a meta-analysis
Other bias	Low risk	The study appears to be free of other sources of bias

Shenoi 1999

Methods	Randomised controlled trial (no placebo) I Blinding of randomisation—Yes II Blinding of intervention—No III Complete follow-up—No IV Blinding of outcome measurement—No
Participants	A total of 58 neonates with suspected infection (suspected clinically to have sepsis with C-reactive protein greater than 6 mg/dL and at least one of the following rapid diagnostic tests with positive results: absolute neutrophil count, thrombocytopenia, toxic granulation in the peripheral smear, and a band count greater than 500/mm^3, as well as negative blood culture). Confirmed sepsis as above plus blood, urine, or cerebrospinal fluid culture yielding an organism Seven neonates who qualified but did not receive either IVIG or placebo were taken into a separate control group, and one neonate who received only one dose of IVIG was excluded from the analysis Three centres, India October 1995 to May 1996
Interventions	25 neonates (mean BW (SEM) 2072 ± 682 g, mean GA (SEM) 35.8 ± 3.52 wk) received 1 g/kg of Sandoglobulin on three consecutive days 25 infants (mean BW (SEM) 2144 ± 675 g; mean GA (SEM) 37.0 ± 3.56 wk) received an equivalent amount of 0.15% saline, 10% dextrose placebo (this placebo was not provided by the pharmaceutical company)
Outcomes	Mortality Duration of hospital stay
Notes	Mortality associated with suspected sepsis and duration of hospital stay could be ascertained from this study. No adverse effects were noted

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A random table was used to assign the randomisation sequence (information provided by the principal investigator on request)
Allocation concealment (selection bias)	Low risk	Random number allocation was done at the co-ordinating centre, and the sealed, numbered envelopes with allocations were sent to three centres. On entry of a neonate into the trial, a sealed, numbered envelope was opened and therapy or placebo instituted
Blinding (performance bias and detection bias) All outcomes	Low risk	No blinding, but the outcome of mortality is not likely to be influenced by lack of blinding. A non-identical placebo was used in the control group. Length of stay could be influenced by lack of blinding
Incomplete outcome data (attrition bias) All outcomes	High risk	58 neonates with suspected sepsis were allocated to IVIG treatment or placebo; 7 neonates who qualified but did not receive either IVIG or placebo were taken into a separate control group, and 1 infant who received only one dose of IVIG was excluded from the analyses

Shenoi 1999 *(Continued)*

		20 infants were confirmed as having a positive blood culture, whereas in 30 infants bacteraemia was not confirmed Outcomes were reported for these 50 randomly assigned participants. No adverse effects were reported
Selective reporting (reporting bias)	Unclear risk	Insufficient information to permit judgement of 'yes' or 'no'
Other bias	Unclear risk	The study was terminated in May 1996, as the company (Sandoz India) withdrew support. The attained sample size is much smaller than intended, but no explanation is given and no stopping rules are reported

Sidiropoulos 1981

Methods	Quasi-randomised controlled trial I Blinding of randomisation — No II Blinding of intervention — No III Complete follow-up — Yes IV Blinding of outcome measurement — No
Participants	A total of 82 newborns with clinical evidence of sepsis (suspected sepsis) Study period 1976 to 1979 Single centre, Switzerland
Interventions	41 infants with clinical evidence of sepsis received IVIG (Immunoglobulin SRK) (preterm infants received 0.5 g/day for 6 days and term infants 1.0 g/day for 6 days) 41 infants with clinical evidence of sepsis received no placebo
Outcomes	Mortality Psychomotor development and growth in the IVIG group (n = 18) at 2 4/12 ± 1 5/12 years of age and in the control group (n = 11) at 2 6/12 ± 1 2/12 years of age were reported only in infants who were ultimately found to be septic Serum IgG Suspected adverse effects: respiratory rate, heart rate, temperature, blood gas analysis
Notes	This is a quasi-randomised trial; infants were allocated to IVIG or no IVIG on an alternating basis Mortality associated with suspected serious infection could be ascertained from this study No adverse effects were reported

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	High risk	Quasi-randomised controlled trial
Allocation concealment (selection bias)	High risk	Blinding of randomisation — No
Blinding (performance bias and detection bias) All outcomes	High risk	Blinding of intervention — No
Incomplete outcome data (attrition bias)	Low risk	Complete follow-up — Yes

