Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes (Review)

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[Intervention Review]

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

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ABSTRACT

Background

It has been unclear whether repeat dose(s) of prenatal corticosteroids are beneficial.

Objectives

To assess the effectiveness and safety of repeat dose(s) of prenatal corticosteroids.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (20 January 2015), searched reference lists of retrieved studies and contacted authors for further data.

Selection criteria

Randomised controlled trials of women who had already received a single course of corticosteroids seven or more days previously and considered still at risk of preterm birth.

Data collection and analysis

We assessed trial quality and extracted data independently.

Main results

We included 10 trials (a total of 4733 women and 5700 babies) with low to moderate risk of bias. Treatment of women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with repeat dose(s), compared with no repeat corticosteroid treatment, reduced the risk of their infants experiencing the primary outcomes *respiratory distress syndrome* (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.91, eight trials, 3206 infants, number needed to treat to benefit (NNTB) 17, 95% CI 11 to 32) and *serious infant outcome* (RR 0.84, 95% CI 0.75 to 0.94, seven trials, 5094 infants, NNTB 30, 95% CI 19 to 79).

Treatment with repeat dose(s) of corticosteroid was associated with a reduction in *mean birthweight* (mean difference (MD) -75.79 g, 95% CI -117.63 to -33.96, nine trials, 5626 infants). However, outcomes that adjusted birthweight for gestational age (birthweight Z scores, birthweight multiples of the median and small-for-gestational age) did not differ between treatment groups.

At early childhood follow-up, no statistically significant differences were seen for infants exposed to repeat prenatal corticosteroids compared with unexposed infants for the primary outcomes (total deaths; survival free of any disability or major disability; disability; or serious outcome) or in the secondary outcome growth assessments. In women, for the two primary outcomes, there was no increase in infectious morbidity of *chorioamnionitis* or *puerperal sepsis*, and the likelihood of a caesarean birth was unchanged.

Authors' conclusions

The short-term benefits for babies of less respiratory distress and fewer serious health problems in the first few weeks after birth support the use of repeat dose(s) of prenatal corticosteroids for women still at risk of preterm birth seven days or more after an initial course. These benefits were associated with a small reduction in size at birth. The current available evidence reassuringly shows no significant harm in early childhood, although no benefit.

Further research is needed on the long-term benefits and risks for the woman and baby. Individual patient data meta-analysis may clarify how to maximise benefit and minimise harm.

PLAIN LANGUAGE SUMMARY

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease

This review shows that a repeat dose of prenatal corticosteroids given to women who remain at risk of an early birth after an initial course of prenatal corticosteroids helps the baby's lungs and reduces serious health problems in the first few weeks of life.

Infants born preterm (before 37 weeks' gestation) are at risk of difficulty breathing and lung disease because their lungs are not fully developed. Women at risk of preterm birth include those with ruptured membranes, antepartum haemorrhage, preterm labour, cervical incompetence, pre-eclampsia or multiple pregnancy. Preterm babies who survive the early weeks of life are also at risk of long-term neurological disabilities such as epilepsy and cerebral palsy. A single course of corticosteroids, given to women who may give birth early, helps develop the baby's lungs. This benefit does not last beyond seven days. This review of 10 randomised controlled trials, involving 4733 women who remained at risk of early birth more than seven days after an initial course of corticosteroids and 5700 babies between 23 and 34 weeks' gestation at trial enrolment showed that repeat dose(s) of prenatal corticosteroids reduced the risk of the baby having breathing difficulties and serious health problems in the first few weeks of life. Some of the trials showed that the baby may be smaller at birth, but not if adjusted for gestational age nor by the time of hospital discharge. In four trials that followed up the babies to early childhood, no long-term benefits or harms were seen at 18 months to two years' corrected age. Further research is needed on the long-term benefits and risks for the woman and baby, which should include later child health, growth and development.

Repeat prenatal corticosteroid treatment could increase the risk of infection and suppress pituitary-adrenal function for the mother and her baby. For the women, there was no increase in infectious morbidity of chorioamnionitis or puerperal sepsis, and the likelihood of a caesarean birth was unchanged.

Betamethasone was the only corticosteroid evaluated. It is uncertain whether the effects seen for betamethasone would be the same for dexamethasone.

BACKGROUND

Description of the condition

Infants born preterm (before 37 weeks' gestation) are at high risk of neonatal lung disease and its sequelae. The more preterm the

baby the greater are the risks, especially when birth occurs before 32 weeks' gestation. In Australia, in 2003, 1.6% of all births were before 32 weeks' gestation (Laws 2005). Respiratory distress syndrome (RDS), as a consequence of immature lung development, is the principal cause of early neonatal mortality and morbidity and contributes significantly to the high costs of neonatal intensive care. Preterm babies who survive the early weeks of life are at risk of long-term neurological disability (Johnson 1993). Parents are understandably worried and distressed when their baby is born preterm. Strategies to reduce the risk of neonatal respiratory disease for infants who are born preterm have received considerable attention (Roberts 2006; Rojas-Reyes 2012).

A single course of prenatal corticosteroids reduces the risk of RDS from 26% to 17% (risk ratio (RR) 0.66, 95% confidence interval (CI) 0.59 to 0.73, 21 trials, 4038 infants) (Roberts 2006). Other beneficial effects include a reduced risk of neonatal death, intraventricular haemorrhage, necrotising enterocolitis and early sepsis (Roberts 2006). Prenatal corticosteroids enhance the benefits of postnatal surfactant therapy (Jobe 1994) and reduce the need for blood pressure support (Moise 1995). Overall, there is a reduction in the cost and duration of neonatal care. The cost benefit of a single course of antenatal corticosteroids is estimated as USD 3000 (NIH 1995). Long-term follow-up into adulthood of babies in the New Zealand trial (Liggins 1972), exposed to prenatal corticosteroids have shown no adverse clinical outcomes (Dalziel 2005a; Dalziel 2005b). However, even though prenatal corticosteroids remain the most effective known strategy for reducing the adverse consequences of preterm birth, and despite postnatal intensive care and exogenous surfactant, there is still significant neonatal morbidity (Rojas-Reyes 2012).

Description of the intervention

Prenatal corticosteroid treatment compared with no prenatal corticosteroid treatment has not been shown to be effective in babies who are born more than seven days after an initial treatment (Roberts 2006). Specifically no reduction in the incidence of RDS or neonatal mortality has been demonstrated (McLaughlin 2003; Roberts 2006), and birthweight is significantly reduced (Roberts 2006). There may be benefit in repeating the dose of prenatal corticosteroids to women who remain at risk of preterm birth more than seven days after the initial course. This was suggested by Liggins and Howie in the first reported controlled trial of antenatal glucocorticoid treatment for the prevention of RDS in premature infants (Liggins 1972). Indeed, in some clinical centres this has been standard practice. However, until recently, there has been little formal assessment of such a policy, and the effect of this practice on the women and infants has been unclear (NIH 2000).

How the intervention might work

Animal studies have suggested that repeat treatment with prenatal corticosteroids may be more effective than a single course in reducing the risk of RDS. In sheep fetuses; there is a dose-dependent improvement in lung function with repeat doses of betamethasone (Ikegami 1997). In human infants, improved cardiovascular responses to preterm birth have been observed (Padbury 1996).

Why it is important to do this review

The potential benefits of repeat prenatal corticosteroid treatment on neonatal lung function and cardiovascular health may be balanced by increased maternal risks such as infection and suppression of hypothalamic-pituitary-adrenal function (Ashwood 2006; McKenna 2000). In addition, experimental reports raise concerns about the use of repeat doses of prenatal corticosteroids because of potential adverse effects for the offspring.

It is well known that corticosteroids inhibit cell growth and DNA replication. Studies in both small and large animals demonstrate that exogenous steroids inhibit fetal growth and increase fetal blood pressure (Fowden 1996; Jensen 2002). In sheep there is a dose-dependent reduction in birthweight in lambs exposed to up to four doses of betamethasone administered to the ewe (Ikegami 1997), although exogenous steroids administered directly to the fetus do not inhibit fetal growth (Newnham 1999).

Other animal experimental studies have shown that repeat doses of corticosteroids may have harmful effects on neuronal myelination (Dunlop 1997), the development of the alveolar septa leaving 'emphysematous' -like alveoli (Tschanz 1995) and hypothalamic-pituitary-adrenal (HPA) function (Ikegami 1997). Effects on the HPA axis can persist into adulthood.

In humans, similar concerns have been raised from non-randomised cohort studies, with adverse effects after repeat doses of corticosteroids on measures of growth at birth (French 1999), risk of neonatal infection, fetal pituitary-adrenal axis function, neonatal blood pressure (Mildenhall 2006), childhood behaviour (French 1998), and high levels of stress in parents (French 1998). Long-term developmental follow-up studies of infants exposed to repeat doses of prenatal corticosteroids are limited to date and have produced conflicting results. Some non-randomised studies suggest delayed development (Esplin 2000) and adverse effects on childhood behaviour (French 1998), whilst other non-randomised studies have shown no difference between exposed and non-exposed children (French 1999; Hasbargen 2001; Thorp 2002), or possible reduced cerebral palsy (French 2004). Another long-term potential adverse outcome that requires further investigation is the possibility that single or repeat doses of antenatal corticosteroids could program cardiovascular settings in the fetus and lead to adult hypertension (Benediktsson 1993), and insulin resistance leading to diabetes mellitus (Dalziel 2005a). Increased exposure of the fetus to glucocorticoids has been proposed as a possible mechanism underlying the epidemiological association between small size at birth and adult cardiovascular and metabolic disease (Seckl 2004).

There remains uncertainty therefore about whether there is benefit in repeating the dose of prenatal corticosteroids for women who remain at risk of preterm birth after an initial course. This review will assess the benefits and harms of repeat doses of prenatal corticosteroids for women at risk of preterm birth seven or more days after an initial course.

OBJECTIVES

To assess the effectiveness and safety, using the best available evidence, of a repeat dose(s) of prenatal corticosteroids, given to women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with the primary aim of reducing fetal, infant and childhood morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised trials with reported data that compared outcomes for women at risk of preterm birth randomised to receive a repeat dose(s) of prenatal corticosteroids with outcomes in controls given a single course of prenatal corticosteroids, with or without additional placebo administration. The trials used some form of random allocation and reported data on one or more of the prestated outcomes. We excluded quasi-randomised trials. Cross-over trials were not eligible for inclusion. Cluster trials were eligible for inclusion.

Types of participants

Women considered to be at risk of preterm birth who have already received a single course of prenatal corticosteroid seven or more days previously.

Predefined subgroups were planned to examine separately the outcomes for women and infants based on the reasons the woman was considered to be at risk for preterm birth (e.g. presence or absence of ruptured membranes, antepartum haemorrhage, preterm labour, cervical incompetence, pre-eclampsia, growth restriction), and the number of infants in utero (singleton, twin or higher order multiple pregnancy).

Types of interventions

Corticosteroid administered to the women intravenously, intramuscularly or orally, compared with either placebo or no placebo. We excluded trials in which the fetus received corticosteroids directly as these are included in another Cochrane review, '*Transplacental versus direct fetal corticosteroid treatment for accelerating fetal lung maturation where there is a risk of preterm birth*' (Utama 2010).

We planned predefined subgroups to examine separately the primary outcomes for women and infants based on the type of corticosteroid given, the planned interval between corticosteroid treatments, the number of repeat courses planned, the number of repeat courses actually given, the planned dose of corticosteroid given per repeat treatment, the planned dose of repeat corticosteroid drug exposure per week, the method of administration, and the gestational age at which the treatment was given.

Types of outcome measures

We prespecified clinically relevant outcomes after discussion amongst the authors.

Primary outcomes

We chose primary outcomes to be most representative of the clinically important measures of effectiveness and safety, including serious outcomes, for the women and their infants, the infant as a child and the infant as an adult.

For the infant

- RDS;
- severe lung disease (however defined by the authors);
- composite serious outcome (however defined by authors);
- birthweight;
- fetal, neonatal or later death;
- chronic lung disease (however defined by authors);
- intraventricular haemorrhage.

For the child

- Total deaths;
- survival free of any disability (however defined by authors);
- survival free of major disability (however defined by authors);
- disability at childhood follow-up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy after 18 months of age) (however defined by authors);
- composite serious outcome (however defined by authors).

For the child as an adult

- Total deaths;
- survival free of any disability (however defined by authors);
- survival free of major disability (however defined by authors);
- disability at adult follow-up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy) (however defined by authors);
- major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient less than two standard deviations below mean));
- composite serious outcome (however defined by authors).

For the women

- Chorioamnionitis (however defined by authors);
- puerperal sepsis (however defined by authors).

Secondary outcomes

These include other measures of effectiveness, complications, satisfaction with care and health service use.

For the infant

- Gestational age at birth (preterm birth less than 37 weeks, very preterm birth less than 34 weeks, extremely preterm birth less than 28 weeks);
- interval between trial entry and birth;
- small-for-gestational age;
- head circumference at birth;
- length at birth;
- skin-fold thickness at birth;
- placental weight;
- Apgar score less than seven at five minutes;
- use of respiratory support (mechanical ventilation or continuous positive airways pressure (CPAP)), or both;
- use of mechanical ventilation;
- use of CPAP;
- duration of respiratory support;
- use of oxygen supplementation;
- duration of oxygen supplementation;
- use of surfactant;
- use of inotropic support;
- use of nitric oxide for respiratory support;
- intraventricular haemorrhage grade 3/4;
- periventricular leukomalacia;
- early systemic neonatal infection (however defined by authors);
- proven infection while in the neonatal intensive care unit;
- admission to neonatal intensive care unit;
- air leak syndrome;
- necrotising enterocolitis (however defined by authors);
- patent ductus arteriosus (however defined by authors);
- retinopathy of prematurity;
- use of postnatal corticosteroids;
- neonatal blood pressure (systolic, diastolic and mean arterial blood pressure);
- cardiac hypertrophy;
- growth assessments at primary hospital discharge (weight, head circumference, length, skin-fold thickness);
- growth assessments at infant follow-up (weight, head circumference, length, skin-fold thickness);
- infant temperament;
- infant behaviour;
- developmental delay at infant follow-up (however defined by the authors);
- hypothalamo/pituitary/adrenal (HPA) axis suppression (however defined by the authors).

For the child

- Growth assessments at childhood follow-up (weight, head circumference, length, skin-fold thickness, body mass index (BMI));
- developmental delay (however defined by the authors);
- intellectual impairment;
- motor impairment;
- blindness/visual impairment (however defined by authors);
- deafness (however defined by authors);
- cerebral palsy;
- child behaviour (however defined by authors);
- child temperament;
- learning difficulties;
- respiratory disease (however defined by authors);
- insulin sensitivity;
- dyslipidaemia;
- blood pressure;
- HPA axis function;
- lung function;
- bone density.

For the child as an adult

- Age at puberty;
- growth assessments in later life (weight, head circumference, length, skin-fold thickness, BMI);
- major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or

intelligence quotient less than two standard deviations below mean));

- developmental delay (however defined by the authors);
- intellectual impairment;
- motor impairment;
- blindness;
- deafness;
- cerebral palsy;
- educational achievements;
- learning difficulties;
- insulin sensitivity;
- dyslipidaemia;
- blood pressure;
- HPA axis function;
- lung function;
- bone density.

For the woman

- Death;
- pulmonary oedema;
- admission to intensive care unit;
- prelabour rupture of the membranes after trial entry;
- hypertension (variously defined by the authors);
- mode of birth;
- length of labour;
- pyrexia after trial entry requiring the use of antibiotics;
- intrapartum fever requiring the use of antibiotics;
- postpartum haemorrhage;
- postnatal pyrexia (however defined by authors);
- breastfeeding after hospital discharge;
- postnatal depression;
- side effects of therapy (including nausea, vomiting, hypertension, glucose intolerance, osteoporosis, adrenal insufficiency, insomnia, pain at the injection site, bruising at the injection site, haematoma at injection site);
- discontinuation of therapy because of maternal side effects;
- adverse drug reaction;
- satisfaction with the therapy;
- quality of life;
- parenting stress.

Use of health services

- Length of antenatal hospitalisation for the women;
- length of postnatal hospitalisation for the women;
- maternal admission to intensive care unit;
- admission to and length of stay in neonatal intensive care unit;
- length of neonatal hospitalisation;
- costs of maternal care;
- cost of neonatal care;
- hospital re-admission at childhood follow-up.

While we sought all the above outcomes from the included trials, only those with data appear in the analysis tables. We included outcomes in the analysis if reasonable measures were taken to minimise observer bias and data were available for analysis according to original allocation.

Search methods for identification of studies

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Electronic searches

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (20 January 2015).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:

1. monthly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
2. weekly searches of MEDLINE (Ovid);
3. weekly searches of Embase (Ovid);
4. monthly searches of CINAHL (EBSCO);
5. handsearches of 30 journals and the proceedings of major conferences;
6. weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Details of the search strategies for CENTRAL, MEDLINE, Embase and CINAHL, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

Trials identified through the searching activities described above are each assigned to a review topic (or topics). The Trials Search Co-ordinator searches the register for each review using the topic list rather than keywords.

Searching other resources

We searched reference lists of trials and other review articles. We contacted authors on two studies listed under 'ongoing studies' in the previous version of the review for further information for this update.

We did not apply any language restrictions.

Data collection and analysis

For methods used in the previous version of this review, *see* 'Crowther 2011'.

For this update, the following methods were used for assessing the reports that were identified as a result of the updated search.

The following methods section of this review is based on a standard template used by the Cochrane Pregnancy and Childbirth Group.

Selection of studies

We independently evaluated trials under consideration for inclusion without consideration of their results. We resolved any differences of opinion by discussion. There was no blinding of authorship.

Data extraction and management

Two review authors independently extracted study data, using a pre-designed data form. Review author Philippa Middleton independently extracted data for the ACTORDS trial (Crowther 2006). We resolved discrepancies through discussion. When information was unclear, we attempted to contact authors of the original reports to provide further details. We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each study using the criteria outlined in the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2011). Any disagreement was resolved by discussion or by involving a third assessor.

(1) Random sequence generation (checking for possible selection bias)

We described for each included study the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups.

We assessed the method as:

- low risk of bias (any truly random process, e.g. random number table; computer random number generator);
- high risk of bias (any non-random process, e.g. odd or even date of birth; hospital or clinic record number);
- unclear risk of bias.

(2) Allocation concealment (checking for possible selection bias)

We described for each included study the method used to conceal allocation to interventions prior to assignment and assessed whether intervention allocation could have been foreseen in advance of, or during recruitment, or changed after assignment.

We assessed the methods as:

- low risk of bias (e.g. telephone or central randomisation; consecutively numbered sealed opaque envelopes);
- high risk of bias (open random allocation; unsealed or non-opaque envelopes, alternation; date of birth);
- unclear risk of bias.

(3.1) Blinding of participants and personnel (checking for possible performance bias)

We described for each included study the methods used, if any, to blind study participants and personnel from knowledge of which intervention a participant received. We considered that studies were at low risk of bias if they were blinded, or if we judged that the lack of blinding unlikely to affect results. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed the methods as:

- low, high or unclear risk of bias for participants;
- low, high or unclear risk of bias for personnel.

(3.2) Blinding of outcome assessment (checking for possible detection bias)

We described for each included study the methods used, if any, to blind outcome assessors from knowledge of which intervention a participant received. We assessed blinding separately for different outcomes or classes of outcomes.

We assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

(4) Incomplete outcome data (checking for possible attrition bias due to the amount, nature and handling of incomplete outcome data)

We described for each included study, and for each outcome or class of outcomes, the completeness of data including attrition and exclusions from the analysis. We stated whether attrition and exclusions were reported and the numbers included in the analysis at each stage (compared with the total randomised participants), reasons for attrition or exclusion where reported, and whether missing data were balanced across groups or were related to outcomes. Where sufficient information was reported, or could be supplied by the trial authors, we planned to re-include missing data in the analyses which we undertook.

We assessed methods as:

- low risk of bias (e.g. no missing outcome data; missing outcome data balanced across groups);
- high risk of bias (e.g. numbers or reasons for missing data imbalanced across groups; 'as treated' analysis done with substantial departure of intervention received from that assigned at randomisation);
- unclear risk of bias.

(5) Selective reporting (checking for reporting bias)

We described for each included study how we investigated the possibility of selective outcome reporting bias and what we found. We assessed the methods as:

- low risk of bias (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 of bias (where not all the study's pre-specified outcomes have been reported; one or more reported primary outcomes were not pre-specified; outcomes of interest are reported incompletely and so cannot be used; study fails to include results of a key outcome that would have been expected to have been reported);
- unclear risk of bias.

(6) Other bias (checking for bias due to problems not covered by (1) to (5) above)

We described for each included study any important concerns we had about other possible sources of bias.

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - *see* Sensitivity analysis.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio (RR) with 95% confidence intervals (CI). We calculated number needed to treat to benefit (NNTB) from the summary risk differences and their 95% confidence limits (Higgins 2011).

Continuous data

For continuous data, we used the mean difference (MD) with 95% CI.

Unit of analysis issues

Cluster-randomised trials

Cluster-randomised trials were eligible for inclusion but we did not identify any. Should we include cluster-randomised trials subsequently, we will include them in the analyses along with individually-randomised trials. We will adjust their sample sizes using the methods described in *Handbook [Section 16.3.4 or 16.3.6]*) using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), or from another source. If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually-randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomisation unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

Cross-over trials

Cross-over trials were not eligible for inclusion.

Dealing with missing data

For included studies, we noted levels of attrition. We planned to explore the impact of including studies with high levels of missing data in the overall assessment of treatment effect by using sensitivity analyses. If missing data were such that they might significantly affect the results, we excluded these data from the analysis. This decision rested with the review authors. If missing data become available subsequently, we will include them in the analyses.

For all outcomes we carried out analyses as far as possible on an intention-to-treat basis. We attempted to include all participants randomised to each group in the analyses, and analysed all participants in the group to which they were allocated, regardless of whether or not they received the allocated intervention. The denominator for each outcome in each trial was taken as the number randomised minus any participants whose outcomes were known to be missing, ('available case' analysis).

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if the Tau^2 was greater than zero and either the I^2 was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity. When we identified high levels of heterogeneity among the trials, we explored this by pre-specified subgroup analysis.

Assessment of reporting biases

Where we suspected reporting bias (see selective reporting bias above), and the missing data were thought to introduce serious bias, we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Where there were 10 or more studies in the meta-analysis, we planned to investigate reporting biases (such as publication bias) using funnel plots, although we identified none. In future updates, if there are 10 or more studies in the meta-analysis, we will investigate reporting biases (such as publication bias) using funnel plots. We will assess funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment, we will perform exploratory analyses to investigate it.

Data synthesis

We carried out statistical analysis using the Review Manager software (RevMan 2014). We used fixed-effect meta-analysis for combining data where it was reasonable to assume that studies were estimating the same underlying treatment effect: i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar.

If there was clinical heterogeneity sufficient to expect that the underlying treatment effects differed between trials, or if substantial statistical heterogeneity was detected, we used random-effects meta-analysis to produce an overall summary, if an average treatment effect across trials was considered clinically meaningful. The random-effects summary was treated as the average of the range of possible treatment effects and we discussed the clinical implications of treatment effects differing between trials. If the average treatment effect was not clinically meaningful, we did not combine trials. Where we used random-effects analyses, the results were presented as the average treatment effect with 95% confidence intervals, and the estimates of Tau^2 and I^2.

Clinical subgroups

We planned secondary analyses to explore clinical diversity by examining separately the outcomes for women exposed to repeat dose(s) of prenatal corticosteroids compared with women receiving no repeat prenatal corticosteroids/placebo based on:

- the reasons the woman was considered to be at risk of preterm birth (e.g. presence or absence of ruptured membranes, antepartum haemorrhage, preterm labour, cervical incompetence, pre-eclampsia and growth restriction);
- the number of babies in utero (singleton, twins or higher order multiples);
- the type of corticosteroid given (betamethasone, dexamethasone);
- the planned interval between corticosteroid treatments (minimum interval of seven days or less, between eight and less than 14 days, 14 days or more);
- the planned number of repeat courses of corticosteroids to be given (one, two, three, four or more repeat courses);
- the number of repeat courses of corticosteroids actually given post-randomisation (one, two, three, four or more repeat courses);
- the planned dosage of corticosteroid given per treatment (12 mg or less, more than 12 mg to 24 mg, more than 24 mg);
- the planned dose of repeat dose of corticosteroid drug exposure/week (12 mg or less/week, more than 12 mg/week to 24 mg/week, more than 24 mg/week);
- the method of treatment administration (intramuscular, intravenous, intra-amniotic); and
- the gestational age at which the first repeat treatment was given (less than 28, 28 to less than 32, 32 to 34, more than 34 completed weeks).

We used primary outcomes for the infant, women and child most representative of the clinically important measures of effectiveness and safety for the women and their infants.

In future updates, we may carry out formal subgroup analysis in order to investigate heterogeneity.

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of trial quality on important outcomes in the review. Where there was risk of bias associated with a particular aspect of study quality (e.g. inadequate allocation concealment), we explored this by sensitivity analysis.

RESULTS

Description of studies

Results of the search

Studies considered and included

We identified 14 trials for potential inclusion (Aghajafari 2002; Bontis 2011; Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; McEvoy 2002; McEvoy 2010; Mercer 2001; Murphy 2008; Peltoniemi 2007; Romejko-Wolniewicz 2013; Thorp 2000; Wapner 2006). There were 11 trials of repeat dose(s) of prenatal corticosteroids given to women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids, of which 10 trials met our inclusion criteria (Aghajafari 2002; Crowther 2006; Garite 2009; Guinn 2002; Mazumder 2008; McEvoy 2002; McEvoy 2010; Murphy 2008;

Peltoniemi 2007; Wapner 2006). We excluded four trials (Bontis 2011; Mercer 2001; Romejko-Wolniewicz 2013; Thorp 2000).

Included studies

A total of 4733 women (and 5700 babies) were recruited into the 10 trials that met the prespecified criteria for inclusion in this review (12 women: 16 babies in Aghajafari 2002; 982 women: 1147 babies in Crowther 2006; 437 women: 577 babies in Garite 2009; 502 women: 496 babies in Guinn 2002; 76 women: 76 babies in Mazumder 2008; 37 women: 37 babies in McEvoy 2002, 85 women: 113 babies in McEvoy 2010; 1858 women: 2318 babies in Murphy 2008; 249 women: 326 babies in Peltoniemi 2007; and 495 women: 594 babies in Wapner 2006).

Five of the trials were conducted in the United States of America (Garite 2009; Guinn 2002; McEvoy 2002; McEvoy 2010; Wapner 2006); one each in Canada (Aghajafari 2002), India (Mazumder 2008), and Finland (Peltoniemi 2007); one in Australia and New Zealand (Crowther 2006); and one involved 20 countries (Murphy 2008).

We are aware of three other trials of repeat prenatal corticosteroids for women at risk of preterm birth. One trial from the UK stopped recruitment and publication is awaited (TEAMS 1999); one trial in women with preterm prelabour rupture of the membranes has only been published in abstract form with no usable data as yet (Sobhrabvand 2001); and one trial from Iran is awaiting classification to establish its eligibility for inclusion. We are awaiting a response from the authors (Atarod 2014).

The gestational age at trial entry varied between the trials: 24 to 30 weeks in Aghajafari 2002; 25 to 32 weeks in Murphy 2008; 25 to less than 33 weeks in Guinn 2002 and Garite 2009; 26 to 33 weeks in Mazumder 2008 and McEvoy 2010; 25 to 33 weeks in McEvoy 2002; 23 to less than 32 weeks in Wapner 2006; less than 32 weeks in Crowther 2006; and less than 34 weeks in Peltoniemi 2007. All women were at increased risk of preterm birth (*see* Characteristics of included studies table) and had received a single course of antenatal corticosteroids one week or more before trial entry. The type, amount and timing regimen for administration of the corticosteroid given for the pre-trial course of antenatal corticosteroids varied between the trials.

In six trials women were eligible for inclusion seven or more days after a pre-trial course (Aghajafari 2002; Crowther 2006; Guinn 2002; Mazumder 2008; McEvoy 2002; Peltoniemi 2007); in one trial between seven and 10 days after a pre-trial course (Wapner 2006); in two trials 14 or more days after a pre-trial course (Garite 2009: McEvoy 2010); and in one trial between 14 and 21 days after a pre-trial course (Murphy 2008).

Exclusion criteria for recruitment to the trials included in this review are listed below

Aghajafari 2002; if women required chronic doses of corticosteroids secondary to medical conditions, had a contra-indication to corticosteroids, had clinical evidence of chorioamnionitis, or if their fetus(es) had a known lethal congenital anomaly.

Crowther 2006; in second stage of labour, chorioamnionitis needing urgent delivery, or if further corticosteroid therapy was judged to be essential.

Garite 2009; major fetal anomaly, cervical dilatation 5 cm or more, higher order multiples, ruptured membranes, documented lung maturity, receiving corticosteroids for other indications, human immunodeficiency virus infection or active tuberculosis.

Guinn 2002; required immediate delivery, fetal anomalies incompatible with life, documented fetal lung maturity, and maternal active tuberculosis or human immunodeficiency virus infection.

Mazumder 2008; unreliable gestational age, frank chorioamnionitis and major fetal malformation, not available for follow-up.

McEvoy 2002; insulin-dependent diabetics, drug-addiction, or known lethal congenital anomaly, multiple pregnancy.

McEvoy 2010; insulin-dependent diabetics, major documented fetal or chromosomal abnormality; multiple pregnancy greater than twins; clinical chorioamnionitis; first course of antenatal corticosteroids given before 24 weeks' gestation; chronic steroid use during pregnancy for clinical care.

Murphy 2008; contraindication to corticosteroid use, needed chronic doses of corticosteroid drugs, had evidence of chorioamnionitis, known lethal congenital abnormality, had an initial course of corticosteroids before 23 weeks' gestation, previously participated in MACS, women with a multiple pregnancy with fetal death after 13 weeks' gestation.

Peltoniemi 2007; long-term maternal corticosteroid use, clinical chorioamnionitis, or lethal disease of the fetus.

Wapner 2006; preterm premature rupture of the membranes prior to randomisation, confirmed fetal lung maturity, chorioamnionitis, a major fetal anomaly, non-reassuring fetal status, systemic corticosteroid use during the current pregnancy, or insulin-dependent diabetes.

Interventions

The type of corticosteroid planned to be given as treatment was betamethasone for all the trials, although the gestational age at which treatment could begin or was continued until varied slightly between the trials.

In five trials a planned treatment course was two doses of 12 mg/dose betamethasone, intramuscularly, at weekly intervals (Aghajafari 2002; Guinn 2002; Mazumder 2008; McEvoy 2002; Wapner 2006). For Aghajafari 2002, a weekly course of betamethasone was given (two doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Canada Inc.) intramuscularly, 24 hours apart) until 33 weeks or birth if the woman remained at increased risk of preterm birth. Guinn 2002 used a weekly course of betamethasone (two doses of 12 mg/dose betamethasone, intramuscularly 24 hours apart) until 34 weeks or birth, whichever came first. Mazumder 2008 used betamethasone 12 mg intramuscu-

larly, two doses, 24 hours apart until the end of the 33rd week of gestation. McEvoy 2002 used a weekly course of betamethasone (two doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, until 34 weeks or birth. Wapner 2006 used a weekly course of betamethasone (two doses of 12 mg betamethasone as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate, intramuscularly in 24 hours) until birth or 33 weeks and six days, limited to four repeat courses after the first 67 women.

One trial, Crowther 2006, used a single intramuscular injection of 11.4 mg Celestone Chronodose (Schering-Plough, Sydney, Australia) containing 7.8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate, repeated weekly if the woman remained undelivered and less than 32 weeks' gestation and the responsible clinician regarded her as at continued risk of preterm birth.

One trial, Murphy 2008, used a course of betamethasone (two doses of 12 mg/dose betamethasone (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate: Celestone Schering-Plough Corporation, Madison, New Jersey, USA), intramuscularly, 24 hours apart, every 14 days (if the woman remained at risk of preterm birth after their first course of study treatment) until 33 weeks' gestation or birth. For women with preterm premature rupture of membranes, it was recommended that treatment stop at 32 weeks' gestation.

Three trials planned only a single repeat course of treatment; Garite 2009 used a single course consisting of two doses of 12 mg betamethasone, intramuscularly, 24 hours apart (preparation not specified); McEvoy 2010 used a single course of two doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, 24 hours apart; and Peltoniemi 2007 used a single intramuscular injection of 12 mg intramuscular of betamethasone, preparation not specified. For Garite 2009, due to unavailability of betamethasone, dexamethasone (6 mg, intramuscularly every 12 hours up to four doses or similar placebo regimen) was used for 61 (14%) of women.

Primary outcomes

The primary outcomes for Aghajafari 2002 were the rate of recruitment over a 12-month period, risk of complications requiring discontinuation of study treatment, concentrations of plasma cortisol and adrenocorticotropic hormone in cord blood and in maternal blood immediately following birth, perinatal or neonatal mortality or significant neonatal morbidity.

For Crowther 2006, the primary outcomes were occurrence of neonatal RDS, severity of any respiratory disease present, use and duration of oxygen therapy, use and duration of mechanical ventilation, and weight, length and head circumference at birth and at discharge from hospital.

In Garite 2009 the primary outcome was a composite of neonatal mortality/morbidity in babies born before 34 weeks' gestation. The composite outcome was defined as one or more of: perinatal death (defined as stillbirth or death before neonatal discharge); RDS (oxygen requirement, clinical diagnosis and consistent chest radiograph); bronchopulmonary dysplasia (defined as a requirement for oxygen at 30 days of age); severe intraventricular haemorrhage (grades 3 or 4); periventricular leukomalacia; blood culture-proven sepsis; or necrotising enterocolitis (not defined in the publication).

The Guinn 2002 trial had a composite neonatal morbidity primary outcome of any of the following: severe RDS, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge.

The primary outcome in Mazumder 2008 was severe RDS, defined as respiratory distress within six hours of birth in a preterm infant with either a negative gastric shake test or a typical chest radiograph. Severe RDS was defined as requiring mechanical ventilation for at least 12 hours. Mechanical ventilation was started in infants with hypoxaemia ($Pa0_2$ < 50 mmHg) or hypercapnic acidosis ($PaC0_2$ > 50 mmHg with pH < 7.25) or worsening acidosis or clinically worsening respiratory fatigue/apnoea/work of breathing despite continuous positive airway pressure (maximum 8 cm water pressure).

The primary outcomes for McEvoy 2002 and McEvoy 2010 were functional residual capacity and respiratory compliance.

Murphy 2008 used a composite primary outcome consisting of one of the following: stillbirth or neonatal death (defined as death during the first 28 days of life or before hospital discharge); severe RDS (defined as needing assisted ventilation via endotracheal tube and supplemental oxygen within the first 24 hours of life and for 24 hours or more, and either a radiographic scan compatible with RDS or surfactant given between the two and 24 hours after birth); bronchopulmonary dysplasia (defined as needing oxygen at a postmenstrual age of 36 completed weeks and radiographic scan compatible with bronchopulmonary dysplasia); intraventricular haemorrhage grade 3 or 4; cystic periventricular leukomalacia, necrotising enterocolitis.

For Peltoniemi 2007 the primary outcome was survival without RDS or severe intraventricular haemorrhage during the first hospitalisation.

For Wapner 2006 the primary outcome was one of the following: severe RDS (defined as clinical features of RDS with the need for oxygen and respiratory support from six to 24 hours or more of age, an abnormal chest x-ray, and either administration of a full course of surfactant or a fraction of inspired oxygen (FiO_2 of at least 60%); grade 3 or 4 intraventricular haemorrhage; periventricular leukomalacia; chronic lung disease (defined as the need for supplemental oxygen at 36 weeks' corrected age in infants born before 34 weeks' gestation); or stillbirth or neonatal death.

All the trials had a range of secondary outcomes of clinical relevance.

At early childhood follow-up, primary outcomes varied by trial.

For Crowther 2006, the pre-specified primary outcomes were survival at two years' corrected age free of major neurodisability (defined as survival free of moderate or severe disability); and body size (weight, height and head circumference). For Murphy 2008, the primary outcome was death or the presence of neurologic impairment at 18 to 24 months of age, corrected for gestational age at birth. Neurologic impairment was defined as the presence of cerebral palsy or cognitive delay. For Peltoniemi 2007, the power analysis at follow-up was based on survival without neurodevelopmental impairment. For Wapner 2006, the power analysis was based on the prespecified developmental outcome of the Bayley Mental Developmental Index score. Other prespecified outcomes for Wapner were the Bayley Psychomotor Developmental Index score: measurements of weight, height and head circumference and the occurrence of cerebral palsy.

Excluded studies

We excluded four trials (Bontis 2011; Mercer 2001; Romejko-Wolniewicz 2013; Thorp 2000). Bontis 2011 was not a 'randomized' trial; in Mercer 2001 women recruited to the trial did not have corticosteroids before entry (the objective of this trial was to evaluate the need for and benefits of weekly antenatal corticosteroids in women at risk of preterm birth; in Romejko-Wolniewicz 2013, this is a head-to-head trial of 2 different regimens and is eligible for the Cochrane review entitled '*Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth*' Brownfoot 2013; and in Thorp 2000 the treatment to which women were randomised was not repeat dose(s) of prenatal corticosteroids.

Risk of bias in included studies

See Included studies, 'Risk of bias' tables and 'Risk of bias' summary figures: Figure 1; Figure 2. Overall, the included trials were assessed as having a low to moderate risk of bias.

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

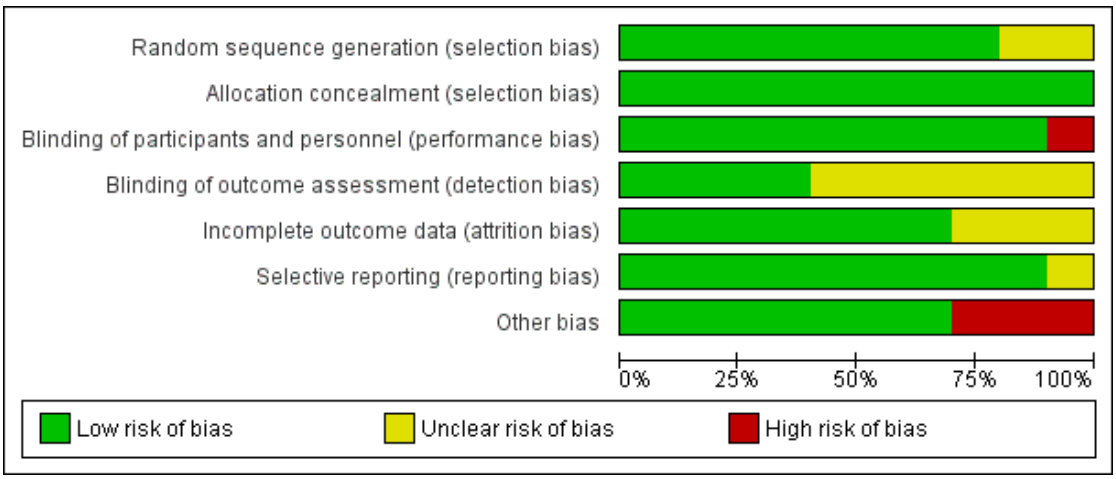
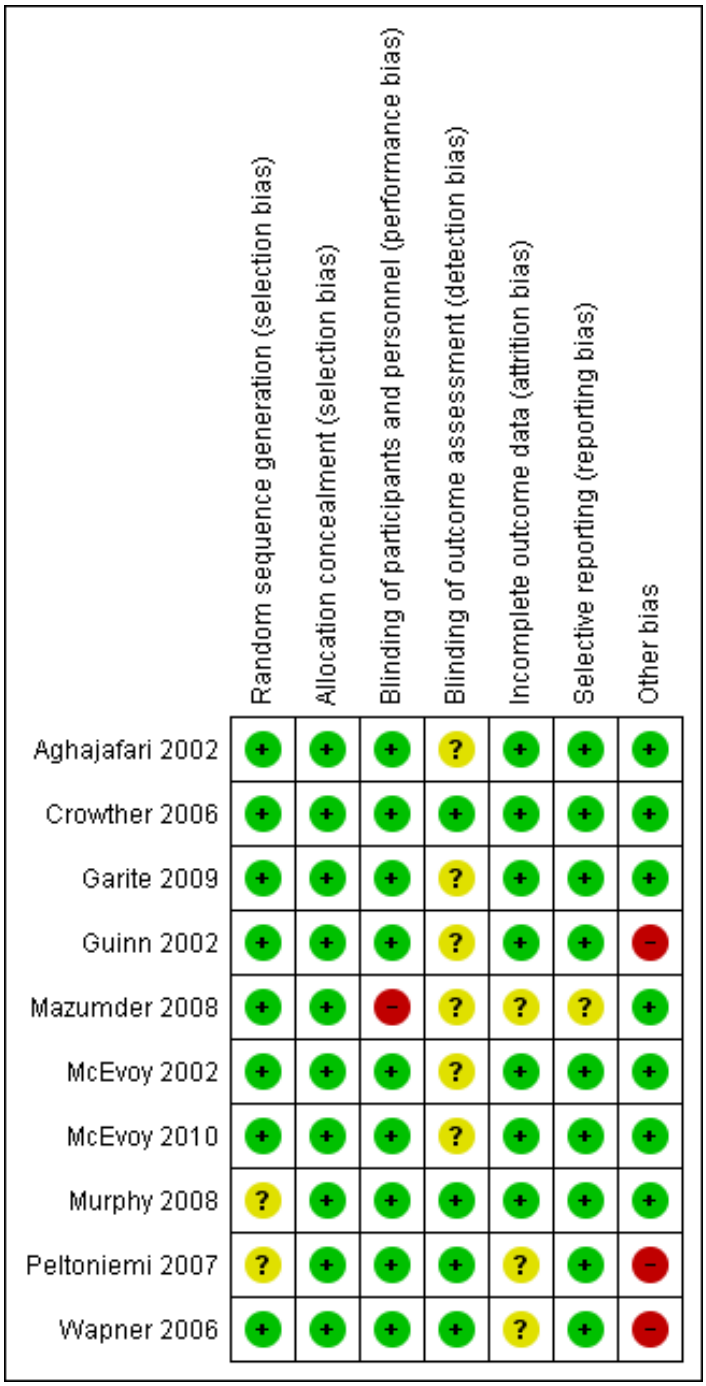


Figure 2. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



Allocation

Sequence generation

Adequate sequence generation was clearly reported for eight trials. For Aghajafari 2002, randomisation was computer-generated and was centrally controlled by one pharmacist at each hospital who kept the randomisation code with stratification by gestational age (24 to 27 weeks versus 28 to 30 weeks), and by hospital using block sizes of two. Crowther 2006 used a central telephone randomisation service for study number and then treatment pack allocation. The randomisation numbers were generated by a computer with variable block sizes, stratified by centre, gestational age (two groups: less than 28 weeks and 28 weeks or more) and number of fetuses (three groups: singleton, twin and triplet). In Garite 2009, a blocked randomisation sequence was used prepared centrally, with the random sequence generated by computer. Guinn 2002 used computer-generated randomisation logs prepared centrally, stratified by centre, and distributed to the research pharmacist at each clinical site. Mazumder 2008 used a website-generated random number list. In McEvoy 2002, assignment was via the pharmacy using a random-number table. No stratification was reported. McEvoy 2010 used a random number table, with stratification of 28 weeks or less versus 28 or more weeks' gestation and multiple gestation (twins versus singletons). For Wapner 2006, randomisation sequences for the treatment kits were generated by the independent data co-ordinating centre with stratification by centre, type of qualifying corticosteroid course and whether an in-patient or out-patient using the urn design.

The method of sequence generation was unclear from the published reports for Peltoniemi 2007 and Murphy 2008. Murphy 2008 used a 24-hour telephone service for randomisation. Information on the generation of the allocation sequence was not provided in the published paper but was probably adequate. For Peltoniemi 2007, randomisation was performed centrally and was stratified according to centre by using four sets of sequentially-labelled, opaque, sealed envelopes (for the four strata of gestational age (28 weeks or less or between 28 and 34 weeks or less) and multiple gestation (singleton or multiple pregnancies)), which were sent to each centre. How the randomisation sequence was generated was not described in the paper but was probably adequate.

Allocation concealment

Adequate allocation concealment was reported in all 10 trials. For Aghajafari 2002, randomisation was controlled by one pharmacist at each hospital who kept the randomisation code. Crowther 2006 used a central telephone randomisation service for study number and then treatment pack allocation. In Garite 2009, the research pharmacist at each site prepared the medication based on the blocked randomisation sequence. In Guinn 2002, the research pharmacist at each clinical site allocated the treatment from the randomisation log. In Mazumder 2008, women were randomised by opening the next serially numbered opaque sealed envelope prepared using the random number list. For McEvoy 2002 and McEvoy 2010, assignment was via the pharmacy where the medication was prepared, and was stratified according to centre by using four sets of sequentially-labelled, opaque, sealed envelopes (for the four strata of gestational age (28 weeks or less or between 28 and 34 weeks or less) and multiple gestation (singleton or multiple pregnancies)), which were sent to each centre. Murphy 2008 used a 24-hour telephone service for randomisation. Peltoniemi 2007 used centrally-labelled, opaque, sealed envelopes sent to each centre, with the sealed envelope opened after informed consent was obtained. For Wapner 2006, the woman was assigned the next sequentially-numbered treatment kit by a centralised research pharmacy.