Sidiropoulos 1981 *(Continued)*
All outcomes

Other bias	Low risk

Abbreviations:
BW = birth weight
g = gram
GA = gestational age
IgG = immunoglobulin G
IV = intravenous(ly)
IVIG = intravenous immunoglobulin
kg = kilogram
LBW = low birth weight (< 2.5 kg)
mg = milligram
NICU = neonatal intensive care unit
SEM = standard error of the mean
SD = standard deviation
wk = week(s)

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

Study	Reason for exclusion
Chen 1996	Participants with suspected infection were randomly assigned to receive a single dose of 500 mg/kg IVIG or placebo (0.9% sodium chloride). Of 141 newborn infants with suspected infection, 56 had a positive blood culture and were included in the results. The study did not fulfil our inclusion criterion of suspected or proven infection at trial entry
Gökalp 1994	The purpose of this study was to determine the role of IVIG administration in preterm infants with *S. typhimurium* infection (including both intestinal and extra-intestinal *S. typhimurium* infections). Intestinal infections did not qualify for inclusion in our review. Randomisation took place after the infants were known to have a positive culture for *Salmonella*. This study did not meet our inclusion criterion of IVIG for treatment of suspected sepsis. In this study, infants were randomly assigned when they were known to be infected with *Salmonella* (information provided by the author). We could not identify the infants who had sepsis from those who had intestinal *Salmonella* infection
Haque 1995	In a prospective, randomised, double-blind study, standard IVIG was compared with IgM-enriched IVIG in the treatment of neonatal sepsis. The two treatment groups were also compared with a group of non-treated matched controls. The 65 controls were selected randomly by an independent member of the staff who was not participating in the study. This is not a true randomised controlled trial as not every infant entering the study had the same chance of entering into one of the three groups (two treatment groups and one control group). No statistical difference (P = 0.25) in mortality was noted between the two immunoglobulin therapy groups (the two groups that were randomly assigned); mortality in the standard IVIG group was 6/42 (14.2%), and in the IgM-enriched IVIG group it was 3/44 (6.8%)
Mancilla-R 1992	In this study, 84 newborns with suspected infection were randomly assigned, and 37 had proven sepsis that was known after study entry. The authors report only on these 37 infants with proven infection. We obtained unpublished information from the authors
Salihoglu 2013	This study reports on 13 preterm infants who received 'pentaglobin' in addition to antibiotics for nosocomial infection. It was a prospective non-randomised study
Weisman 1992	This study reports on 31 infants with early-onset sepsis that was confirmed after the infants entered a large randomised controlled trial of infants to evaluate the impact of IVIG therapy in preventing nosocomial or late-onset infection in high-risk neonates. It was not known at trial entry whether the infants had suspected or proven infection

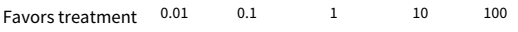
DATA AND ANALYSES

Comparison 1. IVIG versus placebo or no intervention for suspected infection at trial entry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality from any cause during initial hospitalisation	9	2527	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.80, 1.13]
2 Length of hospital stay	3	170	Mean Difference (IV, Fixed, 95% CI)	-4.08 [-6.47, -1.69]
3 Death at 2 years corrected age	1	2047	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.24]
4 Death or major disability at 2 years corrected age	1	1985	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.88, 1.09]

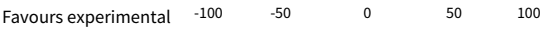
Analysis 1.1. Comparison 1 IVIG versus placebo or no intervention for suspected infection at trial entry, Outcome 1 Mortality from any cause during initial hospitalisation.