Blinding

A placebo was used in all the trials, except Mazumder 2008, to blind participants and caregivers to treatment allocation. Normal saline was used as placebo in Aghajafari 2002, Crowther 2006, Garite 2009 and Peltoniemi 2007. McEvoy 2002 and McEvoy 2010 used 25 mg cortisone acetate, an inactive steroid. Murphy 2008 used a similarly appearing intramuscular injection of dilute concentration of aluminium monostearate (an inert substance used as a filler in pharmaceutical preparations). The type of placebo preparation used was not stated for Guinn 2002 or Wapner 2006. In Aghajafari 2002, the pharmacist prepared the study treatments in a syringe covered with yellow tape and the injection of the study treatment was given by a designated research nurse in each hospital, who was not caring for the woman. For Crowther 2006, the treatment packs looked identical and contained an opaque study-labelled syringe. In Garite 2009 the study syringes were completely covered by a label to conceal the contents. For Guinn 2002, the placebo syringes were indistinguishable from the syringes containing betamethasone. For McEvoy 2002 and McEvoy 2010, the placebo was identical in appearance to betamethasone. In Murphy 2008, the study treatments were similar in appearance. In Peltoniemi 2007 the study medication and placebo were prepared in identical syringes which were masked with opaque tape. In Wapner 2006, the placebo was identical in appearance to betamethasone.

There are no details for blinding of outcome assessors reported by Aghajafari 2002, Garite 2009, Guinn 2002, Mazumder 2008, McEvoy 2002, McEvoy 2010.

Of the four trials reporting early childhood follow-up data in full

(Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006), three stated blinding of outcome assessors. For Crowther 2006 staff making the assessments and the families "were unaware of group assignment"; in Peltoniemi 2007 "the examiners and families were unaware of treatment-group assignment" and in Wapner 2006 assessments were performed by "centrally trained and certified study personnel who were unaware of the treatment assignment". Murphy 2008 does not stipulate whether outcome assessors were blinded to treatment group.

Incomplete outcome data

All 10 trials provided data on women and children up to the time of primary hospital discharge after birth. No losses to follow-up to this time were reported for Aghajafari 2002, Crowther 2006, McEvoy 2002 or Peltoniemi 2007. Garite 2009 reported 19 (3.3%) babies (13 in the repeat corticosteroid group and six in the placebo group) lost to follow-up. In the Guinn 2002 trial, 16 (3.2%) women and one (0.2%) neonate were lost to follow-up. Partial data were available for women who were lost to follow-up for the birth date, weight, and health status for the neonate. The denominators presented in the trial report vary slightly from one variable to another because of missing data (Guinn 2002). For Mazumder 2008 one (1.3%) women was lost to follow-up before birth in the repeat corticosteroid group. In McEvoy 2010, one (0.9%) neonate was lost to follow-up in the placebo group. For Murphy 2008, five (0.3%) babies alive at randomisation were lost to follow-up, two in the repeat corticosteroid group and three in the placebo group. For Wapner 2006, three (0.6%) women were lost to follow-up.

At early childhood follow-up, five trials have reported some data (Crowther 2006; Mazumder 2008; Murphy 2008; Peltoniemi 2007; Wapner 2006), with varied losses to follow-up reported. In Crowther 2006, for 86 (7.5%) children alive at randomisation, no data were available to include in the primary outcome of survival free of major neurosensory disability at two years' corrected age follow-up. In Murphy 2008, for 205 (8.9%) children alive at randomisation no data were available to include in the primary outcome of death or the presence of neurologic impairment at 18 to 24 months corrected age. For Peltoniemi 2007, 69 (21.2%) children from trial entry were not available to include in the primary outcome of survival without severe neurological, cognitive or sensory impairment at follow-up of the children between two to three years of age. For Wapner 2006, at the time of two-year corrected age assessment of the 582 known survivors, 96 (16.5%) were not able to be seen, 46 in the repeat corticosteroid group and 50 in the placebo group; 117 (20.1%) did not have a Bayley assessment performed, 59 in the repeat corticosteroid group and 58 in the placebo group. Only interim data have been reported by Mazumder 2008 on 44 (58%) infants at 18 months of age and final follow-up at 18 months of age on the children remaining is awaited.

Selective reporting

Overall, there was no obvious risk of selective reporting for nine of the trials. There was insufficient detail in the publication to permit judgement for Mazumder 2008. Only outcomes relating to body size were reported by number of repeat corticosteroid courses in Wapner 2006.

Other potential sources of bias

Guinn 2002 made the decision to stop recruitment at 500 women following the first interim analysis when 308 women had been randomised. The reason was because of "safety concerns" and the finding of only a marginal difference in short-term outcomes between treatment groups.

In the Peltoniemi 2007 trial, recruitment was terminated early, after 249 women had been enrolled, primarily because of safety concerns due a decrease in intact survival in the repeat corticosteroid group. There were additional concerns about the long-term adverse effects of glucocorticoid. There was a potential imbalance at trial entry for multiple pregnancy and gestational age that was not addressed by the trial authors.

In the Wapner 2006 trial, recruitment was stopped early based on safety concerns after the recruitment of 495 women. "At the second interim analysis the Data Safety Monitoring Committee recommended that enrolment be halted because of a tendency towards decreased birthweight in the repeat steroid group without evident reduction in the primary morbidity outcome and also because of difficulties with recruitment."

Effects of interventions

We included 10 trials involving more than 4730 women and 5650 babies.

(1) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment (all included trials)

Primary outcomes for the infant

Data were available for all the *primary outcomes for the infant*.

- Significantly fewer infants exposed to repeat dose(s) of corticosteroids had respiratory distress syndrome (RDS) compared with infants exposed to placebo or no treatment (risk ratio (RR) 0.83, 95% confidence interval (CI) 0.75 to 0.91, eight trials, 3206 infants, number needed to treat to benefit (NNTB) 17, 95% CI 11 to 32 - Analysis 1.1).

- Seven trials reported a *composite for serious infant outcome*. Treatment with repeat dose(s) of corticosteroid was associated with a reduction in serious infant outcome (RR 0.84, 95% CI 0.75 to 0.94, seven trials, 5094 infants, NNTB 30, 95% CI 19 to 79 - Analysis 1.3). The composite outcome was variously

defined by the trialists: Aghajafari 2002: one or more of the following: stillborn or neonatal death during the first 28 days of life or before hospital discharge, whichever was sooner; RDS; bronchopulmonary dysplasia (requiring oxygen at 36 corrected postnatal gestational age); grade 3 or 4 intraventricular haemorrhage and necrotising enterocolitis; Crowther 2006: one or more of the following: air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks' postmenstrual age, severe intraventricular haemorrhage (grade 3 or 4), periventricular leukomalacia, proven necrotising enterocolitis or retinopathy of prematurity; Garite 2009: one or more of: perinatal death in babies born before 34 weeks' gestation, perinatal death (defined as stillbirth or death before neonatal discharge); RDS (oxygen requirement, clinical diagnosis and consistent chest radiograph); bronchopulmonary dysplasia (defined as a requirement for oxygen at 30 days of age); severe intraventricular haemorrhage (grades 3 or 4); periventricular leukomalacia; blood culture-proven sepsis; or necrotising enterocolitis (not defined); Guinn 2002: the presence of any of the following: severe RDS, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge; Murphy 2008: one of the following: stillbirth or neonatal death (defined as death during the first 28 days of life or before hospital discharge); severe RDS (defined as needing assisted ventilation via endotracheal tube and supplemental oxygen within the first 24 hours of life and for 24 hours or more, and either a radiographic scan compatible with RDS or surfactant given between the first two to 24 hours of life); bronchopulmonary dysplasia (defined as needing oxygen at a postmenstrual age of 36 completed weeks and radiographic scan compatible with bronchopulmonary dysplasia); intraventricular haemorrhage grade 3 or 4; cystic periventricular leukomalacia, necrotising enterocolitis; Peltoniemi 2007: death or RDS or severe intraventricular haemorrhage (expressed as survival without RDS or severe intraventricular haemorrhage during the first hospitalisation); Wapner 2006: one of the following: severe RDS, grade 3 or 4 intraventricular haemorrhage; periventricular leukomalacia, chronic lung disease (defined as the need for supplemental oxygen at 36 weeks' corrected age in infants born before 34 weeks' gestation), or stillbirth or neonatal death.

Treatment with repeat dose(s) of corticosteroid was associated with a reduction in unadjusted mean birthweight. However, birthweight outcomes that adjusted for gestational age (birthweight Z scores, birthweight multiples of the median and small-for-gestational age) did not differ statistically between treatment groups.

- *Mean birthweight* (mean difference (MD) -75.79 g, 95% CI -117.63 to -33.96, nine trials, 5626 infants - Analysis 1.4);
- *birthweight Z scores* (MD -0.11, 95% CI -0.23 to 0.00, two trials, 1256 infants - Analysis 1.5);
- *birthweight multiples of the median* (MD 0.00, 95% CI -0.03 to 0.03, one trial, 590 infants - Analysis 1.6).

No statistically significant differences were seen in infants in the repeat corticosteroid group compared with infants in the placebo/no treatment group for any of the other primary clinical outcomes:

- *severe lung disease* (average RR 0.80, 95% CI 0.56 to 1.14, I^2 = 76%, Tau^2 = 0.12; random-effects, six trials, 4826 infants - Analysis 1.2);
- *fetal and neonatal mortality* (RR 0.94, 95% CI 0.71 to 1.23, nine trials, 5554 infants - Analysis 1.8);
- *chronic lung disease* (RR 1.06, 95% CI 0.87 to 1.30, eight trials, 5393 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 0.94, 95% CI 0.75 to 1.18, six trials, 3065 infants - Analysis 1.12).

Primary outcomes for the child

Only four trials have reported data in full from early childhood follow-up (Crowther 2006, Murphy 2008; Peltoniemi 2007, Wapner 2006) and we have included these in the meta-analysis. We have not included the interim data reported by Mazumder 2008 on 44 (58%) infants at 18 months of age, due to the high proportion of unavailable data (42%).

Data were available for all the primary outcomes for the child, but not from all the trials. No statistically significant differences were seen for infants in the repeat corticosteroids group compared with infants in the placebo or no treatment for any of the primary outcomes for the child:

- *total deaths up to early childhood follow-up* (RR 1.06, 95% CI 0.80 to 1.41, four trials, 4370 infants - Analysis 1.65);
- *survival free of any disability* (RR 1.01, 95% CI 0.97 to 1.05, two trials, 3155 infants - Analysis 1.66);
- *survival free of any major disability* (average RR 1.01, 95% CI 0.92 to 1.11; I^2 = 88%, Tau^2 = 0.00, random-effects, two trials, 1317 infants - Analysis 1.67);
- *any disability at childhood follow-up* (RR 0.98, 95% CI 0.83 to 1.16, one trial, 999 infants - Analysis 1.69);
- *major disability at childhood follow-up* (RR 1.08, 95% CI 0.31 to 3.76, two trials, 1256 infants - Analysis 1.68);
- *composite serious outcome at childhood follow-up* (RR 0.99, 95% CI 0.87 to 1.12, two trials, 3164 infants - Analysis 1.70), defined in Crowther 2006 as death or any neurosensory disability; and defined in Murphy 2008 as death or any neurologic impairment.

Primary outcomes for the child as an adult

No data available for inclusion.

Primary outcomes for the women

No statistically significant differences were seen for women treated with repeat dose(s) of prenatal corticosteroids compared with women given placebo or no treatment for the two primary outcomes for the women of maternal infectious morbidity:

- *chorioamnionitis* (RR 1.16, 95% CI 0.92 to 1.46, six trials, 4261 women - Analysis 1.15);
- *puerperal sepsis* (RR 1.15, 95% CI 0.83 to 1.60, five trials, 3091 women - Analysis 1.16).

Secondary outcomes for the infant

In keeping with the reduction in RDS seen, treatment with repeat dose(s) of corticosteroid compared with placebo or no treatment was associated with a reduction in the use of:

- *mechanical ventilation* (average RR 0.84, 95% CI 0.71 to 0.99; I^2 = 61%, Tau^2 = 0.02, random-effects, six trials, 4918 infants - Analysis 1.27);
- *oxygen supplementation* (RR 0.92, 95% CI 0.85 to 0.99, two trials, 3448 infants - Analysis 1.29);
- *surfactant* (average RR 0.78, 95% CI 0.65 to 0.95; I^2 = 66%, Tau^2 = 0.05, random-effects, nine trials, 5525 infants - Analysis 1.31);
- *inotropic support* (RR 0.80, 95% CI 0.66 to 0.97, two trials, 1470 infants - Analysis 1.32).

Fewer infants exposed to repeat corticosteroids compared with infants exposed to placebo or no treatment had a patent ductus arteriosus (RR 0.80, 95% CI 0.64 to 0.98, six trials, 4356 infants - Analysis 1.39).

At birth, treatment with repeat dose(s) of corticosteroid was associated with a reduction in *mean head circumference* (MD -0.32 cm, 95% CI -0.49 to -0.15, nine trials, 5626 infants - Analysis 1.21), *head circumference Z scores* (MD -0.14, 95% CI -0.27 to -0.00, two trials, 1256 infants - Analysis 1.22), *mean length* (average MD -0.56 cm, 95% CI -0.89 to -0.23, six trials, 4550 infants - Analysis 1.23) and in one trial, significantly *lower length multiples of the mean* at birth (MD -0.01, 95% CI -0.02 to 0.00, one trial, 590 infants - Analysis 1.25). In contrast, *length Z scores* were not significantly reduced by treatment with repeat dose(s) of corticosteroid in two trials (MD -0.05, 95% CI -0.19 to 0.09, two trials, 1256 infants - Analysis 1.24). There was no statistically significant difference associated with repeat antenatal corticosteroids for *small-for-gestational age* (RR 1.18, 95% CI 0.97 to 1.43, seven trials, 3975 infants - Analysis 1.7).

At primary hospital discharge, two trials (1195 infants) reported infant growth assessments. No significant differences were seen between infants exposed to repeat corticosteroids or placebo/no treatment for *mean weight, head circumference or length, or in Z scores for weight, head circumference or length.*

The *mean gestational age at birth* for the infants (MD -0.09 weeks, 95% CI -0.33 to 0.15, eight trials, 3179 infants - Analysis 1.17) was not significantly different between treatment groups, nor was the proportion of infants born before 37 weeks', 34 weeks' or 28 weeks' gestation. However, data are not available to include in these analyses from Murphy 2008, the largest trial, where there was a significant difference in the mean gestational age women gave birth reported (34.5 weeks (standard deviation (SD) 3.6 for the repeat corticosteroid group and 34.9 weeks (SD 3.6) for the placebo group, MD -0.40 weeks, 95% CI -0.73 to -0.07).

No statistically significant differences were seen in infants exposed to repeat dose(s) of corticosteroids compared with infants exposed to placebo or no treatment for the other reported secondary respiratory outcomes (including *duration of respiratory support, duration of oxygen supplementation, use of postnatal corticosteroids*), infectious morbidity outcomes (*early systemic neonatal infection, proven infection while in the neonatal intensive care unit*), and other neonatal morbidity (including *air leak syndrome, intraventricular haemorrhage grade 3 or 4, periventricular leukomalacia, necrotising enterocolitis, and retinopathy of prematurity).*

In the one trial (Crowther 2006) that reported blood pressure and cardiac outcomes in a subgroup of infants (recruited at two of the collaborating hospitals), no significant differences were seen between treatment groups for *mean blood pressure* on the first day of life or at six weeks postnatally, or in the risk of *neonatal cardiac hypertrophy*. In the one trial that reported on hypothalamo/pituitary/adrenal axis suppression in a subgroup of infants (recruited at one of the collaborating hospitals), infants exposed to repeat dose(s) of corticosteroids had significantly lower *mean cortisol concentrations at birth* (MD -44.90 nmol/L, 95% CI -78.41 to -11.39, one trial, 67 infants - Analysis 1.46).

Secondary outcomes for the child

From the limited data available from four trials (Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006), no statistically significant differences were seen for infants in the repeat corticosteroids group compared with infants in the placebo or no treatment groups for any of the reported *secondary developmental outcomes for the child*. These included *developmental delay, blindness, deafness, and cerebral palsy, mental development index (MDI), and psychomotor developmental index (PDI):*

- *developmental delay* (RR 0.97, 95% CI 0.84 to 1.13, three trials, 3202 infants - Analysis 1.80);
- *blindness* (RR 1.17, 95% CI 0.65 to 2.10, two trials, 3151 infants - Analysis 1.83);
- *deafness* (RR 0.85, 95% CI 0.29 to 2.52, three trials, 3405 infants - Analysis 1.84);
- *cerebral palsy* (RR 1.03, 95% CI 0.71 to 1.50, four trials, 3800 infants - Analysis 1.85) (More than a 10-fold variation in the rate of cerebral palsy was seen between the trials);
- *mental developmental index* (MDI) (MD 1.23, -0.65 to 3.11, two trials, 1162 infants - Analysis 1.81);
- *psychomotor developmental index* (PDI) (MD 0.40, -1.75 to 2.55, one trial, 958 infants - Analysis 1.82).

Data were not able to be included in the meta-analysis for Murphy 2008 for MDI or PDI scores expressed as means, as standard deviations were not available in the published report. In this trial, the mean MDI scores were 93.91 and 94.74 and the PDI scores

were 97.86 and 98.98 for the prenatal corticosteroid therapy and placebo groups, respectively.

At early childhood follow-up, all four trials reported some *growth assessments for the children*. Unlike assessments of body size at birth, at childhood follow-up no significant differences were seen for children exposed to repeat corticosteroids compared with children in the control group for a variety of measures of body size, including*mean weight, head circumference and length, Z scores for weight, head circumference and height, and assessments of small for age for weight, head circumference and or height:*

- *mean weight* (MD -0.03 kg, 95% CI -0.21 to 0.15, three trials, 1776 infants - Analysis 1.74);
- *mean head circumference* (MD -0.05 cm, 95% CI -0.22 to 0.11, three trials, 1776 infants - Analysis 1.75);
- *mean height* (MD -0.13 cm, 95% CI -0.55 to 0.30, three trials, 1776 infants - Analysis 1.76);
- *weight Z scores* (MD -0.03, 95% CI -0.19 to 0.13, one trial, 1047 infants - Analysis 1.77);
- *head circumference Z scores* (MD 0.04, 95% CI -0.09 to 0.18, two trials, 1290 infants - Analysis 1.78);
- *height Z scores* (MD -0.04, 95% CI -0.17 to 0.09, two trials, 1290 infants - Analysis 1.79);
- *weight small for age* (RR 0.92, 95% CI 0.71 to 1.19, two trials, 1448 infants - Analysis 1.71);
- *head circumference small for age* (average RR 1.10, 95% CI 0.77 to 1.56, two trials; I^2 = 57%, Tau^2 = 0.04, random-effects, 1442 infants - Analysis 1.72);
- *height small for age* (average RR 1.12, 95% CI 0.63 to 2.02, two trials; I^2 = 65%, Tau^2 = 0.12, random-effects, 1441 infants - Analysis 1.73).

Data were not able to be included in the meta-analysis for Murphy 2008 for anthropometric assessments expressed as means, as standard deviations were not available in the published report. In this trial, mean weight, head circumference and height for children exposed to repeated courses of prenatal corticosteroids were not significantly different from those for children who were exposed to a single course.

Using a random-effects model because of heterogeneity, we found no impact on *asthma or wheezing* at early childhood follow-up on average between treatment groups (average RR 0.89, 95% CI 0.63 to 1.27; I^2 = 62%, Tau^2 = 0.06, random-effects, three trials, 1720 children - Analysis 1.87). Two trials reported on *blood pressure* at early childhood follow-up. One trial (Wapner 2006) reported a significantly lower *mean systolic blood pressure* for children who had been exposed to repeat corticosteroids compared with children exposed to a single course (MD -2.90 mmHg, 95% CI -5.40 to -0.40, one trial, 486 children - Analysis 1.89), although no differences were seen for *mean diastolic blood pressure,* or, in another trial (Crowther 2006), in the *proportion of children who were hypertensive.*

Two trials (Crowther 2006; Murphy 2008) reported on *behaviour.* Crowther 2006 used the Child Behavior Checklist, a rating scale that screens for behavioural and emotional problems. The trial showed no significant differences between the groups in the total or individual mean scores for internalising, externalising, emotional reactivity, anxiety or depression, somatic complaints, withdrawal, sleep problems, attention problems, or aggressive behaviour between treatment groups. No differences were seen in the proportion of children with a behaviour score within the clinical range (RR 1.09, 95% CI 0.79 to 1.51, one trial, 1045 children - Analysis 1.86). Murphy 2008 used the Behavior Rating Scale of the BSID-II and found scores were non-optimal or questionable for 285 (31.6%) of 902 children in the prenatal corticosteroid therapy group and 239 (27.3%) of 874 children in the placebo group.

Secondary outcomes for the child as an adult

No information is currently available for outcomes for the child when an adult.

Secondary outcomes for the women

There was one maternal death reported for a women allocated to the placebo group and withdrawn from the trial before study treatment was given (Garite 2009). No statistically significant differences were seen between treatment groups, where data were available, for the following outcomes: *risk of prelabour rupture of the membranes after trial entry, hypertension, mode of birth, postpartum haemorrhage* or*postnatal pyrexia.*

The two trials that reported on the outcome *any side effects of therapy* showed significant heterogeneity. Crowther 2006 reported a significant increase in side effects with treatment with repeat dose(s) of corticosteroid compared with saline placebo (RR 1.97, 95% CI 1.23 to 3.18, one trial, 982 women), whilst Wapner 2006 reported a significant reduction in side effects with repeat dose(s) corticosteroid treatment compared with an unnamed placebo (RR 0.49, 95% CI 0.39 to 0.61, one trial, 492 women). Using a random-effects model, no impact was seen for side effects of therapy on average between treatment groups (average RR 0.97, 95% CI 0.24 to 3.90, random-effects, two trials, 1474 women - Analysis 1.60). Similar heterogeneity was seen for *pain at the site of the injection*; Crowther 2006 reported a non-significant increase in side effects with treatment with repeat dose(s) of corticosteroid compared with placebo (RR 2.02, 95% CI 0.95 to 4.26, one trial, 982 women), whilst Wapner 2006 a significant reduction (RR 0.28, 95% CI 0.19 to 0.41, one trial, 492 women). Overall, no average difference was seen using a random-effects model (average RR 0.73, 95% CI 0.11 to 5.05, random-effects, two trials, 1474 women - Analysis 1.63). Wapner 2006 reported a significant reduction in *bruising at the site of the injection* with treatment with repeat dose(s) of corticosteroid compared with an unnamed placebo (RR 0.38, 95% CI 0.21 to 0.71, one trial, 492 women - Analysis 1.64). Three trials reported on insomnia (Aghajafari 2002; Crowther 2006; Wapner 2006). More women receiving repeat corticosteroids compared with no repeat treatment reported

insomnia (RR 2.63, 95% CI 1.10 to 6.30, three trials, 1486 women - Analysis 1.62). Wapner 2006 found no significant differences for maternal *glucose intolerance* between treatment groups. No data from any of the trials were reported on other secondary systematic review outcomes for the women including *postnatal depression, parenting stress, breastfeeding after discharge from hospital, satisfaction with the therapy,* and*quality of life.*

Secondary outcomes on use of health services

Few data were reported that related to health services use. No differences were seen between treatment groups for the two trials (Crowther 2006; Murphy 2008) that reported on need for *admission to the neonatal intensive care unit.* Similarly, no differences were seen between treatment groups for *length of postnatal hospitalisation for the women* in the one trial with data (Guinn 2002). All four trials reported on *readmission to hospital by early childhood follow-up* and no significant differences were seen on readmission to hospital between treatment groups (RR 1.02, 95% CI 0.93 to 1.11, four trials, 3824 children - Analysis 1.91).

(2) Sensitivity analyses based on trial quality

All 10 trials were rated as being adequate for allocation concealment, so sensitivity analyses were not performed based on trial quality.

(3) Planned population subgroup analyses

(3.1) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by reason for being at risk of preterm birth (e.g. presence or absence of ruptured membranes, antepartum haemorrhage, preterm labour, cervical incompetence, pre-eclampsia and growth restriction)

Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the presence or absence of ruptured membranes at trial entry or after trial entry

Only one trial (Guinn 2002), reported data for a subgroup of 161 women with preterm prelabour rupture of membranes (120 with ruptured membranes at trial entry and 41 women who ruptured membranes after trial entry). For the infants, no statistically significant differences were seen for any of the primary outcomes where data were available, namely *RDS; fetal, neonatal, infant death;* and*chronic lung disease.* In this small subgroup of women with ruptured membranes, treatment with repeat dose(s) of corticosteroid compared with placebo was associated with an increased risk of *chorioamnionitis* (RR 1.56, 95% 1.05 to 2.31, one trial, 160 women - Analysis 1.15), although no differences were seen for *puerperal sepsis* between treatment groups (RR 0.65, 95% CI 0.19 to 2.22, one trial, 160 women - Analysis 1.16).

Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the presence or absence at trial entry of antepartum haemorrhage, preterm labour, cervical incompetence, pre-eclampsia and growth restriction

No data have been reported on these clinical subgroups to date.

(3.2) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by number of babies in utero (singleton, twins or higher order multiples)

No data have been reported on these clinical subgroups to date.

(3.3) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by type of corticosteroid given (e.g. betamethasone, dexamethasone, hydrocortisone)

All 10 trials planned to use betamethasone, so we were not able to perform subgroup analyses as to the type of repeat corticosteroid treatment given.

(3.4) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the planned interval between corticosteroid treatments (at a minimum interval of seven days or less, at a minimum interval between eight and less than 14 days, at a minimum interval of 14 days or greater)

Planned interval between corticosteroid treatments of a minimum interval of seven days or less

Seven trials used a minimum interval of seven days or less between corticosteroid treatments. (Aghajafari 2002; Crowther 2006; Guinn 2002; Mazumder 2008; McEvoy 2002; Peltoniemi 2007; Wapner 2006).

Women were eligible for inclusion seven or more days after a pre-trial course in six trials (Aghajafari 2002; Crowther 2006; Guinn 2002; Mazumder 2008; McEvoy 2002; Peltoniemi 2007), and in Wapner 2006 between seven and 10 days after a pre-trial course. The upper gestational age at trial entry varied between the trials: being up to 30 weeks in Aghajafari 2002, less than 32 weeks in Crowther 2006 and Wapner 2006, less than 33 weeks in Guinn 2002, Mazumder 2008 and McEvoy 2002, and up to 34 weeks in Peltoniemi 2007.

In five trials a planned treatment course was two doses of 12 mg/dose betamethasone (Aghajafari 2002; Guinn 2002; Mazumder 2008; McEvoy 2002; Wapner 2006), repeated at weekly intervals up to 33 weeks in Aghajafari 2002, until less than 34 weeks in Wapner 2006 and until 34 weeks in Guinn 2002, Mazumder 2008, and McEvoy 2002. In two trials (Crowther 2006; Peltoniemi

2007), a planned treatment course was a single injection of 12 mg betamethasone, given only once in Peltoniemi 2007 and repeated weekly if still considered at risk of preterm birth up to less than 32 weeks' gestation in Crowther 2006.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid treatments at a minimum interval of seven days or less compared with no repeat treatment was associated with a reduction in:

- *respiratory distress syndrome* (RR 0.86, 95% CI 0.77 to 0.96, six trials, 2538 infants - Analysis 1.1);
- *composite serious outcome* (RR 0.78, 95% CI 0.66 to 0.91, five trials, 2232 infants - Analysis 1.3).

No significant differences were seen between treatment groups for the other primary clinical outcomes:

- *severe lung disease* (average RR 0.72, 95% CI 0.47 to 1.12, I^2 = 78%, Tau^2 = 0.15 random-effects, five trials, 2522 infants - Analysis 1.2);
- *fetal and neonatal mortality* (RR 0.96, 95% CI 0.67 to 1.37, six trials, 2871 infants - Analysis 1.8);
- *chronic lung disease* (RR 0.97, 95% CI 0.78 to 1.21, six trials, 2538 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 0.98, 95% CI 0.77 to 1.26, five trials, 2519 infants - Analysis 1.12).

Most of the outcomes related to birthweight were significantly less for infants exposed to repeat corticosteroid treatment at intervals of seven days, or less compared with infants exposed to placebo. Infants exposed to repeat corticosteroids had lower mean birthweights, lower birthweight Z scores and were more likely to be small-for-gestational age, although there was no difference in birthweight multiples of the median:

- *birthweight* (MD -63.68 g, 95% CI -128.59 to 1.24, five trials, 2328 infants - Analysis 1.4);
- *birthweight Z score* (MD -0.13, 95% CI -0.26 to 0.00, one trial, 1144 infants - Analysis 1.5);
- *birthweight multiples of the median* (MD 0.00, 95% CI -0.03 to 0.03, one trial, 590 infants - Analysis 1.6);
- *small-for-gestational age* (RR 1.38, 95% CI 1.04 to 1.82, four trials, 1006 infants - Analysis 1.7).

Primary outcomes for the child

At early childhood follow-up, no significant differences were seen when treatment was given at a minimum interval of seven days or less between treatment groups for any of the primary outcomes:

- *total deaths up to early childhood follow-up* (RR 1.11, 95% CI 0.74 to 1.67, three trials, 2066 infants - Analysis 1.65);
- *survival free of any disability* (RR 1.02, 95% CI 0.92 to 1.12, one trial, 1060 infants - Analysis 1.66);
- *survival free of any major disability* (average RR 1.01, 95% CI 0.92 to 1.11, random-effects, two trials, 1317 infants - Analysis 1.67);
- *any disability at childhood follow-up* (RR 0.98, 95% CI 0.83 to 1.16, one trial, 999 infants - Analysis 1.69);
- *major disability at childhood follow-up* (RR 1.08, 95% CI 0.31 to 3.76, two trials, 1256 infants - Analysis 1.68);
- *composite serious outcome at childhood follow-up* (RR 0.98, 95% CI 0.84 to 1.13, one trial, 1060 infants - Analysis 1.70), defined in this trial as death or any neurosensory disability.

Primary outcomes for the women

No statistically significant differences for the two primary outcomes of maternal infectious morbidity were seen for women treated with repeat dose(s) of prenatal corticosteroids at a minimum interval of seven days or less compared with women given placebo/no treatment:

- *chorioamnionitis* (RR 1.23, 95% CI 0.95 to 1.59, four trials, 1971 women - Analysis 1.15);
- *puerperal sepsis* (average RR 1.01, 95% CI 0.58 to 1.74, I^2 = 32%, Tau^2 = 0.08 random-effects not shown in forest plot, four trials, 1238 women - Analysis 1.16.4).

Planned interval between corticosteroid treatments of a minimum interval of eight and less than 14 days

No trial used a minimum interval between eight and less than 14 days so no data have been reported on these subgroups to date.

Planned interval between corticosteroid treatments of a minimum interval of 14 days or more

Three trials used a minimum interval of 14 days or more between corticosteroid treatment(s) (Garite 2009; McEvoy 2010; Murphy 2008), with Garite 2009 and McEvoy 2010 only planning a single repeat course of treatment.

The gestational age at trial entry was similar between the trials: 25 to 32 weeks in Murphy 2008, 25 to less than 33 weeks in Garite 2009, and 26 to 33 weeks in McEvoy 2010. Women were eligible for inclusion 14 or more days after a pre-trial course in Garite 2009 and McEvoy 2010 and between 14 and 21 days after a pre-trial course in Murphy 2008.

In all three trials the planned treatment course was two doses of 12 mg/dose betamethasone (Garite 2009; McEvoy 2010; Murphy 2008) given singly for Garite 2009 and McEvoy 2010, and for Murphy 2008, given every 14 days if the woman remained at risk of preterm birth, until 33 weeks' gestation or birth.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid treatments at a minimum interval of 14 days or more between treatments compared with placebo was associated with a reduction in RDS (RR 0.72, 95% CI 0.58 to 0.89, two trials, 668 infants - Analysis 1.1). No significant differences were seen between treatment groups for the other primary clinical outcomes:

- *severe lung disease* (average RR 1.11, 95% CI 0.82 to 1.49, random-effects, one trial, 2304 infants - Analysis 1.2);
- *composite serious outcome* (average RR 0.88, 95% CI 0.64 to 1.20, I^2 = 76%, Tau^2 = 0.04 random-effects not shown in forest plot, two trials, 2862 infants - Analysis 1.3.6);
- *fetal and neonatal mortality* (RR 1.02, 95% CI 0.69 to 1.51, three trials, 2993 infants - Analysis 1.8);
- *chronic lung disease* (RR 1.49, 95% CI 0.96 to 2.32, two trials, 2855 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 0.77, 95% CI 0.43 to 1.36, one trial, 546 infants - Analysis 1.12).

Birthweight and birthweight Z scores were significantly reduced for infants exposed to repeat corticosteroid treatment at intervals of 14 days or more compared with infants exposed to placebo, although not the proportion of infants small- for- gestational age:

- *birthweight* (MD -79.61 g, 95% CI -143.23 to -16.00, three trials, 2972 infants - Analysis 1.4);
- *birthweight Z score* (MD 0.0, 95% CI -0.34 to 0.34, one trial, 112 infants - Analysis 1.5);
- *small-for-gestational age* (RR 1.03, 95% CI 0.79 to 1.35, three trials, 2969 infants - Analysis 1.7).

Primary outcomes for the child

Data from early childhood follow-up were available for inclusion from one trial (Murphy 2008).

Limited data were available for the *primary outcomes for the child for this subgroup*. No statistically significant differences were seen for infants exposed to repeat dose(s) of corticosteroid treatments at a minimum interval of 14 days or more between treatments compared with placebo for any of the primary outcomes for the child reported:

- *total deaths up to early childhood follow-up* (RR 1.02, 95% CI 0.69 to 1.51, one trial, 2304 infants - Analysis 1.65);
- *survival free of any disability to early childhood follow-up* (RR 1.00, 95% CI 0.97 to 1.03, one trial, 2104 infants - Analysis 1.66);
- *composite serious outcome at childhood follow-up* (RR 1.01, 95% CI 0.81 to 1.25, one trial, 2104 infants - Analysis 1.70), defined in Murphy 2008 as death or any neurologic impairment.

Primary outcomes for the women

No statistically significant differences were seen for the two outcomes of maternal infectious morbidity *chorioamnionitis* and *puerperal sepsis* for women treated with repeat dose(s) of prenatal corticosteroids at a minimum interval of 14 days or more between treatments compared with women given placebo.

(3.5) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the number of repeat courses actually given post-randomisation (one, two, three, four or more repeat courses of prenatal corticosteroids)

One repeat course of corticosteroids planned or actually given

One single repeat course (variously defined) was planned for three trials (Garite 2009; McEvoy 2010; Peltoniemi 2007). Two trials used a single course consisting of two doses of 12 mg betamethasone (Garite 2009; McEvoy 2010) and for one trial the course of repeat corticosteroids was a single dose of 12 mg betamethasone (Peltoniemi 2007). Women were eligible for inclusion seven or more days after a pre-trial course in Peltoniemi 2007, and 14 or more days after a pre-trial course in Garite 2009 and McEvoy 2010. The eligible gestational age at trial entry was similar between these three trials: being 25 to less than 33 weeks in Garite 2009, 26 to 33 weeks McEvoy 2010, and up to 34 weeks in Peltoniemi 2007.

Primary outcomes for the infant

Treatment with one planned repeat course of corticosteroid treatment compared with placebo was associated with a reduction in a *composite serious outcome* (RR 0.75, 95% CI 0.60 to 0.93, one trial, 558 infants - Analysis 1.3);

No significant differences were seen between treatment groups for the other primary clinical outcomes. There was significant heterogeneity for some of the outcomes (respiratory distress syndrome, and intraventricular haemorrhage):

- *RDS* (average RR 0.83, 95% CI 0.61 to 1.15, I^2 = 72%, Tau^2 = 0.05 random-effects not shown in forest plot, three trials, 994 infants - Analysis 1.1.7);
- *severe lung disease* (RR 1.23, 95% CI 0.94 to 1.60, one trial, 326 infants - Analysis 1.2);
- *fetal and neonatal mortality* (RR 1.41, 95% CI 0.64 to 3.08, three trials, 1015 infants - Analysis 1.8);
- *chronic lung disease* (RR 1.27, 95% CI 0.83 to 1.96, two trials, 877 infants - Analysis 1.11);
- *intraventricular haemorrhage* (average RR 0.99, 95% CI 0.64 to 1.54, I^2 = 31%, Tau^2 = 0.03 random-effects not shown in forest plot, two trials, 872 infants - Analysis 1.12).

No significant effects were seen on birthweight, birthweight Z scores or the proportion of infants small-for-gestational age for infants exposed to one planned repeat course of corticosteroid treatment compared with infants exposed to placebo:

- *birthweight* (MD -57.20 g, 95% CI -132.99 to 18.59, three trials, 994 infants - Analysis 1.4);
- *birthweight Z score* (MD 0.00, 95% CI -0.34 to 0.34, one trial, 112 infants - Analysis 1.5);
- *small-for-gestational age* (RR 1.16, 95% CI 0.87 to 1.54, three trials, 991 infants - Analysis 1.7).

Primary outcomes for the child

Data from early childhood follow-up were available for inclusion from one trial (Peltoniemi 2007).
Limited data were available for all the *primary outcomes for the child for this subgroup*. No statistically significant differences were seen for infants exposed to one planned repeat course of corticosteroid compared with infants exposed to placebo for any of the primary outcomes for the child:

- *total deaths up to early childhood follow-up* (RR 2.31, 95% CI 0.82 to 6.50, one trial, 326 infants - Analysis 1.65);
- *survival free of any major disability* (RR 0.98, 95% CI 0.95 to 1.01, one trial, 257 infants - Analysis 1.67);
- *major disability at childhood follow-up* (RR 3.53, 95% CI 0.37 to 33.52, one trial, 257 infants - Analysis 1.68).

Primary outcomes for the women

No statistically significant differences were seen for women treated with one planned repeat course of corticosteroid compared with placebo for the two *primary outcomes for the women* of maternal infectious morbidity:

- *chorioamnionitis* (RR 0.64, 95% CI 0.23 to 1.77, one trial, 437 women - Analysis 1.15);
- *puerperal sepsis* (RR 1.57, 95% CI 0.80 to 3.10, one trial, 249 women - Analysis 1.16).

Four or more courses of repeat corticosteroids planned or actually given.

One trial reported anthropometric outcomes but not clinical outcomes for infants when four or more courses of repeat corticosteroids actually had been given (Wapner 2006). Women were eligible for inclusion in the trial from 23 to less than 32 weeks' gestation and between seven and 10 days after a pre-trial course of corticosteroids. This trial used a weekly course of two doses of 12 mg betamethasone until birth or 33 weeks and six days whichever was earlier, limited to four study courses after the first 67 women.

Primary outcomes for the infant

Infants exposed to four or more repeat courses of betamethasone compared with infants not exposed to repeat corticosteroids had a reduction in *mean birthweight* (MD -161.00 g, 95% CI -290.52 to -31.48, one trial, 368 infants - Analysis 1.4), lower *birthweight multiples of the median* (MD -0.04, 95% CI -0.07 to -0.01, one trial, 368 infants - Analysis 1.6), and were more likely to be small-for-gestational age (RR 2.00, 95% CI 1.07 to 3.73, one trial, 368 infants - Analysis 1.7).
No data were reported for the other primary outcomes.

Primary outcomes for the child

No data reported for this subgroup.

Primary outcomes for the women

No data reported for this subgroup.

(3.6) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the planned dose of betamethasone or equivalent given per treatment (12 mg or less of betamethasone or equivalent, greater than 12 mg to 24 mg or less of betamethasone or equivalent, greater than 24 mg or more of betamethasone or equivalent)

Planned treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone or equivalent compared with placebo

The planned dose of corticosteroid given per treatment was 12 mg or less of betamethasone for two trials (Crowther 2006; Peltoniemi 2007). Women were eligible for inclusion seven or more days after a pre-trial course in both trials. The eligible gestational age at trial entry was less than 32 weeks in Crowther 2006 and up to 34 weeks in Peltoniemi 2007. A course of study treatment consisted of one 12 mg injection of betamethasone in both trials, given only once in Peltoniemi 2007 and in Crowther 2006 repeated weekly if the woman remained at risk of preterm birth up to 32 weeks' gestation.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone compared with placebo was associated with a reduction in *composite serious neonatal outcome* in the one trial that reported data (RR 0.77, 95% CI 0.62 to 0.96, one trial, 1144 infants - Analysis 1.3).
There was significant heterogeneity when comparing the effects of treatment on mean birthweight for these two trials. Using a random-effects model there was no significant reduction in *mean birthweight* on average (average MD -50.36 g, 95% CI -136.30 to 35.58, random-effects, two trials, 1470 infants - Analysis 1.4). No difference between treatment groups was reported in one trial for the risk of being *small-for-gestational age* (RR 1.33, 95% CI 0.92 to 1.94, one trial, 326 infants - Analysis 1.7). One trial reported

a reduction in *birthweight Z scores* (MD -0.13, 95% CI -0.26 to -0.00, one trial, 1144 infants - Analysis 1.5).

No significant differences were seen between treatment groups for the other primary clinical outcomes. There was significant heterogeneity for several of the outcomes (respiratory distress syndrome, severe lung disease, and fetal and neonatal mortality), where a random-effects model was used:

- *RDS* (average RR 0.91, 95% CI 0.68 to 1.24, I^2 = 81%, Tau^2 = 0.04 random-effects not shown in forest plot, two trials, 1470 infants - Analysis 1.1);
- *severe lung disease* (average RR 0.84, 95% CI 0.40 to 1.78, I^2 = 93%, Tau^2 = 0.27 random-effects, two trials, 1470 infants - Analysis 1.2);
- *fetal and neonatal mortality* (average RR 1.37, 95% CI 0.50 to 3.75, random-effects not shown in forest plot, two trials, 1472 infants - Analysis 1.8);
- *chronic lung disease* (RR 0.97, 95% CI 0.74 to 1.27, two trials, 1470 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 1.02, 95% CI 0.74 to 1.40, two trials, 1470 infants - Analysis 1.12).

Primary outcomes for the child

At early childhood follow-up no significant differences were seen for any of the primary outcomes when treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone was compared with placebo, although there was significant heterogeneity for several of the outcomes:

- *total deaths up to early childhood follow-up* (average RR 1.30, 95% CI 0.54 to 3.10, I^2 = 60%, Tau^2 = 0.25 random-effects not shown in forest plot, two trials, 1472 infants - Analysis 1.65);
- *survival free of any disability* (RR 1.02, 95% CI 0.92 to 1.12, one trial, 1060 infants - Analysis 1.66);
- *survival free of any major disability* (average RR 1.01, 95% CI 0.92 to 1.11, I^2 = 88%, Tau^2 = 0.00 random-effects, two trials, 1317 infants - Analysis 1.67);
- *any disability at childhood follow-up* (RR 0.98, 95% CI 0.83 to 1.16, one trial, 999 infants - Analysis 1.69);
- *major neurosensory disability at childhood follow-up* (average RR 1.08, 95% CI 0.31 to 3.76, I^2 = 42%, Tau^2 = 0.49 random-effects, two trials, 1256 infants - Analysis 1.68);
- *composite serious outcome at childhood follow-up* (RR 0.98, 95% CI 0.84 to 1.13, one trial, 1060 infants - Analysis 1.70), defined in this trial as death or any neurosensory disability.

Primary outcomes for the women

No statistically significant differences were seen for women treated with repeat dose(s) of prenatal corticosteroids of 12 mg or less of betamethasone compared with women given placebo for the two primary outcomes of maternal infectious morbidity;

- *chorioamnionitis* (RR 1.08, 95% CI 0.72 to 1.62, P = 0.70, one trial, 982 women - Analysis 1.15);
- *puerperal sepsis* (RR 1.57, 95% CI 0.80 to 3.10, P = 0.19, one trial, 249 women - Analysis 1.16.

Planned treatment with repeat dose(s) of corticosteroid of greater than 12 mg to 24 mg or less of betamethasone compared with placebo or no treatment

The planned dose of corticosteroid given per treatment was greater than 12 mg to 24 mg or less of betamethasone for eight trials (Aghajafari 2002; Garite 2009; Guinn 2002; Mazumder 2008; McEvoy 2002; McEvoy 2010; Murphy 2008; Wapner 2006).