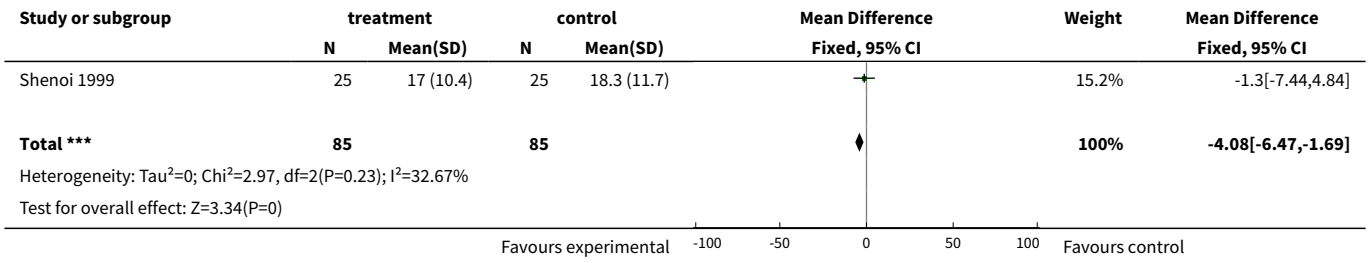
Study or subgroup	treatment n/N	control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Ahmed 2006	4/30	10/30		4.42%	0.4[0.14,1.14]
Akdag 2014	4/51	2/51		0.88%	2[0.38,10.44]
Christensen 1991	0/11	0/11			Not estimable
Erdem 1993	6/20	9/24		3.62%	0.8[0.34,1.86]
Haque 1988	1/30	6/30		2.65%	0.17[0.02,1.3]
INIS 2011	185/1030	176/1017		78.27%	1.04[0.86,1.25]
Samatha 1997	5/30	8/30		3.54%	0.63[0.23,1.69]
Shenoi 1999	7/25	7/25		3.09%	1[0.41,2.43]
Sidiropoulos 1981	4/41	8/41		3.54%	0.5[0.16,1.53]
Total (95% CI)	**1268**	**1259**		**100%**	**0.95[0.8,1.13]**
Total events: 216 (treatment), 226 (control)					
Heterogeneity: Tau^2=0; Chi^2=9.14, df=7(P=0.24); I^2=23.4%					
Test for overall effect: Z=0.57(P=0.57)					



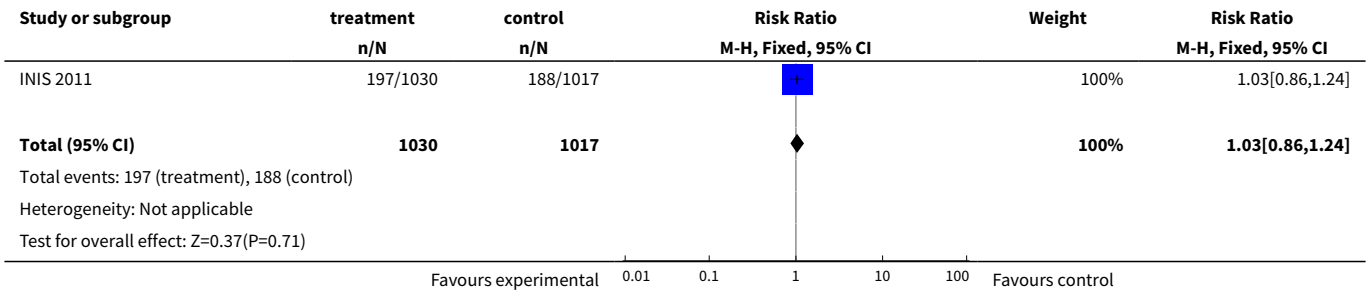
Analysis 1.2. Comparison 1 IVIG versus placebo or no intervention for suspected infection at trial entry, Outcome 2 Length of hospital stay.

Study or subgroup	treatment N	treatment Mean(SD)	control N	control Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Ahmed 2006	30	14.5 (3.9)	30	18.3 (6.9)		71.65%	-3.77[-6.6,-0.94]
Samatha 1997	30	20 (12)	30	29 (14)		13.15%	-9[-15.6,-2.4]

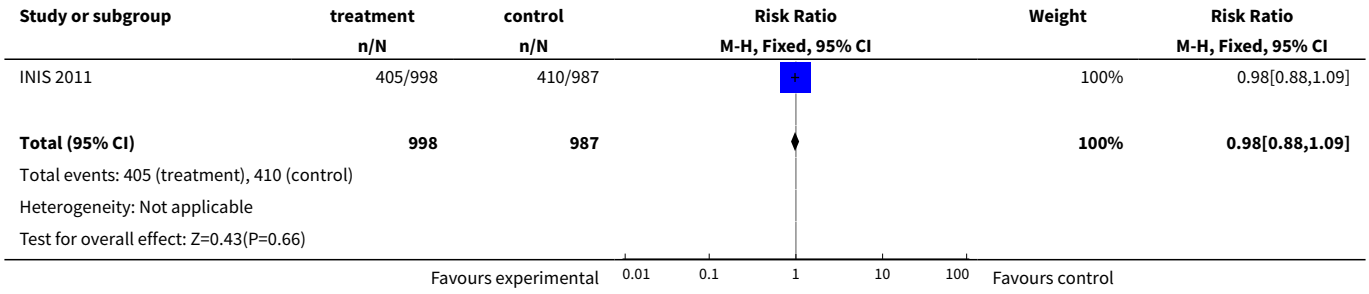




Analysis 1.3. Comparison 1 IVIG versus placebo or no intervention for suspected infection at trial entry, Outcome 3 Death at 2 years corrected age.