Women were eligible for inclusion seven or more days after a pre-trial course in four trials (Aghajafari 2002; Guinn 2002; Mazumder 2008; McEvoy 2002); between seven and 10 days after a pre-trial course in Wapner 2006; between 14 to 21 days after a pre-trial course in Murphy 2008; and 14 or more days after a pre-trial course in Garite 2009 and McEvoy 2010.

The upper gestational age at trial entry varied between the trials: being up to 30 weeks in Aghajafari 2002, less than 32 weeks in Wapner 2006, to 32 weeks in Murphy 2008; less than 33 weeks in Garite 2009 ,Guinn 2002, Mazumder 2008 and McEvoy 2002 and McEvoy 2010.

In all eight trials a planned treatment course was two doses of 12 mg/dose betamethasone given only once for Garite 2009 and McEvoy 2010; repeated at weekly intervals up to 33 weeks in Aghajafari 2002, until before 34 weeks in Wapner 2006 and until 34 weeks in Guinn 2002, Mazumder 2008 and McEvoy 2002; and repeated every 14 days up to 33 weeks' gestation in Murphy 2008.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid treatments of greater than 12 mg to 24 mg or less of betamethasone compared with no repeat treatment was associated with a reduction in:

- *RDS* (RR 0.78, 95% CI 0.67 to 0.92, six trials, 1736 infants - Analysis 1.1);
- *composite serious outcome* (RR 0.87, 95% CI 0.76 to 0.99, six trials, 3950 infants - Analysis 1.3).

These benefits were associated with a significantly lower mean birthweight (MD -90.12 g, 95% CI -141.85 to -38.39, seven trials, 4156 infants - Analysis 1.4), although no differences between treatment groups were seen when adjustment was made for gestational age using birthweight Z scores (MD 0.00, 95% CI -0.34 to 0.34, one trial, 112 infants - Analysis 1.5) or birthweight multiples of the median (MD 0.00, 95% CI -0.03 to 0.03, one trial, 590 infants - Analysis 1.6) or in the number of infants small-for-gestational age (RR1.13, 95% CI 0.90 to 1.42, six trials, 3649 infants - Analysis 1.7).

No significant differences were seen between treatment groups for the other primary outcomes:

- *severe lung disease* (average RR 0.78, 95% CI 0.50 to 1.20, I^2 = 56%, Tau^2 = 0.09 random-effects, four trials, 3356 infants - Analysis 1.2);
- *fetal and neonatal mortality* (RR 0.85, 95% CI 0.61 to 1.19, seven trials, 4082 infants - Analysis 1.8);
- *chronic lung disease* (RR 1.18, 95% CI 0.88 to 1.59 six trials, 3923 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 0.88, 95% CI 0.64 to 1.21, four trials, 1595 infants - Analysis 1.12).

Primary outcomes for the child

Data from early childhood follow-up were available for inclusion from two trials (Murphy 2008; Wapner 2006).

No significant differences between treatment groups when treatment was given of greater than 12 mg to 24 mg or less of betamethasone for *total deaths* (RR 1.04, 95% CI 0.72 to 1.50, two trials, 2898 infants - Analysis 1.65); *survival free of any disability to early childhood follow-up* (RR 1.00, 95% CI 0.97 to 1.03, one trial, 2104 infants - Analysis 1.66); and *composite serious outcome at childhood follow-up* (RR 1.01, 95% CI 0.81 to 1.25, one trial, 2104 infants - Analysis 1.70), defined in Murphy 2008 as death or any neurologic impairment.

Primary outcomes for the women

No statistically significant differences were seen for women treated with repeat dose(s) of prenatal corticosteroids of greater than 12 mg to 24 mg or less of betamethasone compared with women not given repeat corticosteroids for the two outcomes of maternal infectious morbidity of *chorioamnionitis* and *puerperal sepsis.*

Planned treatment with repeat dose(s) of corticosteroid greater than 24 mg or more of betamethasone or equivalent compared with placebo/no treatment

No data have been reported on this subgroup.

(3.7). Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the planned repeat drug exposure per week (12 mg/week or less of betamethasone or equivalent, greater than 12 mg/week to 24 mg/week of betamethasone or equivalent, greater than 24 mg/week or more of betamethasone or equivalent). Trials only included if able to give multiple trial treatments.

Planned treatment with repeat dose(s) of corticosteroid of 12 mg/week or less of betamethasone or equivalent compared with placebo/no treatment

The planned repeat drug exposure per week was 12 mg/week or less of betamethasone or equivalent for two trials (Crowther 2006; Murphy 2008). Women were eligible for inclusion seven or more days after a pre-trial course in Crowther 2006 and between 14 to 21 days after a pre-trial course in Murphy 2008. The eligible gestational age at trial entry was similar being less than 32 weeks in Crowther 2006 and 25 to 32 weeks in Murphy 2008. A course of study treatment consisted of one 12 mg injection of betamethasone repeated weekly if still at risk up to less than 32 weeks' gestation in Crowther 2006 and two 12 mg betamethasone injections repeated every 14 days up to 33 weeks' gestation in Murphy 2008.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid where the planned repeat drug exposure per week was 12 mg/week or less of betamethasone compared with placebo was associated with a reduction the risk of RDS, in the one trial that reported data:

- RDS (RR 0.79, 95% CI 0.68 to 0.92, one trial, 1144 infants - Analysis 1.1).

Significant heterogeneity was seen for all the other primary outcomes except fetal and neonatal mortality where data were reported from both trials. No significant differences were seen between treatment groups for the other primary outcomes:

- severe lung disease (average RR 0.80, 95% CI 0.42 to 1.51, I^2 = 90%, Tau^2 = 0.19 random-effects, two trials, 3448 infants - Analysis 1.2);
- composite serious outcome (average RR 0.89, 95% CI 0.67 to 1.18, I^2 = 70%, Tau^2 = 0.03 random-effects not shown in forest plot two trials, 3448 infants - Analysis 1.3);
- fetal and neonatal mortality (RR 1.01, 95% CI 0.73 to 1.40, two trials, 3450 infants - Analysis 1.8);
- chronic lung disease (average RR 1.14, 95% CI 0.67 to 1.95, I^2 = 52%, Tau^2 = 0.09 random-effects not shown in forest plot, two trials, 3448 infants - Analysis 1.11);
- intraventricular haemorrhage (RR 0.89, 95% CI 0.57 to 1.38, one trial, 1144 infants - Analysis 1.12);
- birthweight (average MD -57.89 g, 95% CI -159.49 to 43.71, I^2 = 49%, Tau^2 = 2628.81 random-effects not shown in forest plot, two trials, 3448 infants - Analysis 1.4);
- birthweight Z score (MD -0.13, 95% CI -0.26 to 0.00, one trial, 1144 infants - Analysis 1.5);
- small-for-gestational age at birth (RR 1.06,95% CI 0.75 to 1.50, one trial, 2304 infants - Analysis 1.7).

Primary outcomes for the child

At early childhood follow-up two trials reported data (Crowther 2006; Murphy 2008). No significant differences were seen between treatment groups for any of the primary outcomes when the planned repeat drug exposure per week was 12 mg/week or less of betamethasone compared with placebo:

- *total deaths up to early childhood follow-up* (RR 0.98, 95% CI 0.72 to 1.33, two trials, 3450 - Analysis 1.65);
- *survival free of any disability* (RR 1.00, 95% CI 0.97 to 1.04, two trials, 3164 infants - Analysis 1.66);
- *survival free of any major disability* (average RR 1.04, 95% CI 0.99 to 1.10, one trial, 1060 infants - Analysis 1.67);
- *any disability at childhood follow-up* (RR 0.98, 95% CI 0.83 to 1.16, one trial, 999 infants - Analysis 1.69);
- *major disability at childhood follow-up* (RR 0.77, 95% CI 0.55 to 1.08, one trial, 999 infants - Analysis 1.68);
- *composite serious outcome at childhood follow-up* (RR 0.99, 95% CI 0.87 to 1.12, two trials, 3164 infants - Analysis 1.70), defined in Crowther 2006 as death or any neurosensory disability; and defined in Murphy 2008 as death or any neurologic impairment.

Primary outcomes for the women

No statistically significant differences were seen for women treated with repeat dose(s) of prenatal corticosteroids for the two outcomes of maternal infectious morbidity when the planned repeat drug exposure per week was 12 mg/week or less of betamethasone compared with placebo:

- *chorioamnionitis* (RR 1.08, 95% CI 0.77 to 1.51, two trials, 2835 women - Analysis 1.15);
- *puerperal sepsis* (RR 1.34, 95% CI 0.80 to 2.22, one trial, 1853 women - Analysis 1.16).

Planned treatment with repeat dose(s) of corticosteroid of greater than 12 mg/week to 24 mg/week or less of betamethasone or equivalent compared with placebo/no treatment

The planned repeat drug exposure per week was greater than 12 mg/week to 24 mg/week or less of betamethasone or equivalent for five trials (Aghajafari 2002; Guinn 2002; Mazumder 2008; McEvoy 2002; Wapner 2006).

Women were eligible for inclusion seven or more days after a pre-trial course in four trials (Aghajafari 2002; Guinn 2002; Mazumder 2008; McEvoy 2002) and between seven and 10 days after a pre-trial course in Wapner 2006.

The upper gestational age at trial entry varied between the trials: being up to 30 weeks in Aghajafari 2002, less than 32 weeks in Wapner 2006, and less than 33 weeks in Guinn 2002, Mazumder 2008 and McEvoy 2002.

In all five trials a planned treatment course was two doses of 12 mg/dose betamethasone repeated at weekly intervals up to 33 weeks in Aghajafari 2002, until less than 34 weeks in Wapner 2006 and until 34 weeks in Guinn 2002, Mazumder 2008 and McEvoy 2002.

Primary outcomes for the infant

Treatment with repeat dose(s) of corticosteroid, where the planned repeat drug exposure per week was greater than 12 mg/week to 24 mg/week or less of betamethasone, compared with placebo was associated with a reduction in the risk of severe lung disease, composite serious outcome and fetal and neonatal mortality:

- *severe lung disease* (average RR 0.62, 95% CI 0.44 to 0.87, random-effects, three trials, 1052 infants - Analysis 1.2);
- *composite serious outcome* (average RR 0.77, 95% CI 0.60 to 0.99, random-effects, four trials, 1088 infants - Analysis 1.3);
- *fetal and neonatal mortality* (RR 0.51, 95% CI 0.26 to 1.00, four trials, 1089 infants - Analysis 1.8).

No significant heterogeneity was seen for the other primary outcomes reported. No significant differences were seen between treatment groups for the other primary clinical outcomes. Although mean birthweight was lower in exposed infants compared with unexposed infants there was no difference in the risk of being small-for-gestational age or birthweight multiples of the median:

- *RDS* (RR 0.86, 95% CI 0.68 to 1.10, four trials, 1068 infants - Analysis 1.1);
- *chronic lung disease* (RR 0.97, 95% CI 0.65 to 1.44, four trials, 1068 infants - Analysis 1.11);
- *intraventricular haemorrhage* (RR 0.95, 95% CI 0.64 to 1.40, three trials, 1017 infants - Analysis 1.12);
- *birthweight* (MD -110.62 g, 95% CI -199.49 to -21.74, four trials, 1184 infants - Analysis 1.4);
- *small-for-gestational age at birth* (RR 1.29,95% CI 0.88 to 1.90, four trials, 792 infants - Analysis 1.7);
- *birthweight multiples of the median* (MD 0.00, 95% CI -0.03 to 0.03, one trial, 590 infants - Analysis 1.6).

Primary outcomes for the child

At early childhood follow-up one trial reported data (Wapner 2006). No significant differences were seen between treatment groups for the only primary outcome with data when the planned repeat drug exposure per week was greater than 12 mg/week to 24 mg/week or less of betamethasone compared with placebo:

- *total deaths up to early childhood follow-up* (RR 1.15, 95% CI 0.39 to 3.38, one trial, 594 infants - Analysis 1.65).

Primary outcomes for the women

No statistically significant differences were seen for women treated with repeat dose(s) of prenatal corticosteroids for the two outcomes of maternal infectious morbidity when the planned repeat drug exposure per week was greater than 12 mg/week to 24 mg/week or less of betamethasone compared with placebo:

- *chorioamnionitis* (RR 1.35, 95% CI 0.96 to 1.88, three trials, 989 women - Analysis 1.15);
- *puerperal sepsis* (RR 0.76, 95% CI 0.42 to 1.36, three trials, 989 women - Analysis 1.16).

Planned treatment with repeat dose(s) of corticosteroid greater than 24 mg/week or more of betamethasone or equivalent compared with placebo or no treatment

No data have been reported on this subgroup.

(3.8) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the method of administration (intramuscular, intravenous, oral)

No data have been reported on these subgroups to date. All the included trials used intramuscular injection as the method of administration of the treatment.

(3.9) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by the gestational age at entry to the trial

No data have been reported on these subgroups to date.

DISCUSSION

Summary of main results

A total of 4733 women (5700 babies) were randomised into trials comparing women given repeat dose(s) of prenatal corticosteroids seven or more days after an initial course with women not receiving repeat corticosteroids after an initial course of prenatal corticosteroids seven or more days earlier. The use of repeat dose(s) of corticosteroid for women at risk of preterm birth reduced the risk of neonatal respiratory distress syndrome (RDS) by 17% (number needed to treat to benefit (NNTB) 17 (95% CI 11 to 32) women; 60 fewer babies with RDS per 1000 women treated) with a similar reduction, 16%, in the risk of serious infant outcome (NNTB 30 (95% CI 19 to 79) women; 33 fewer babies with a serious health outcome per 1000 women treated). These are clinically important neonatal benefits and there is clear evidence that repeat doses leads to a reduction in the use of mechanical ventilation, less need for oxygen supplementation, less inotropic support treatment, less use of surfactant and a reduced risk of a patent ductus arteriosus. No substantive effect was seen on fetal or neonatal mortality or for total mortality at early childhood follow-up.

The reduction in risk of RDS and/or composite serious neonatal outcomes was consistent across most of the planned subgroups providing data (timing of repeat corticosteroid treatment seven days or less, or 14 days or more; planned number of doses only one; dose per treatment 12 mg or less, or more than 12 mg to 24 mg or less betamethasone; or dose per week).

In contrast to these clinical benefits, at birth, infants exposed to repeat corticosteroids compared with infants not exposed to repeat corticosteroids had a reduction in some measures of growth (mean weight, mean length and mean head circumference, head circumference Z scores, length multiples of the mean), although not in Z scores for weight or length, or multiples of the median for weight, or in the risk of being small-for-gestational age. By the time of discharge from hospital after birth and at later childhood follow-up, no differences were seen between children exposed to repeat prenatal corticosteroids and those not exposed for weight, head circumference and height. Measures of body size are dependant on gestational age at birth and without adjustment for gestational age, as in Z scores or multiples of the mean/median, it is not possible to fully assess the effects repeat prenatal corticosteroid treatment may have on fetal growth.

In the update of this review in 2011, data from early childhood follow-up were added from four trials. These data show no substantive differences in children exposed to repeat prenatal corticosteroids compared with unexposed children for survival or neurosensory disability at 18 months to two years' corrected age, childhood behaviour, or general health. Further information from one existing trial on outcome in early childhood is awaited (Mazumder 2008). The evidence available provides some reassurance about the health of the infants into early childhood when repeat prenatal corticosteroids are used for women at risk of preterm birth. However, there are as yet no information on the health, neurodevelopmental, growth, cardiovascular and metabolic status in later childhood, adulthood to assess the long-term significance of the observed neonatal clinical benefits or the effects on anthropometric assessments observed at birth. Such information will be needed to assess overall benefits and risks of using repeat prenatal corticosteroids for women at risk of preterm birth. Several trials have conducted later assessment of their children (Crowther 2006 - early school-age follow-up at six to eight years' corrected age; and Murphy 2008 - childhood follow-up at five years of age) and publications arising will be included in the next update of this review.

For the women, there was no increase in infectious morbidity of chorioamnionitis or puerperal sepsis, and the likelihood of a caesarean birth was unchanged providing some reassurance about the safety of repeat prenatal corticosteroid treatment for the mothers. There was significant heterogeneity for the trials reporting on side effects with no differences overall for women reporting any side effects. Although few women reported insomnia (2.3% in the repeat prenatal corticosteroid group, 0.8% in the non repeat corticosteroid group), this was more likely for women treated with repeat prenatal corticosteroids. Reduction in bruising at the injection site was reported in one trial for women given repeat corticosteroid injections compared with placebo.

Overall completeness and applicability of evidence

Women in these trials have been recruited in a range of countries and settings. The trials were all conducted at either tertiary or provincial hospitals, but apart from one trial, they were conducted

in high-income countries. The results are considered applicable to hospital settings worldwide. Betamethasone has been the only corticosteroid evaluated in randomised trials of repeat prenatal corticosteroids prior to preterm birth. Dexamethasone is often used because it is less expensive and often more easily available, particularly in low- to middle-income countries. It is uncertain whether the effects seen for betamethasone would be the same for dexamethasone. Appropriate trials are needed.

There has been no cost-effectiveness analysis of the use of repeat prenatal corticosteroids for women at risk of preterm birth seven or more days after initial corticosteroid treatment.

Quality of the evidence

The quality of the studies included in this review ranged from moderate to excellent. Of the 10 included trials, all are recent publications of moderate to high methodological quality. All had adequate allocation concealment, all except one used a placebo, and losses to follow-up to the time of primary hospital discharge after birth were nil or minimal. At early childhood follow-up losses to follow-up in the three trials that have reported data ranged between 7.5% and 21.2%.

Potential biases in the review process

The evidence for this review is derived from studies identified from a detailed, systematic search process without language restriction. It is possible (but unlikely) that additional trials comparing the use of repeat corticosteroids prior to preterm birth versus placebo or no treatment have been published but not identified. It is also possible that there are other studies, additional to those of which we are aware, that have been conducted but are not yet published. Should any such studies be identified, we will include them in future updates of this review.

Two of the review authors (CAC, JEH) were investigators for the ACTORDS trial (Crowther 2006). Data extraction for this trial was performed by the other review authors (PM and CM).

Agreements and disagreements with other studies or reviews

Since the update of this review in 2011, further follow-up data from the Crowther 2006 (two publications), McEvoy 2010 (one publication) and Murphy 2008 (two publications) have been published adding to the evidence base assessing whether repeat dose(s) of prenatal corticosteroids improve fetal lung maturation, and thereby reduce infant morbidity and mortality. This systematic review presents strong evidence that repeat dose(s) of prenatal corticosteroid for women at risk of preterm birth provides significant clinical benefits in the short term for the infant and is not associated with any evidence of any effect on benefit or harm for either the woman or the child at early childhood follow-up.

AUTHORS' CONCLUSIONS

Implications for practice

The short-term benefits seen for babies support the use of repeat dose(s) of prenatal corticosteroids for women who have received an initial course of prenatal corticosteroids seven of more days previously and who remain at risk of preterm birth.

Repeat dose(s) of prenatal corticosteroids given to women at risk of preterm birth, compared to no repeat treatment, reduce the occurrence of respiratory distress syndrome (RDS) by 17% and the risk of serious health problems in the first few weeks of life for the infant by 16%. For one baby to benefit by not developing RDS, 17 women (95% CI 11 to 32) would need to be treated with repeat prenatal corticosteroids. The number needed to treat to benefit (NNTB) for serious neonatal outcome is 30 women (95% CI 19 to 79). At birth the neonatal benefits are associated with a reduction in some measures of mean body size (mean weight, head circumference and length), although not for anthropometric assessments that adjusted for gestational age. These differences in body size measurements are no longer seen by hospital discharge in the two trials that report data. The limited evidence available from early childhood reassuringly shows no significant harm, although no benefit. No differences are seen in mortality, neurodisability or childhood weight, head circumference or height. There is insufficient evidence on the longer-term benefits and risks.

Corticosteroids should be available in all hospitals providing care for women at risk of preterm birth (Roberts 2006). Repeat prenatal corticosteroids should be considered for women who have received a course of prenatal corticosteroids seven or more days previously, and who remain at risk of preterm birth before 34 weeks' gestation. Women eligible for repeat prenatal corticosteroid treatment should be informed of the known benefits and risks and counselled about the available but limited information about childhood health outcomes. Until clearer information is available on optimal dose of treatment, and frequency of administration it would seem prudent to use a treatment regimen of one of the trials reporting neonatal benefit.

Implications for research

Further information is awaited from one existing trial on outcome in early childhood (Mazumder 2008). There are still no data published for later childhood or adulthood on health, neurodevelopmental, growth, cardiovascular and metabolic status. Such information is needed to assess overall benefits and risks of using repeat

prenatal corticosteroids for women at risk of preterm birth. Several trials have completed later assessment of their children (Crowther 2006 - early school-age follow-up at six to eight years' corrected age; and Murphy 2008 - childhood follow-up at five years of age). Data from these later assessments will be included in the next planned update of this review.

We are aware of three other trials of repeat prenatal corticosteroids for women at risk of preterm birth. One trial from the UK stopped recruitment and publication is awaited (TEAMS 1999); one trial in women with preterm prelabour rupture of the membranes has only been published in abstract form with data not suitable for inclusion in the meta-analysis (Sobhrabvand 2001); and one trial from Iran is awaiting classification to establish its eligibility for inclusion. We are awaiting a response from the authors (Atarod 2014).

Individual patient data meta-analysis using the existing trials is ongoing and may clarify how to maximise benefit and minimise harm using factors relating to the women (*reasons the woman was considered at risk of preterm birth*), her pregnancy (*number of babies in-utero, gestational age repeat prenatal corticosteroid treatment was given, time prior to birth repeat prenatal corticosteroid treatment was given*), and *drug frequency and dosage (*Crowther 2012).

Further trials are difficult to justify until the results of the individual patient data meta-analysis are available. Any further trials of repeat dose(s) of prenatal corticosteroids for women who remain at risk of preterm birth after a course of corticosteroids should be of high quality; be large enough to assess mortality and serious morbidity; consider comparing different corticosteroid preparations (all trials to date have used betamethasone for repeat treatment); provide further evaluation of the times between repeat courses; evaluate the optimal amount of corticosteroid given at each course; provide data on all relevant maternal and infant outcomes; ensure assessment of neurodevelopmental status of the child at follow-up and organise assessment of longer-term outcomes including behaviour, educational achievement, cardiovascular status, bone density, hypothalamic-pituitary-adrenal axis function, glucose intolerance and lung function.

Cost-effectiveness analysis of the use of repeat corticosteroids should be conducted.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

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

Aghajafari 2002

Methods	Type of study: randomised trial. Small pilot study to determine the feasibility of a larger trial
Participants	Location: 2 hospitals in Toronto, Canada. Timeframe: September 1999-August 2000. Eligibility criteria: women at 24-30 weeks' gestation at continued increased risk of preterm birth who remained undelivered 7 or more days following a single course of antenatal corticosteroids (defined as 2 doses of 12 mg/dose intramuscular betamethasone, given at 12- or 24-hour intervals; or 4 doses of 5-6 mg/dose intramuscular dexamethasone, given at 12-hour intervals. To be at increased risk of preterm birth, women had to have 1 or more of the following: regular uterine contractions; a shortened cervical length or cervical dilatation; preterm prelabour rupture of the membranes; antepartum bleeding secondary to placental separation or placenta praevia; history of preterm birth; maternal hypertension; other medical condition increasing the risk of preterm delivery or intrauterine growth restriction; or other fetal conditions increasing the risk of preterm delivery. Gestational age range: 24-30 weeks. Exclusion criteria: women were excluded if they required chronic doses of corticosteroids secondary to medical conditions, had a contra-indication to corticosteroids, had clinical evidence of chorioamnionitis, or of their fetus(es) had a known lethal congenital anomaly. Total recruited: 12 in total: 6 in the multiple course of antenatal corticosteroid group and 6 in the placebo group
Interventions	Multiple course of antenatal corticosteroid group: a weekly course of betamethasone (2 doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Canada Inc) intramuscularly, 24 hours apart) until 33 weeks or delivery if the woman remained at increased risk of preterm birth. In the placebo group: a weekly course of placebo consisting of 2 doses of normal saline, intramuscularly 24 hours apart, until 33 weeks or birth if the woman remained at increased risk of preterm birth
Outcomes	Outcomes: rate of recruitment over 12-month period, risk of complications requiring discontinuation of study treatment, concentrations of plasma cortisol and ACTH in cord blood and in maternal blood immediately following birth. Perinatal or neonatal mortality or significant neonatal morbidity, defined as one or more of the following: stillborn or neonatal death during the first 28 days of life or prior to hospital discharge, whichever was sooner; respiratory distress syndrome; BPD (requiring oxygen at 36 corrected postnatal gestational age); IVH (grade 3 or 4; and necrotising enterocolitis
Funding Support	Funding: support from Canadian Institutes of Health Research Senior Scientist Award
Notes	Sample-size calculation: no.

Aghajafari 2002 (*Continued*)

Risk of bias		
Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Randomisation sequence was computer-generated and was centrally controlled by 1 pharmacist at each hospital who kept the randomisation code Stratification: by gestational age (24-27 weeks; 28-30 weeks) and by hospital using block sizes of 2
Allocation concealment (selection bias)	Low risk	Method of treatment allocation: 1 pharmacist at each hospital who kept the randomisation code
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The injection of the study treatment was given by a designated research nurse in each hospital who was not caring for the woman. Placebo of normal saline was used. The physical appearance of the study solutions had to be kept masked since the betamethasone is opaque, while saline is clear. To minimise unblinding, the pharmacist prepared the study treatments in a syringe covered with yellow tape
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	No losses to follow-up reported. Intention-to-treat analyses: yes.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported.
Other bias	Low risk	The study appears to be free of other sources of bias.

Crowther 2006

Methods	Type of study: ACTORDS randomised controlled trial.
Participants	Location: 23 hospitals in Australia and New Zealand. Timeframe: April 1998 to July 2004. Included: single, twin or triplet pregnancy at less than 32 weeks' gestation if women had received an initial treatment of corticosteroid 7 or more days previously and their responsible clinician regarded them to be at continued risk of preterm birth, and there

	was no contraindication to further corticosteroid therapy. Exclusion criteria: in second stage of labour, had chorioamnionitis needing urgent delivery, or if further corticosteroid therapy was judged to be essential. Gestational age recruited up to less than 32 weeks. Total recruited 982 women (1146 babies). 489 women in the repeat corticosteroid group and 493 women in the placebo group
Interventions	Repeat corticosteroids: 11.4 mg Celestone Chronodose (as 7.8 mg betamethasone sodium phosphate and 6 mg betamethasone acetate. Placebo: saline intramuscular injection. Every week, if the woman remained undelivered and less than 32 weeks' gestation, and the responsible clinician regarded her as at continued risk of preterm birth, a further treatment pack from the same treatment group was allocated by the telephone randomisation service
Outcomes	To time of primary hospital discharge: primary outcomes: frequency and severity of RDS (defined as clinical signs of respiratory distress and a ground-glass appearance on chest radiograph); weight, length and head circumference at birth and primary discharge from hospital. Secondary outcomes included clinical chorioamnionitis (defined as requiring intrapartum antibiotics); maternal postpartum pyrexia (38.0 degrees Centrigrade or greater); any side effects of the injection for the mother and other measures of neonatal morbidity. Composite outcome was post hoc (defined as one of air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks' post menstrual age, severe IVH (grade 3 or 4), periventricular haemorrhage, proven necrotising enterocolitis, or retinopathy of prematurity) For the early childhood follow-up at 2 years' corrected age: primary outcomes: survival at 2 years' corrected age free of major neurosensory disability, defined as survival free of moderate to severe disability. Body size (weight, height and head circumference). Secondary outcomes were general health, including the use of health services since primary hospital discharge; respiratory morbidity; blood-pressure; child behaviour; incidence of neurosensory impairments and disabilities; total number of deaths by 2 years of corrected age; and the combined adverse outcome of death or any neurosensory disability at 2 years' corrected age
Funding Support	Funding: Australian National Health and Medical Research Council, The Channel 7 Research Foundation of South Australia, The Women's and Children's Hospital Research Foundation, Adelaide, and The Department of Obstetrics and Gynaecology, The University of Adelaide, South Australia
Notes	Sample-size calculation: yes. 980 women needed to detect a 25% reduction in the risk of respiratory distress syndrome form 30% to 22.5% with 80% power and a 2-sided significance level of 5%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Random-number sequence generated by computer with variable block sizes and stratification by centre, gestational age and

Crowther 2006 (*Continued*)

		number of fetuses
Allocation concealment (selection bias)	Low risk	Method of treatment allocation: central telephone randomisation
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Normal saline placebo was used. Study treatment packs and study syringes identical appearance (opaque study-labelled syringe)
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the follow-up at 2 years' corrected age: staff making the assessments and the families "were unaware of group assignment."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up to time of primary hospital discharge: none Losses to follow-up to time of 2 year corrected age assessment: 38 survivors (4%) had no paediatric assessment, 18 in the repeat corticosteroid group and 20 in the placebo group; 86 (8%) had no psychological tests, 44 in the repeat corticosteroid group and 42 in the placebo group Intention-to-treat analyses: yes.
Selective reporting (reporting bias)	Low risk	All expected outcomes reported. No obvious risk of selective reporting
Other bias	Low risk	No other obvious risk of bias identified. Pre-specified that analyses would be adjusted for gestational age at trial entry and for prognostic variables with imbalance (antepartum haemorrhage and preterm, prelabour rupture of the membranes)

Garite 2009

Methods	Type of study: randomised placebo-controlled trial.
Participants	Location: 15 private and 3 university centres, USA. The participants were largely private/non-goverment funded Time frame: May 2003 to February 2008. Included: women with singleton or twin pregnancies from 25 weeks' to less than 33 weeks' gestation who had received a course of betamethasone 14 or more days previously and who were judged to have recurrent or continued risk of preterm birth Exclusion criteria: major fetal anomaly, cervical dilatation 5 cm or more, higher order multiples, ruptured membranes, documented lung maturity, receiving corticosteroids for other indications, human immunodeficiency virus infection or active tuberculosis

Garite 2009 (*Continued*)

	Total recruited: 437 women (223 repeat corticosteroid, 214 placebo). 577 infants were enrolled (289 repeat corticosteroid, 288 placebo), although 1 fetal twin in the corticosteroid group died before randomisation
Interventions	Repeat corticosteroid: a single course of intramuscular betamethasone given as 2 doses of 12 mg, 24 hours apart (preparation not specified) Placebo: a similarly administered saline intramuscular injection In some centres betamethasone became unavailable and was replaced with dexamethasone 6 mg intramuscularly, 4 doses, every 12 hours. 31 women received dexamethasone and 30 women received an equivalent placebo
Outcomes	Primary outcome: composite neonatal mortality/morbidity in babies born before 34 weeks' gestation. The composite outcome was defined as 1 or more of: perinatal death (defined as stillbirth or death before neonatal discharge); RDS (oxygen requirement, clinical diagnosis and consistent chest radiograph); BPD (defined as a requirement for oxygen at 30 days of age); severe IVH (grades 3 or 4); PVL; blood culture-proven sepsis; or necrotising enterocolitis (not defined) Secondary outcomes: preterm birth before 34 weeks' gestation; RDS; gestational age at birth; small-for-gestational age (< 10th percentile); head circumference; birthweight; surfactant therapy; pneumothorax; maternal infectious morbidity
Funding Support	Funding: Pediatrix Medical Group.
Notes	Sample-size calculation: yes, based on a 40% reduction in the primary outcome, which was estimated to be 28% in the control group. The planned sample size was 217 women in each arm (2 tailed alpha 0.05, beta 0.2)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	A "blocked randomisation sequence" was used that was "prepared centrally". Although not described in the paper, the study protocol states that the random sequence was generated by computer
Allocation concealment (selection bias)	Low risk	The research pharmacist (unblinded) at each site prepared the medication based on the blocked randomisation sequence
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Normal saline placebo was used. The study syringes (betamethasone or saline) were completely covered by a label to conceal the contents
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.

Incomplete outcome data (attrition bias) All outcomes	Low risk	Neonatal data were unavailable on 13 babies in the repeat corticosteroid group and 6 babies in the placebo group. No reason was given for the missing data and no sensitivity analysis was performed. Data were missing for some of the secondary outcomes in a few participants (for example BPD missing data for 2 babies in the repeat corticosteroid group and 3 in the placebo group; and similarly for PVL, missing data for 6 versus 9 babies) Intention-to-treat analysis was performed on babies with known outcomes
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No other obvious risk of bias identified.

Guinn 2002

Methods	Type of study: randomised controlled trial.
Participants	Location: 13 academic centres in USA. Timeframe: February 1996-April 2000. Eligibility criteria: 502 women (502 babies) at 24 weeks to < 33 weeks' gestation at high risk of preterm birth who remained undelivered 1 week following an initial course of antenatal corticosteroids (defined as 2 doses of 12 mg/dose intramuscular betamethasone, repeated at 24 hours; or 4 doses of 6 mg/dose intramuscular dexamethasone, given at 12 hour-intervals. To be at high risk of preterm birth qualifying criteria were: preterm labour with intact membranes (either a history of regular uterine contractions associated with cervical dilatation of > 2 cm and effacement > 80% in a nulliparous participant or cervical dilatation of > 3 cm and > 80% effacement in a multiparous participant at the time of presentation: or regular uterine contractions with documented cervical change); preterm premature rupture of the membranes (rupture of the membranes occurring > 1 hour prior to the onset of preterm labour); maternal medical illness (pre-eclampsia, hypertension, diabetes, renal disease, systemic lupus erythematosus, trauma); or suspected fetal jeopardy (intrauterine growth restriction < 10th percentile, oligohydramnios, abnormal antepartum testing, progression of a fetal anomaly compatible with like, twin-twin transfusion syndrome). Gestational age range: 24 weeks to < 33 weeks' gestation. Exclusion criteria: women were excluded if they required immediate delivery, there were fetal anomalies incompatible with life, documented fetal lung maturity, and maternal active tuberculosis or human immunodeficiency virus infection. Total recruited: 502-256 in the weekly-course group and 246 in the single-course group
Interventions	In the weekly-course group: a weekly course of betamethasone (2 doses of 12 mg/dose betamethasone repeated after 24 hours, intramuscularly), until 34 weeks or birth whichever came first.

Guinn 2002 (*Continued*)

	In the single-course group: a similarly administered placebo
Outcomes	Primary outcomes: composite neonatal morbidity defined as presence of any of the following: severe RDS, BPD, severe IVH, PVL, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge. Secondary outcomes: frequency and severity of RDS; need for and duration of oxygen therapy; need for and duration of ventilatory support; BPD (defined as need for oxygen > 21% and usually ventilatory therapy for at least 28 days of life; in cases were no additional ventilatory support was needed but oxygen was required, chest radiographs consistent with BPD were used; in the case of neonatal death, BPD was diagnosed on autopsy findings); severe IVH was defined as intraventricular bleeding with dilatation of the cerebral ventricles (grade 3) or parenchymal haemorrhage (grade 4), as diagnosed with an imaging technique or autopsy, PVL was defined as the presence of more than 1 obvious hypoechoic cyst in the periventricular white matter; necrotising enterocolitis (defined as proven); proven sepsis; perinatal death defined as death of a fetus or neonate at any time between randomisation and nursery discharge
Funding Support	Funding: March of Dimes grant, the Berlex Foundation, the Wisconsin Perinatal Association, the Perinatal Clinical Research Center at the University of Colorado Health Sciences Center (grant from the General Clinical Research Centers Program, National Centers for Research Resources, National Institutes of Health), and the participating departments
Notes	Sample-size calculation: yes. A sample of 1000 women was required to have a 90% power to detect a one-third reduction in composite morbidity from 25.0% to 16.5% (2-tailed alpha = 0.05). 2 interim analyses were planned for efficacy and safety. Recruitment was stopped early based on safety concerns

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Computer-generated randomisation logs prepared centrally and distributed to the research pharmacist at each clinical site. Stratification: by centre
Allocation concealment (selection bias)	Low risk	Method of treatment allocation: participants were assigned by the pharmacy to a treatment group
Blinding of participants and personnel (performance bias) All outcomes	Low risk	The placebo syringes were indistinguishable from the syringes containing betamethasone. Patients and healthcare workers were blinded to study group
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported

Guinn 2002 (*Continued*)

Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses: yes. Losses to follow-up: 16 women and 1 neonate were lost to follow-up. Partial data were available for participants who were lost to follow-up. In some cases the investigators were able to ascertain the birth date, weight, and health status for the neonate. The denominators presented very slightly from 1 variable to another because of missing data
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	High risk	After the first interim analysis when 308 women have been randomised the decision was made to stop recruitment at 500 women, because of "safety concerns" and the finding of only a marginal difference in short-term outcomes between treatment groups

Mazumder 2008

Methods	Type of study: open-label, randomised trial.
Participants	Location: tertiary hospital in northern India. Time frame: August 2004 onwards. Included: mothers from 26 to 33 weeks' gestation who were at risk of preterm birth and who had received a course of betamethasone 7 or more days previously. Mothers had to be available for follow-up every week until birth Exclusion criteria: unreliable gestational age, frank chorioamnionitis, and major fetal malformation Total recruited: 76 mothers (38 repeat corticosteroid, 38 control). 83 babies were born to 75 mothers but only the first born of multiple pregnancies were assessed (37 repeat corticosteroid, 38 control)
Interventions	Repeat corticosteroid: betamethasone 12 mg intramuscularly, 2 doses, 24 hours apart. The course was repeated every 7 days until delivery or the end of the 33rd week of gestation Control: no intervention.
Outcomes	Primary outcome: severe RDS. RDS was defined as respiratory distress within 6 hours of birth in a preterm infant with either a negative gastric shake test or a typical chest radiograph. Severe RDS was defined as requiring mechanical ventilation for at least 12 hours. Mechanical ventilation was started in infants with hypoxaemia ($Pa0_2$ < 50 mmHg) or hypercapnic acidosis ($PaC0_2$ > 50mmHg with pH < 7.25) or worsening acidosis or clinically worsening respiratory fatigue/apnoea/work of breathing despite continuous positive airway pressure (maximum 8 cm water pressure)

	Secondary outcomes: RDS; IVH; necrotising enterocolitis (not defined); patent ductus arteriosus (not defined); BPD (not defined), sepsis (not defined), retinopathy of prematurity, stillbirth and neonatal death, weight, length and occipital-frontal circumference at birth and at 6 months' corrected age, and body size and development (evaluated by the Denver Development Screening Test II) at 6 months' corrected age
Funding Support	None.
Notes	Sample-size calculation: yes, based on a reduction in severe RDS from an estimated 33% in the control group to 6% in the repeat corticosteroid group (2 tailed alpha 0.05, beta 0.2). The planned sample size was 70 (35 women in each arm)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Website-generated random number list.
Allocation concealment (selection bias)	Low risk	Participants were "randomised" to receive by a process of simple randomisation. "Slips bearing the random allocation" (generated from the random number list) "were placed in opaque envelopes, sealed and numbered serially on the outside"
Blinding of participants and personnel (performance bias) All outcomes	High risk	Placebo not used so no blinding of participants or staff.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	One mother in the repeat corticosteroid group was lost to follow-up before birth. Outcomes were recorded only for the first-born of multiple pregnancies. Intention-to-treat analysis was performed on babies with known outcomes. Neonatal outcomes reported on 75 (99%) infants, 37 in the repeat corticosteroid group and 38 in the control group. Infant outcomes reported to date for 44 (58%) infants, 21 in the repeat corticosteroid group and 23 in the control group

Mazumder 2008 (*Continued*)

Selective reporting (reporting bias)	Unclear risk	Insufficient detail to permit judgement. Outcomes specified in the research methods reported
Other bias	Low risk	No other obvious risk of bias identified.

McEvoy 2002

Methods	Type of study: randomised trial.
Participants	Location: single centre in USA (Sacred Heart Hospital, University of Florida, Pensacola, Florida). Timeframe: 3-year period ending in December 1999. Eligibility criteria: women at 25-33 weeks' gestation who remained undelivered 1 week after a single course of antenatal corticosteroids (defined as 2 doses of 12 mg/dose intramuscular betamethasone), given because of increased risk of preterm delivery. Gestational age range: 25-33 weeks. Exclusion criteria: women were excluded if they were insulin-dependent diabetics, had a drug-addiction, or fetus had a known lethal congenital anomaly. Total recruited: 37 women (37 babies). 18 women in the repetitive courses of antenatal corticosteroid group and 19 women in the single course remote group
Interventions	In the repetitive courses of antenatal corticosteroid group: a weekly course of betamethasone (2 doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, until birth or 34 weeks' gestation. In the single-course remote group: weekly courses of placebo intramuscularly, until 34 weeks or birth
Outcomes	Primary outcomes: functional residual capacity, respiratory compliance. Secondary outcomes: admission head circumference, surfactant administration, days on oxygen, and mechanical ventilation
Funding Support	American Lung Association.
Notes	Sample-size calculation: yes. Based on 37 women the average functional residual capacity in the single course remote group is not > 12% smaller than the functional residual capacity in the repetitive group (P = 0.05, power 80%)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Group assignment done through pharmacy using a randomisation table. Stratification: none stated
Allocation concealment (selection bias)	Low risk	Method of treatment allocation: "group assignment done through pharmacy using a randomisation table.

McEvoy 2002 (*Continued*)

		" "The study medication was prepared by the pharmacy." Stratification: none stated.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Investigators and clinical care providers were unaware of the treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: none stated. Intention-to-treat analyses: yes
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No other obvious risk of bias detected.

McEvoy 2010

Methods	Type of study: randomised trial.
Participants	Location: 2 centres in USA (Sacred Heart Hospital, University of Florida, Pensacola, Florida recruited first 8 patients; Oregon Health and Science University). Timeframe: From June 2001 to May 2007. Eligibility criteria: women at 26 to < 34 weeks' gestation; at least 14 days after first course of antenatal corticosteroids (93% received betamethasone); at continued risk of preterm delivery as determined by their care provider; who provided informed consent Gestational age range: 26 to < 34 weeks' gestation. Exclusion criteria: women were excluded if they were insulin-dependent diabetics, had a major documented fetal or chromosomal abnormality; multiple pregnancy greater than twins; clinical chorioamnionitis; first course of antenatal corticosteroids given < 24 weeks' gestation; chronic steroid use during pregnancy for clinical care Total recruited: 85 women randomised (113 babies alive at randomisation). 44 women (56 babies) in the rescue corticosteroids group and 41 women (57 babies) in the placebo group
Interventions	In the rescue group: course of antenatal corticosteroids (2 doses of 12 mg/dose betamethasone (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, 24 hours apart. In the placebo group: 2 doses of placebo (identical in appearance to betamethasone: 25 mg cortisone acetate, an inactive steroid)
Outcomes	Primary outcomes: respiratory compliance and functional residual capacity (measured within 72 hours of birth (before any surfactant) Secondary outcomes: growth measurements including weight, head circumference and length at birth and hospital discharge; surfactant administration; RDS (defined as clinical signs of respiratory distress with radiographic appearance and

	needing supplemental oxygen with FiO_2 > 0.21); respiratory distress requiring ≥ 0.30 and ≥ 0.40 at 24 hours of age; days on mechanical ventilation and days on supplemental oxygen
Funding Support	Oregon Health and Science University, GCRC/PHS Grant 5 MO1 RR000334; OCTRI UL1 RR02414001; and The American Lung Association
Notes	

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Group assignment performed using a randomisation table. A staff pharmacist performed randomisation and study drug preparation at each institution. Stratification: ≤ 28 versus > 28 weeks' gestation; multiple gestation (twins versus singletons)
Allocation concealment (selection bias)	Low risk	Method of treatment allocation: "group assignment was performed using a randomisation table. A staff pharmacist performed randomisation and study drug preparation" Stratification: ≤ 28 versus > 28 weeks' gestation; multiple gestation (twins versus singletons)
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"All patients, investigators and care providers were unaware of the treatment allocation."
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	No details reported.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Losses to follow-up: neonatal data not available for 1 baby in the placebo group. Intention-to-treat analyses: yes
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting.
Other bias	Low risk	No other obvious risk of bias detected.

Murphy 2008

Methods	Type of study: MACS randomised controlled trial.
Participants	Location: 80 centres, 20 countries. Timeframe: April 2001 to August 2006. Included: single, twin or triplet pregnancy between 25 and 32 weeks' gestation if women remained undelivered 14-21 days after an initial course of antenatal corticosteroids (either betamethasone or dexamethasone) and continued to be at high risk of preterm birth. Exclusion criteria: contraindication to corticosteroid use, needed chronic doses of these drugs, had evidence of chorioamnionitis, carried a fetus with a known lethal congenital abnormality, had an initial course of corticosteroids before 23 weeks' gestation, previously participated in MACS, women with a multiple pregnancy with fetal death after 13 weeks' gestation. Gestational age recruited up to less than 32 weeks. Total recruited 1858 women (2304 babies). 935 women in the antenatal corticosteroid group and 918 women in the placebo group
Interventions	Repeat corticosteroid group: each course consisted of 2 intramuscular injections of betamethasone 12 mg (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate; Celestone Schering-Plough Corporation, Madison, NJ, USA)) 24 hours apart. Placebo group: similarly appearing intramuscular injection of dilute concentration of aluminium monostearate (an inert substance used as a filler in pharmaceutical preparations). Women who remained at risk of preterm birth after their first course of study medication continued to receive 2 doses of 12 mg betamethasone or placebo, 24 hours apart, every 14 days until 33 weeks' gestation or birth, whichever happened first. For women with preterm rupture of the membranes the recommendation was to stop the study medication at 32 weeks' gestation
Outcomes	Primary outcome: composite of perinatal or neonatal mortality and neonatal morbidity; 1 of the following: stillbirth or neonatal death (defined as death during the first 28 days of life or before hospital discharge); severe RDS (defined as needing assisted ventilation via endotracheal tube and supplemental oxygen within the first 24 hours of life and for 24 hours or more, and either a radiographic scan compatible with RDS or surfactant given between the first 2-24 hours of life); BPD (defined as needing oxygen at a postmenstrual age of 36 completed weeks and radiographic scan compatible with BPD); IVH grade III or IV; cystic PVL, necrotising enterocolitis For the early childhood follow-up at 2 years' corrected age: primary outcome was death or the presence of a neurologic impairment at 18 to 24 months of age, corrected for gestational age at birth. Neurologic impairment was defined as the presence of cerebral palsy or a cognitive delay. Cerebral palsy was diagnosed if the child had a non-progressive motor impairment characterised by abnormal muscle tone and decreased range of movements. Cognitive delay were defined as Mental Developmental Index scores of 70 (2 SDs below the mean of 100) on the BSID-II or equivalent scores on another standardised assessment Secondary outcomes were anthropometric measurements (weight, height, and head circumference), general health, illnesses, and operations occurring after the primary hospitalisation was recorded, Psychomotor Developmental Index and the Behavior Rating Scale of the BSID-II

Funding Support	Funding: Canadian Institutes of Health Research (CIHR).
Notes	ISRCTN 72654148 Sample-size calculation: yes. A sample size of 1900 women (950 per group) was needed to have 80% probability of achieving a significant difference between the 2 groups (2-tailed type 1 error 0.05, if multiple courses of antenatal corticosteroids reduced the risk of RDS from 12% to 8%

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	"Randomisation was done with a 24-hour telephone service". Information on the generation of the allocation sequence not provided in the paper. Comment: probably done "The study was stratified by gestational age and centre."
Allocation concealment (selection bias)	Low risk	"Randomisation was done with a 24-hour telephone service after patient eligibility and baseline information were recorded. A study number was assigned corresponding to a box of study medication at the participating centre."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants were probably blinded as the injections were of similar appearance
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Later publication reporting follow-up data state that "the children's families, clinicians, and researchers associated with the trial remained unaware of the random assignments ...."
Incomplete outcome data (attrition bias) All outcomes	Low risk	Intention-to-treat analyses: yes. Losses to follow-up to time of primary hospital discharge: 9 fetuses/infants (5 in the repeat antenatal corticosteroid group and 4 in the placebo group) were stillbirths within multiple pregnancies that took place before randomisation and were excluded from the analyses 5 women (0.3%) with 5 fetuses were lost to follow-up (2 women and 2 fetuses in the repeat antenatal corticosteroid group and 3

Murphy 2008 (*Continued*)

		women and 3 fetuses in the placebo group)
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting bias detected.
Other bias	Low risk	No obvious risk of other bias detected.

Peltoniemi 2007

Methods	Type of study: placebo-controlled randomised trial.
Participants	Location: 5 Finnish university and 3 central hospitals. Time frame: May 2001 to March 2005. Included: women at < 34 weeks' gestation who had received a single course of betamethasone > 7 days previously and were to have elective delivery within 48 hours or were at very high risk of spontaneous delivery within 48 hours (cervical opening 3 cm or more, and regular contractions at 5- to 10-minute intervals) Exclusion criteria: long-term maternal corticosteroid use, clinical chorioamnionitis, or lethal disease of the fetus Total recruited: 249 women (125 betamethasone, 124 placebo), 326 infants (159 betamethasone, 167 placebo)
Interventions	Repeat corticosteroid: a single dose of betamethasone 12 mg intramuscularly Placebo: isotonic saline intramuscularly.
Outcomes	To time of primary hospital discharge: primary outcome: survival without severe RDS or severe IVH (grade 3 or 4) during the first hospital admission. RDS was defined on the basis of typical chest radiograph findings, requirement for continuous distending airway pressure, supplemental oxygen for 48 hours or more, or requirement for surfactant in cases of established respiratory failure. Severe IVH was defined as IVH with ventricular dilation (grade 3) or parenchymal haemorrhage (grade 4). Cranial ultrasound was performed for all infants at 4 to 8 days of age and at 36 weeks post-menstrual age or before discharge. The most severe grade of IVH was recorded Secondary outcomes: cystic PVL; necrotising enterocolitis grade 2 or higher; BPD (defined as a requirement for supplemental oxygen or any form of ventilation with continuous distending pressures at postnatal age of 36 weeks or at postnatal age of 4 weeks for those born after postmenstrual age of 31 weeks); patent ductus arteriosus requiring treatment (defined as a requirement for prostaglandin inhibitor therapy or surgery for closure) For the early childhood follow-up at 2 years' corrected age: a range of outcomes were assessed. Survival without serious neurological, cognitive or sensory impairment (NDI) ; respiratory problems; infections, medical history; child's weight, length and head circumference; cerebral palsy; speech; deafness; blindness; child behaviour
Funding Support	Funding: foundation for paediatric research in Finland, Alma and KA Snellmann Foundation, Sigrid Juselius foundation, hospital research funds

Notes	Tocolytics were not used and 79% of mothers gave birth < 24 hours after the intervention. All infants were born < 36 weeks' gestation Sample-size calculation: yes. Sample size based on a 25% increase in the primary outcome rate, from an estimated 50% in the control group to 62.5% in the repeat group. The planned sample size was 220 women in each arm (2 tailed alpha 0.05, beta 0.2) Recruitment was terminated early, after 249 women had been enrolled, primarily because of safety concerns due a decrease in intact survival in the repeat corticosteroid group. In addition, recruitment was slower than expected

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Unclear risk	The method by which the sequence was generated was not described
Allocation concealment (selection bias)	Low risk	"Randomization was performed centrally and was stratified according to centre by using 4 sets of sequentially-labelled, opaque, sealed envelopes (for the 4 strata of gestational age (< 28 weeks or between 28 and $\leq$ 34 weeks and multiple gestation), which were sent to each centre." "Both gestation groups were stratified additionally on the basis of number of fetuses (singleton or multiple pregnancies)." "The sealed envelopes were opened after informed consent was obtained."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The doctors and nurses as well as the study investigators were blinded."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At the follow-up at 2 years' corrected age: "The examiners and families were unaware of treatment-group assignment."
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Losses to follow-up to time of primary hospital discharge: none reported Analysis was by "intention-to-treat". Losses to follow-up to time of 2-year corrected age assessment: 259 of 312 (83%) survivors completed 2-year follow-up. 66 survivors (21%) had no paediatric assessment, 32 (21%) in the repeat corticosteroid group and 34 (21%) in the placebo group; 116 (37%) had no psychological tests, 61 (41%) in the repeat corticosteroid group

Peltoniemi 2007 (*Continued*)

		and 56 (34%) in the placebo group
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting detected.
Other bias	High risk	Recruitment was terminated early, after 249 women had been enrolled, primarily because of safety concerns due a decrease in intact survival in the repeat corticosteroid group. There were additional concerns about the long-term adverse effects of glucocorticoid Potential imbalance at trial entry for multiple pregnancy and gestational age not addressed

Wapner 2006

Methods	Type of study: randomised controlled trial.
Participants	Location: 18 US hospitals (NICHD MFMU network centres). Timeframe: March 2000 to April 2003. Eligibility criteria: pregnant women with intact membranes between 23 weeks 0 days and 31 weeks and 6 days if they had received a single full course of betamethasone or dexamethasone between 7 and 10 days earlier and were at high risk for spontaneous preterm birth, or had the diagnosis of placenta praevia or chronic abruption Exclusions: preterm premature rupture of the membranes prior to randomisation, confirmed fetal lung maturity, chorioamnionitis, a major fetal anomaly, non-reassuring fetal status, systemic corticosteroid use during the current pregnancy, or insulin-dependent diabetes. Gestational age was determined from the last menstrual period provided that ultrasonography confirmed the estimate. When there was discordance, the duration of gestation at randomisation was determined from the first sonogram performed. Gestational age range: 23 weeks 0 days to 31 weeks 6 days gestation. Total recruited: 495 women (planned for 2400) = 591 fetuses/infants. 252 to the repeat corticosteroid arm and 243 to the placebo
Interventions	Repeat corticosteroid group: each course consisted of 2 injections of betamethasone 12 mg (as 6 mg betamethasone sodium phosphate and 6 mg betamethasone acetate) repeated once in 24 hours. Placebo group: 'matching placebo' - no other details of preparation given. Initially women received courses until birth or 33 weeks 6 days' gestation, whichever was sooner. After 67 women had been enrolled, the number of courses (not including the qualifying course) was limited to 4 because of difficulty in recruitment and published literature suggesting possible harmful effects of multiple courses. 63.4% of women received 4 or more study courses
Outcomes	To time of primary hospital discharge: the primary outcome was a composite endpoint of 1 of the following: severe RDS (defined as clinical features of RDS with the need for oxygen and respiratory support from 6 to 24 hours or more of age, an abnormal chest

	x-ray, and either administration of a full course of surfactant or a fraction of inspired oxygen (FiO_2 of at least 60%); grade 3 or 3 IVH; PVL; chronic lung disease (defined as the need for supplemental oxygen at 36 weeks' corrected age in infants born before 34 weeks' gestation); or stillbirth or neonatal death. Secondary outcomes not stated in the paper For the early childhood follow-up at 2 years' corrected age: the pre-specified developmental outcome was the Bayley Mental Developmental Index Score. Other outcomes included Bayley Psychomotor Developmental Index Score; measurements of weight, height and head circumference; and the occurrence of cerebral palsy
Funding Support	Funding: National Institute of Child Health and Human Development
Notes	Sample-size calculation: yes. Planned sample size was 2400 women. "A primary outcome rate of 11.5% was anticipated for patients assigned to placebo. Detection of a 30% reduction for patients assigned to repeat corticosteroids required a sample of 1200 patients in each group" (80% power and type 1 error rate of 5% (2-sided) Recruitment was stopped early based on safety concerns (because of a tendency towards decreased birthweight in the repeat corticosteroid group without any reduction in the primary morbidity outcome and also because of difficulties in recruitment)

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Method of treatment allocation: numbered kits were prepared using randomisation sequences created by an independent data coordinating centre. Sequences were generated using the urn design and were stratified by clinical centre, type of qualifying course, and inpatient/outpatient. Woman was assigned to the next sequentially-numbered kit - betamethasone or identical looking placebo prepared by a centralised research pharmacy
Allocation concealment (selection bias)	Low risk	Assessed as adequate. Women were assigned to the next sequentially-numbered kit - betamethasone or identical looking placebo prepared by a centralised research pharmacy
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Participants are likely to be blinded due to the use of a matching placebo
Blinding of outcome assessment (detection bias) All outcomes	Low risk	At early childhood follow-up the assessments were performed by centrally trained and certified study personnel who were un-

Wapner 2006 (*Continued*)

		aware of the treatment assignment
Incomplete outcome data (attrition bias) All outcomes	Unclear risk	Intention-to-treat analyses: yes. "For categorical infant outcomes the statistical unit was pregnancy rather than infant, because of the correlation between twins." Continuous variables were compared with an adjustment for the correlation between twins, for infants Losses to follow-up to time of primary hospital discharge: 3 (< 1%) women lost to follow-up (2 in the repeat group and 1 in the placebo group) Losses to follow-up to time of 2-year corrected age assessment: There were 582 known survivors. Of the survivors, 96 (16.5%) were not able to be seen, 46 in the repeat corticosteroid group and 50 in the placebo group; 117 (20.1%) did not have a Bayley assessment performed, 59 in the repeat corticosteroid group and 58 in the placebo group Intention-to-treat analyses: yes.
Selective reporting (reporting bias)	Low risk	No obvious risk of selective reporting bias detected.
Other bias	High risk	Recruitment was stopped early based on safety concerns after the recruitment of 495 women. "At the second interim analysis the Data Safety Monitoring Committee recommended that enrolment be halted because of a tendency towards decreased birthweight in the repeat corticosteroid group without evident reduction in the primary morbidity outcome and also because of difficulties with recruitment."

ACTH: adrenocorticotropic hormone
BPD: bronchopulmonary dysplasia
IVH: intraventricular haemorrhageMFMU: Maternal Fetal Medicine Units
NICHD: National Institute of Child Health and Human Development
PVL: periventricular leukomalacia
RDS: respiratory distress syndrome
SD: standard deviation

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

Study	Reason for exclusion
Bontis 2011	This is a 'non-randomized' trial.
Mercer 2001	Women recruited to the trial did not have corticosteroids before entry The objective of the trial was to evaluate the need for and benefits of weekly antenatal corticosteroids in women at risk of preterm birth. 189 women between 23 and 32 weeks at risk of preterm birth were randomised to weekly antenatal corticosteroids or to a control group where corticosteroids were given if indicated before 35 weeks, if the pregnancy was expected to last more than 1 week The primary outcome was antenatal corticosteroids given within 7 days of preterm birth (< 35 weeks) (optimal exposure). In the control group only one-third of infants < 35 weeks' gestation received optimal antenatal corticosteroid exposure. Weekly corticosteroids doubled optimal exposure although the vast majority gave birth > 34 weeks
Romejko-Wolniewicz 2013	This is a head-to-head trial of 2 different regimens and is eligible for the Cochrane review entitled '*Different corticosteroids and regimens for accelerating fetal lung maturation for women at risk of preterm birth*' Brownfoot 2013.
Thorp 2000	Women recruited to the trial were not randomised to receive repeat corticosteroids but antenatal phenobarbital. The abstract is a secondary multivariate analysis of this trial assessing if duration of antenatal betamethasone is associated with perinatal outcome

Characteristics of studies awaiting assessment *[ordered by study ID]*

Atarod 2014

Methods	Randomised trial.
Participants	Women at risk of preterm birth between 28 and 35 weeks' gestation
Interventions	Repeat betamethasone compared with no repeat.
Outcomes	RDS, need for oxygen, surfactant, need for ventilation, duration of hospital stay, mortality to hospital discharge, birthweight, height, head circumference
Notes	It is unclear as to the time point at which randomisation to repeat betamethasone or no repeat occurred. The authors have been contacted for this information in February 2015 and we are awaiting a response

Crowther 2011

Methods	8 conference abstracts reporting on follow-up data and 1 report on the follow-up of a subgroup of the original trial population of the ACTORDS trial (Crowther 2006).
Participants	
Interventions	
Outcomes	
Notes	The review authors will add any data eligible for inclusion when the ACTORDS follow-up data have been published in full

Murphy 2012

Methods	4 papers reporting further follow-up data from the Murphy 2008 trial.
Participants	
Interventions	
Outcomes	
Notes	The review authors will add any data eligible for inclusion in the next update of this systematic review

RDS: respiratory distress syndrome

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

Sobhrabvand 2001

Trial name or title	Effects of single versus multiple courses of corticosteroid therapy on pregnancy results in women with PPROM
Methods	
Participants	
Interventions	
Outcomes	
Starting date	
Contact information	
Notes	

TEAMS 1999

Trial name or title	Trial of the effects of antenatal multiple courses of steroids versus a single course (TEAMS)
Methods	RCT.
Participants	Women who had received a course of antenatal corticosteroids
Interventions	2 intramuscular injections of betamethasone versus placebo.
Outcomes	Death within first year after birth; developmental quotient less than 85 at 2 years.
Starting date	1/10/1999. End date (recruitment): 1/05/2001.
Contact information	Ms Helen Adams, TEAMS administrator.
Notes	ISRCTN46614711

PPROM: preterm prelabour rupture of the membranes
RCT: randomised controlled trial

DATA AND ANALYSES

Comparison 1. Repeat doses of corticosteroids versus single course

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Respiratory distress syndrome	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
1.1 In all babies	8	3206	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.91]
1.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.60, 1.24]
1.3 In babies exposed to repeat corticosteroids as betamethasone	8	3206	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.75, 0.91]
1.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	6	2538	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.77, 0.96]
1.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	668	Risk Ratio (M-H, Fixed, 95% CI)	0.72 [0.58, 0.89]
1.7 In babies exposed to one repeat course of prenatal corticosteroids	3	994	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.73, 0.99]
1.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
1.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1470	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.98]
1.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	6	1736	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.67, 0.92]
1.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

1.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.92]
1.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	4	1068	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.68, 1.10]
1.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
2 Severe lung disease	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
2.1 In all babies	6	4826	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.14]
2.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.3 In babies exposed to repeat corticosteroids as betamethasone	6	4826	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.56, 1.14]
2.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2522	Risk Ratio (M-H, Random, 95% CI)	0.72 [0.47, 1.12]
2.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2304	Risk Ratio (M-H, Random, 95% CI)	1.11 [0.82, 1.49]
2.7 In babies exposed to one repeat course of prenatal corticosteroids	1	326	Risk Ratio (M-H, Random, 95% CI)	1.23 [0.94, 1.60]
2.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1470	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.40, 1.78]
2.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	4	3356	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.50, 1.20]

2.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
2.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3448	Risk Ratio (M-H, Random, 95% CI)	0.80 [0.42, 1.51]
2.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	3	1052	Risk Ratio (M-H, Random, 95% CI)	0.62 [0.44, 0.87]
2.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
3 Composite serious outcome (variously defined)	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
3.1 In all babies	7	5094	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.94]
3.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.3 In babies exposed to repeat corticosteroids as betamethasone	7	5094	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.75, 0.94]
3.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2232	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.66, 0.91]
3.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2862	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
3.7 In babies exposed to one repeat course of prenatal corticosteroids	1	558	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.60, 0.93]
3.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

3.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.62, 0.96]
3.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	6	3950	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 0.99]
3.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
3.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3448	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
3.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	4	1088	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.60, 1.00]
3.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
4 Mean birthweight (g)	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
4.1 In all babies	9	5626	Mean Difference (IV, Fixed, 95% CI)	-75.79 [-117.63, -33.96]
4.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.3 In babies exposed to repeat corticosteroids as betamethasone	9	5626	Mean Difference (IV, Fixed, 95% CI)	-75.79 [-117.63, -33.96]
4.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2328	Mean Difference (IV, Fixed, 95% CI)	-63.68 [-128.59, 1.24]
4.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2972	Mean Difference (IV, Fixed, 95% CI)	-79.61 [-143.23, -14.00]
4.7 In babies exposed to one repeat course of prenatal corticosteroids	3	994	Mean Difference (IV, Fixed, 95% CI)	-57.20 [-132.99, 18.59]
4.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]

4.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	1	368	Mean Difference (IV, Fixed, 95% CI)	-161.0 [-290.52, -31.48]
4.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1470	Mean Difference (IV, Fixed, 95% CI)	-48.72 [-119.84, 22.40]
4.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	7	4156	Mean Difference (IV, Fixed, 95% CI)	-90.12 [-141.85, -38.39]
4.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
4.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3448	Mean Difference (IV, Fixed, 95% CI)	-52.00 [-126.19, 18.19]
4.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	4	1184	Mean Difference (IV, Fixed, 95% CI)	-110.62 [-199.49, -21.74]
4.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5 Birthweight Z scores	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
5.1 In all babies	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.23, 0.00]
5.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.3 In babies exposed to repeat corticosteroids as betamethasone	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.11 [-0.23, 0.00]
5.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	1	1144	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.26, -0.00]
5.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	112	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.34, 0.34]

5.7 In babies exposed to one repeat course of prenatal corticosteroids	1	112	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.34, 0.34]
5.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	1144	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.26, -0.00]
5.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	1	112	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.34, 0.34]
5.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	1144	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.26, -0.00]
5.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
5.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6 Birthweight multiples of the median	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
6.1 In all babies	1	590	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]
6.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.3 In babies exposed to repeat corticosteroids as betamethasone	1	590	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]
6.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	1	590	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]

6.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.7 In babies exposed to one repeat course of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	1	368	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.07, -0.01]
6.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	1	590	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]
6.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
6.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	1	590	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.03, 0.03]
6.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Mean Difference (IV, Fixed, 95% CI)	0.0 [0.0, 0.0]
7 Small-for-gestational age at birth	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
7.1 In all babies	7	3975	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.97, 1.43]
7.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

7.3 In babies exposed to repeat corticosteroids as betamethasone	7	3975	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.97, 1.43]
7.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	4	1006	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [1.04, 1.82]
7.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2969	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
7.7 In babies exposed to one repeat course of prenatal corticosteroids	3	991	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.87, 1.54]
7.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	1	368	Risk Ratio (M-H, Fixed, 95% CI)	2.00 [1.07, 3.73]
7.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	326	Risk Ratio (M-H, Fixed, 95% CI)	1.33 [0.92, 1.94]
7.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	6	3649	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.42]
7.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
7.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	2304	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.75, 1.50]
7.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	4	792	Risk Ratio (M-H, Fixed, 95% CI)	1.29 [0.88, 1.90]
7.16 In babies where planned repeat drug exposure was >24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8 Fetal and neonatal mortality	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
8.1 In all babies	9	5554	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.23]

8.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.49 [0.13, 1.88]
8.3 In babies exposed to repeat corticosteroids as betamethasone	9	5554	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.71, 1.23]
8.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	6	2871	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.67, 1.37]
8.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2993	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.51]
8.7 In babies exposed to one repeat course of prenatal corticosteroids	3	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.41 [0.64, 3.08]
8.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1472	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.79]
8.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	7	4082	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.61, 1.19]
8.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
8.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3450	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
8.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	4	1089	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.26, 1.00]

8.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9 Fetal death	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
9.1 In all babies	7	2755	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
9.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.3 In babies exposed to repeat corticosteroids as betamethasone	7	2755	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
9.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	4	1740	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.57]
9.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	689	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.86]
9.7 In babies exposed to one repeat course of prenatal corticosteroids	3	1015	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.23]
9.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1472	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 7.31]
9.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	5	1283	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.14, 3.55]
9.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
9.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.23]

9.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	3	594	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.08, 4.42]
9.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10 Neonatal death	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
10.1 In all babies	7	2713	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
10.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.3 In babies exposed to repeat corticosteroids as betamethasone	7	2713	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
10.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2045	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.61, 1.38]
10.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	668	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.28, 2.66]
10.7 In babies exposed to one repeat course of prenatal corticosteroids	3	994	Risk Ratio (M-H, Fixed, 95% CI)	1.47 [0.65, 3.33]
10.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.80]
10.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	5	1243	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.32, 1.20]

10.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
10.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.59]
10.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	3	575	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.23, 1.18]
10.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11 Chronic lung disease	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
11.1 In all babies	8	5393	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
11.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.41]
11.3 In babies exposed to repeat corticosteroids as betamethasone	8	5393	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.87, 1.30]
11.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	6	2538	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.21]
11.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2855	Risk Ratio (M-H, Fixed, 95% CI)	1.49 [0.96, 2.32]
11.7 In babies exposed to one repeat course of prenatal corticosteroids	2	877	Risk Ratio (M-H, Fixed, 95% CI)	1.27 [0.83, 1.96]
11.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

11.11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent	2	1470	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
11.12 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent	6	3923	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.88, 1.59]
11.13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
11.14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	2	3448	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
11.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent	4	1068	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.65, 1.44]
11.16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12 Intraventricular haemorrhage	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1 In all babies	6	3065	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
12.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.3 In babies exposed to repeat corticosteroids as betamethasone	6	3065	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.75, 1.18]
12.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2519	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.77, 1.26]
12.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	546	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.43, 1.36]
12.7 In babies exposed to one repeat course of prenatal corticosteroids	2	872	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.42]
12.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

12.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent	2	1470	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.74, 1.40]
12.12 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent	4	1595	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
12.13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
12.14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	1	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.57, 1.38]
12.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent	3	1017	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.40]
12.16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
13 Intraventricular haemorrhage grade 3/4	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
13.1 In all babies	6	4819	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
14 Periventricular leukomalacia	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
14.1 In all babies	7	4888	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.43, 1.37]
15 Chorioamnionitis	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
15.1 In all women	6	4261	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.92, 1.46]
15.2 In women where pregnancy complicated by preterm prelabour rupture of membranes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	1.56 [1.05, 2.31]
15.3 In women given repeat corticosteroids as betamethasone	6	4261	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [0.92, 1.46]
15.4 In women given repeat corticosteroids at a minimum interval of 7 days or less	4	1971	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.95, 1.59]
15.5 In women given repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

15.6 In women given repeat corticosteroids at a minimum interval of 14 days or more	2	2290	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.57]
15.7 In women given one repeat course of prenatal corticosteroids	1	437	Risk Ratio (M-H, Fixed, 95% CI)	0.64 [0.23, 1.77]
15.8 In women given two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.9 In women given three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.10 In women given four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.11 In women where planned dose per treatment course 12 mg or less of betamethasone or equivalent	1	982	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.72, 1.62]
15.12 In women where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent	5	3279	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.90, 1.58]
15.13 In women where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
15.14 In women where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	2	2835	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.77, 1.51]
15.15 In women where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivale	3	989	Risk Ratio (M-H, Fixed, 95% CI)	1.35 [0.96, 1.88]
15.16 In women where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16 Puerperal sepsis	5		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
16.1 In all women	5	3091	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.83, 1.60]
16.2 In women where pregnancy complicated by preterm prelabour rupture of membranes	1	160	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.19, 2.22]
16.3 In women given repeat corticosteroids as betamethasone	5	3091	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.83, 1.60]
16.4 In women given repeat corticosteroids at a minimum interval of 7 days or less	4	1238	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.66, 1.59]

16.5 In women given repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.6 In women given repeat corticosteroids at a minimum interval of 14 days or more	1	1853	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.80, 2.22]
16.7 In women given one repeat course of prenatal corticosteroids	1	249	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.80, 3.10]
16.8 In women given two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.9 In women given three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.10 In women given four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.11 In women where planned dose per treatment course 12 mg or less of betamethasone or equivalent	1	249	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.80, 3.10]
16.12 In women where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalen	4	2842	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.72, 1.54]
16.13 In women where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
16.14 In women where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	1	1853	Risk Ratio (M-H, Fixed, 95% CI)	1.34 [0.80, 2.22]
16.15 In women where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivale	3	989	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.42, 1.36]
16.16 In women where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
17 Mean gestational age at birth (weeks)	8		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
17.1 In all babies	8	3179	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.33, 0.15]
18 Preterm birth before 37 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
18.1 In all babies	2	1181	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.92, 1.02]
19 Very preterm birth before 34 weeks	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
19.1 In all babies	4	2140	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]

20 Extremely preterm birth before 28 weeks	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
20.1 In all babies	2	1632	Risk Ratio (M-H, Fixed, 95% CI)	1.07 [0.83, 1.38]
21 Mean head circumference at birth (cm)	9		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
21.1 In all babies	9	5626	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.49, -0.15]
22 Head circumference Z scores at birth	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
22.1 In all babies	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.27, -0.00]
23 Mean length at birth (cm)	6		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
23.1 In all babies	6	4550	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.89, -0.23]
24 Length Z scores at birth	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
24.1 In all babies	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.19, 0.09]
25 Length multiples of the median at birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
25.1 In all babies	1	590	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, -0.00]
26 Apgar score less than 7 at 5 minutes	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
26.1 In all babies	3	4004	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.64, 1.10]
27 Use of mechanical ventilation	6		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
27.1 In all babies	6	4918	Risk Ratio (M-H, Random, 95% CI)	0.84 [0.71, 0.99]
28 Duration of respiratory support in days	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
28.1 In all babies	1	37	Mean Difference (IV, Fixed, 95% CI)	0.30 [-0.90, 1.50]
29 Use of oxygen supplementation	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
29.1 In all babies	2	3448	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.85, 0.99]
30 Duration of oxygen supplementation in days	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
30.1 In all babies	1	37	Mean Difference (IV, Fixed, 95% CI)	3.3 [-2.31, 8.91]
31 Use of surfactant	9		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
31.1 In all babies	9	5525	Risk Ratio (M-H, Random, 95% CI)	0.78 [0.65, 0.95]
32 Use of inotropic support	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
32.1 In all babies	2	1470	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]
33 Use of nitric oxide for respiratory support	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
33.1 In all babies	1	1144	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.29, 1.17]
34 Early systemic neonatal infection (variously defined)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
34.1 In all babies	3	1544	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.11]
35 Proven infection while in the neonatal intensive care unit	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
35.1 In all babies	6	5002	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.20]
36 Admission to the neonatal intensive care unit	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
36.1 In all babies	2	3448	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
37 Air leak syndrome	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
37.1 In all babies	3	2192	Risk Ratio (M-H, Random, 95% CI)	0.76 [0.29, 1.97]
38 Necrotising enterocolitis	8		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
38.1 In all babies	8	5394	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.51, 1.08]
39 Patent ductus arteriosus	6		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
39.1 In all babies	6	4356	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.64, 0.98]
40 Retinopathy of prematurity	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only

40.1 In all babies	7	4883	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.81, 1.28]
41 Use of postnatal steroids	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
41.1 In all babies	3	3931	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.99, 1.93]
42 Mean neonatal blood pressure on first day after birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
42.1 In all babies	1	175	Mean Difference (IV, Fixed, 95% CI)	0.70 [-2.47, 3.87]
43 Mean neonatal blood pressure 6 weeks after birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
43.1 In all babies	1	175	Mean Difference (IV, Fixed, 95% CI)	-1.40 [-5.06, 2.26]
44 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
44.1 In all babies	1	175	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.24, 0.26]
45 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
45.1 In all babies	1	175	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.27, 0.19]
46 Mean basal cortisol concentrations (nmol/L) at birth	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
46.1 In all babies	1	67	Mean Difference (IV, Fixed, 95% CI)	-44.9 [-78.41, -11.39]
47 Mean weight (g) at primary hospital discharge	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
47.1 In all babies	1	1090	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-77.15, 75.15]
48 Weight Z scores at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
48.1 In all babies	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.16, 0.06]
49 Mean head circumference (cm) at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
49.1 In all babies	2	1195	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.10, 0.35]
50 Head circumference Z scores at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
50.1 In all babies	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.15, 0.10]
51 Mean length (cm) at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
51.1 In all babies	2	1189	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.44, 0.47]
52 Length Z score at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
52.1 In all babies	2	1189	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.23, 0.10]
53 Prelabour rupture of membranes after trial entry	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
53.1 In all women	1	492	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.67, 1.57]
54 Maternal Hypertension (variously defined by the authors)	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
54.1 In all women	3	3327	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.32]
55 Vaginal birth	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
55.1 In all women	7	4062	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.87, 1.00]
56 Caesarean section	7		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
56.1 In all women	7	4062	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.99, 1.10]

57 Postpartum haemorrhage	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
57.1 In all women	1	485	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.33, 1.07]
58 Postnatal pyrexia (variously defined by authors)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
58.1 In all women	1	982	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.55, 1.38]
59 Length of postnatal hospitalisation (days)	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
59.1 In all babies	1	483	Mean Difference (IV, Fixed, 95% CI)	0.0 [-0.22, 0.22]
60 Any maternal side effects of therapy	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
60.1 In all women	2	1474	Risk Ratio (M-H, Random, 95% CI)	0.97 [0.24, 3.90]
61 Maternal hyperglycaemia (variously defined by authors)	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
61.1 In all women	1	492	Risk Ratio (M-H, Fixed, 95% CI)	1.31 [0.89, 1.93]
62 Insomnia	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
62.1 In all women	3	1486	Risk Ratio (M-H, Fixed, 95% CI)	2.63 [1.10, 6.30]
63 Pain at injection site	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
63.1 In all women	2	1474	Risk Ratio (M-H, Random, 95% CI)	0.73 [0.11, 5.05]
64 Bruising at injection site	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
64.1 In all women	1	492	Risk Ratio (M-H, Fixed, 95% CI)	0.38 [0.21, 0.71]
65 Total mortality up to early childhood follow up	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
65.1 In all babies	4	4370	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.41]
65.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
65.3 In babies exposed to repeat corticosteroids as betamethasone	4	4370	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.80, 1.41]
65.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	3	2066	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.74, 1.67]
65.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
65.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2304	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.51]
65.7 In babies exposed to one repeat course of prenatal corticosteroids	1	326	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.82, 6.50]
65.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
65.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]

65.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
65.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1472	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]
65.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	2	2898	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.72, 1.50]
65.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
65.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3450	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.33]
65.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	1	594	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.39, 3.38]
65.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66 Survival free of any disability to early childhood follow up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
66.1 In all babies	2	3155	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.97, 1.05]
66.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.3 In babies exposed to repeat corticosteroids as betamethasone	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
66.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.12]
66.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]

66.7 In babies exposed to one repeat course of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.12]
66.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
66.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
66.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
66.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
67 Survival free of major neurosensory disability to early childhood follow up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
67.1 In all babies	2	1317	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]
67.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.3 In babies exposed to repeat corticosteroids as betamethasone	2	1317	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]
67.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	2	1317	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]

67.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.7 In babies exposed to one repeat course of prenatal corticosteroids	1	257	Risk Ratio (M-H, Random, 95% CI)	0.98 [0.95, 1.01]
67.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1317	Risk Ratio (M-H, Random, 95% CI)	1.01 [0.92, 1.11]
67.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	1060	Risk Ratio (M-H, Random, 95% CI)	1.04 [0.99, 1.10]
67.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
67.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68 Major neurosensory disablity at early childhood follow-up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
68.1 In all babies	2	1256	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.31, 3.76]
68.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

68.3 In babies exposed to repeat corticosteroids as betamethasone	2	1256	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.31, 3.76]
68.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	2	1256	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.31, 3.76]
68.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.7 In babies exposed to one repeat course of prenatal corticosteroids	1	257	Risk Ratio (M-H, Random, 95% CI)	3.53 [0.37, 33.52]
68.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	2	1256	Risk Ratio (M-H, Random, 95% CI)	1.08 [0.31, 3.76]
68.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	999	Risk Ratio (M-H, Random, 95% CI)	0.77 [0.55, 1.08]
68.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]
68.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Random, 95% CI)	0.0 [0.0, 0.0]

69 Disability at early childhood follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
69.1 In all babies	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
69.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.3 In babies exposed to repeat corticosteroids as betamethasone	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
69.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
69.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.7 In babies exposed to one repeat course of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
69.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]

69.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
69.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70 Composite serious outcome at early childhood follow-up (however defined by authors)	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
70.1 In all babies	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
70.2 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.3 In babies exposed to repeat corticosteroids as betamethasone	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
70.4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.13]
70.5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.25]
70.7 In babies exposed to one repeat course of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.8 In babies exposed to two repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.9 In babies exposed to three repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.10 In babies exposed to four or more repeat courses of prenatal corticosteroids	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.84, 1.13]
70.12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.25]

70.13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.87, 1.12]
70.15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
70.16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	0.0 [0.0, 0.0]
71 Weight small for age at early childhood follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
71.1 In all babies	2	1448	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.71, 1.19]
72 Head circumference small for age at early childhood follow-up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
72.1 In all babies	2	1442	Risk Ratio (M-H, Random, 95% CI)	1.10 [0.77, 1.56]
73 Height small for age at early childhood follow-up	2		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
73.1 In all babies	2	1441	Risk Ratio (M-H, Random, 95% CI)	1.12 [0.63, 2.02]
74 Mean weight at early childhood follow-up	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
74.1 In all babies	3	1776	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.21, 0.15]
75 Mean head circumference at early childhood follow-up	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
75.1 In all babies	3	1776	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.22, 0.11]
76 Mean height at early childhood follow-up	3		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
76.1 In all babies	3	1776	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.55, 0.30]
77 Weight Z score at early childhood follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
77.1 In all babies	1	1047	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
78 Head circumference Z score at early childhood follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
78.1 In all babies	2	1290	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.18]
79 Height Z score at early childhood follow-up	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
79.1 In all babies	2	1290	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.17, 0.09]
80 Developmental delay at early childhood follow-up	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
80.1 In all babies	3	3202	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.84, 1.13]
81 Mental Developmental Index at early childhood follow-up	2	1162	Mean Difference (IV, Fixed, 95% CI)	1.23 [-0.65, 3.11]
81.1 In all babies	2	1162	Mean Difference (IV, Fixed, 95% CI)	1.23 [-0.65, 3.11]

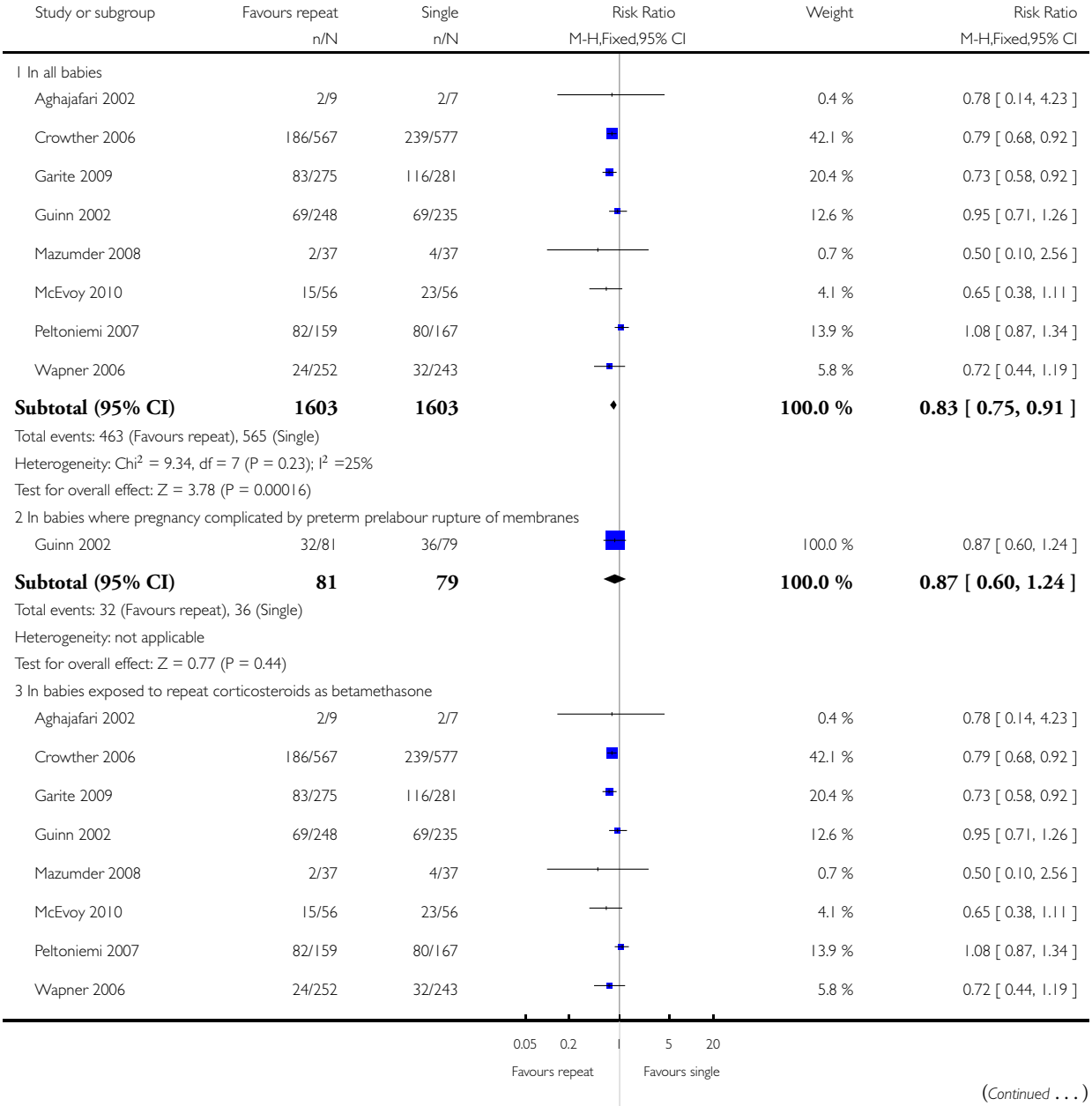
82 Psychomotor Developmental Index at early childhood follow-up	1	958	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.75, 2.55]
82.1 In all babies	1	958	Mean Difference (IV, Fixed, 95% CI)	0.40 [-1.75, 2.55]
83 Bindness at early childhood follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
83.1 In all babies	2	3151	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.65, 2.10]
84 Deafness at early childhood follow-up	3		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
84.1 In all babies	3	3405	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.29, 2.52]
85 Cerebral palsy at early childhood follow-up	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
85.1 In all babies	4	3800	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.50]
86 Behaviour score at early childhood follow-up within clinical range	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
86.1 In all babies	1	1045	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.51]
87 Asthma/Wheezing at early childhood follow-up	3		Risk Ratio (M-H, Random, 95% CI)	Subtotals only
87.1 In all babies	3	1720	Risk Ratio (M-H, Random, 95% CI)	0.89 [0.63, 1.27]
88 Hypertensive at early childhood follow-up	1		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
88.1 In all babies	1	628	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
89 Mean systolic blood pressure at early childhood follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
89.1 In all babies	1	486	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-5.40, -0.40]
90 Mean diasystolic blood pressure at early childhood follow-up	1		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
90.1 In all babies	1	486	Mean Difference (IV, Fixed, 95% CI)	-1.0 [-2.86, 0.86]
91 Hospital re-admission by early childhood follow-up	4		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
91.1 In all babies	4	3824	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]

Analysis 1.1. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 1 Respiratory distress syndrome.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 1 Respiratory distress syndrome



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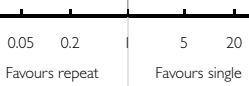
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**1603**	**1603**	♦	**100.0 %**	**0.83 [0.75, 0.91]**
Total events: 463 (Favours repeat), 565 (Single)					
Heterogeneity: Chi^2 = 9.34, df = 7 (P = 0.23); I^2 =25%					
Test for overall effect: Z = 3.78 (P = 0.00016)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	2/9	2/7		0.5 %	0.78 [0.14, 4.23]
Crowther 2006	186/567	239/577		55.8 %	0.79 [0.68, 0.92]
Guinn 2002	69/248	69/235		16.7 %	0.95 [0.71, 1.26]
Mazumder 2008	2/37	4/37		0.9 %	0.50 [0.10, 2.56]
Peltoniemi 2007	82/159	80/167		18.4 %	1.08 [0.87, 1.34]
Wapner 2006	24/252	32/243		7.7 %	0.72 [0.44, 1.19]
Subtotal (95% CI)	**1272**	**1266**	♦	**100.0 %**	**0.86 [0.77, 0.96]**
Total events: 365 (Favours repeat), 426 (Single)					
Heterogeneity: Chi^2 = 6.51, df = 5 (P = 0.26); I^2 =23%					
Test for overall effect: Z = 2.60 (P = 0.0094)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Garite 2009	83/275	116/281		83.3 %	0.73 [0.58, 0.92]
McEvoy 2010	15/56	23/56		16.7 %	0.65 [0.38, 1.11]
Subtotal (95% CI)	**331**	**337**	♦	**100.0 %**	**0.72 [0.58, 0.89]**
Total events: 98 (Favours repeat), 139 (Single)					
Heterogeneity: Chi^2 = 0.15, df = 1 (P = 0.70); I^2 =0.0%					
Test for overall effect: Z = 3.10 (P = 0.0019)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Garite 2009	83/275	116/281		53.2 %	0.73 [0.58, 0.92]
McEvoy 2010	15/56	23/56		10.7 %	0.65 [0.38, 1.11]
Peltoniemi 2007	82/159	80/167		36.2 %	1.08 [0.87, 1.34]
Subtotal (95% CI)	**490**	**504**	♦	**100.0 %**	**0.85 [0.73, 0.99]**
Total events: 180 (Favours repeat), 219 (Single)					
Heterogeneity: Chi^2 = 7.15, df = 2 (P = 0.03); I^2 =72%					
Test for overall effect: Z = 2.13 (P = 0.033)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