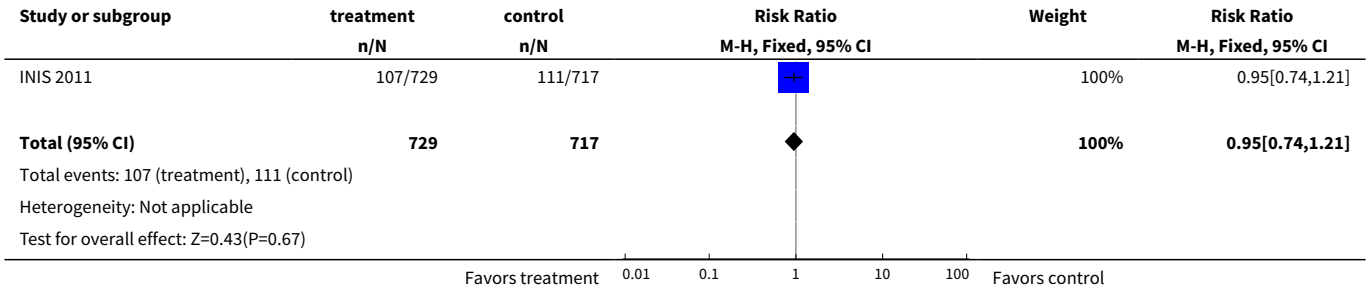
Analysis 1.4. Comparison 1 IVIG versus placebo or no intervention for suspected infection at trial entry, Outcome 4 Death or major disability at 2 years corrected age.



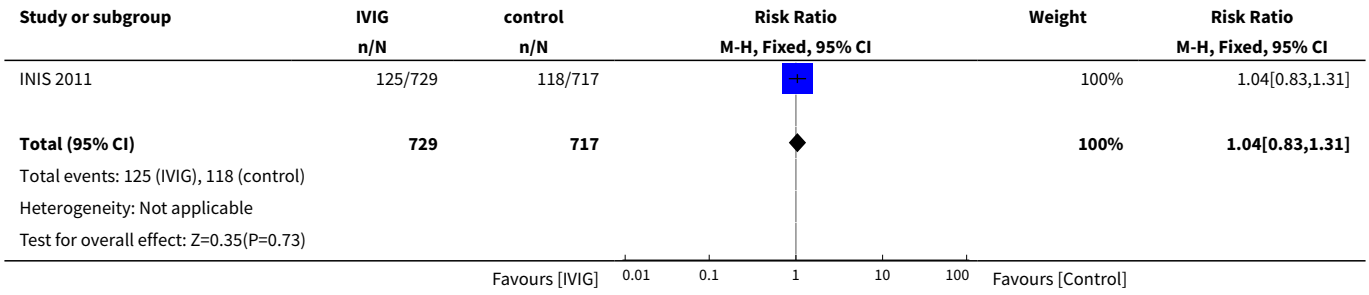
Comparison 2. IVIG versus placebo or no intervention for proven infection at trial entry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality from any cause during hospital stay	1	1446	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.74, 1.21]
2 Death at 2 years corrected age	1	1446	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.83, 1.31]
3 Death or major disability at 2 years corrected age	1	1393	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.91, 1.18]

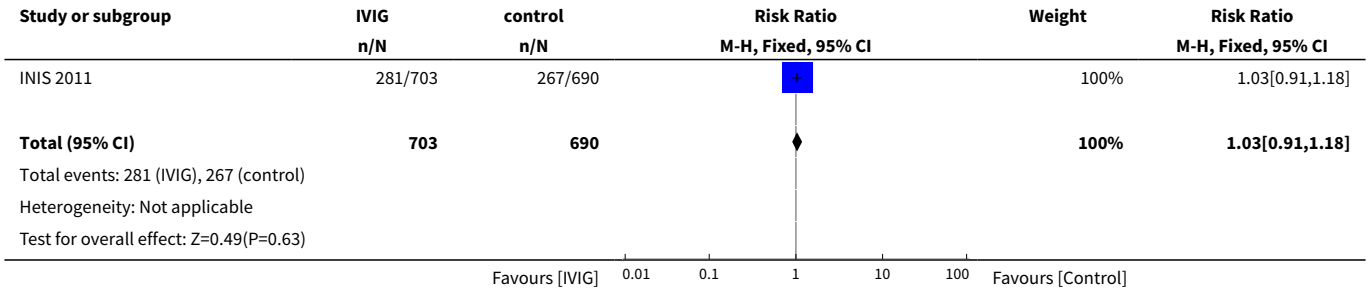
Analysis 2.1. Comparison 2 IVIG versus placebo or no intervention for proven infection at trial entry, Outcome 1 Mortality from any cause during hospital stay.