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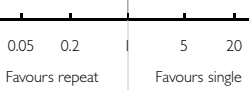
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	186/567	239/577		75.2 %	0.79 [0.68, 0.92]
Peltoniemi 2007	82/159	80/167		24.8 %	1.08 [0.87, 1.34]
Subtotal (95% CI)	**726**	**744**		**100.0 %**	**0.86 [0.76, 0.98]**
Total events: 268 (Favours repeat), 319 (Single)					
Heterogeneity: Chi^2 = 5.16, df = 1 (P = 0.02); I^2 =81%					
Test for overall effect: Z = 2.31 (P = 0.021)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Aghajafari 2002	2/9	2/7		0.9 %	0.78 [0.14, 4.23]
Garite 2009	83/275	116/281		46.4 %	0.73 [0.58, 0.92]
Guinn 2002	69/248	69/235		28.6 %	0.95 [0.71, 1.26]
Mazumder 2008	2/37	4/37		1.6 %	0.50 [0.10, 2.56]
McEvoy 2010	15/56	23/56		9.3 %	0.65 [0.38, 1.11]
Wapner 2006	24/252	32/243		13.2 %	0.72 [0.44, 1.19]
Subtotal (95% CI)	**877**	**859**		**100.0 %**	**0.78 [0.67, 0.92]**
Total events: 195 (Favours repeat), 246 (Single)					
Heterogeneity: Chi^2 = 2.94, df = 5 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 3.05 (P = 0.0023)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	186/567	239/577		100.0 %	0.79 [0.68, 0.92]
Subtotal (95% CI)	**567**	**577**		**100.0 %**	**0.79 [0.68, 0.92]**
Total events: 186 (Favours repeat), 239 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 3.00 (P = 0.0027)					



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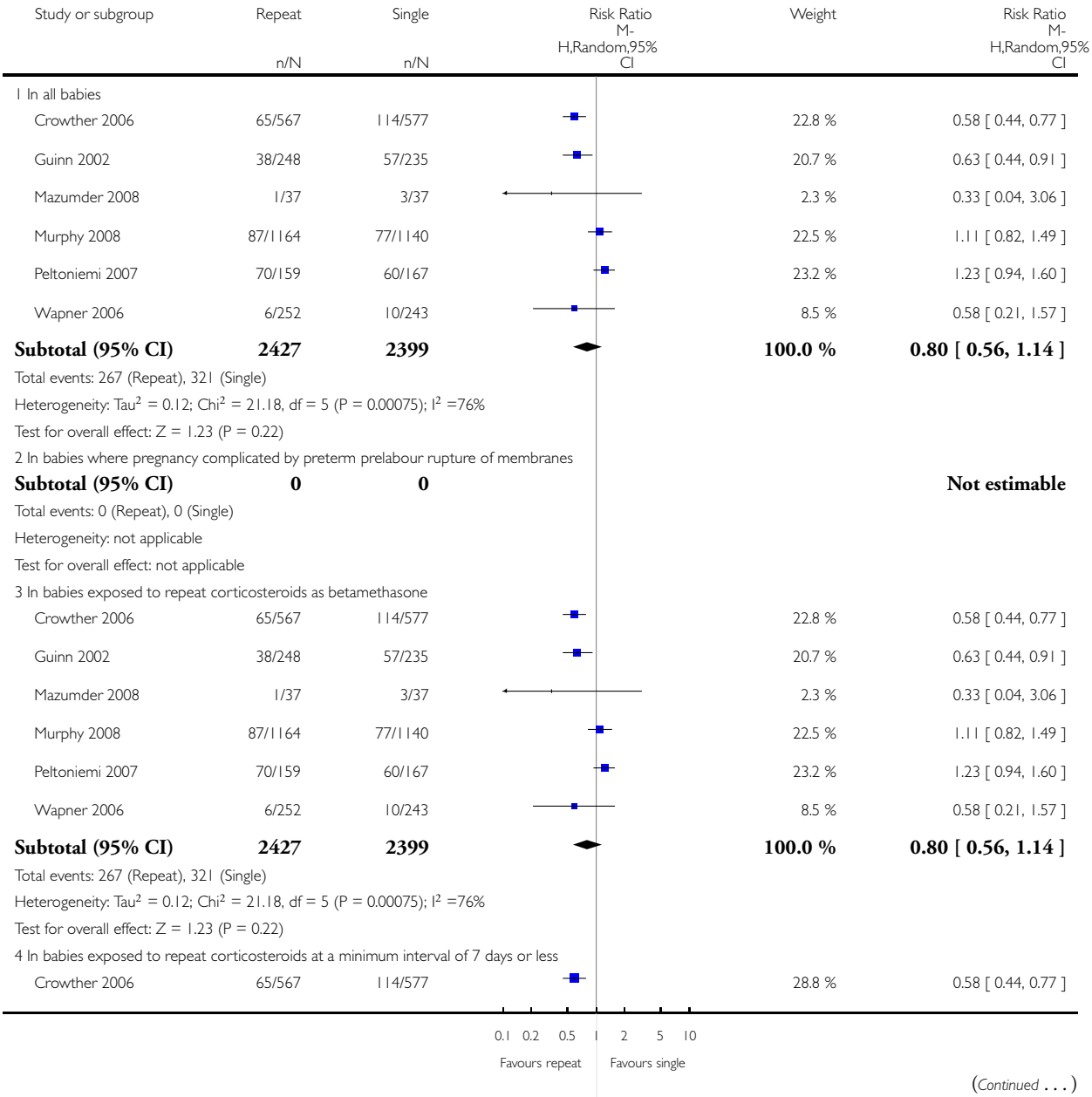
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Aghajafari 2002	2/9	2/7		2.1 %	0.78 [0.14, 4.23]
Guinn 2002	69/248	69/235		64.6 %	0.95 [0.71, 1.26]
Mazumder 2008	2/37	4/37		3.6 %	0.50 [0.10, 2.56]
Wapner 2006	24/252	32/243		29.7 %	0.72 [0.44, 1.19]
Subtotal (95% CI)	**546**	**522**		**100.0 %**	**0.86 [0.68, 1.10]**
Total events: 97 (Favours repeat), 107 (Single)					
Heterogeneity: Chi^2 = 1.35, df = 3 (P = 0.72); I^2 =0.0%					
Test for overall effect: Z = 1.22 (P = 0.22)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.2. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 2 Severe lung disease.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 2 Severe lung disease



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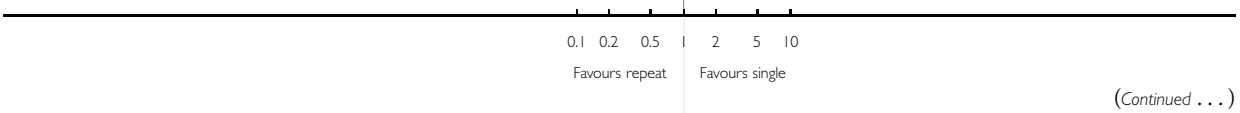
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Guinn 2002	38/248	57/235		26.5 %	0.63 [0.44, 0.91]
Mazumder 2008	1/37	3/37		3.5 %	0.33 [0.04, 3.06]
Peltoniemi 2007	70/159	60/167		29.1 %	1.23 [0.94, 1.60]
Wapner 2006	6/252	10/243		12.1 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**1263**	**1259**		**100.0 %**	**0.72 [0.47, 1.12]**
Total events: 180 (Repeat), 244 (Single)					
Heterogeneity: Tau² = 0.15; Chi² = 17.81, df = 4 (P = 0.001); I² =78%					
Test for overall effect: Z = 1.45 (P = 0.15)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Murphy 2008	87/1164	77/1140		100.0 %	1.11 [0.82, 1.49]
Subtotal (95% CI)	**1164**	**1140**		**100.0 %**	**1.11 [0.82, 1.49]**
Total events: 87 (Repeat), 77 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.67 (P = 0.50)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Peltoniemi 2007	70/159	60/167		100.0 %	1.23 [0.94, 1.60]
Subtotal (95% CI)	**159**	**167**		**100.0 %**	**1.23 [0.94, 1.60]**
Total events: 70 (Repeat), 60 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.49 (P = 0.14)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					



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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Crowther 2006	65/567	114/577		49.8 %	0.58 [0.44, 0.77]
Peltoniemi 2007	70/159	60/167		50.2 %	1.23 [0.94, 1.60]
Subtotal (95% CI)	**726**	**744**		**100.0 %**	**0.84 [0.40, 1.78]**
Total events: 135 (Repeat), 174 (Single)					
Heterogeneity: Tau² = 0.27; Chi² = 14.72, df = 1 (P = 0.00012); I² =93%					
Test for overall effect: Z = 0.44 (P = 0.66)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Guinn 2002	38/248	57/235		38.9 %	0.63 [0.44, 0.91]
Mazumder 2008	1/37	3/37		3.6 %	0.33 [0.04, 3.06]
Murphy 2008	87/1164	77/1140		43.3 %	1.11 [0.82, 1.49]
Wapner 2006	6/252	10/243		14.2 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**1701**	**1655**		**100.0 %**	**0.78 [0.50, 1.20]**
Total events: 132 (Repeat), 147 (Single)					
Heterogeneity: Tau² = 0.09; Chi² = 6.78, df = 3 (P = 0.08); I² =56%					
Test for overall effect: Z = 1.13 (P = 0.26)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	65/567	114/577		50.3 %	0.58 [0.44, 0.77]
Murphy 2008	87/1164	77/1140		49.7 %	1.11 [0.82, 1.49]
Subtotal (95% CI)	**1731**	**1717**		**100.0 %**	**0.80 [0.42, 1.51]**
Total events: 152 (Repeat), 191 (Single)					
Heterogeneity: Tau² = 0.19; Chi² = 9.61, df = 1 (P = 0.002); I² =90%					
Test for overall effect: Z = 0.69 (P = 0.49)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Guinn 2002	38/248	57/235		85.8 %	0.63 [0.44, 0.91]
Mazumder 2008	1/37	3/37		2.4 %	0.33 [0.04, 3.06]
Wapner 2006	6/252	10/243		11.8 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**537**	**515**		**100.0 %**	**0.62 [0.44, 0.87]**
Total events: 45 (Repeat), 70 (Single)					
Heterogeneity: Tau² = 0.0; Chi² = 0.33, df = 2 (P = 0.85); I² =0.0%					
Test for overall effect: Z = 2.78 (P = 0.0055)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

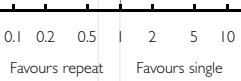
Analysis 1.3. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 3 Composite serious outcome (variously defined).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 3 Composite serious outcome (variously defined)

Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	4/9	5/7		1.1 %	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		28.6 %	0.77 [0.62, 0.96]
Garite 2009	88/276	120/282		22.8 %	0.75 [0.60, 0.93]
Guinn 2002	56/256	66/246		12.9 %	0.82 [0.60, 1.11]
Mazumder 2008	6/37	13/38		2.5 %	0.47 [0.20, 1.11]
Murphy 2008	150/1164	143/1140		27.8 %	1.03 [0.83, 1.27]
Wapner 2006	20/252	22/243		4.3 %	0.88 [0.49, 1.56]
Subtotal (95% CI)	**2561**	**2533**		**100.0 %**	**0.84 [0.75, 0.94]**
Total events: 438 (Favours repeat), 519 (Single)					
Heterogeneity: Chi^2 = 7.24, df = 6 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					



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Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	4/9	5/7		1.1 %	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		28.6 %	0.77 [0.62, 0.96]
Garite 2009	88/276	120/282		22.8 %	0.75 [0.60, 0.93]
Guinn 2002	56/256	66/246		12.9 %	0.82 [0.60, 1.11]
Mazumder 2008	6/37	13/38		2.5 %	0.47 [0.20, 1.11]
Murphy 2008	150/1164	143/1140		27.8 %	1.03 [0.83, 1.27]
Wapner 2006	20/252	22/243		4.3 %	0.88 [0.49, 1.56]
Subtotal (95% CI)	**2561**	**2533**		**100.0 %**	**0.84 [0.75, 0.94]**
Total events: 438 (Favours repeat), 519 (Single)					
Heterogeneity: Chi^2 = 7.24, df = 6 (P = 0.30); I^2 =17%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	4/9	5/7		2.2 %	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		57.9 %	0.77 [0.62, 0.96]
Guinn 2002	56/256	66/246		26.2 %	0.82 [0.60, 1.11]
Mazumder 2008	6/37	13/38		5.0 %	0.47 [0.20, 1.11]
Wapner 2006	20/252	22/243		8.7 %	0.88 [0.49, 1.56]
Subtotal (95% CI)	**1121**	**1111**		**100.0 %**	**0.78 [0.66, 0.91]**
Total events: 200 (Favours repeat), 256 (Single)					
Heterogeneity: Chi^2 = 1.79, df = 4 (P = 0.77); I^2 =0.0%					
Test for overall effect: Z = 3.06 (P = 0.0022)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Garite 2009	88/276	120/282		45.1 %	0.75 [0.60, 0.93]
Murphy 2008	150/1164	143/1140		54.9 %	1.03 [0.83, 1.27]
Subtotal (95% CI)	**1440**	**1422**		**100.0 %**	**0.90 [0.77, 1.05]**
Total events: 238 (Favours repeat), 263 (Single)					
Heterogeneity: Chi^2 = 4.17, df = 1 (P = 0.04); I^2 =76%					
Test for overall effect: Z = 1.31 (P = 0.19)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Garite 2009	88/276	120/282		100.0 %	0.75 [0.60, 0.93]

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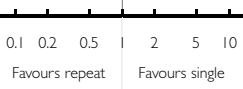
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**276**	**282**		**100.0 %**	**0.75 [0.60, 0.93]**
Total events: 88 (Favours repeat), 120 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.58 (P = 0.0099)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	114/567	150/577		100.0 %	0.77 [0.62, 0.96]
Subtotal (95% CI)	**567**	**577**		**100.0 %**	**0.77 [0.62, 0.96]**
Total events: 114 (Favours repeat), 150 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 2.35 (P = 0.019)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Aghajafari 2002	4/9	5/7		1.5 %	0.62 [0.26, 1.48]
Garite 2009	88/276	120/282		32.0 %	0.75 [0.60, 0.93]
Guinn 2002	56/256	66/246		18.1 %	0.82 [0.60, 1.11]
Mazumder 2008	6/37	13/38		3.5 %	0.47 [0.20, 1.11]
Murphy 2008	150/1164	143/1140		38.9 %	1.03 [0.83, 1.27]
Wapner 2006	20/252	22/243		6.0 %	0.88 [0.49, 1.56]
Subtotal (95% CI)	**1994**	**1956**		**100.0 %**	**0.87 [0.76, 0.99]**
Total events: 324 (Favours repeat), 369 (Single)					
Heterogeneity: Chi^2 = 6.73, df = 5 (P = 0.24); I^2 =26%					
Test for overall effect: Z = 2.15 (P = 0.032)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					



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Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	114/567	150/577		50.7 %	0.77 [0.62, 0.96]
Murphy 2008	150/1164	143/1140		49.3 %	1.03 [0.83, 1.27]
Subtotal (95% CI)	**1731**	**1717**		**100.0 %**	**0.90 [0.77, 1.05]**
Total events: 264 (Favours repeat), 293 (Single)					
Heterogeneity: Chi^2 = 3.39, df = 1 (P = 0.07); I^2 =70%					
Test for overall effect: Z = 1.39 (P = 0.17)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Aghajafari 2002	4/9	5/7		5.2 %	0.62 [0.26, 1.48]
Guinn 2002	56/256	66/246		62.2 %	0.82 [0.60, 1.11]
Mazumder 2008	6/37	13/38		11.9 %	0.47 [0.20, 1.11]
Wapner 2006	20/252	22/243		20.7 %	0.88 [0.49, 1.56]
Subtotal (95% CI)	**554**	**534**		**100.0 %**	**0.78 [0.60, 1.00]**
Total events: 86 (Favours repeat), 106 (Single)					
Heterogeneity: Chi^2 = 1.80, df = 3 (P = 0.62); I^2 =0.0%					
Test for overall effect: Z = 1.96 (P = 0.050)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

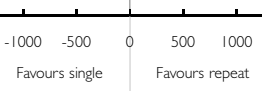
Analysis 1.4. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 4 Mean birthweight (g).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 4 Mean birthweight (g)

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	567	1867 (824)	577	1877 (816)		19.4 %	-10.00 [-105.04, 85.04]
Garite 2009	275	1905 (738)	281	1920 (667)		12.8 %	-15.00 [-132.00, 102.00]
Guinn 2002	248	2009.1 (858.7)	235	2138.8 (875.8)		7.3 %	-129.70 [-284.49, 25.09]
Mazumder 2008	37	1553.4 (441.4)	37	1645.6 (627)		2.9 %	-92.20 [-339.27, 154.87]
McEvoy 2002	18	1767 (659)	19	1975 (740)		0.9 %	-208.00 [-659.00, 243.00]
McEvoy 2010	56	1806 (778)	56	1830 (657)		2.5 %	-24.00 [-290.70, 242.70]
Murphy 2008	1164	2216 (966)	1140	2330 (970)		28.0 %	-114.00 [-193.06, -34.94]
Peltoniemi 2007	159	1460 (500)	167	1558 (487)		15.2 %	-98.00 [-205.22, 9.22]
Wapner 2006	296	2194.3 (762.3)	294	2289.6 (791.8)		11.1 %	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	**2820**		**2806**			**100.0 %**	**-75.79 [-117.63, -33.96]**
Heterogeneity: Chi^2 = 4.99, df = 8 (P = 0.76); I^2 =0.0%							
Test for overall effect: Z = 3.55 (P = 0.00038)							
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	1867 (824)	577	1877 (816)		19.4 %	-10.00 [-105.04, 85.04]
Garite 2009	275	1905 (738)	281	1920 (667)		12.8 %	-15.00 [-132.00, 102.00]
Guinn 2002	248	2009.1 (858.7)	235	2138.8 (875.8)		7.3 %	-129.70 [-284.49, 25.09]
Mazumder 2008	37	1553.4 (441.4)	37	1645.6 (627)		2.9 %	-92.20 [-339.27, 154.87]
McEvoy 2002	18	1767 (659)	19	1975 (740)		0.9 %	-208.00 [-659.00, 243.00]
McEvoy 2010	56	1806 (778)	56	1830 (657)		2.5 %	-24.00 [-290.70, 242.70]
Murphy 2008	1164	2216 (966)	1140	2330 (970)		28.0 %	-114.00 [-193.06, -34.94]
Peltoniemi 2007	159	1460 (500)	167	1558 (487)		15.2 %	-98.00 [-205.22, 9.22]
Wapner 2006	296	2194.3 (762.3)	294	2289.6 (791.8)		11.1 %	-95.30 [-220.73, 30.13]



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Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Subtotal (95% CI)	**2820**		**2806**			**100.0 %**	**-75.79 [-117.63, -33.96]**
Heterogeneity: Chi² = 4.99, df = 8 (P = 0.76); I² =0.0%							
Test for overall effect: Z = 3.55 (P = 0.00038)							
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	1867 (824)	577	1877 (816)		46.7 %	-10.00 [-105.04, 85.04]
Guinn 2002	248	2009.1 (858.7)	235	2138.8 (875.8)		17.6 %	-129.70 [-284.49, 25.09]
Mazumder 2008	37	1553.4 (441.4)	37	1645.6 (627)		6.9 %	-92.20 [-339.27, 154.87]
McEvoy 2002	18	1767 (659)	19	1975 (740)		2.1 %	-208.00 [-659.00, 243.00]
Wapner 2006	296	2194.3 (762.3)	294	2289.6 (791.8)		26.8 %	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	**1166**		**1162**			**100.0 %**	**-63.68 [-128.59, 1.24]**
Heterogeneity: Chi² = 2.61, df = 4 (P = 0.62); I² =0.0%							
Test for overall effect: Z = 1.92 (P = 0.055)							
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more							
Garite 2009	275	1905 (738)	281	1920 (667)		29.6 %	-15.00 [-132.00, 102.00]
McEvoy 2010	56	1806 (778)	56	1830 (657)		5.7 %	-24.00 [-290.70, 242.70]
Murphy 2008	1164	2216 (966)	1140	2330 (970)		64.7 %	-114.00 [-193.06, -34.94]
Subtotal (95% CI)	**1495**		**1477**			**100.0 %**	**-79.61 [-143.23, -16.00]**
Heterogeneity: Chi² = 2.07, df = 2 (P = 0.36); I² =3%							
Test for overall effect: Z = 2.45 (P = 0.014)							
7 In babies exposed to one repeat course of prenatal corticosteroids							
Garite 2009	275	1905 (738)	281	1920 (667)		42.0 %	-15.00 [-132.00, 102.00]
McEvoy 2010	56	1806 (778)	56	1830 (657)		8.1 %	-24.00 [-290.70, 242.70]
Peltoniemi 2007	159	1460 (500)	167	1558 (487)		50.0 %	-98.00 [-205.22, 9.22]
Subtotal (95% CI)	**490**		**504**			**100.0 %**	**-57.20 [-132.99, 18.59]**
Heterogeneity: Chi² = 1.12, df = 2 (P = 0.57); I² =0.0%							
Test for overall effect: Z = 1.48 (P = 0.14)							
8 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
9 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
10 In babies exposed to four or more repeat courses of prenatal corticosteroids							

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Favours single Favours repeat

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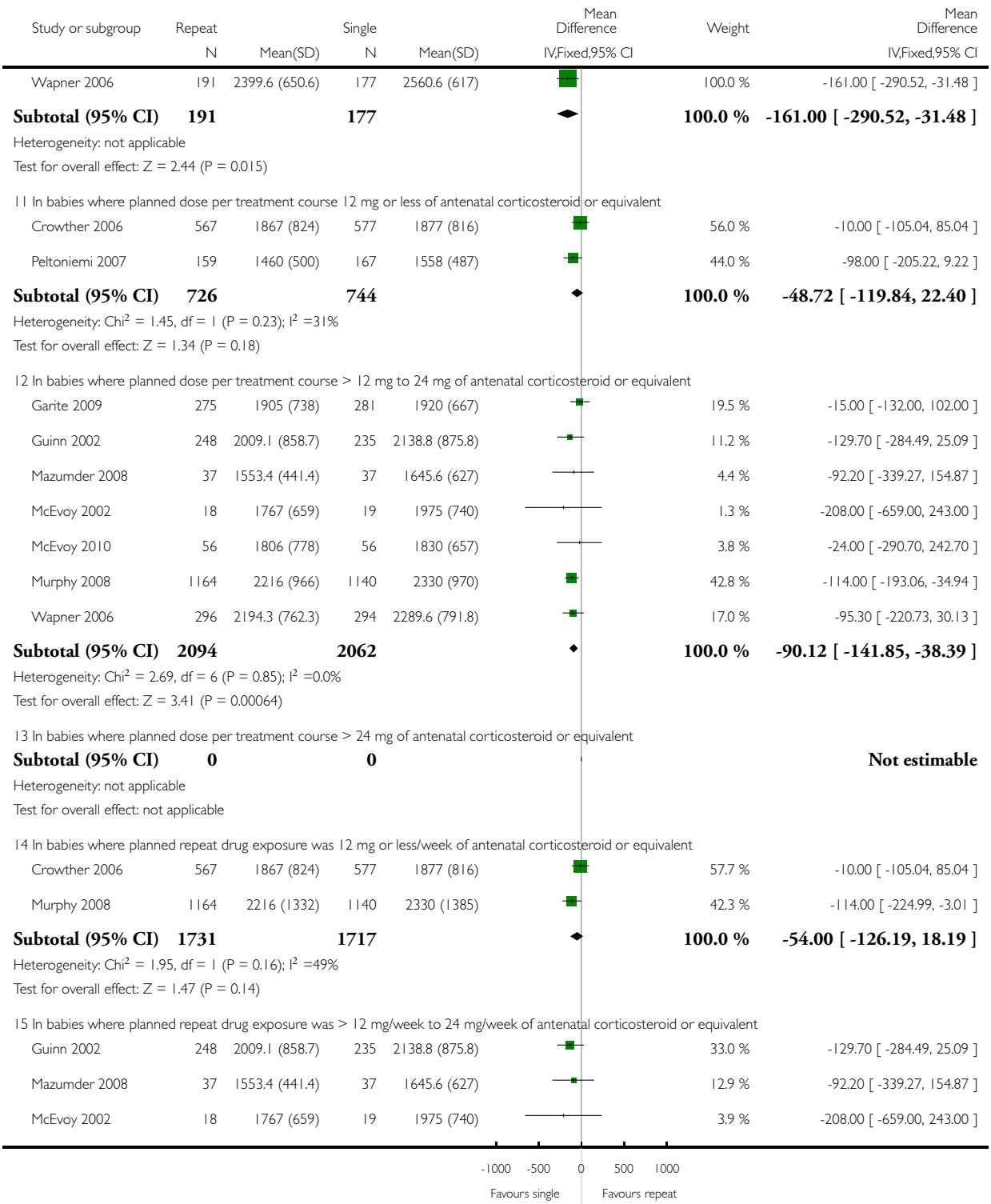

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Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Wapner 2006	296	2194.3 (762.3)	294	2289.6 (791.8)		50.2 %	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	**599**		**585**			**100.0 %**	**-110.62 [-199.49, -21.74]**
Heterogeneity: Chi^2 = 0.32, df = 3 (P = 0.96); I^2 =0.0%							
Test for overall effect: Z = 2.44 (P = 0.015)							
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 1.5. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 5 Birthweight Z scores.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 5 Birthweight Z scores

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	567	-0.4 (1.05)	577	-0.27 (1.14)		87.9 %	-0.13 [-0.26, 0.00]
McEvoy 2010	56	-0.14 (0.86)	56	-0.14 (0.98)		12.1 %	0.0 [-0.34, 0.34]
Subtotal (95% CI)	**623**		**633**			**100.0 %**	**-0.11 [-0.23, 0.00]**
Heterogeneity: Chi^2 = 0.49, df = 1 (P = 0.48); I^2 =0.0%							
Test for overall effect: Z = 1.88 (P = 0.060)							
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 In babies exposed to repeat corticosteroids as betamethasone							

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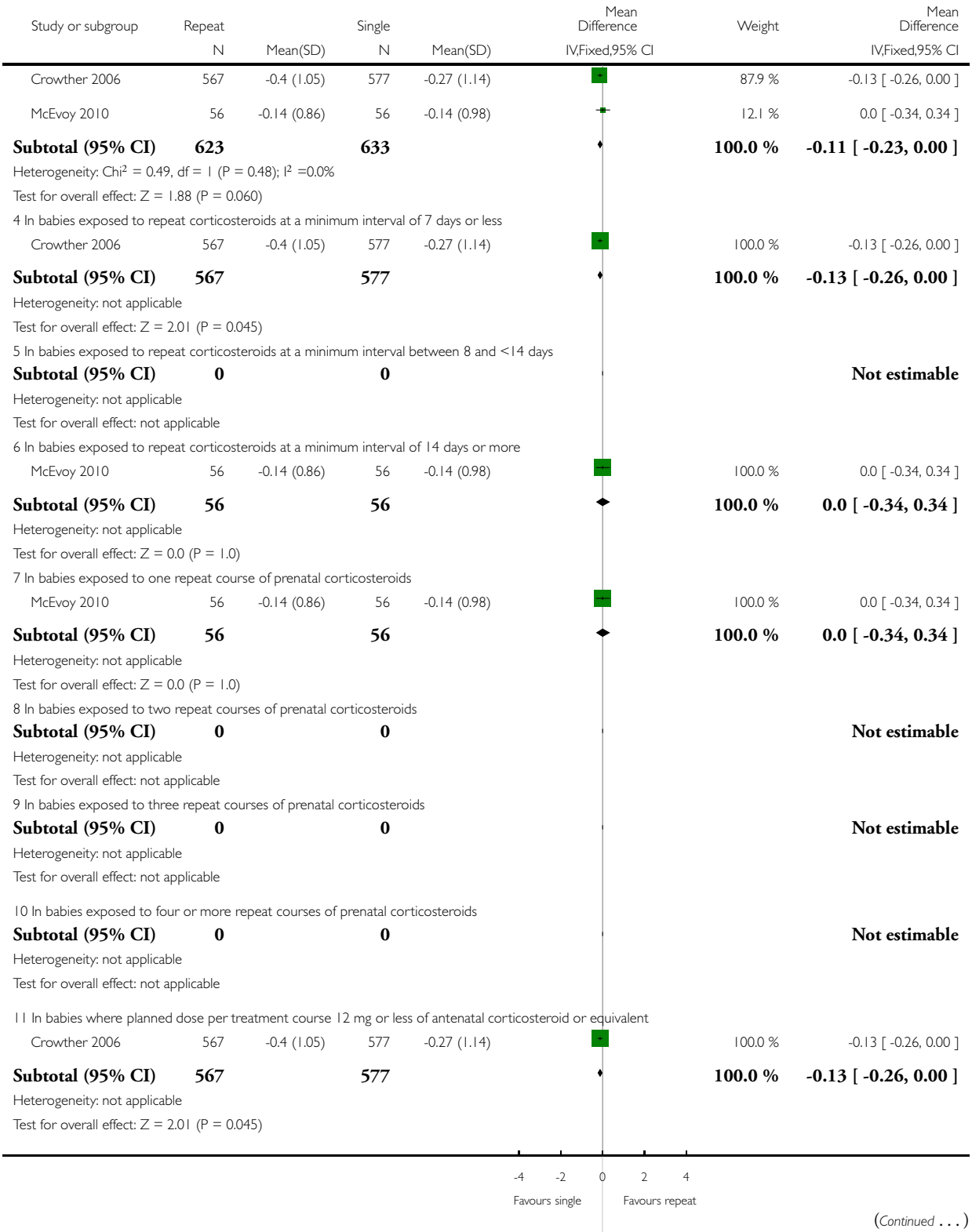

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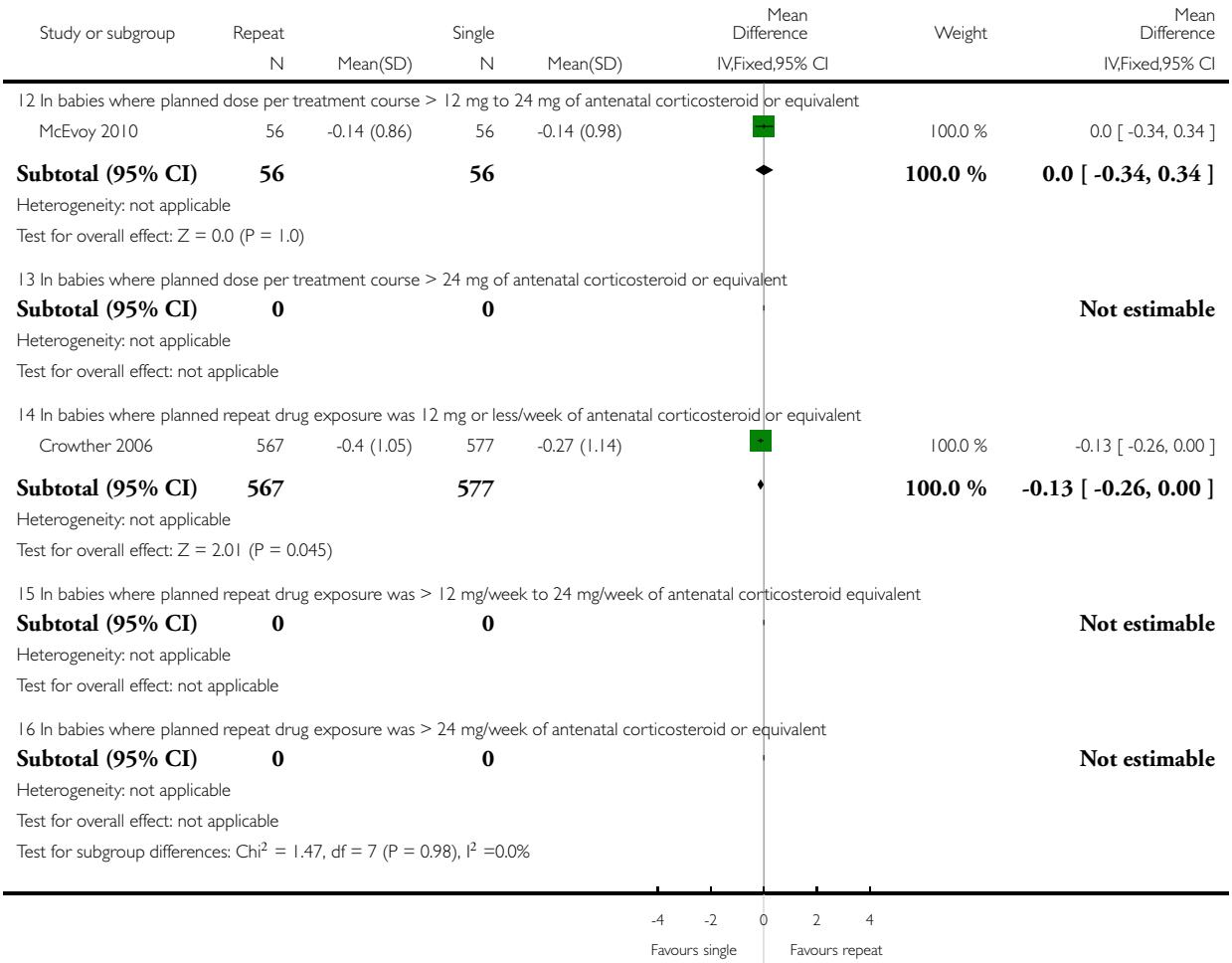


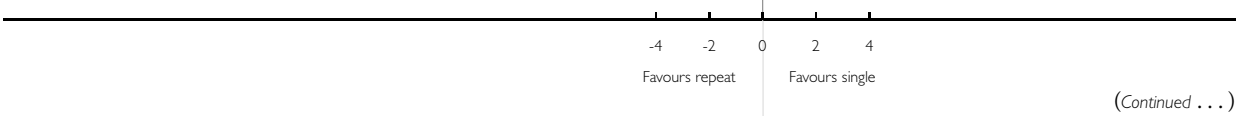
Analysis 1.6. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 6 Birthweight multiples of the median.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 6 Birthweight multiples of the median

Study or subgroup	Repeat		Single		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 In all babies							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**0.0 [-0.03, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
3 In babies exposed to repeat corticosteroids as betamethasone							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**0.0 [-0.03, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**0.0 [-0.03, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
7 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
8 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	**0**		**0**				**Not estimable**



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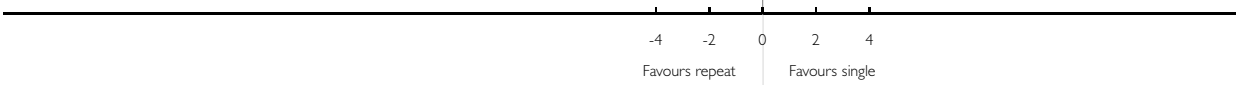
Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
Heterogeneity: not applicable							
Test for overall effect: not applicable							
9 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
10 In babies exposed to four or more repeat courses of prenatal corticosteroids							
Wapner 2006	191	0.86 (0.15)	177	0.9 (0.14)		100.0 %	-0.04 [-0.07, -0.01]
Subtotal (95% CI)	**191**		**177**			**100.0 %**	**-0.04 [-0.07, -0.01]**
Heterogeneity: not applicable							
Test for overall effect: Z = 2.65 (P = 0.0081)							
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**0.0 [-0.03, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0 %	0.0 [-0.03, 0.03]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**0.0 [-0.03, 0.03]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.0 (P = 1.0)							
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent							
Subtotal (95% CI)	**0**		**0**				**Not estimable**
Heterogeneity: not applicable							
Test for overall effect: not applicable							
Test for subgroup differences: Chi^2 = 6.13, df = 5 (P = 0.29), I^2 =18%							



Analysis 1.7. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 7 Small-for-gestational age at birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 7 Small-for-gestational age at birth

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	2/9	0/7		0.3 %	4.00 [0.22, 72.01]
Garite 2009	29/275	28/278		17.1 %	1.05 [0.64, 1.71]
Mazumder 2008	11/37	10/37		6.1 %	1.10 [0.53, 2.27]
McEvoy 2010	6/56	8/56		4.9 %	0.75 [0.28, 2.02]
Murphy 2008	64/1164	59/1140		36.5 %	1.06 [0.75, 1.50]
Peltoniemi 2007	47/159	37/167		22.1 %	1.33 [0.92, 1.94]
Wapner 2006	32/296	21/294		12.9 %	1.51 [0.89, 2.56]
Subtotal (95% CI)	**1996**	**1979**		**100.0 %**	**1.18 [0.97, 1.43]**
Total events: 191 (Repeat), 163 (Single)					
Heterogeneity: Chi^2 = 3.39, df = 6 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.62 (P = 0.10)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	2/9	0/7		0.3 %	4.00 [0.22, 72.01]
Garite 2009	29/275	28/278		17.1 %	1.05 [0.64, 1.71]
Mazumder 2008	11/37	10/37		6.1 %	1.10 [0.53, 2.27]
McEvoy 2010	6/56	8/56		4.9 %	0.75 [0.28, 2.02]
Murphy 2008	64/1164	59/1140		36.5 %	1.06 [0.75, 1.50]
Peltoniemi 2007	47/159	37/167		22.1 %	1.33 [0.92, 1.94]
Wapner 2006	32/296	21/294		12.9 %	1.51 [0.89, 2.56]
Subtotal (95% CI)	**1996**	**1979**		**100.0 %**	**1.18 [0.97, 1.43]**
Total events: 191 (Repeat), 163 (Single)					

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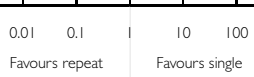
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 3.39, df = 6 (P = 0.76); I² =0.0%					
Test for overall effect: Z = 1.62 (P = 0.10)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	2/9	0/7		0.8 %	4.00 [0.22, 72.01]
Mazumder 2008	11/37	10/37		14.8 %	1.10 [0.53, 2.27]
Peltoniemi 2007	47/159	37/167		53.3 %	1.33 [0.92, 1.94]
Wapner 2006	32/296	21/294		31.1 %	1.51 [0.89, 2.56]
Subtotal (95% CI)	**501**	**505**		**100.0 %**	**1.38 [1.04, 1.82]**
Total events: 92 (Repeat), 68 (Single)					
Heterogeneity: Chi² = 1.04, df = 3 (P = 0.79); I² =0.0%					
Test for overall effect: Z = 2.24 (P = 0.025)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Garite 2009	29/275	28/278		29.2 %	1.05 [0.64, 1.71]
McEvoy 2010	6/56	8/56		8.4 %	0.75 [0.28, 2.02]
Murphy 2008	64/1164	59/1140		62.4 %	1.06 [0.75, 1.50]
Subtotal (95% CI)	**1495**	**1474**		**100.0 %**	**1.03 [0.79, 1.35]**
Total events: 99 (Repeat), 95 (Single)					
Heterogeneity: Chi² = 0.43, df = 2 (P = 0.81); I² =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Garite 2009	29/275	28/278		38.7 %	1.05 [0.64, 1.71]
McEvoy 2010	6/56	8/56		11.1 %	0.75 [0.28, 2.02]
Peltoniemi 2007	47/159	37/167		50.2 %	1.33 [0.92, 1.94]
Subtotal (95% CI)	**490**	**501**		**100.0 %**	**1.16 [0.87, 1.54]**
Total events: 82 (Repeat), 73 (Single)					
Heterogeneity: Chi² = 1.46, df = 2 (P = 0.48); I² =0.0%					
Test for overall effect: Z = 1.01 (P = 0.31)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					



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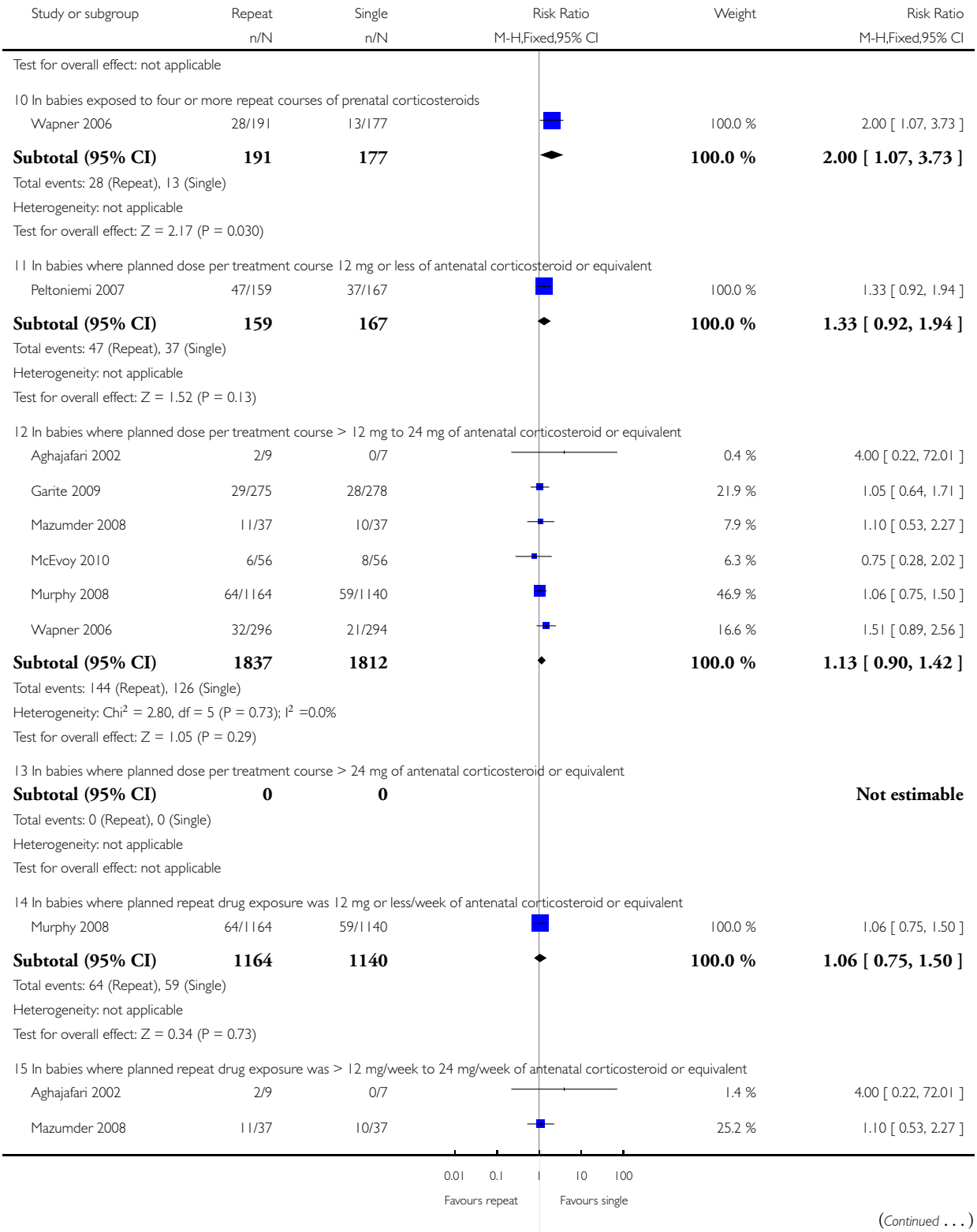

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McEvoy 2010	6/56	8/56		20.2 %	0.75 [0.28, 2.02]
Wapner 2006	32/296	21/294		53.2 %	1.51 [0.89, 2.56]
Subtotal (95% CI)	**398**	**394**		**100.0 %**	**1.29 [0.88, 1.90]**
Total events: 51 (Repeat), 39 (Single)					
Heterogeneity: Chi^2 = 2.28, df = 3 (P = 0.52); I^2 =0.0%					
Test for overall effect: Z = 1.29 (P = 0.20)					
16 In babies where planned repeat drug exposure was >24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

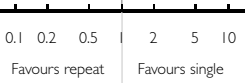
Analysis 1.8. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 8 Fetal and neonatal mortality.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 8 Fetal and neonatal mortality

Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	0/9	0/7			Not estimable
Crowther 2006	27/568	29/578		27.9 %	0.95 [0.57, 1.58]
Garite 2009	5/289	7/288		6.8 %	0.71 [0.23, 2.22]
Guinn 2002	5/256	9/246		8.9 %	0.53 [0.18, 1.57]
Mazumder 2008	4/38	8/38		7.8 %	0.50 [0.16, 1.52]
McEvoy 2010	1/56	0/56		0.5 %	3.00 [0.12, 72.10]
Murphy 2008	43/1164	40/1140		39.3 %	1.05 [0.69, 1.61]
Peltoniemi 2007	8/159	3/167		2.8 %	2.80 [0.76, 10.37]
Wapner 2006	3/252	6/243		5.9 %	0.48 [0.12, 1.91]
Subtotal (95% CI)	**2791**	**2763**		**100.0 %**	**0.94 [0.71, 1.23]**
Total events: 96 (Favours repeat), 102 (Single)					
Heterogeneity: Chi^2 = 6.89, df = 7 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Guinn 2002	3/81	6/79		100.0 %	0.49 [0.13, 1.88]
Subtotal (95% CI)	**81**	**79**		**100.0 %**	**0.49 [0.13, 1.88]**
Total events: 3 (Favours repeat), 6 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.04 (P = 0.30)					
3 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	0/9	0/7			Not estimable
Crowther 2006	27/568	29/578		27.9 %	0.95 [0.57, 1.58]
Garite 2009	5/289	7/288		6.8 %	0.71 [0.23, 2.22]
Guinn 2002	5/256	9/246		8.9 %	0.53 [0.18, 1.57]
Mazumder 2008	4/38	8/38		7.8 %	0.50 [0.16, 1.52]
McEvoy 2010	1/56	0/56		0.5 %	3.00 [0.12, 72.10]
Murphy 2008	43/1164	40/1140		39.3 %	1.05 [0.69, 1.61]



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Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Peltoniemi 2007	8/159	3/167		2.8 %	2.80 [0.76, 10.37]
Wapner 2006	3/252	6/243		5.9 %	0.48 [0.12, 1.91]
Subtotal (95% CI)	**2791**	**2763**		**100.0 %**	**0.94 [0.71, 1.23]**
Total events: 96 (Favours repeat), 102 (Single)					
Heterogeneity: Chi^2 = 6.89, df = 7 (P = 0.44); I^2 =0.0%					
Test for overall effect: Z = 0.48 (P = 0.63)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	8/159	3/167		5.1 %	2.80 [0.76, 10.37]
Crowther 2006	27/568	29/578		49.7 %	0.95 [0.57, 1.58]
Guinn 2002	5/256	9/246		15.9 %	0.53 [0.18, 1.57]
Mazumder 2008	4/38	8/38		13.8 %	0.50 [0.16, 1.52]
Peltoniemi 2007	8/159	3/167		5.1 %	2.80 [0.76, 10.37]
Wapner 2006	3/252	6/243		10.6 %	0.48 [0.12, 1.91]
Subtotal (95% CI)	**1432**	**1439**		**100.0 %**	**0.96 [0.67, 1.37]**
Total events: 55 (Favours repeat), 58 (Single)					
Heterogeneity: Chi^2 = 8.56, df = 5 (P = 0.13); I^2 =42%					
Test for overall effect: Z = 0.23 (P = 0.82)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Garite 2009	5/289	7/288		14.6 %	0.71 [0.23, 2.22]
McEvoy 2010	1/56	0/56		1.0 %	3.00 [0.12, 72.10]
Murphy 2008	43/1164	40/1140		84.3 %	1.05 [0.69, 1.61]
Subtotal (95% CI)	**1509**	**1484**		**100.0 %**	**1.02 [0.69, 1.51]**
Total events: 49 (Favours repeat), 47 (Single)					
Heterogeneity: Chi^2 = 0.85, df = 2 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.12 (P = 0.91)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Garite 2009	5/289	7/288		67.2 %	0.71 [0.23, 2.22]
McEvoy 2010	1/56	0/56		4.8 %	3.00 [0.12, 72.10]
Peltoniemi 2007	8/159	3/167		28.0 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**504**	**511**		**100.0 %**	**1.41 [0.64, 3.08]**
Total events: 14 (Favours repeat), 10 (Single)					
Heterogeneity: Chi^2 = 2.66, df = 2 (P = 0.26); I^2 =25%					
Test for overall effect: Z = 0.86 (P = 0.39)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					

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Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	27/568	29/578		90.8 %	0.95 [0.57, 1.58]
Peltoniemi 2007	8/159	3/167		9.2 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**727**	**745**		**100.0 %**	**1.12 [0.70, 1.79]**
Total events: 35 (Favours repeat), 32 (Single)					
Heterogeneity: Chi^2 = 2.29, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.47 (P = 0.64)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Aghajafari 2002	0/9	0/7			Not estimable
Garite 2009	5/289	7/288		9.8 %	0.71 [0.23, 2.22]
Guinn 2002	5/256	9/246		12.9 %	0.53 [0.18, 1.57]
Mazumder 2008	4/38	8/38		11.2 %	0.50 [0.16, 1.52]
McEvoy 2010	1/56	0/56		0.7 %	3.00 [0.12, 72.10]
Murphy 2008	43/1164	40/1140		56.8 %	1.05 [0.69, 1.61]
Wapner 2006	3/252	6/243		8.6 %	0.48 [0.12, 1.91]
Subtotal (95% CI)	**2064**	**2018**		**100.0 %**	**0.85 [0.61, 1.19]**
Total events: 61 (Favours repeat), 70 (Single)					
Heterogeneity: Chi^2 = 3.92, df = 5 (P = 0.56); I^2 =0.0%					
Test for overall effect: Z = 0.92 (P = 0.36)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					

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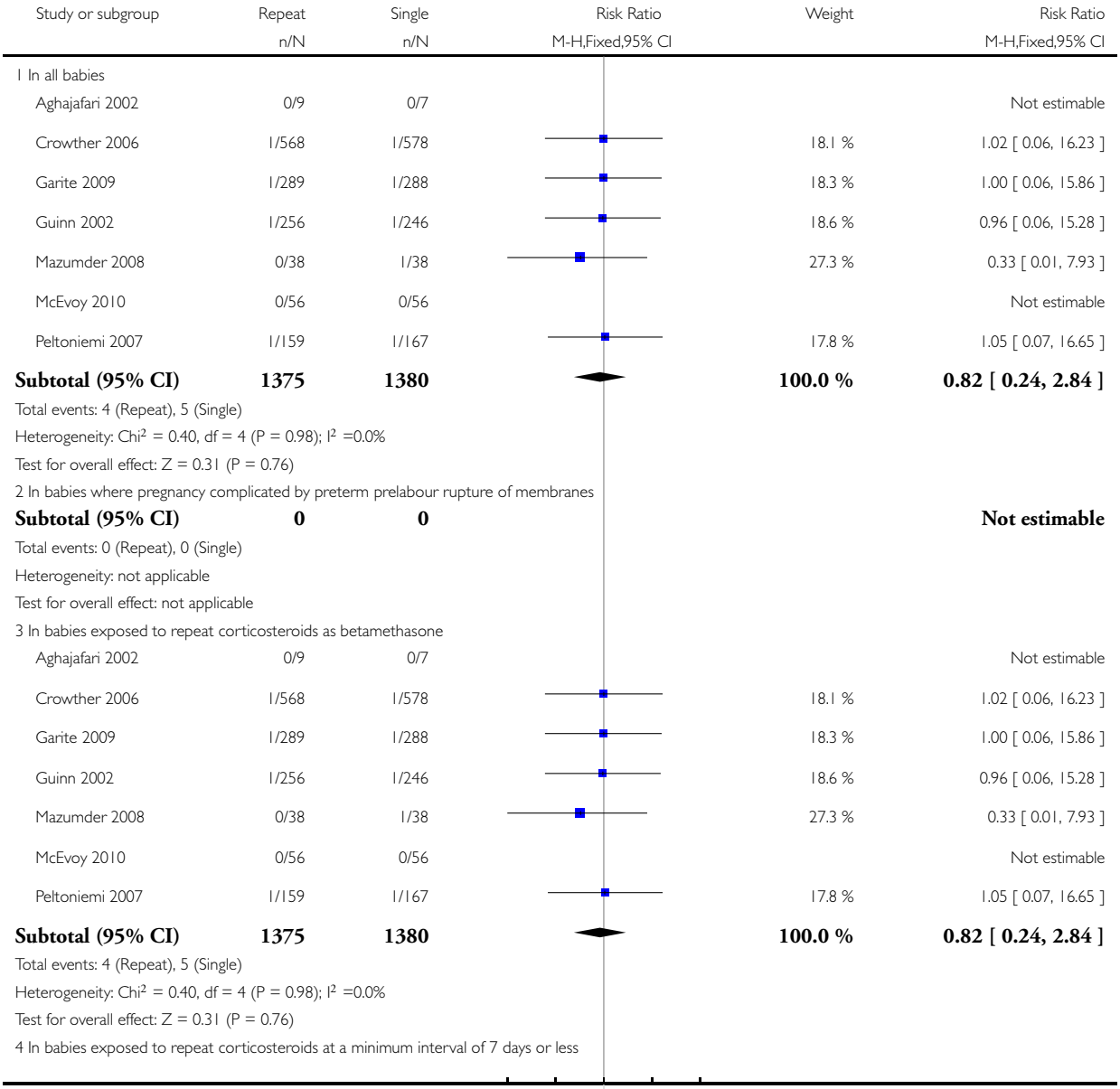
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Crowther 2006	27/568	29/578		41.6 %	0.95 [0.57, 1.58]
Murphy 2008	43/1164	40/1140		58.4 %	1.05 [0.69, 1.61]
Subtotal (95% CI)	**1732**	**1718**		**100.0 %**	**1.01 [0.73, 1.40]**
Total events: 70 (Favours repeat), 69 (Single)					
Heterogeneity: Chi^2 = 0.10, df = 1 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.05 (P = 0.96)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Aghajafari 2002	0/9	0/7			Not estimable
Guinn 2002	5/256	9/246		39.4 %	0.53 [0.18, 1.57]
Mazumder 2008	4/38	8/38		34.4 %	0.50 [0.16, 1.52]
Wapner 2006	3/252	6/243		26.2 %	0.48 [0.12, 1.91]
Subtotal (95% CI)	**555**	**534**		**100.0 %**	**0.51 [0.26, 1.00]**
Total events: 12 (Favours repeat), 23 (Single)					
Heterogeneity: Chi^2 = 0.01, df = 2 (P = 0.99); I^2 =0.0%					
Test for overall effect: Z = 1.96 (P = 0.050)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.9. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 9 Fetal death.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 9 Fetal death



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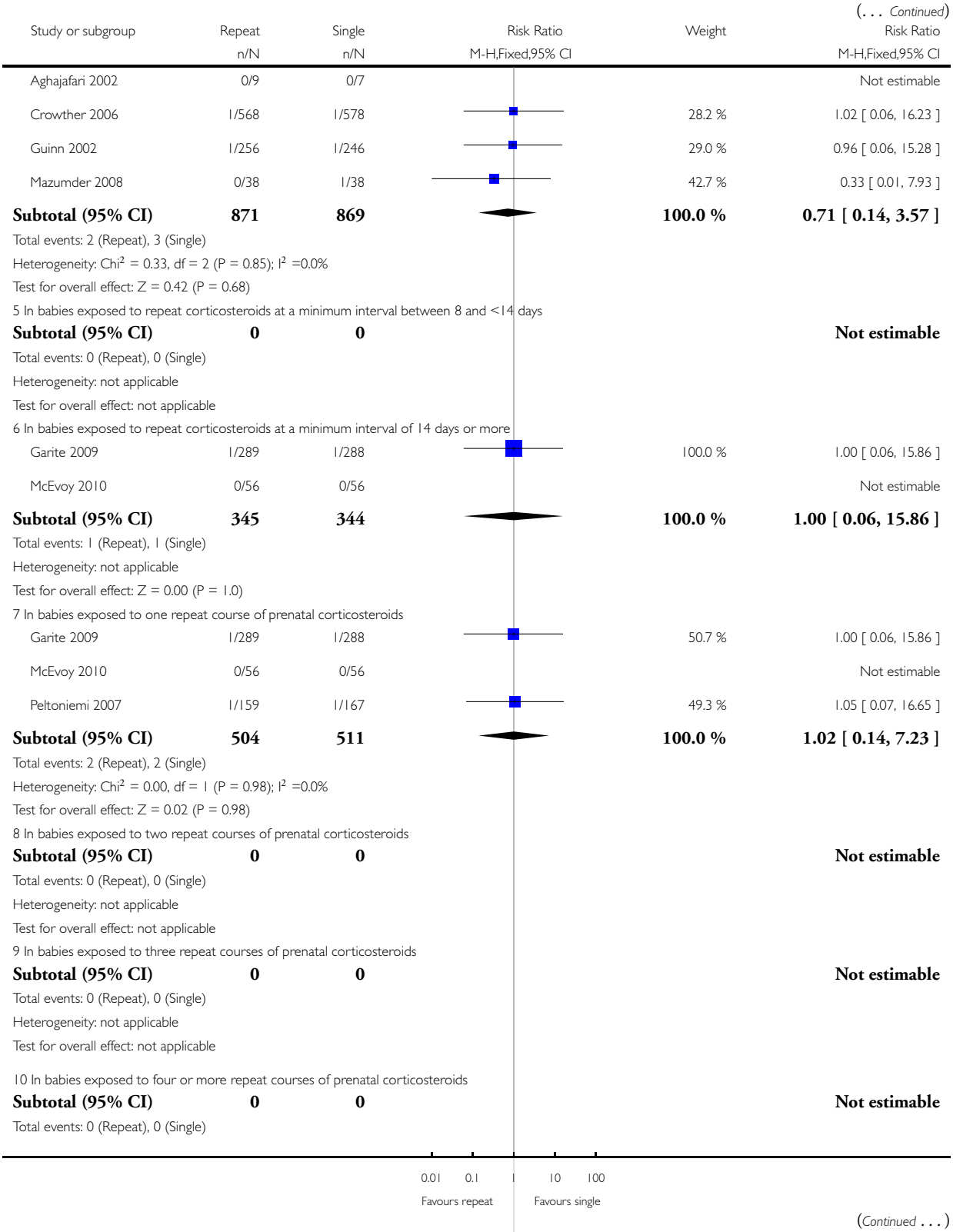

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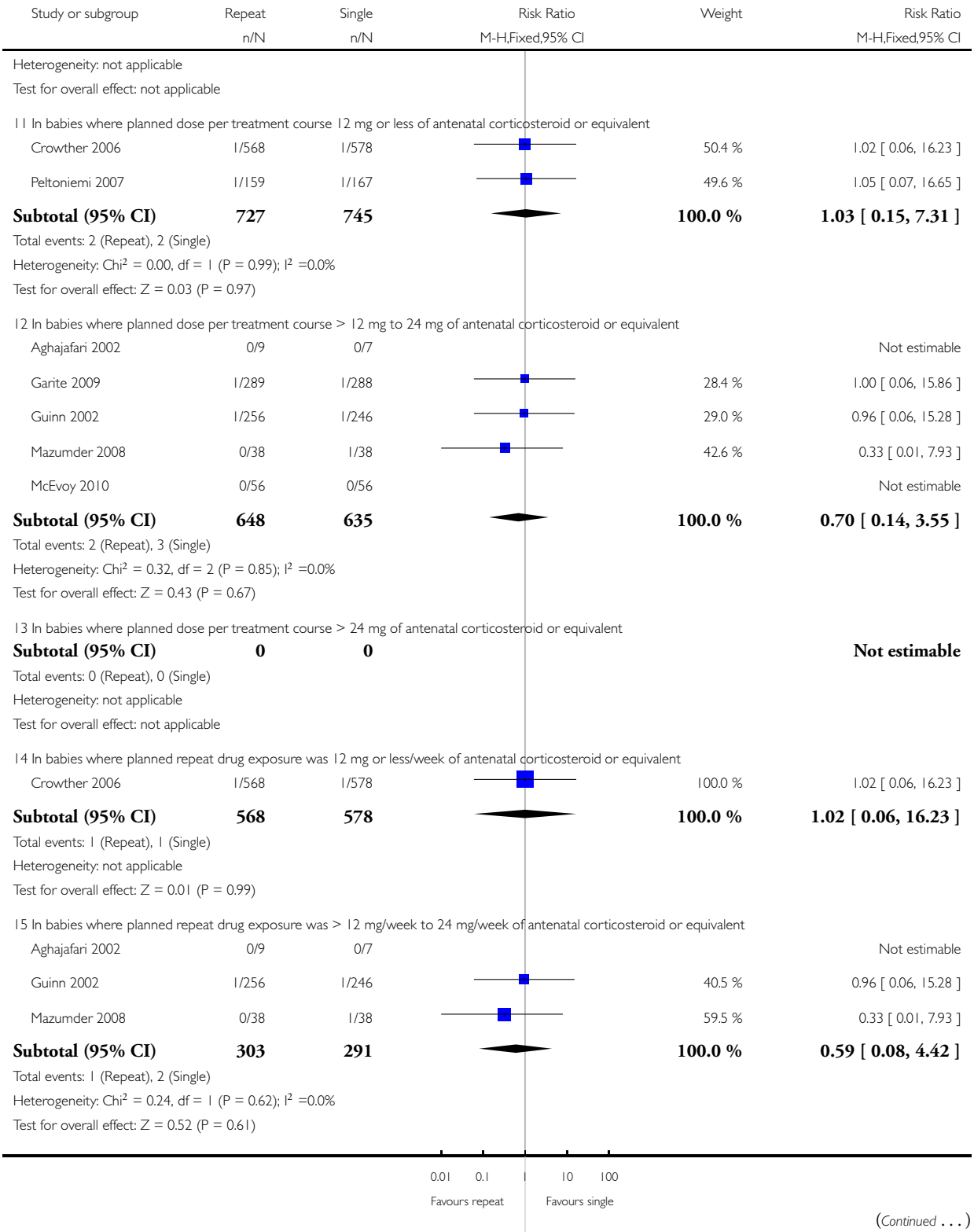

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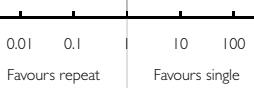
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



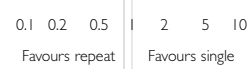
Analysis 1.10. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 10 Neonatal death.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 10 Neonatal death

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	0/9	0/7			Not estimable
Crowther 2006	26/567	28/577		53.0 %	0.94 [0.56, 1.59]
Garite 2009	4/275	6/281		11.3 %	0.68 [0.19, 2.39]
Guinn 2002	4/248	8/235		15.7 %	0.47 [0.14, 1.55]
Mazumder 2008	4/38	7/38		13.4 %	0.57 [0.18, 1.79]
McEvoy 2010	1/56	0/56		1.0 %	3.00 [0.12, 72.10]
Peltoniemi 2007	8/159	3/167		5.6 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**1352**	**1361**		**100.0 %**	**0.91 [0.62, 1.34]**
Total events: 47 (Repeat), 52 (Single)					
Heterogeneity: Chi^2 = 5.40, df = 5 (P = 0.37); I^2 =7%					
Test for overall effect: Z = 0.46 (P = 0.65)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**



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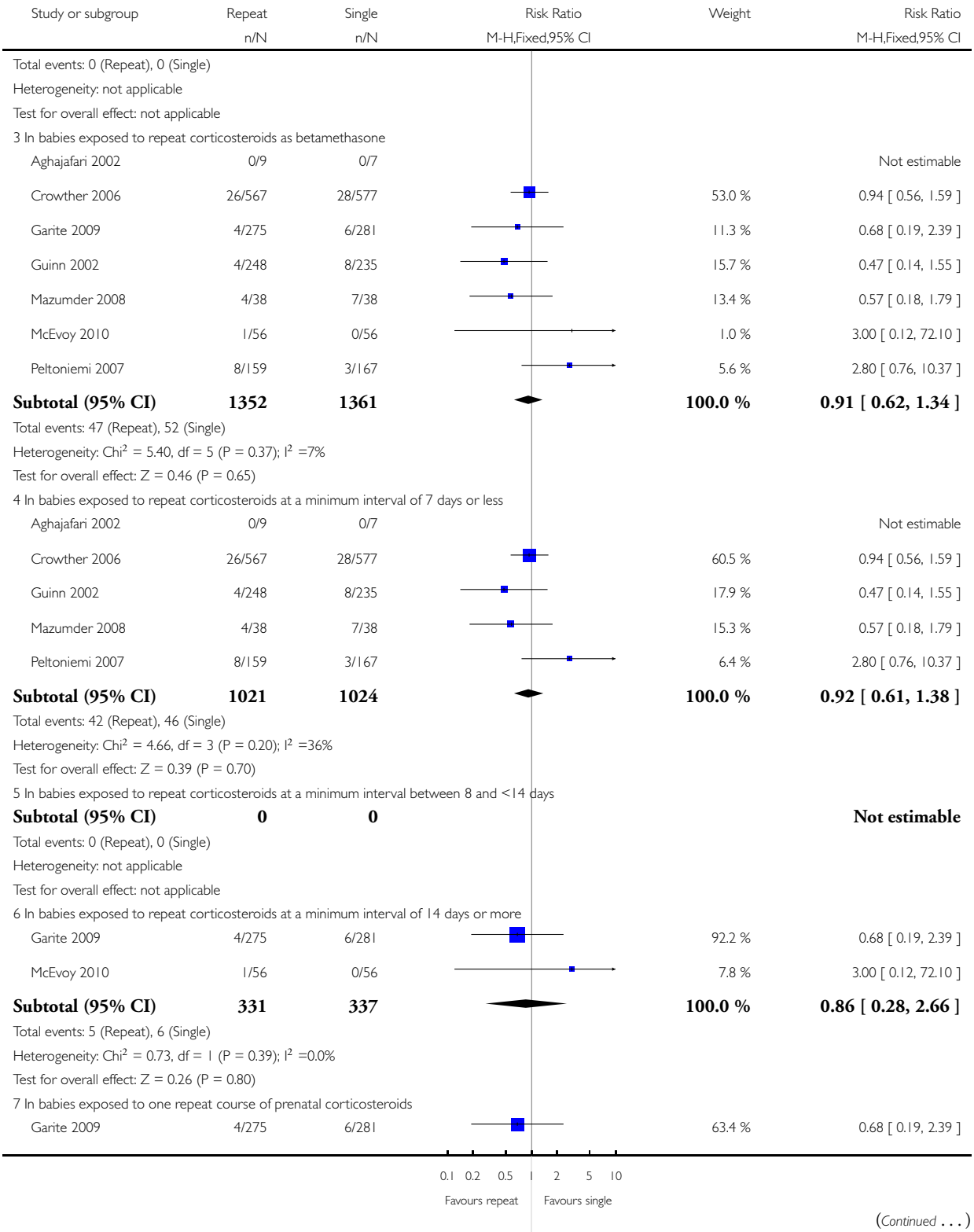

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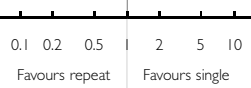
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
McEvoy 2010	1/56	0/56		5.3 %	3.00 [0.12, 72.10]
Peltoniemi 2007	8/159	3/167		31.3 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**490**	**504**		**100.0 %**	**1.47 [0.65, 3.33]**
Total events: 13 (Repeat), 9 (Single)					
Heterogeneity: Chi^2 = 2.57, df = 2 (P = 0.28); I^2 =22%					
Test for overall effect: Z = 0.92 (P = 0.36)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	26/567	28/577		90.5 %	0.94 [0.56, 1.59]
Peltoniemi 2007	8/159	3/167		9.5 %	2.80 [0.76, 10.37]
Subtotal (95% CI)	**726**	**744**		**100.0 %**	**1.12 [0.70, 1.80]**
Total events: 34 (Repeat), 31 (Single)					
Heterogeneity: Chi^2 = 2.29, df = 1 (P = 0.13); I^2 =56%					
Test for overall effect: Z = 0.47 (P = 0.64)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Aghajafari 2002	0/9	0/7			Not estimable
Garite 2009	4/275	6/281		27.4 %	0.68 [0.19, 2.39]
Guinn 2002	4/248	8/235		37.9 %	0.47 [0.14, 1.55]
Mazumder 2008	4/38	7/38		32.3 %	0.57 [0.18, 1.79]
McEvoy 2010	1/56	0/56		2.3 %	3.00 [0.12, 72.10]
Subtotal (95% CI)	**626**	**617**		**100.0 %**	**0.62 [0.32, 1.20]**
Total events: 13 (Repeat), 21 (Single)					
Heterogeneity: Chi^2 = 1.18, df = 3 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 1.42 (P = 0.16)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					



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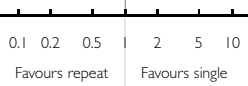
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	26/567	28/577		100.0 %	0.94 [0.56, 1.59]
Subtotal (95% CI)	**567**	**577**		**100.0 %**	**0.94 [0.56, 1.59]**
Total events: 26 (Repeat), 28 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.21 (P = 0.83)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Aghajafari 2002	0/9	0/7			Not estimable
Guinn 2002	4/248	8/235		54.0 %	0.47 [0.14, 1.55]
Mazumder 2008	4/38	7/38		46.0 %	0.57 [0.18, 1.79]
Subtotal (95% CI)	**295**	**280**		**100.0 %**	**0.52 [0.23, 1.18]**
Total events: 8 (Repeat), 15 (Single)					
Heterogeneity: Chi^2 = 0.05, df = 1 (P = 0.82); I^2 =0.0%					
Test for overall effect: Z = 1.56 (P = 0.12)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



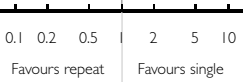
Analysis 1.11. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 11 Chronic lung disease.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 11 Chronic lung disease

Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	2/9	2/7		1.3 %	0.78 [0.14, 4.23]
Crowther 2006	76/567	82/577		47.8 %	0.94 [0.71, 1.26]
Garite 2009	27/273	20/278		11.7 %	1.37 [0.79, 2.39]
Guinn 2002	28/248	26/235		15.7 %	1.02 [0.62, 1.69]
Mazumder 2008	0/37	0/37			Not estimable
Murphy 2008	19/1164	11/1140		6.5 %	1.69 [0.81, 3.54]
Peltoniemi 2007	15/159	14/167		8.0 %	1.13 [0.56, 2.26]
Wapner 2006	14/252	15/243		9.0 %	0.90 [0.44, 1.82]
Subtotal (95% CI)	**2709**	**2684**		**100.0 %**	**1.06 [0.87, 1.30]**
Total events: 181 (Favours repeat), 170 (Single)					
Heterogeneity: Chi^2 = 3.40, df = 6 (P = 0.76); I^2 =0.0%					
Test for overall effect: Z = 0.61 (P = 0.54)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Guinn 2002	15/81	19/79		100.0 %	0.77 [0.42, 1.41]
Subtotal (95% CI)	**81**	**79**		**100.0 %**	**0.77 [0.42, 1.41]**
Total events: 15 (Favours repeat), 19 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.85 (P = 0.39)					
3 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	2/9	2/7		1.3 %	0.78 [0.14, 4.23]
Crowther 2006	76/567	82/577		47.8 %	0.94 [0.71, 1.26]
Garite 2009	27/273	20/278		11.7 %	1.37 [0.79, 2.39]
Guinn 2002	28/248	26/235		15.7 %	1.02 [0.62, 1.69]
Mazumder 2008	0/37	0/37			Not estimable
Murphy 2008	19/1164	11/1140		6.5 %	1.69 [0.81, 3.54]
Peltoniemi 2007	15/159	14/167		8.0 %	1.13 [0.56, 2.26]
Wapner 2006	14/252	15/243		9.0 %	0.90 [0.44, 1.82]



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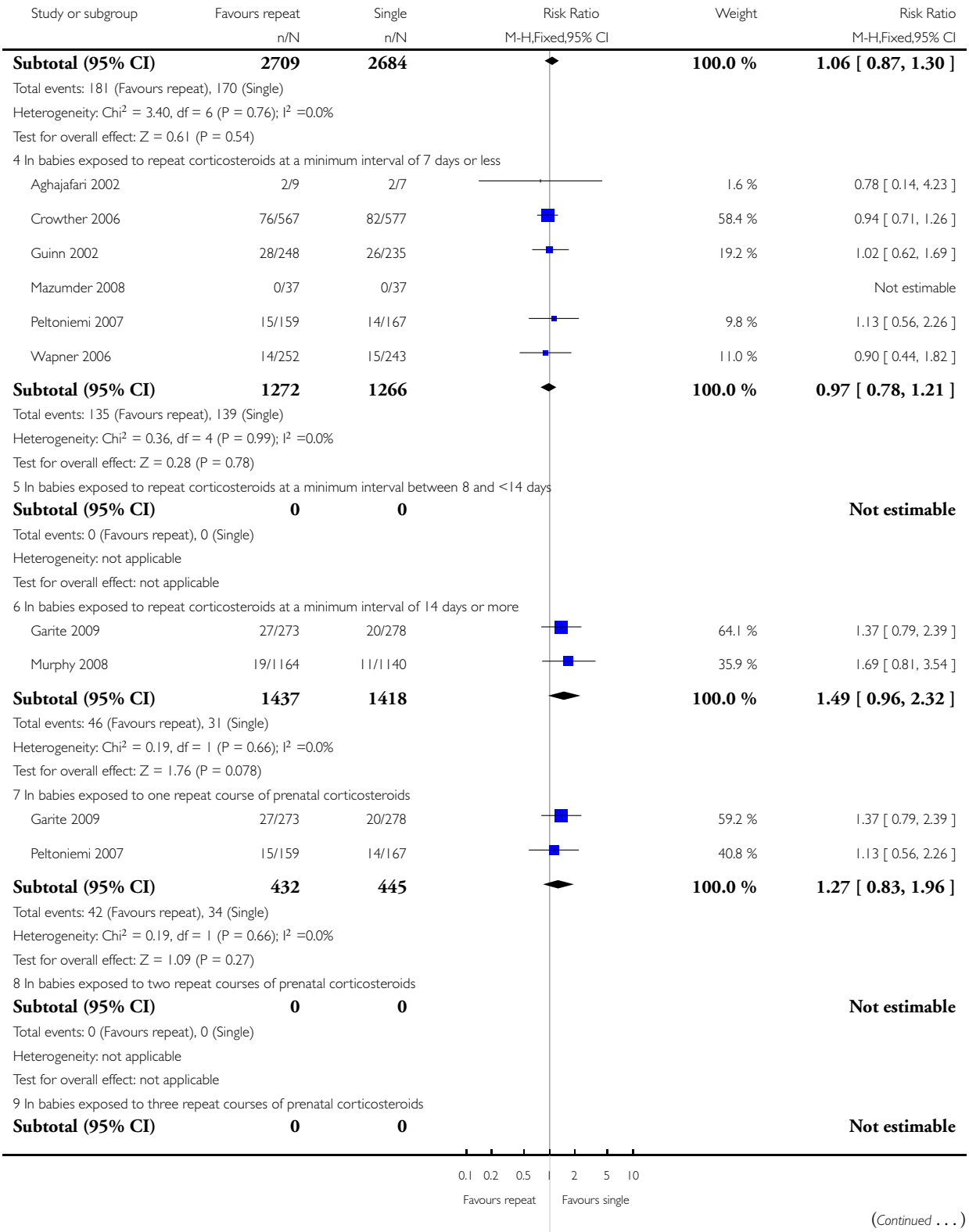

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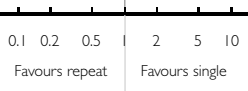
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent					
Crowther 2006	76/567	82/577		85.6 %	0.94 [0.71, 1.26]
Peltoniemi 2007	15/159	14/167		14.4 %	1.13 [0.56, 2.26]
Subtotal (95% CI)	**726**	**744**		**100.0 %**	**0.97 [0.74, 1.27]**
Total events: 91 (Favours repeat), 96 (Single)					
Heterogeneity: Chi^2 = 0.21, df = 1 (P = 0.65); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent					
Aghajafari 2002	2/9	2/7		3.0 %	0.78 [0.14, 4.23]
Garite 2009	27/273	20/278		26.4 %	1.37 [0.79, 2.39]
Guinn 2002	28/248	26/235		35.5 %	1.02 [0.62, 1.69]
Mazumder 2008	0/37	0/37			Not estimable
Murphy 2008	19/1164	11/1140		14.8 %	1.69 [0.81, 3.54]
Wapner 2006	14/252	15/243		20.3 %	0.90 [0.44, 1.82]
Subtotal (95% CI)	**1983**	**1940**		**100.0 %**	**1.18 [0.88, 1.59]**
Total events: 90 (Favours repeat), 74 (Single)					
Heterogeneity: Chi^2 = 2.33, df = 4 (P = 0.68); I^2 =0.0%					
Test for overall effect: Z = 1.11 (P = 0.27)					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	76/567	82/577		88.0 %	0.94 [0.71, 1.26]
Murphy 2008	19/1164	11/1140		12.0 %	1.69 [0.81, 3.54]
Subtotal (95% CI)	**1731**	**1717**		**100.0 %**	**1.03 [0.79, 1.35]**
Total events: 95 (Favours repeat), 93 (Single)					
Heterogeneity: Chi^2 = 2.09, df = 1 (P = 0.15); I^2 =52%					
Test for overall effect: Z = 0.24 (P = 0.81)					



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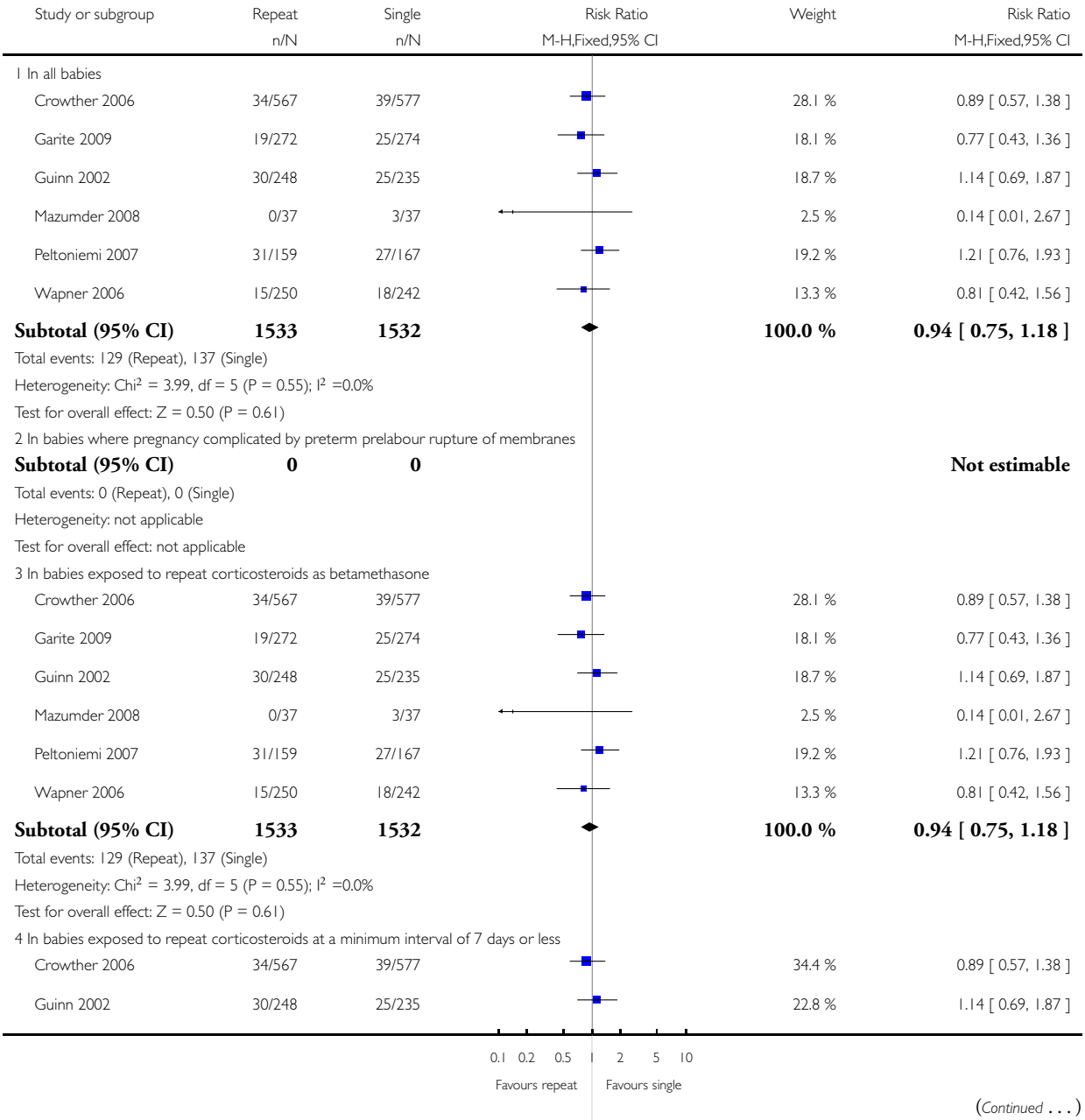
Study or subgroup	Favours repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Aghajafari 2002	2/9	2/7		5.1 %	0.78 [0.14, 4.23]
Guinn 2002	28/248	26/235		60.4 %	1.02 [0.62, 1.69]
Mazumder 2008	0/37	0/37			Not estimable
Wapner 2006	14/252	15/243		34.5 %	0.90 [0.44, 1.82]
Subtotal (95% CI)	**546**	**522**		**100.0 %**	**0.97 [0.65, 1.44]**
Total events: 44 (Favours repeat), 43 (Single)					
Heterogeneity: Chi^2 = 0.15, df = 2 (P = 0.93); I^2 =0.0%					
Test for overall effect: Z = 0.17 (P = 0.87)					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.12. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 12 Intraventricular haemorrhage.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 12 Intraventricular haemorrhage



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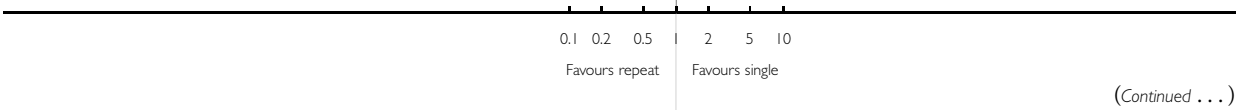
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Mazumder 2008	0/37	3/37		3.1 %	0.14 [0.01, 2.67]
Peltoniemi 2007	31/159	27/167		23.4 %	1.21 [0.76, 1.93]
Wapner 2006	15/250	18/242		16.3 %	0.81 [0.42, 1.56]
Subtotal (95% CI)	**1261**	**1258**		**100.0 %**	**0.98 [0.77, 1.26]**
Total events: 110 (Repeat), 112 (Single)					
Heterogeneity: Chi² = 3.27, df = 4 (P = 0.51); I² =0.0%					
Test for overall effect: Z = 0.14 (P = 0.89)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Garite 2009	19/272	25/274		100.0 %	0.77 [0.43, 1.36]
Subtotal (95% CI)	**272**	**274**		**100.0 %**	**0.77 [0.43, 1.36]**
Total events: 19 (Repeat), 25 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.91 (P = 0.36)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Garite 2009	19/272	25/274		48.6 %	0.77 [0.43, 1.36]
Peltoniemi 2007	31/159	27/167		51.4 %	1.21 [0.76, 1.93]
Subtotal (95% CI)	**431**	**441**		**100.0 %**	**0.99 [0.69, 1.42]**
Total events: 50 (Repeat), 52 (Single)					
Heterogeneity: Chi² = 1.46, df = 1 (P = 0.23); I² =31%					
Test for overall effect: Z = 0.04 (P = 0.96)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent					



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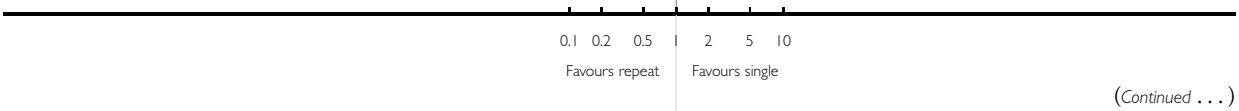
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Crowther 2006	34/567	39/577		59.5 %	0.89 [0.57, 1.38]
Peltoniemi 2007	31/159	27/167		40.5 %	1.21 [0.76, 1.93]
Subtotal (95% CI)	**726**	**744**		**100.0 %**	**1.02 [0.74, 1.40]**
Total events: 65 (Repeat), 66 (Single)					
Heterogeneity: Chi^2 = 0.87, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.10 (P = 0.92)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent					
Garite 2009	19/272	25/274		34.4 %	0.77 [0.43, 1.36]
Guinn 2002	30/248	25/235		35.5 %	1.14 [0.69, 1.87]
Mazumder 2008	0/37	3/37		4.8 %	0.14 [0.01, 2.67]
Wapner 2006	15/250	18/242		25.3 %	0.81 [0.42, 1.56]
Subtotal (95% CI)	**807**	**788**		**100.0 %**	**0.88 [0.64, 1.21]**
Total events: 64 (Repeat), 71 (Single)					
Heterogeneity: Chi^2 = 2.79, df = 3 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.79 (P = 0.43)					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	34/567	39/577		100.0 %	0.89 [0.57, 1.38]
Subtotal (95% CI)	**567**	**577**		**100.0 %**	**0.89 [0.57, 1.38]**
Total events: 34 (Repeat), 39 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.53 (P = 0.60)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Guinn 2002	30/248	25/235		54.4 %	1.14 [0.69, 1.87]
Mazumder 2008	0/37	3/37		7.4 %	0.14 [0.01, 2.67]
Wapner 2006	15/230	18/230		38.2 %	0.83 [0.43, 1.61]
Subtotal (95% CI)	**515**	**502**		**100.0 %**	**0.95 [0.64, 1.40]**
Total events: 45 (Repeat), 46 (Single)					
Heterogeneity: Chi^2 = 2.26, df = 2 (P = 0.32); I^2 =11%					
Test for overall effect: Z = 0.27 (P = 0.79)					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					



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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: not applicable					

Analysis 1.13. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 13 Intraventricular haemorrhage grade 3/4.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 13 Intraventricular haemorrhage grade 3/4

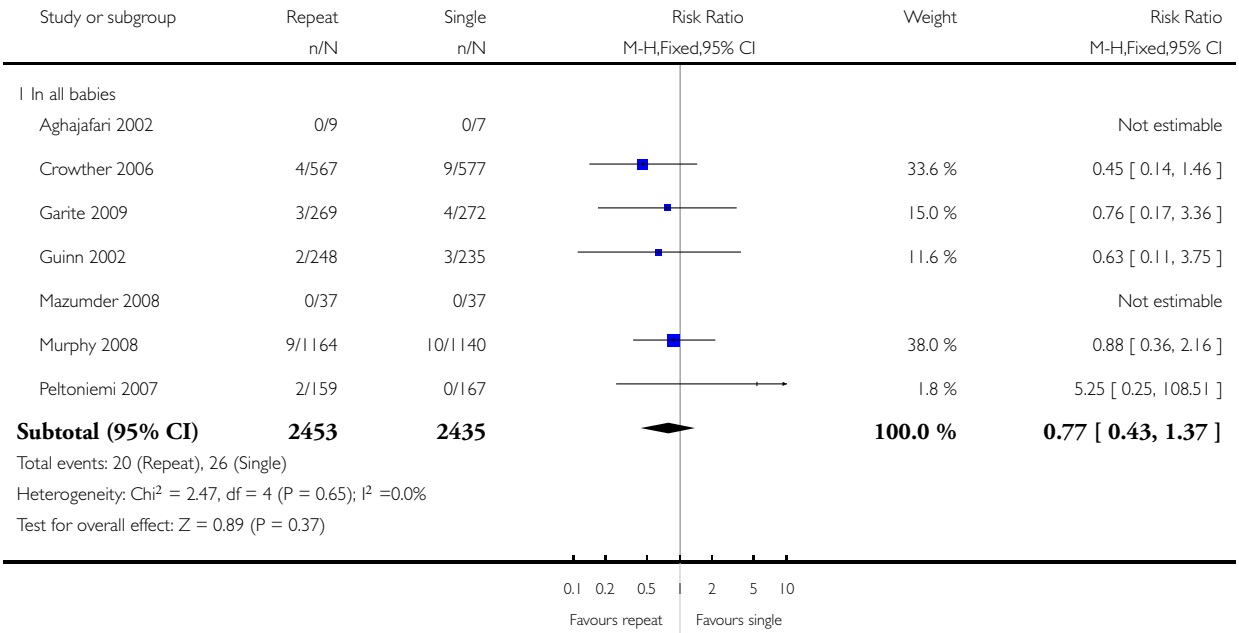
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	0/9	1/7		5.8 %	0.27 [0.01, 5.70]
Crowther 2006	5/567	8/577		27.7 %	0.64 [0.21, 1.93]
Garite 2009	6/272	4/274		13.9 %	1.51 [0.43, 5.30]
Guinn 2002	9/248	2/235		7.2 %	4.26 [0.93, 19.53]
Murphy 2008	6/1164	9/1140		31.8 %	0.65 [0.23, 1.83]
Peltoniemi 2007	6/159	4/167		13.6 %	1.58 [0.45, 5.48]
Subtotal (95% CI)	**2419**	**2400**		**100.0 %**	**1.13 [0.69, 1.86]**
Total events: 32 (Repeat), 28 (Single)					
Heterogeneity: Chi^2 = 6.38, df = 5 (P = 0.27); I^2 =22%					
Test for overall effect: Z = 0.48 (P = 0.63)					

Analysis 1.14. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 14 Periventricular leukomalacia.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 14 Periventricular leukomalacia