Analysis 2.2. Comparison 2 IVIG versus placebo or no intervention for proven infection at trial entry, Outcome 2 Death at 2 years corrected age.



Analysis 2.3. Comparison 2 IVIG versus placebo or no intervention for proven infection at trial entry, Outcome 3 Death or major disability at 2 years corrected age.



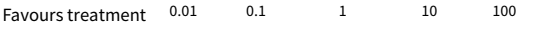
Comparison 3. IVIG versus placebo for suspected or proven infection at trial entry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality from any cause during hospital stay	1	3493	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.86, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2 Use of supplemental oxygen on day 28	1	2785	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.92, 1.04]
3 Major cerebral abnormality	1	3493	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.96, 1.37]
4 Necrotizing enterocolitis (new episode)	1	3493	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.85, 1.38]
5 Duration of hospital stay (days)	1	3493	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.61, 0.61]
6 Death at 2 years corrected age	1	3493	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.90, 1.20]
7 Death or major disability at 2 years (corrected age)	1	3493	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.92, 1.09]
8 Nonmajor disability at 2 years corrected age	1	2865	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.91, 1.13]
9 Major disability at 2 years corrected age	1	2865	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.86, 1.10]

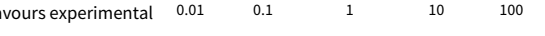
Analysis 3.1. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 1 Mortality from any cause during hospital stay.

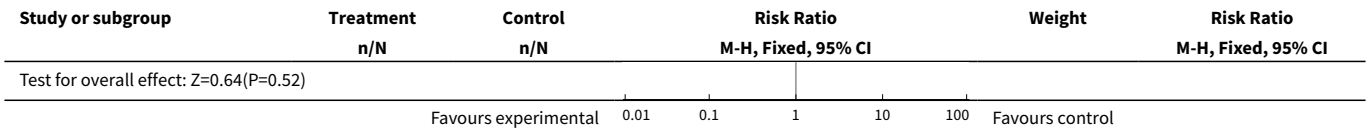
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	292/1759	287/1734		100%	1[0.86,1.16]
Total (95% CI)	**1759**	**1734**		**100%**	**1[0.86,1.16]**
Total events: 292 (Experimental), 287 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.04(P=0.97)					



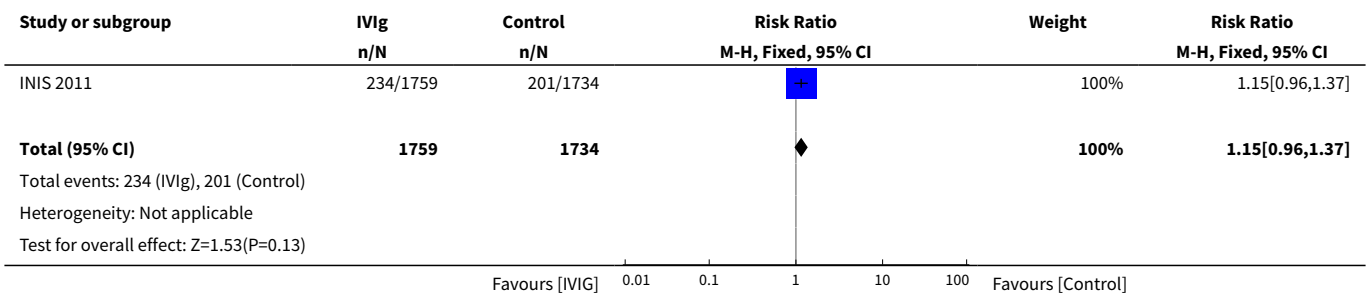
Analysis 3.2. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 2 Use of supplemental oxygen on day 28.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	779/1394	794/1391		100%	0.98[0.92,1.04]
Total (95% CI)	**1394**	**1391**		**100%**	**0.98[0.92,1.04]**
Total events: 779 (Treatment), 794 (Control)					
Heterogeneity: Not applicable					