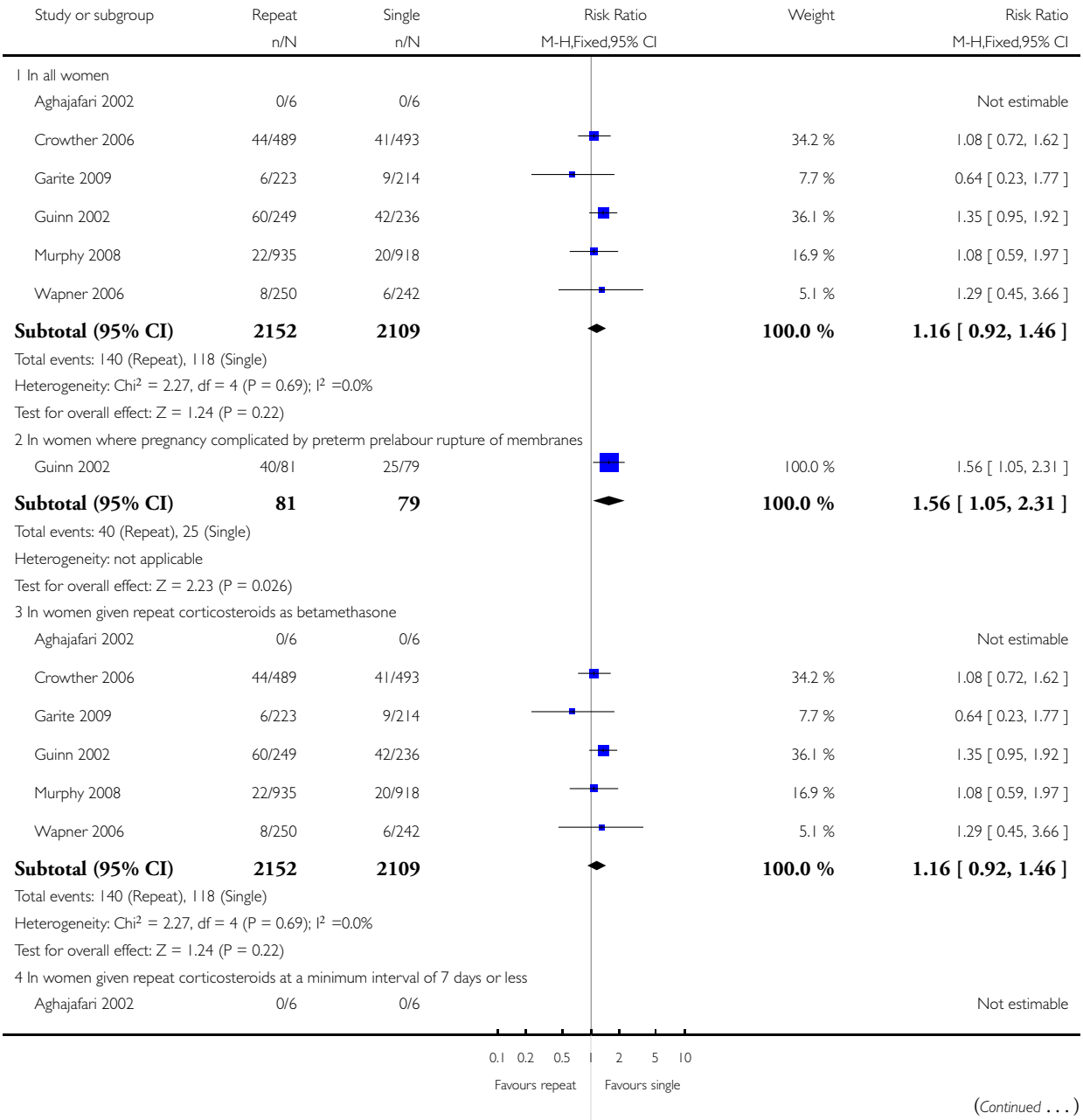


Analysis 1.15. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 15 Chorioamnionitis.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 15 Chorioamnionitis



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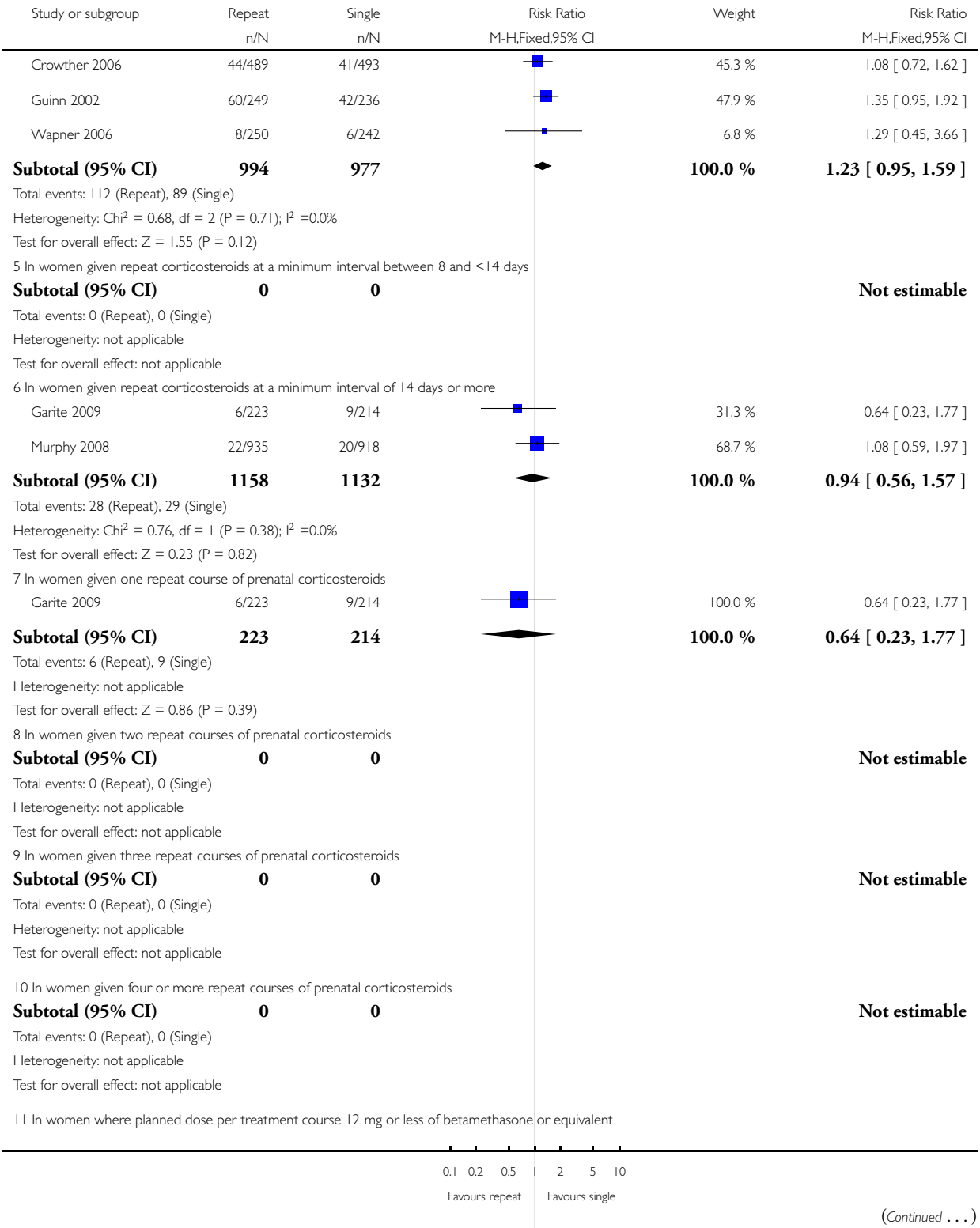

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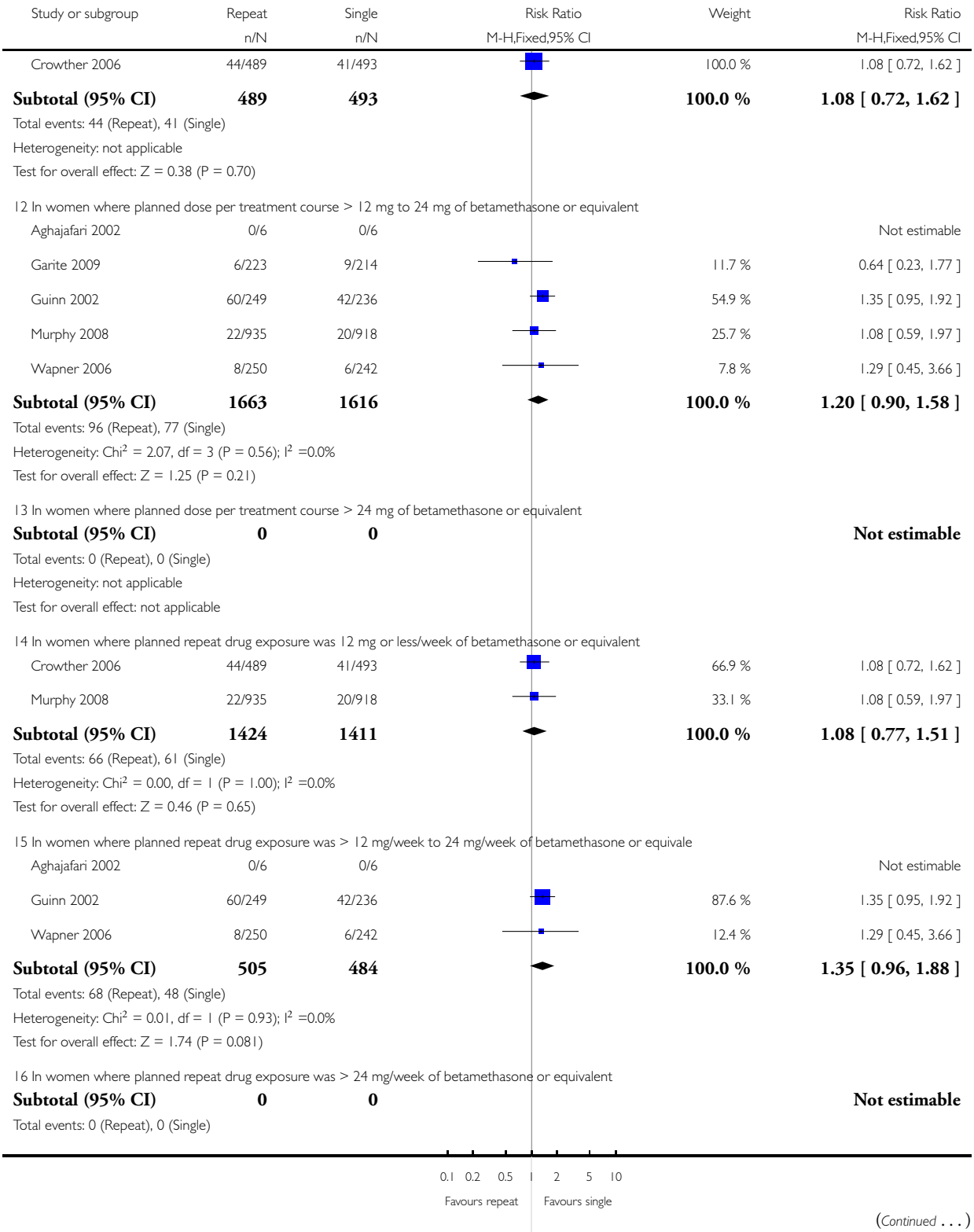

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.16. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 16 Puerperal sepsis.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 16 Puerperal sepsis

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Aghajafari 2002	0/6	0/6			Not estimable
Guinn 2002	13/249	14/236		23.3 %	0.88 [0.42, 1.83]
Murphy 2008	34/935	25/918		40.8 %	1.34 [0.80, 2.22]
Peltoniemi 2007	19/125	12/124		19.5 %	1.57 [0.80, 3.10]
Wapner 2006	6/250	10/242		16.4 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**1565**	**1526**		**100.0 %**	**1.15 [0.83, 1.60]**
Total events: 72 (Repeat), 61 (Single)					
Heterogeneity: Chi^2 = 3.46, df = 3 (P = 0.33); I^2 =13%					
Test for overall effect: Z = 0.83 (P = 0.40)					
2 In women where pregnancy complicated by preterm prelabour rupture of membranes					
Guinn 2002	4/81	6/79		100.0 %	0.65 [0.19, 2.22]
Subtotal (95% CI)	**81**	**79**		**100.0 %**	**0.65 [0.19, 2.22]**
Total events: 4 (Repeat), 6 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.69 (P = 0.49)					
3 In women given repeat corticosteroids as betamethasone					

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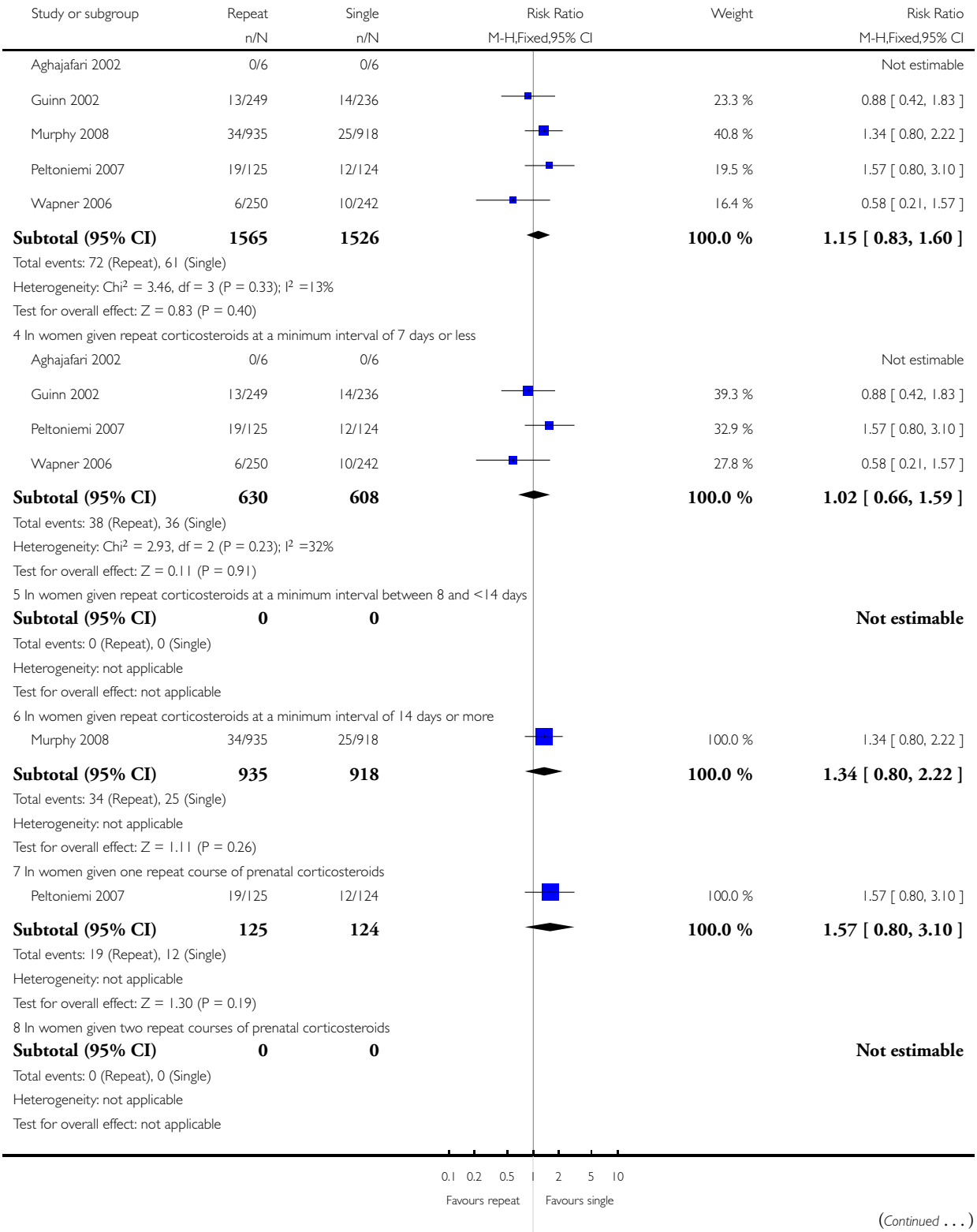

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
9 In women given three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In women given four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In women where planned dose per treatment course 12 mg or less of betamethasone or equivalent					
Peltoniemi 2007	19/125	12/124		100.0 %	1.57 [0.80, 3.10]
Subtotal (95% CI)	**125**	**124**		**100.0 %**	**1.57 [0.80, 3.10]**
Total events: 19 (Repeat), 12 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.30 (P = 0.19)					
12 In women where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalen					
Aghajafari 2002	0/6	0/6			Not estimable
Guinn 2002	13/249	14/236		28.9 %	0.88 [0.42, 1.83]
Murphy 2008	34/935	25/918		50.7 %	1.34 [0.80, 2.22]
Wapner 2006	6/250	10/242		20.4 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**1440**	**1402**		**100.0 %**	**1.05 [0.72, 1.54]**
Total events: 53 (Repeat), 49 (Single)					
Heterogeneity: Chi^2 = 2.44, df = 2 (P = 0.30); I^2 =18%					
Test for overall effect: Z = 0.25 (P = 0.80)					
13 In women where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In women where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Murphy 2008	34/935	25/918		100.0 %	1.34 [0.80, 2.22]
Subtotal (95% CI)	**935**	**918**		**100.0 %**	**1.34 [0.80, 2.22]**
Total events: 34 (Repeat), 25 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.11 (P = 0.26)					
15 In women where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivale					
Aghajafari 2002	0/6	0/6			Not estimable
Guinn 2002	13/249	14/236		58.6 %	0.88 [0.42, 1.83]

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wapner 2006	6/250	10/242		41.4 %	0.58 [0.21, 1.57]
Subtotal (95% CI)	**505**	**484**		**100.0 %**	**0.76 [0.42, 1.36]**
Total events: 19 (Repeat), 24 (Single)					
Heterogeneity: Chi^2 = 0.43, df = 1 (P = 0.51); I^2 =0.0%					
Test for overall effect: Z = 0.93 (P = 0.35)					
16 In women where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.17. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 17 Mean gestational age at birth (weeks).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 17 Mean gestational age at birth (weeks)

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Aghajafari 2002	6	31 (4)	6	35 (5)		0.2 %	-4.00 [-9.12, 1.12]
Crowther 2006	567	32.5 (3.9)	577	32.4 (3.9)		28.7 %	0.10 [-0.35, 0.55]
Garite 2009	275	33.1 (3.1)	281	33 (3.1)		22.1 %	0.10 [-0.42, 0.62]
Guinn 2002	255	33.1 (4)	245	33.5 (4)		11.9 %	-0.40 [-1.10, 0.30]
McEvoy 2002	18	32.2 (3.3)	19	32.8 (2.7)		1.5 %	-0.60 [-2.55, 1.35]
McEvoy 2010	56	31.9 (3.3)	56	32.3 (2.9)		4.4 %	-0.40 [-1.55, 0.75]
Peltoniemi 2007	159	30.7 (2.7)	167	31 (2.5)		18.4 %	-0.30 [-0.87, 0.27]
Wapner 2006	250	34.8 (3.8)	242	34.8 (3.9)		12.7 %	0.0 [-0.68, 0.68]
Subtotal (95% CI)	**1586**		**1593**			**100.0 %**	**-0.09 [-0.33, 0.15]**

Heterogeneity: $Chi^2 = 5.33$, df = 7 (P = 0.62); $I^2 = 0.0\%$

Test for overall effect: Z = 0.71 (P = 0.48)

Analysis 1.18. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 18 Preterm birth before 37 weeks.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 18 Preterm birth before 37 weeks

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	458/567	483/577		96.5 %	0.96 [0.91, 1.02]
McEvoy 2002	17/18	18/19		3.5 %	1.00 [0.85, 1.16]
Subtotal (95% CI)	**585**	**596**		**100.0 %**	**0.97 [0.92, 1.02]**
Total events: 475 (Repeat), 501 (Single)					
Heterogeneity: Chi^2 = 0.16, df = 1 (P = 0.69); I^2 =0.0%					
Test for overall effect: Z = 1.29 (P = 0.20)					

Analysis 1.19. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 19 Very preterm birth before 34 weeks.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 19 Very preterm birth before 34 weeks

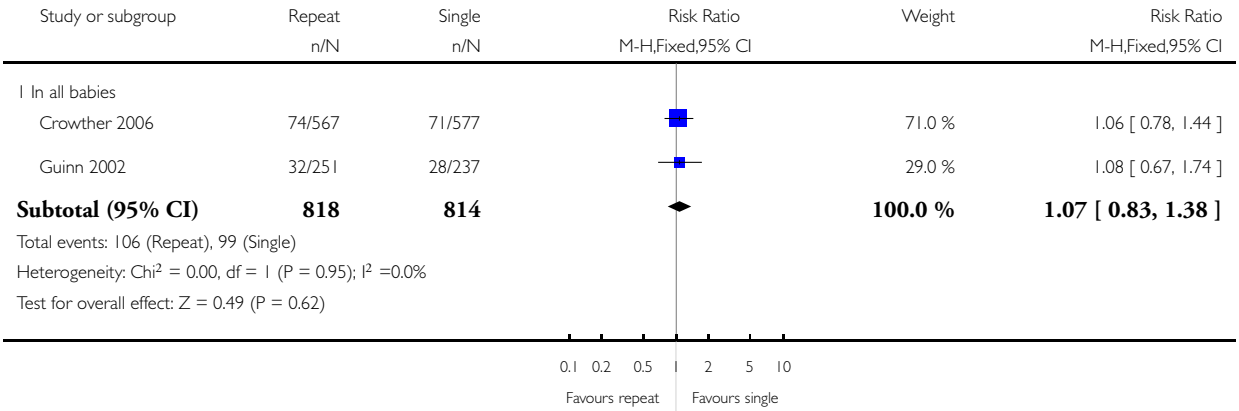
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	362/567	373/577		51.4 %	0.99 [0.91, 1.08]
Garite 2009	163/276	165/282		22.7 %	1.01 [0.88, 1.16]
McEvoy 2010	44/56	39/56		5.4 %	1.13 [0.90, 1.41]
Peltoniemi 2007	148/159	151/167		20.5 %	1.03 [0.96, 1.10]
Subtotal (95% CI)	**1058**	**1082**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 717 (Repeat), 728 (Single)					
Heterogeneity: Chi^2 = 1.59, df = 3 (P = 0.66); I^2 =0.0%					
Test for overall effect: Z = 0.30 (P = 0.77)					

Analysis 1.20. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 20 Extremely preterm birth before 28 weeks.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 20 Extremely preterm birth before 28 weeks



Analysis 1.21. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 21 Mean head circumference at birth (cm).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 21 Mean head circumference at birth (cm)

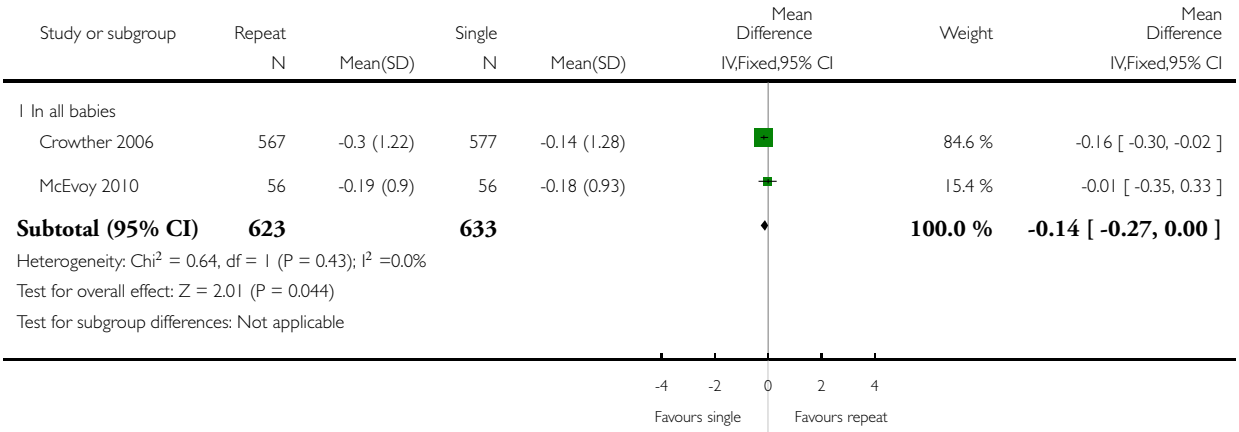
Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	567	29.6 (3.7)	577	29.7 (3.6)		16.8 %	-0.10 [-0.52, 0.32]
Garite 2009	275	30.2 (3)	281	30 (2.9)		12.5 %	0.20 [-0.29, 0.69]
Guinn 2002	248	29.1 (4)	235	29.4 (3.4)		6.9 %	-0.30 [-0.96, 0.36]
Mazumder 2008	37	29.7 (2)	37	29.6 (2.7)		2.6 %	0.10 [-0.98, 1.18]
McEvoy 2002	18	29.4 (3)	19	29.6 (2.7)		0.9 %	-0.20 [-2.04, 1.64]
McEvoy 2010	56	28.7 (3)	56	29.2 (2.9)		2.5 %	-0.50 [-1.59, 0.59]
Murphy 2008	1164	31.1 (3.4)	1140	31.7 (3.4)		38.9 %	-0.60 [-0.88, -0.32]
Peltoniemi 2007	159	28.1 (2.9)	167	28.6 (2.8)		7.8 %	-0.50 [-1.12, 0.12]
Wapner 2006	296	30.6 (3.1)	294	30.8 (3.3)		11.2 %	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	**2820**		**2806**			**100.0 %**	**-0.32 [-0.49, -0.15]**
Heterogeneity: Chi^2 = 10.49, df = 8 (P = 0.23); I^2 =24%							
Test for overall effect: Z = 3.61 (P = 0.00030)							

Analysis 1.22. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 22 Head circumference Z scores at birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 22 Head circumference Z scores at birth



Analysis 1.23. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 23 Mean length at birth (cm).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 23 Mean length at birth (cm)

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	567	42.1 (5.9)	577	42.1 (5.6)		24.7 %	0.0 [-0.67, 0.67]
Mazumder 2008	37	41.2 (3.7)	37	41.5 (4.8)		2.9 %	-0.30 [-2.25, 1.65]
McEvoy 2010	56	41.9 (4.7)	56	42.4 (4.4)		3.9 %	-0.50 [-2.19, 1.19]
Murphy 2008	1164	44.5 (6.8)	1140	45.4 (6.8)		35.6 %	-0.90 [-1.46, -0.34]
Peltoniemi 2007	159	39.4 (4.1)	167	40.2 (3.7)		15.2 %	-0.80 [-1.65, 0.05]
Wapner 2006	296	44.2 (4.6)	294	44.7 (5.1)		17.8 %	-0.50 [-1.28, 0.28]
Subtotal (95% CI)	**2279**		**2271**			**100.0 %**	**-0.56 [-0.89, -0.23]**

Heterogeneity: Chi^2 = 4.55, df = 5 (P = 0.47); I^2 =0.0%

Test for overall effect: Z = 3.31 (P = 0.00094)

Analysis 1.24. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 24 Length Z scores at birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 24 Length Z scores at birth

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	567	-0.53 (1.31)	577	-0.48 (1.22)		85.8 %	-0.05 [-0.20, 0.10]
McEvoy 2010	56	-0.11 (0.99)	56	-0.06 (0.96)		14.2 %	-0.05 [-0.41, 0.31]
Subtotal (95% CI)	**623**		**633**			**100.0 %**	**-0.05 [-0.19, 0.09]**

Heterogeneity: $Chi^2 = 0.00$, df = 1 (P = 1.00); $I^2 = 0.0\%$

Test for overall effect: Z = 0.72 (P = 0.47)

Test for subgroup differences: Not applicable

Analysis 1.25. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 25 Length multiples of the median at birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 25 Length multiples of the median at birth

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Wapner 2006	296	0.98 (0.06)	294	0.99 (0.05)		100.0 %	-0.01 [-0.02, 0.00]
Subtotal (95% CI)	**296**		**294**			**100.0 %**	**-0.01 [-0.02, 0.00]**

Heterogeneity: not applicable

Test for overall effect: Z = 2.20 (P = 0.028)

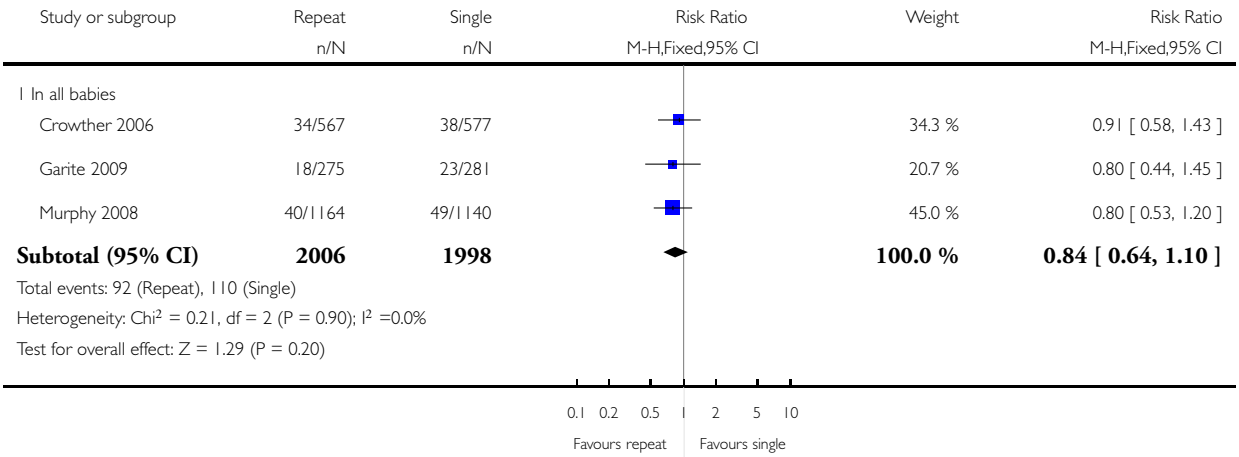
Test for subgroup differences: Not applicable

Analysis 1.26. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 26 Apgar score less than 7 at 5 minutes.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 26 Apgar score less than 7 at 5 minutes



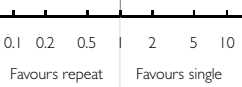
Analysis 1.27. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 27 Use of mechanical ventilation.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 27 Use of mechanical ventilation

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 In all babies					
Crowther 2006	167/567	204/577		22.6 %	0.83 [0.70, 0.99]
Garite 2009	70/267	95/273		17.0 %	0.75 [0.58, 0.98]
McEvoy 2010	15/56	18/56		6.3 %	0.83 [0.47, 1.48]
Murphy 2008	175/1164	204/1140		21.6 %	0.84 [0.70, 1.01]
Peltoniemi 2007	93/159	87/167		20.9 %	1.12 [0.92, 1.37]
Wapner 2006	36/250	60/242		11.6 %	0.58 [0.40, 0.84]
Subtotal (95% CI)	**2463**	**2455**		**100.0 %**	**0.84 [0.71, 0.99]**
Total events: 556 (Repeat), 668 (Single)					
Heterogeneity: $Tau^2 = 0.02$; $Chi^2 = 12.95$, df = 5 (P = 0.02); $I^2 = 61\%$					
Test for overall effect: Z = 2.14 (P = 0.033)					

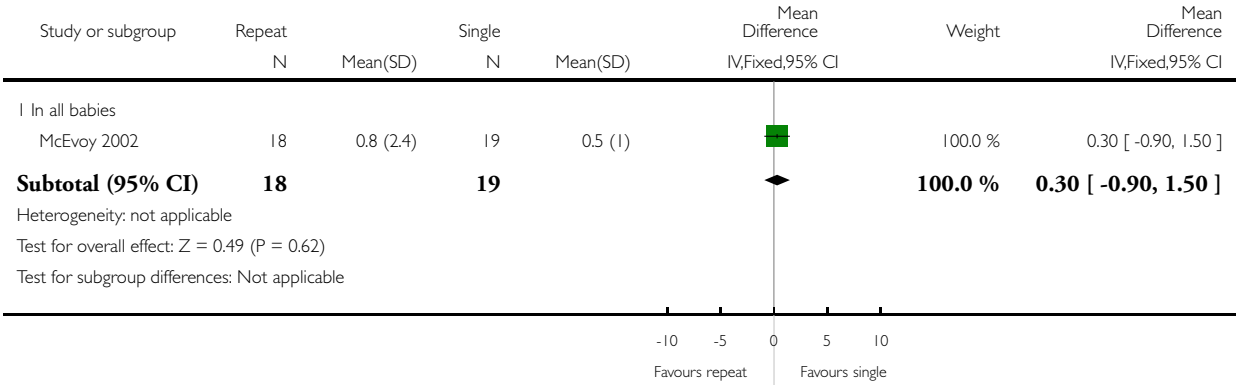


Analysis 1.28. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 28 Duration of respiratory support in days.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 28 Duration of respiratory support in days

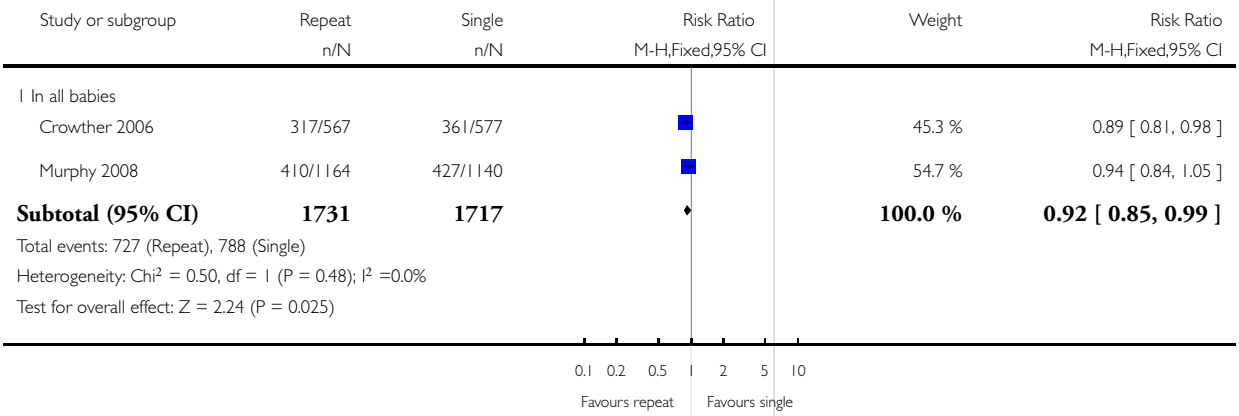


Analysis 1.29. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 29 Use of oxygen supplementation.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 29 Use of oxygen supplementation



Analysis 1.30. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 30 Duration of oxygen supplementation in days.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 30 Duration of oxygen supplementation in days

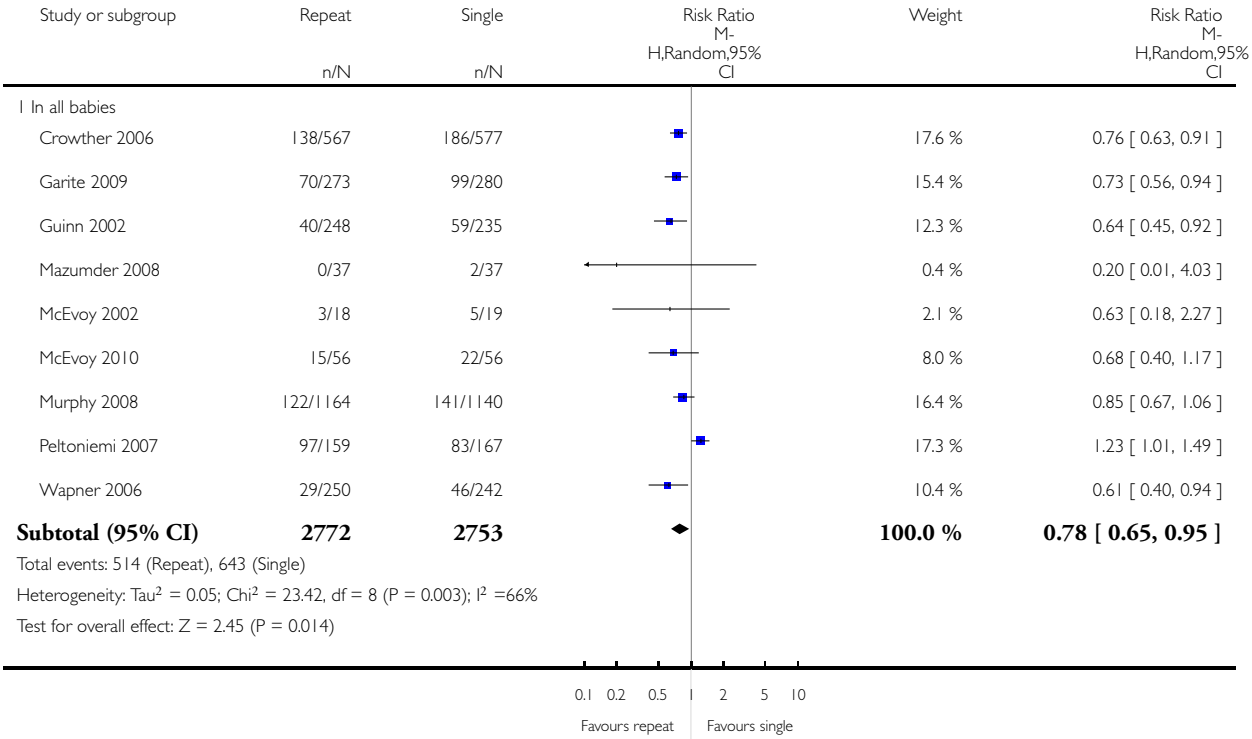
Study or subgroup	Repeat		Single		Mean Difference	Weight	Mean Difference
	N	Mean(SD)	N	Mean(SD)	IV,Fixed,95% CI		IV,Fixed,95% CI
1 In all babies							
McEvoy 2002	18	4 (12)	19	0.7 (1.9)		100.0 %	3.30 [-2.31, 8.91]
Subtotal (95% CI)	**18**		**19**			**100.0 %**	**3.30 [-2.31, 8.91]**
Heterogeneity: not applicable							
Test for overall effect: Z = 1.15 (P = 0.25)							
Test for subgroup differences: Not applicable							

Analysis 1.31. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 31 Use of surfactant.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 31 Use of surfactant

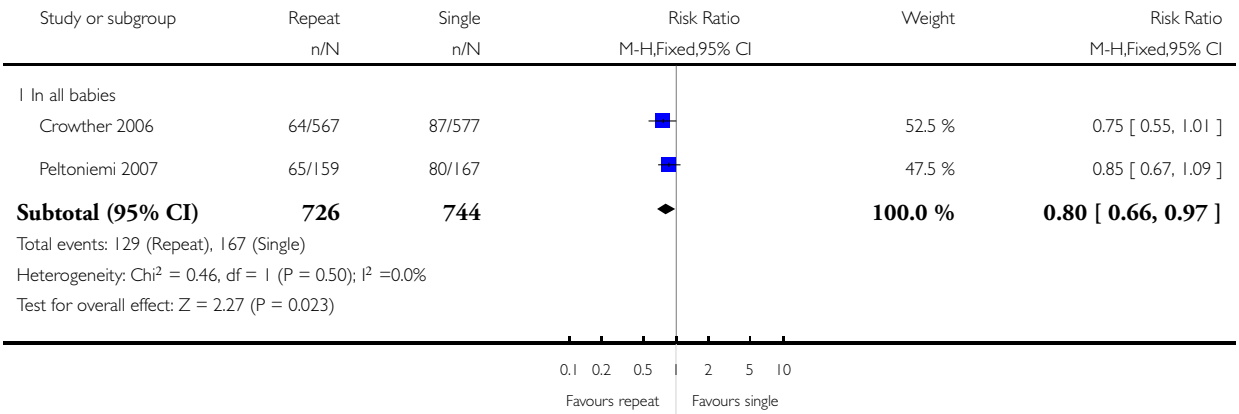


Analysis 1.32. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 32 Use of inotropic support.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 32 Use of inotropic support

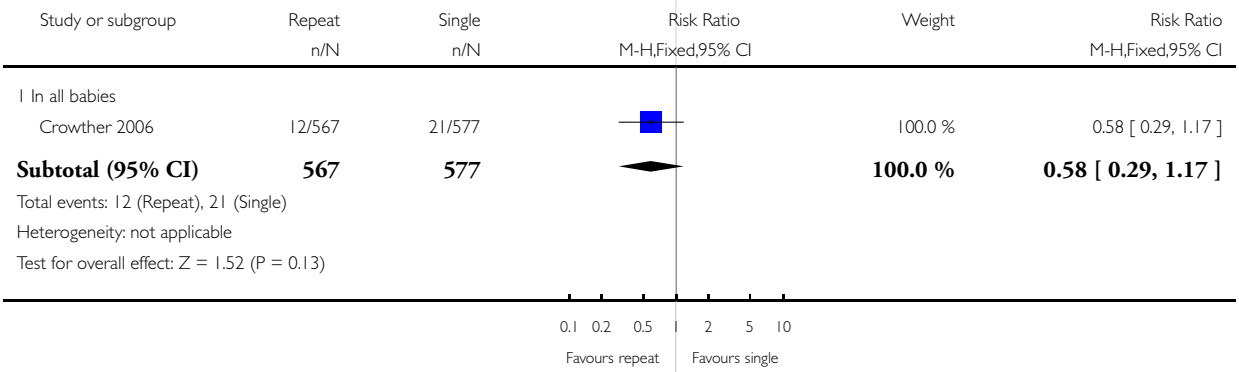


Analysis 1.33. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 33 Use of nitric oxide for respiratory support.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 33 Use of nitric oxide for respiratory support



Analysis 1.34. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 34 Early systemic neonatal infection (variously defined).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 34 Early systemic neonatal infection (variously defined)

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	173/567	188/577		97.4 %	0.94 [0.79, 1.11]
Mazumder 2008	3/37	2/37		1.0 %	1.50 [0.27, 8.46]
Peltoniemi 2007	1/159	3/167		1.5 %	0.35 [0.04, 3.33]
Subtotal (95% CI)	**763**	**781**		**100.0 %**	**0.93 [0.79, 1.11]**
Total events: 177 (Repeat), 193 (Single)					
Heterogeneity: Chi^2 = 1.02, df = 2 (P = 0.60); I^2 =0.0%					
Test for overall effect: Z = 0.80 (P = 0.43)					

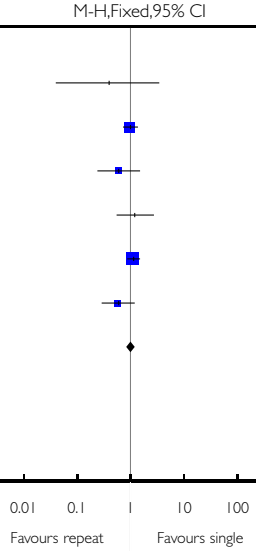
Analysis 1.35. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 35 Proven infection while in the neonatal intensive care unit.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 35 Proven infection while in the neonatal intensive care unit

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	1/9	2/7		1.1 %	0.39 [0.04, 3.47]
Crowther 2006	70/567	72/577		34.7 %	0.99 [0.73, 1.35]
Garite 2009	7/275	12/288		5.7 %	0.61 [0.24, 1.53]
Guinn 2002	13/248	10/235		5.0 %	1.23 [0.55, 2.75]
Murphy 2008	105/1164	91/1140		44.7 %	1.13 [0.86, 1.48]
Wapner 2006	11/250	18/242		8.9 %	0.59 [0.29, 1.23]
Subtotal (95% CI)	**2513**	**2489**		**100.0 %**	**1.00 [0.83, 1.20]**
Total events: 207 (Repeat), 205 (Single)					
Heterogeneity: Chi^2 = 4.87, df = 5 (P = 0.43); I^2 =0.0%					
Test for overall effect: Z = 0.01 (P = 0.99)					



Analysis 1.36. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 36 Admission to the neonatal intensive care unit.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 36 Admission to the neonatal intensive care unit

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	407/567	399/577		45.8 %	1.04 [0.96, 1.12]
Murphy 2008	465/1164	464/1140		54.2 %	0.98 [0.89, 1.08]
Subtotal (95% CI)	**1731**	**1717**		**100.0 %**	**1.01 [0.95, 1.07]**
Total events: 872 (Repeat), 863 (Single)					
Heterogeneity: Chi^2 = 0.88, df = 1 (P = 0.35); I^2 =0.0%					
Test for overall effect: Z = 0.23 (P = 0.82)					

Analysis 1.37. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 37 Air leak syndrome.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 37 Air leak syndrome

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 In all babies					
Crowther 2006	19/567	18/577		55.0 %	1.07 [0.57, 2.03]
Garite 2009	4/275	4/281		28.8 %	1.02 [0.26, 4.04]
Wapner 2006	1/250	7/242		16.1 %	0.14 [0.02, 1.12]
Subtotal (95% CI)	**1092**	**1100**		**100.0 %**	**0.76 [0.29, 1.97]**
Total events: 24 (Repeat), 29 (Single)					
Heterogeneity: Tau^2 = 0.32; Chi^2 = 3.53, df = 2 (P = 0.17); I^2 =43%					
Test for overall effect: Z = 0.56 (P = 0.57)					

Analysis 1.38. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 38 Necrotising enterocolitis.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 38 Necrotising enterocolitis