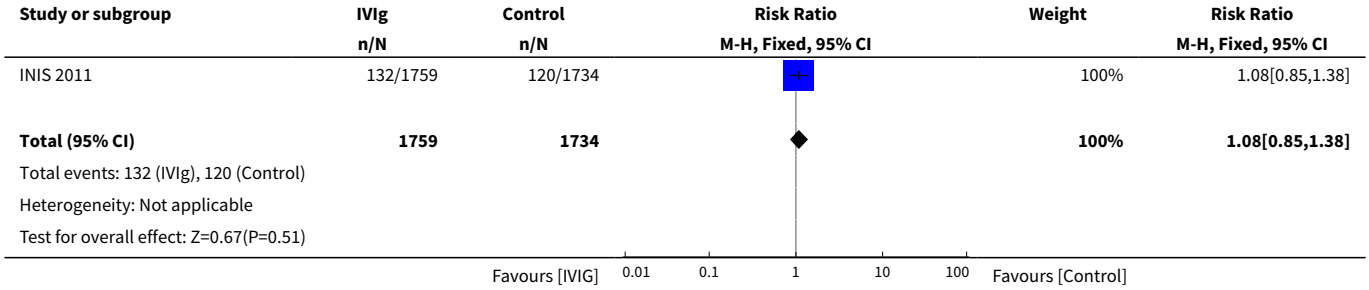




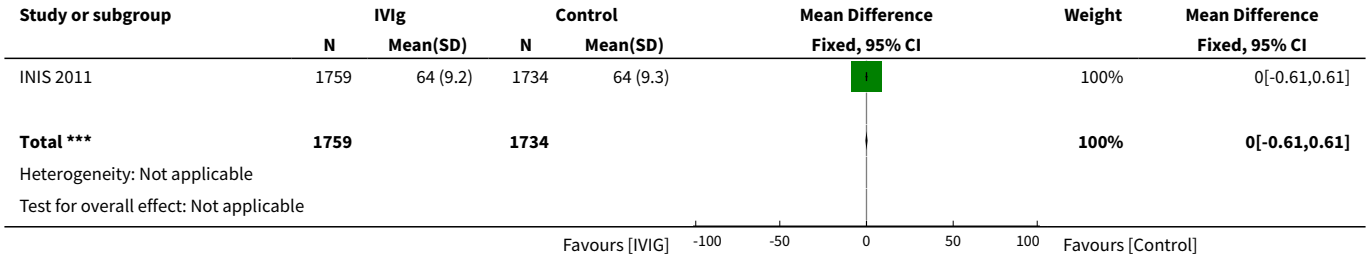
Analysis 3.3. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 3 Major cerebral abnormality.



Analysis 3.4. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 4 Necrotizing enterocolitis (new episode).



Analysis 3.5. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 5 Duration of hospital stay (days).



Analysis 3.6. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 6 Death at 2 years corrected age.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	322/1759	306/1734		100%	1.04[0.9,1.2]
Total (95% CI)	**1759**	**1734**		**100%**	**1.04[0.9,1.2]**
Total events: 322 (Treatment), 306 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.51(P=0.61)					

Analysis 3.7. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 7 Death or major disability at 2 years (corrected age).

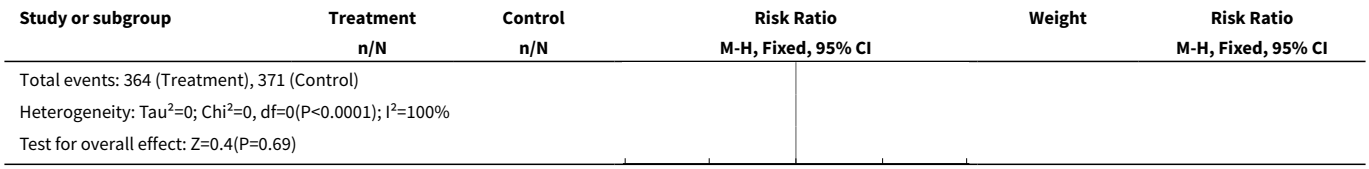
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	686/1759	677/1734		100%	1[0.92,1.09]
Total (95% CI)	**1759**	**1734**		**100%**	**1[0.92,1.09]**
Total events: 686 (Treatment), 677 (Control)					
Heterogeneity: $Tau^2=0$; $Chi^2=0$, df=0(P<0.0001); $I^2=100\%$					
Test for overall effect: Z=0.03(P=0.98)					

Analysis 3.8. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 8 Nonmajor disability at 2 years corrected age.

Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	480/1437	470/1428		100%	1.01[0.91,1.13]
Total (95% CI)	**1437**	**1428**		**100%**	**1.01[0.91,1.13]**
Total events: 480 (Treatment), 470 (Control)					
Heterogeneity: Not applicable					
Test for overall effect: Z=0.28(P=0.78)					

Analysis 3.9. Comparison 3 IVIG versus placebo for suspected or proven infection at trial entry, Outcome 9 Major disability at 2 years corrected age.

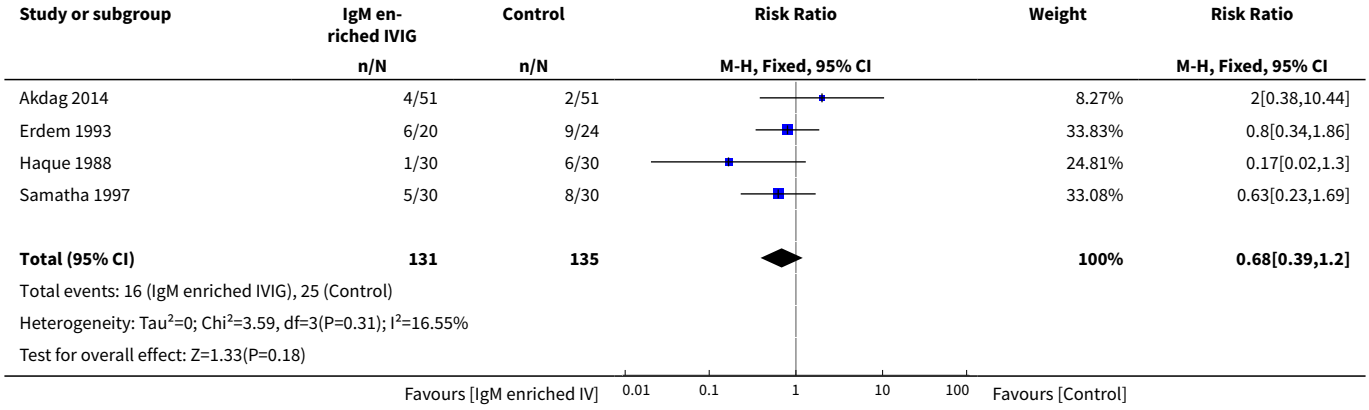
Study or subgroup	Treatment n/N	Control n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
INIS 2011	364/1437	371/1428		100%	0.97[0.86,1.1]
Total (95% CI)	**1437**	**1428**		**100%**	**0.97[0.86,1.1]**



Comparison 4. IgM-enriched IVIG for suspected infection at trial entry

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Mortality from any cause during initial hospitalisation	4	266	Risk Ratio (M-H, Fixed, 95% CI)	0.68 [0.39, 1.20]

Analysis 4.1. Comparison 4 IgM-enriched IVIG for suspected infection at trial entry, Outcome 1 Mortality from any cause during initial hospitalisation.



WHAT'S NEW

Date	Event	Description
29 January 2020	New citation required but conclusions have not changed	Contact author changed, and contact details updated.
29 January 2020	Amended	Arne Ohlsson deceased.

HISTORY

Protocol first published: Issue 4, 1998
Review first published: Issue 4, 1998

Date	Event	Description
11 January 2015	New search has been performed	This updates the review 'Intravenous immunoglobulin (IVIG) for suspected or subsequently proven infection in neonates', published in the Cochrane Database of Systematic Reviews 2013, Issue 7 (Ohlsson 2013). One previously ongoing trial has now been published and we include 102 infants from that trial, 51 randomised to immunoglobulin M (IgM)-enriched IVIG and 51 randomised to normal saline (placebo). The results from that trial confirm our previous conclusions that IVIG or IgM-enriched IVIG does not significantly reduce mortality in infants with suspected or proven infection.
24 June 2013	New citation required and conclusions have changed	The title has been changed to: 'Intravenous immunoglobulin for suspected or proven infection in neonates'. One additional published trial and one ongoing trial were identified. The trial by INIS (INIS 2011) enrolled infants with proven or suspected infection at the time of randomisation. This is the largest trial published to date, adding 3493 infants to this systematic review. We report the results for the combined cohort of infants with suspected and proven infection at the time of randomisation. This approach represents a deviation from previous versions of this review. In addition, the authors provided us with results separately for infants with suspected infection and with proven infection at the time of entry to the trial. We report the results separately for infants with suspected infection, with proven infection and with suspected or proven infection at treatment initiation. Also in this update, we have included in a subgroup analysis the outcome of mortality for infants who were treated with IgM-enriched IVIG. For this update, we excluded the comparison: IVIG versus placebo or no intervention for 'subsequently' proven infection; such estimates are meaningless as the clinician is unaware, at the point of starting treatment, whether the infant will or will not have proven sepsis at a later time point. With the addition of data from the INIS trial (INIS 2011), it is now clear that IVIG does not have a significant effect on important outcomes such as in-hospital death or death and disability at 2 years corrected age. In a secondary analysis of trials using IgM-enriched immunoglobulin, no significant reduction in mortality during hospital stay was reported. One ongoing trial of IgM-enriched immunoglobulin was identified. Conclusions changed: there is now no indication that the use of IVIG or IgM-enriched IVIG in infants with suspected or proven infection at the time of initiation of treatment improves important outcomes. No further research is recommended to test current IVIG preparations for suspected or proven serious infection.
24 April 2008	Amended	Converted to new review format.
18 July 2007	New search has been performed	This updates the review "Intravenous immunoglobulin for suspected or subsequently proven infection in neonates" published in The Cochrane Library, Issue 1, 2004 (Ohlsson 2004).

Date	Event	Description
		No new trials for inclusion were identified for this update conducted in July, 2007. Trials using species specific immunoglobulins (such as for staphylococcus aureus or epidermidis) were not included as they are reviewed separately by others within the Cochrane Collaboration. The ongoing trial (INIS) by Brocklehurst et al. has recruited 3425 infants as of June 2007. Recruitment will close at 3500 patients after a decision by the Data Monitoring Committee in December 2005 (http://www.npeu.ox.ac.uk/inis/inis_downloads/INIS_update_06-07.pdf.). There have been two previous updates of this review (2001, 2004). In the 2001 update of this review two additional trials (Shenoi 1999; Samatha 1997), both conducted in India, were included in this review. Additional information on published trials was provided by Drs. Erdem, Gokalp, Haque, Mancilla-Ramirez and Shenoi. In the first version sensitivity analyses according to trial quality were performed. For some trials it was difficult to accurately assess, whether the trial was a true randomized controlled trial or a quasi randomized trial from the publications. When additional information was obtained from authors, the categorization of some trials changed. Sensitivity analyses excluding quasi-randomized trials were therefore abandoned for the 2001 and this update. For the update, conducted in October 2003 no new trials were identified from the Cochrane Library, MEDLINE nor from EMBASE. In February 2002 Mancilla-Ramirez et al. provided unpublished information that changed the rating of their trial from B to A. For this update, the absolute risk difference and the number needed to treat was not calculated for the subset of patients who entered the trials with suspected sepsis and who were subsequently proven to have sepsis. Such estimates are meaningless as the clinician is unaware at the point of starting treatment whether the infant will have proven sepsis or not. For this update, the I squared statistic was added. In the 2001 version, the addition of results from two small studies changed the statistical significance of effect on two major outcomes: mortality in suspected cases of infection (previously significant - currently of borderline statistical significance) and mortality in subsequently proven infection (previously not significant - currently significant). Thus, there is the need for further well-designed research to identify the role of IVIG in suspected/subsequently proved neonatal infection.
11 November 2003	New citation required and conclusions have changed	Substantive amendment

CONTRIBUTIONS OF AUTHORS

Arne Ohlsson
Literature search and identification of trials for inclusion
Evaluation of methodological quality of included trials

Abstraction of data
Verification and entry of data into RevMan
Writing of review text

Janet B Lacy
Literature search and identification of trials for inclusion
Evaluation of methodological quality of included trials
Abstraction of data. Verification and entry of data into RevMan
Writing of review text

Both review authors contributed to the current update of the review.

DECLARATIONS OF INTEREST

None

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External sources

- Eunice Kennedy Shriver National Institute of Child Health and Human Development National Institutes of Health, Department of Health and Human Services, USA.

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

For the 2013 update, and as a deviation from the protocol, we included a study that enrolled infants with suspected or proven serious infection at the time of randomisation (INIS 2011). We obtained unpublished data from that study, which enabled us to include a subgroup of infants with suspected infection at trial entry for our primary outcome of death during hospital stay.

INDEX TERMS

Medical Subject Headings (MeSH)

Immunoglobulins, Intravenous [*therapeutic use]; Infant, Low Birth Weight; Infant, Premature; Infant, Premature, Diseases [prevention & control]; Infections [*drug therapy] [mortality]; Length of Stay; Randomized Controlled Trials as Topic; Treatment Outcome

MeSH check words

Humans; Infant, Newborn