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	0/9	0/7			Not estimable
Crowther 2006	5/567	11/577		18.1 %	0.46 [0.16, 1.32]
Garite 2009	8/275	11/280		18.1 %	0.74 [0.30, 1.81]
Guinn 2002	10/248	9/235		15.3 %	1.05 [0.44, 2.55]
Mazumder 2008	1/37	2/37		3.3 %	0.50 [0.05, 5.28]
Murphy 2008	10/1164	12/1140		20.1 %	0.82 [0.35, 1.88]
Peltoniemi 2007	1/159	4/167		6.5 %	0.26 [0.03, 2.32]
Wapner 2006	10/250	11/242		18.6 %	0.88 [0.38, 2.03]
Subtotal (95% CI)	**2709**	**2685**		**100.0 %**	**0.74 [0.51, 1.08]**
Total events: 45 (Repeat), 60 (Single)					
Heterogeneity: Chi^2 = 2.57, df = 6 (P = 0.86); I^2 =0.0%					
Test for overall effect: Z = 1.54 (P = 0.12)					

Analysis 1.39. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 39 Patent ductus arteriosus.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 39 Patent ductus arteriosus

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	2/9	1/7		0.7 %	1.56 [0.17, 13.87]
Crowther 2006	40/567	67/577		39.0 %	0.61 [0.42, 0.88]
Mazumder 2008	1/37	3/37		1.8 %	0.33 [0.04, 3.06]
Murphy 2008	44/1164	42/1140		24.9 %	1.03 [0.68, 1.55]
Peltoniemi 2007	41/159	44/167		25.2 %	0.98 [0.68, 1.41]
Wapner 2006	7/250	14/242		8.4 %	0.48 [0.20, 1.18]
Subtotal (95% CI)	**2186**	**2170**		**100.0 %**	**0.80 [0.64, 0.98]**
Total events: 135 (Repeat), 171 (Single)					
Heterogeneity: Chi^2 = 6.82, df = 5 (P = 0.23); I^2 =27%					
Test for overall effect: Z = 2.10 (P = 0.036)					

Analysis 1.40. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 40 Retinopathy of prematurity.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 40 Retinopathy of prematurity

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Aghajafari 2002	3/9	3/7		2.5 %	0.78 [0.22, 2.74]
Crowther 2006	40/567	43/577		31.1 %	0.95 [0.63, 1.43]
Garite 2009	21/260	19/267		13.7 %	1.14 [0.63, 2.06]
Mazumder 2008	1/37	1/37		0.7 %	1.00 [0.06, 15.40]
Murphy 2008	46/1164	34/1140		25.1 %	1.33 [0.86, 2.05]
Peltoniemi 2007	14/159	17/167		12.1 %	0.86 [0.44, 1.70]
Wapner 2006	15/250	20/242		14.8 %	0.73 [0.38, 1.38]
Subtotal (95% CI)	**2446**	**2437**		**100.0 %**	**1.02 [0.81, 1.28]**
Total events: 140 (Repeat), 137 (Single)					
Heterogeneity: Chi^2 = 3.11, df = 6 (P = 0.80); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					

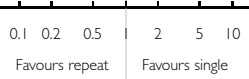
Analysis 1.41. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 41 Use of postnatal steroids.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 41 Use of postnatal steroids

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	43/567	31/577		54.6 %	1.41 [0.90, 2.21]
Guinn 2002	20/248	17/235		31.0 %	1.11 [0.60, 2.08]
Murphy 2008	15/1164	8/1140		14.4 %	1.84 [0.78, 4.31]
Subtotal (95% CI)	**1979**	**1952**		**100.0 %**	**1.38 [0.99, 1.93]**
Total events: 78 (Repeat), 56 (Single)					
Heterogeneity: Chi^2 = 0.89, df = 2 (P = 0.64); I^2 =0.0%					
Test for overall effect: Z = 1.90 (P = 0.058)					

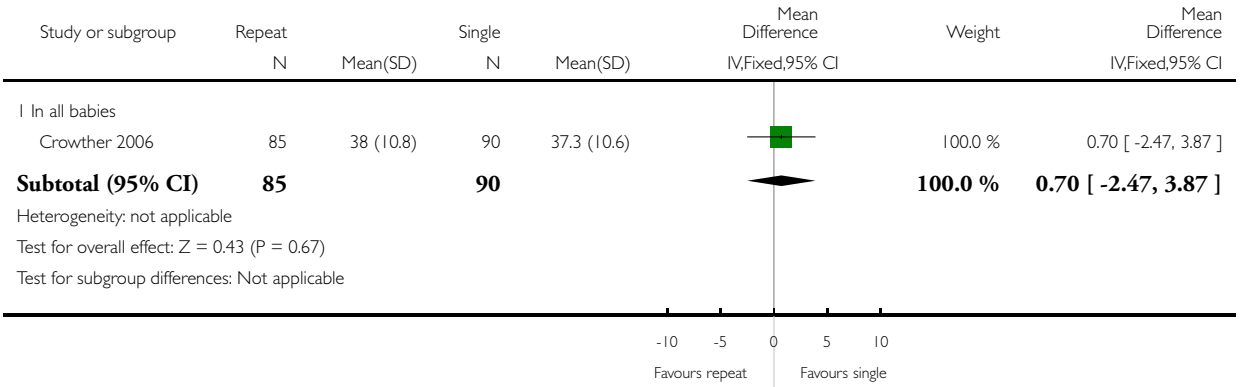


Analysis 1.42. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 42 Mean neonatal blood pressure on first day after birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 42 Mean neonatal blood pressure on first day after birth

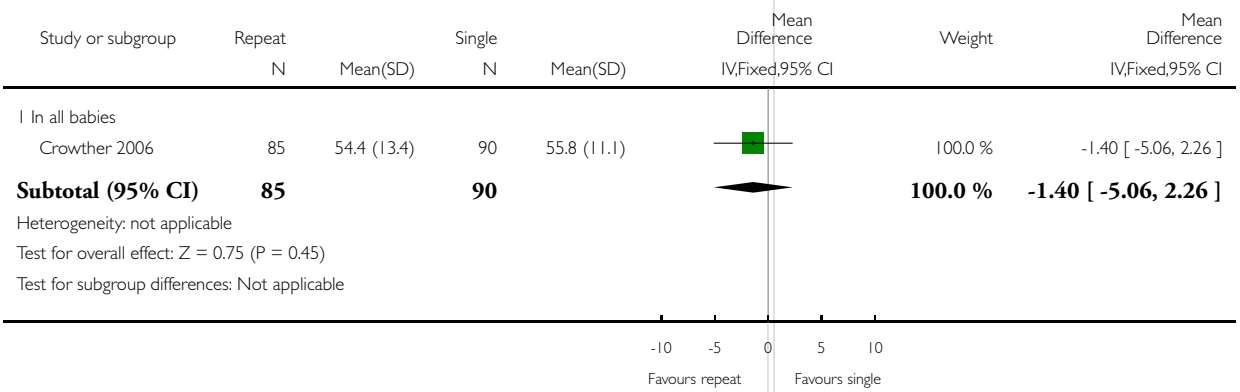


Analysis 1.43. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 43 Mean neonatal blood pressure 6 weeks after birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 43 Mean neonatal blood pressure 6 weeks after birth



Analysis 1.44. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 44 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 44 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd)

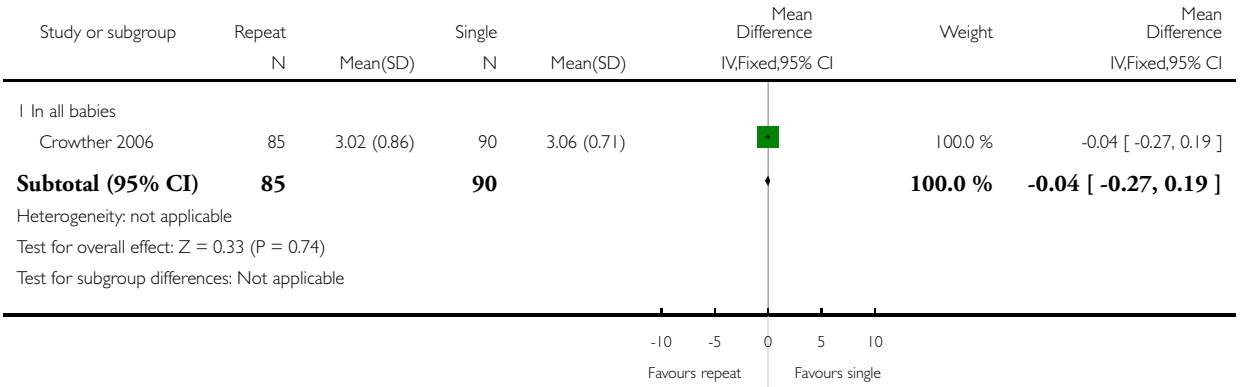
Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	85	2.95 (0.86)	90	2.94 (0.83)		100.0 %	0.01 [-0.24, 0.26]
Subtotal (95% CI)	**85**		**90**			**100.0 %**	**0.01 [-0.24, 0.26]**
Heterogeneity: not applicable							
Test for overall effect: Z = 0.08 (P = 0.94)							
Test for subgroup differences: Not applicable							

Analysis 1.45. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 45 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 45 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole

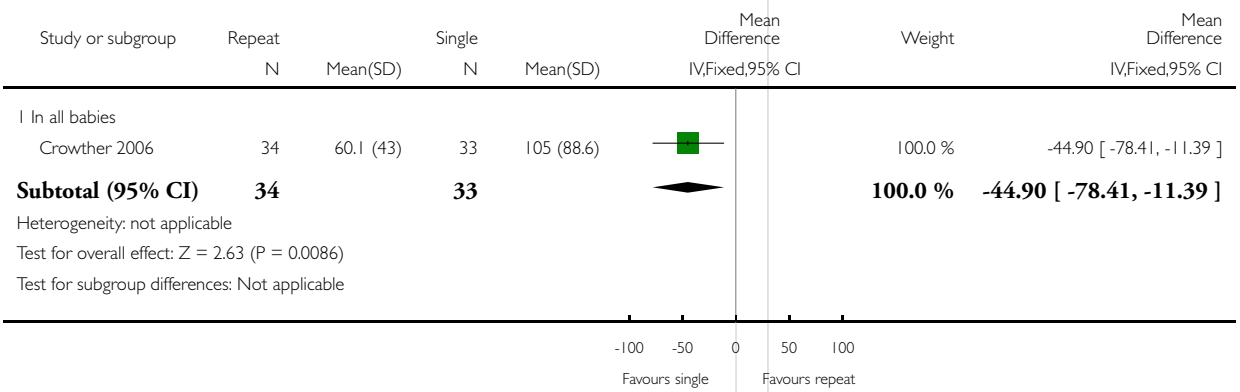


Analysis 1.46. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 46 Mean basal cortisol concentrations (nmol/L) at birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 46 Mean basal cortisol concentrations (nmol/L) at birth

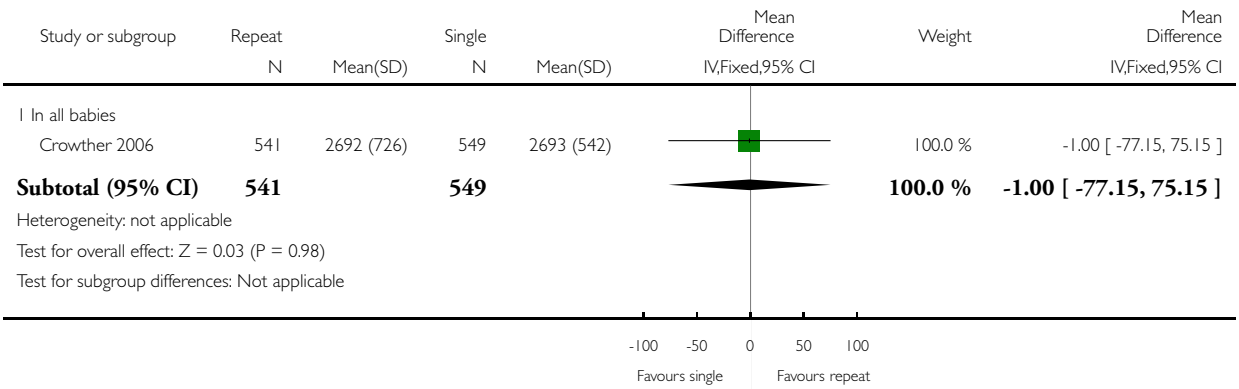


Analysis 1.47. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 47 Mean weight (g) at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 47 Mean weight (g) at primary hospital discharge



Analysis 1.48. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 48 Weight Z scores at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 48 Weight Z scores at primary hospital discharge

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	541	-1.07 (0.98)	549	-1.02 (0.93)		91.2 %	-0.05 [-0.16, 0.06]
McEvoy 2010	50	-0.8 (0.88)	55	-0.77 (1.03)		8.8 %	-0.03 [-0.40, 0.34]
Subtotal (95% CI)	**591**		**604**			**100.0 %**	**-0.05 [-0.16, 0.06]**

Heterogeneity: $Chi^2 = 0.01$, df = 1 (P = 0.92); $I^2 = 0.0\%$

Test for overall effect: Z = 0.87 (P = 0.38)

Test for subgroup differences: Not applicable

Analysis 1.49. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 49 Mean head circumference (cm) at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 49 Mean head circumference (cm) at primary hospital discharge

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	541	33.7 (2.1)	549	33.6 (1.9)		87.6 %	0.10 [-0.14, 0.34]
McEvoy 2010	50	32.6 (1.7)	55	32.3 (1.6)		12.4 %	0.30 [-0.33, 0.93]
Subtotal (95% CI)	**591**		**604**			**100.0 %**	**0.12 [-0.10, 0.35]**

Heterogeneity: $Chi^2 = 0.34$, df = 1 (P = 0.56); $I^2 = 0.0\%$

Test for overall effect: Z = 1.10 (P = 0.27)

Test for subgroup differences: Not applicable

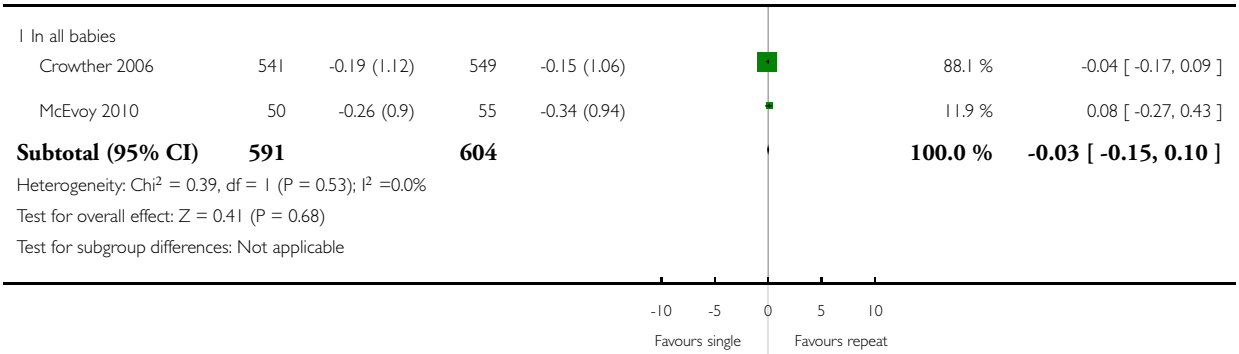
Analysis 1.50. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 50 Head circumference Z scores at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 50 Head circumference Z scores at primary hospital discharge

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	541	-0.19 (1.12)	549	-0.15 (1.06)		88.1 %	-0.04 [-0.17, 0.09]
McEvoy 2010	50	-0.26 (0.9)	55	-0.34 (0.94)		11.9 %	0.08 [-0.27, 0.43]
Subtotal (95% CI)	**591**		**604**			**100.0 %**	**-0.03 [-0.15, 0.10]**
Heterogeneity: Chi^2 = 0.39, df = 1 (P = 0.53); I^2 =0.0%							
Test for overall effect: Z = 0.41 (P = 0.68)							
Test for subgroup differences: Not applicable							



Analysis 1.51. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 51 Mean length (cm) at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 51 Mean length (cm) at primary hospital discharge

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	541	47.4 (4.3)	549	47.4 (4)		83.8 %	0.0 [-0.49, 0.49]
McEvoy 2010	49	46.5 (2.9)	50	46.4 (2.8)		16.2 %	0.10 [-1.02, 1.22]
Subtotal (95% CI)	**590**		**599**			**100.0 %**	**0.02 [-0.44, 0.47]**

Heterogeneity: $Chi^2 = 0.03$, df = 1 (P = 0.87); $I^2 = 0.0\%$

Test for overall effect: Z = 0.07 (P = 0.94)

Test for subgroup differences: Not applicable

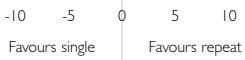
Analysis 1.52. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 52 Length Z score at primary hospital discharge.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 52 Length Z score at primary hospital discharge

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	541	-1.11 (1.47)	549	-1.08 (1.55)		85.7 %	-0.03 [-0.21, 0.15]
McEvoy 2010	49	-0.63 (1.14)	50	-0.37 (1.09)		14.3 %	-0.26 [-0.70, 0.18]
Subtotal (95% CI)	**590**		**599**			**100.0 %**	**-0.06 [-0.23, 0.10]**
Heterogeneity: Chi^2 = 0.90, df = 1 (P = 0.34); I^2 =0.0%							
Test for overall effect: Z = 0.74 (P = 0.46)							
Test for subgroup differences: Not applicable							



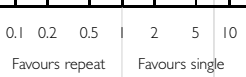
Analysis 1.53. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 53 Prelabour rupture of membranes after trial entry.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 53 Prelabour rupture of membranes after trial entry

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Wapner 2006	37/250	35/242		100.0 %	1.02 [0.67, 1.57]
Subtotal (95% CI)	**250**	**242**		**100.0 %**	**1.02 [0.67, 1.57]**
Total events: 37 (Repeat), 35 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.11 (P = 0.92)					



Analysis 1.54. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 54 Maternal Hypertension (variously defined by the authors).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 54 Maternal Hypertension (variously defined by the authors)

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Crowther 2006	62/489	67/493		43.2 %	0.93 [0.68, 1.29]
Murphy 2008	90/935	79/918		51.6 %	1.12 [0.84, 1.49]
Wapner 2006	15/250	8/242		5.3 %	1.82 [0.78, 4.20]
Subtotal (95% CI)	**1674**	**1653**		**100.0 %**	**1.08 [0.87, 1.32]**
Total events: 167 (Repeat), 154 (Single)					
Heterogeneity: $Chi^2 = 2.31$, df = 2 (P = 0.31); $I^2 = 14\%$					
Test for overall effect: Z = 0.68 (P = 0.49)					

Analysis 1.55. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 55 Vaginal birth.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 55 Vaginal birth

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Aghajafari 2002	1/6	2/6		0.2 %	0.50 [0.06, 4.15]
Crowther 2006	163/489	206/493		22.9 %	0.80 [0.68, 0.94]
Garite 2009	72/223	62/214		7.0 %	1.11 [0.84, 1.48]
McEvoy 2002	9/18	11/19		1.2 %	0.86 [0.47, 1.57]
Murphy 2008	396/935	415/918		46.7 %	0.94 [0.84, 1.04]
Peltoniemi 2007	48/125	44/124		4.9 %	1.08 [0.78, 1.50]
Wapner 2006	157/250	151/242		17.1 %	1.01 [0.88, 1.15]
Subtotal (95% CI)	**2046**	**2016**		**100.0 %**	**0.93 [0.87, 1.00]**
Total events: 846 (Repeat), 891 (Single)					
Heterogeneity: Chi^2 = 7.42, df = 6 (P = 0.28); I^2 =19%					
Test for overall effect: Z = 1.88 (P = 0.060)					

Analysis 1.56. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 56 Caesarean section.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 56 Caesarean section

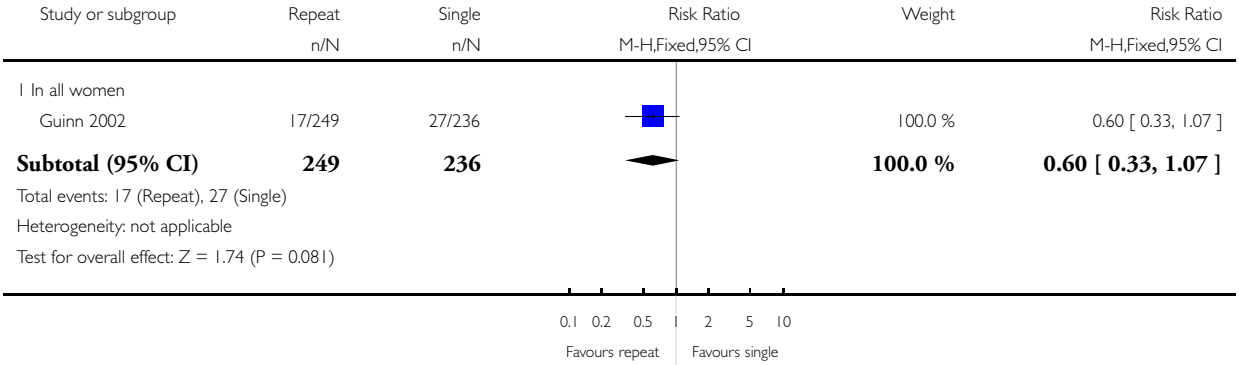
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Aghajafari 2002	5/6	4/6		0.4 %	1.25 [0.64, 2.44]
Crowther 2006	326/489	287/493		25.4 %	1.15 [1.04, 1.26]
Garite 2009	139/223	146/214		13.2 %	0.91 [0.80, 1.05]
McEvoy 2002	9/18	8/19		0.7 %	1.19 [0.59, 2.39]
Murphy 2008	537/935	501/918		44.9 %	1.05 [0.97, 1.14]
Peltoniemi 2007	77/125	80/124		7.1 %	0.95 [0.79, 1.15]
Wapner 2006	93/250	91/242		8.2 %	0.99 [0.79, 1.24]
Subtotal (95% CI)	**2046**	**2016**		**100.0 %**	**1.05 [0.99, 1.10]**
Total events: 1186 (Repeat), 1117 (Single)					
Heterogeneity: Chi^2 = 8.59, df = 6 (P = 0.20); I^2 =30%					
Test for overall effect: Z = 1.70 (P = 0.090)					

Analysis 1.57. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 57 Postpartum haemorrhage.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 57 Postpartum haemorrhage

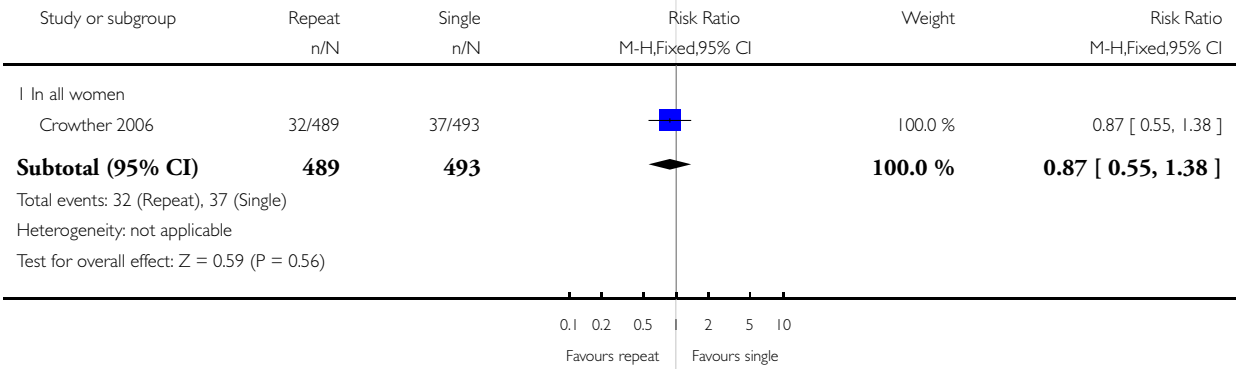


Analysis 1.58. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 58 Postnatal pyrexia (variously defined by authors).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 58 Postnatal pyrexia (variously defined by authors)

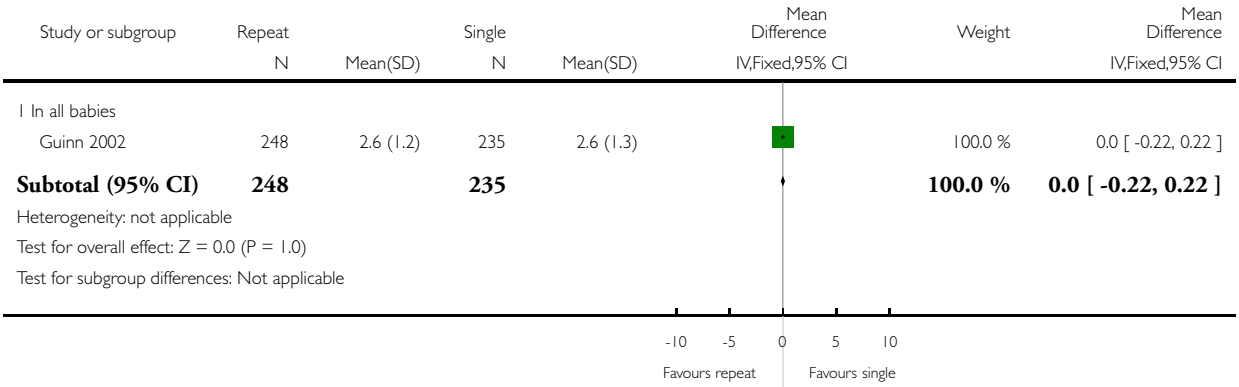


Analysis 1.59. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 59 Length of postnatal hospitalisation (days).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 59 Length of postnatal hospitalisation (days)

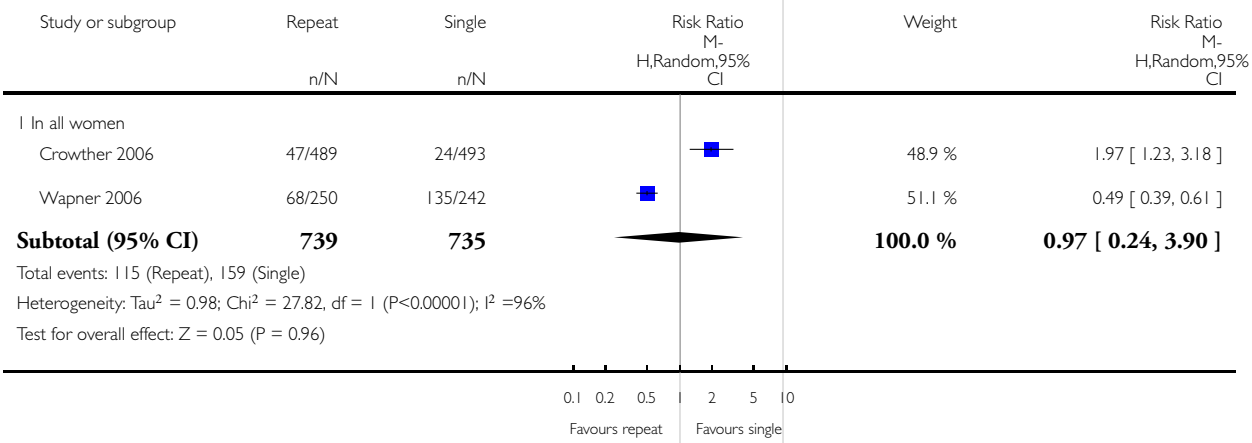


Analysis 1.60. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 60 Any maternal side effects of therapy.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 60 Any maternal side effects of therapy



Analysis 1.61. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 61 Maternal hyperglycaemia (variously defined by authors).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 61 Maternal hyperglycaemia (variously defined by authors)

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Wapner 2006	50/250	37/242		100.0 %	1.31 [0.89, 1.93]
Subtotal (95% CI)	**250**	**242**		**100.0 %**	**1.31 [0.89, 1.93]**
Total events: 50 (Repeat), 37 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.36 (P = 0.17)					

Analysis 1.62. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 62 Insomnia.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 62 Insomnia

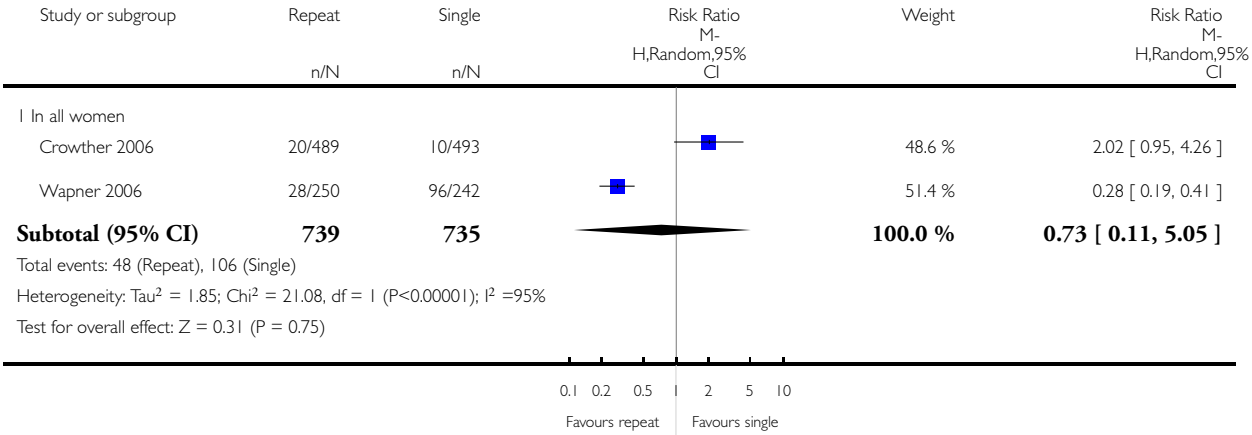
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all women					
Aghajafari 2002	3/6	1/6		15.2 %	3.00 [0.42, 21.30]
Crowther 2006	3/489	0/493		7.6 %	7.06 [0.37, 136.26]
Wapner 2006	11/250	5/242		77.2 %	2.13 [0.75, 6.04]
Subtotal (95% CI)	**745**	**741**		**100.0 %**	**2.63 [1.10, 6.30]**
Total events: 17 (Repeat), 6 (Single)					
Heterogeneity: Chi^2 = 0.60, df = 2 (P = 0.74); I^2 =0.0%					
Test for overall effect: Z = 2.18 (P = 0.029)					

Analysis 1.63. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 63 Pain at injection site.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 63 Pain at injection site

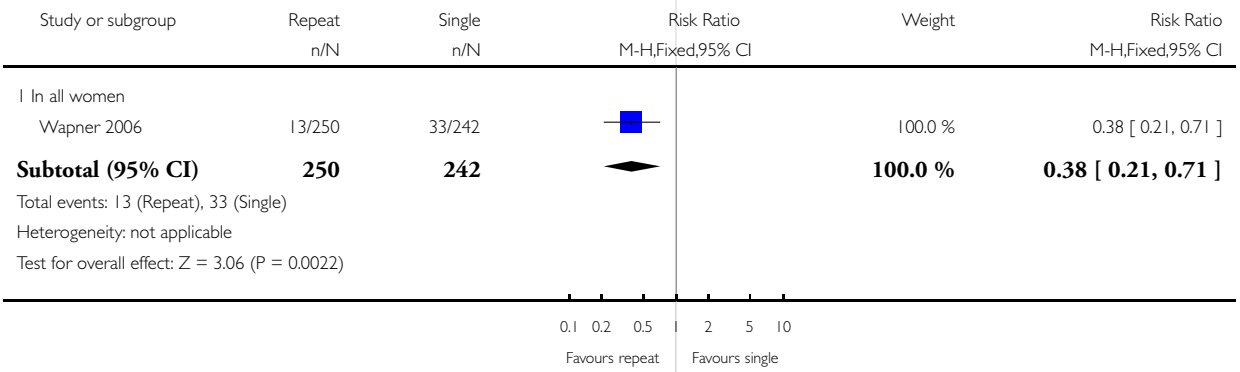


Analysis 1.64. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 64 Bruising at injection site.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 64 Bruising at injection site



Analysis 1.65. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 65 Total mortality up to early childhood follow up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 65 Total mortality up to early childhood follow up

Study or subgroup	Favours experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	29/568	32/578		35.2 %	0.92 [0.57, 1.50]
Murphy 2008	49/1164	47/1140		52.7 %	1.02 [0.69, 1.51]
Peltoniemi 2007	11/159	5/167		5.4 %	2.31 [0.82, 6.50]
Wapner 2006	7/299	6/295		6.7 %	1.15 [0.39, 3.38]
Subtotal (95% CI)	**2190**	**2180**		**100.0 %**	**1.06 [0.80, 1.41]**
Total events: 96 (Favours experimental), 90 (Control)					
Heterogeneity: Chi^2 = 2.55, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	29/568	32/578		35.2 %	0.92 [0.57, 1.50]
Murphy 2008	49/1164	47/1140		52.7 %	1.02 [0.69, 1.51]
Peltoniemi 2007	11/159	5/167		5.4 %	2.31 [0.82, 6.50]
Wapner 2006	7/299	6/295		6.7 %	1.15 [0.39, 3.38]
Subtotal (95% CI)	**2190**	**2180**		**100.0 %**	**1.06 [0.80, 1.41]**
Total events: 96 (Favours experimental), 90 (Control)					
Heterogeneity: Chi^2 = 2.55, df = 3 (P = 0.47); I^2 =0.0%					
Test for overall effect: Z = 0.44 (P = 0.66)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	29/568	32/578		74.4 %	0.92 [0.57, 1.50]
Peltoniemi 2007	11/159	5/167		11.4 %	2.31 [0.82, 6.50]

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Study or subgroup	Favours experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Wapner 2006	7/299	6/295		14.2 %	1.15 [0.39, 3.38]
Subtotal (95% CI)	**1026**	**1040**		**100.0 %**	**1.11 [0.74, 1.67]**
Total events: 47 (Favours experimental), 43 (Control)					
Heterogeneity: Chi^2 = 2.49, df = 2 (P = 0.29); I^2 =20%					
Test for overall effect: Z = 0.52 (P = 0.60)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Murphy 2008	49/1164	47/1140		100.0 %	1.02 [0.69, 1.51]
Subtotal (95% CI)	**1164**	**1140**		**100.0 %**	**1.02 [0.69, 1.51]**
Total events: 49 (Favours experimental), 47 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.10 (P = 0.92)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Peltoniemi 2007	11/159	5/167		100.0 %	2.31 [0.82, 6.50]
Subtotal (95% CI)	**159**	**167**		**100.0 %**	**2.31 [0.82, 6.50]**
Total events: 11 (Favours experimental), 5 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.59 (P = 0.11)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	29/568	32/578		86.7 %	0.92 [0.57, 1.50]
Peltoniemi 2007	11/159	5/167		13.3 %	2.31 [0.82, 6.50]
Subtotal (95% CI)	**727**	**745**		**100.0 %**	**1.11 [0.72, 1.71]**
Total events: 40 (Favours experimental), 37 (Control)					

0.01 0.1 1 10 100

Favours experimental Favours control

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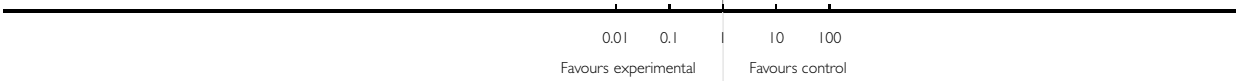
Study or subgroup	Favours experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: Chi² = 2.48, df = 1 (P = 0.12); I² =60%					
Test for overall effect: Z = 0.46 (P = 0.65)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Murphy 2008	49/1164	47/1140		88.7 %	1.02 [0.69, 1.51]
Wapner 2006	7/299	6/295		11.3 %	1.15 [0.39, 3.38]
Subtotal (95% CI)	**1463**	**1435**		**100.0 %**	**1.04 [0.72, 1.50]**
Total events: 56 (Favours experimental), 53 (Control)					
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² =0.0%					
Test for overall effect: Z = 0.19 (P = 0.85)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	29/568	32/578		40.0 %	0.92 [0.57, 1.50]
Murphy 2008	49/1164	47/1140		60.0 %	1.02 [0.69, 1.51]
Subtotal (95% CI)	**1732**	**1718**		**100.0 %**	**0.98 [0.72, 1.33]**
Total events: 78 (Favours experimental), 79 (Control)					
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² =0.0%					
Test for overall effect: Z = 0.12 (P = 0.90)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Wapner 2006	7/299	6/295		100.0 %	1.15 [0.39, 3.38]
Subtotal (95% CI)	**299**	**295**		**100.0 %**	**1.15 [0.39, 3.38]**
Total events: 7 (Favours experimental), 6 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.26 (P = 0.80)					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Favours experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 1.66. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 66 Survival free of any disability to early childhood follow up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 66 Survival free of any disability to early childhood follow up

Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	320/524	322/536		26.1 %	1.02 [0.92, 1.12]
Murphy 2008	921/1060	893/1035		73.9 %	1.01 [0.97, 1.04]
Subtotal (95% CI)	**1584**	**1571**		**100.0 %**	**1.01 [0.97, 1.05]**
Total events: 1241 (Experimental), 1215 (Control)					
Heterogeneity: Chi^2 = 0.04, df = 1 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.52 (P = 0.60)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	320/524	322/536		26.0 %	1.02 [0.92, 1.12]
Murphy 2008	921/1069	893/1035		74.0 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**1593**	**1571**		**100.0 %**	**1.00 [0.97, 1.04]**
Total events: 1241 (Experimental), 1215 (Control)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	320/524	322/536		100.0 %	1.02 [0.92, 1.12]
Subtotal (95% CI)	**524**	**536**		**100.0 %**	**1.02 [0.92, 1.12]**
Total events: 320 (Experimental), 322 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Murphy 2008	921/1069	893/1035		100.0 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**1069**	**1035**		**100.0 %**	**1.00 [0.97, 1.03]**

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Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Total events: 921 (Experimental), 893 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	320/524	322/536		100.0 %	1.02 [0.92, 1.12]
Subtotal (95% CI)	**524**	**536**		**100.0 %**	**1.02 [0.92, 1.12]**
Total events: 320 (Experimental), 322 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Murphy 2008	921/1069	893/1035		100.0 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**1069**	**1035**		**100.0 %**	**1.00 [0.97, 1.03]**
Total events: 921 (Experimental), 893 (Control)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	320/524	322/536		26.0 %	1.02 [0.92, 1.12]

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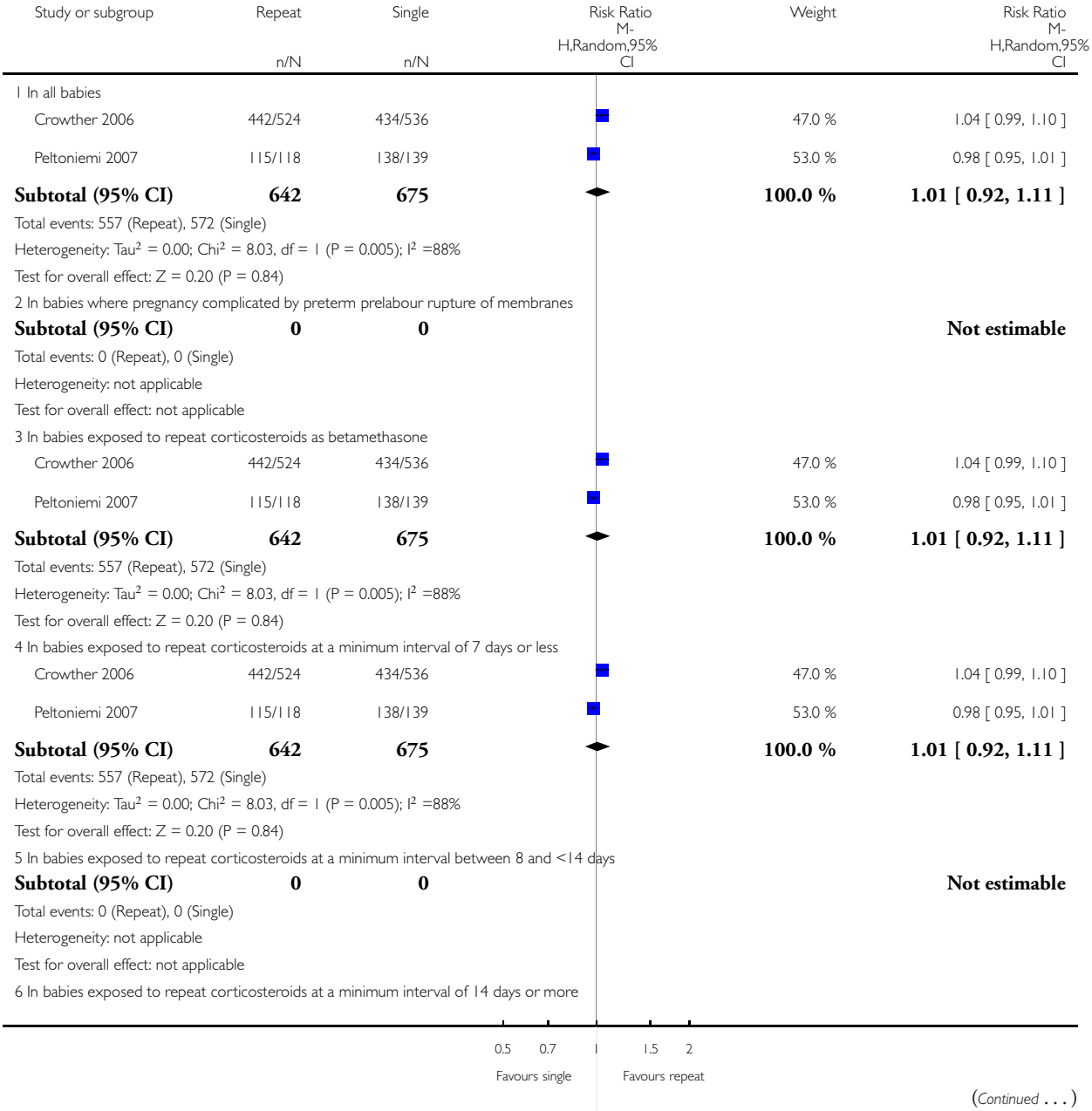
Study or subgroup	Experimental n/N	Control n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Murphy 2008	921/1069	893/1035		74.0 %	1.00 [0.97, 1.03]
Subtotal (95% CI)	**1593**	**1571**		**100.0 %**	**1.00 [0.97, 1.04]**
Total events: 1241 (Experimental), 1215 (Control)					
Heterogeneity: Chi^2 = 0.14, df = 1 (P = 0.71); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Experimental), 0 (Control)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.67. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 67 Survival free of major neurosensory disability to early childhood follow up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 67 Survival free of major neurosensory disability to early childhood follow up



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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Peltoniemi 2007	115/118	138/139		100.0 %	0.98 [0.95, 1.01]
Subtotal (95% CI)	**118**	**139**		**100.0 %**	**0.98 [0.95, 1.01]**
Total events: 115 (Repeat), 138 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.12 (P = 0.26)					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	442/524	434/536		47.0 %	1.04 [0.99, 1.10]
Peltoniemi 2007	115/118	138/139		53.0 %	0.98 [0.95, 1.01]
Subtotal (95% CI)	**642**	**675**		**100.0 %**	**1.01 [0.92, 1.11]**
Total events: 557 (Repeat), 572 (Single)					
Heterogeneity: Tau^2 = 0.00; Chi^2 = 8.03, df = 1 (P = 0.005); I^2 =88%					
Test for overall effect: Z = 0.20 (P = 0.84)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	442/524	434/536		100.0 %	1.04 [0.99, 1.10]
Subtotal (95% CI)	**524**	**536**		**100.0 %**	**1.04 [0.99, 1.10]**
Total events: 442 (Repeat), 434 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.45 (P = 0.15)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

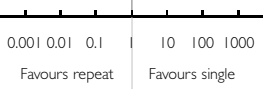
Analysis 1.68. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 68 Major neurosensory disablity at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 68 Major neurosensory disablity at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
1 In all babies					
Crowther 2006	53/495	70/504		77.7 %	0.77 [0.55, 1.08]
Peltoniemi 2007	3/118	1/139		22.3 %	3.53 [0.37, 33.52]
Subtotal (95% CI)	**613**	**643**		**100.0 %**	**1.08 [0.31, 3.76]**
Total events: 56 (Repeat), 71 (Single)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 1.73, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 0.13 (P = 0.90)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	53/495	70/504		77.7 %	0.77 [0.55, 1.08]
Peltoniemi 2007	3/118	1/139		22.3 %	3.53 [0.37, 33.52]
Subtotal (95% CI)	**613**	**643**		**100.0 %**	**1.08 [0.31, 3.76]**
Total events: 56 (Repeat), 71 (Single)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 1.73, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 0.13 (P = 0.90)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	53/495	70/504		77.7 %	0.77 [0.55, 1.08]
Peltoniemi 2007	3/118	1/139		22.3 %	3.53 [0.37, 33.52]
Subtotal (95% CI)	**613**	**643**		**100.0 %**	**1.08 [0.31, 3.76]**
Total events: 56 (Repeat), 71 (Single)					
Heterogeneity: Tau^2 = 0.49; Chi^2 = 1.73, df = 1 (P = 0.19); I^2 =42%					
Test for overall effect: Z = 0.13 (P = 0.90)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					



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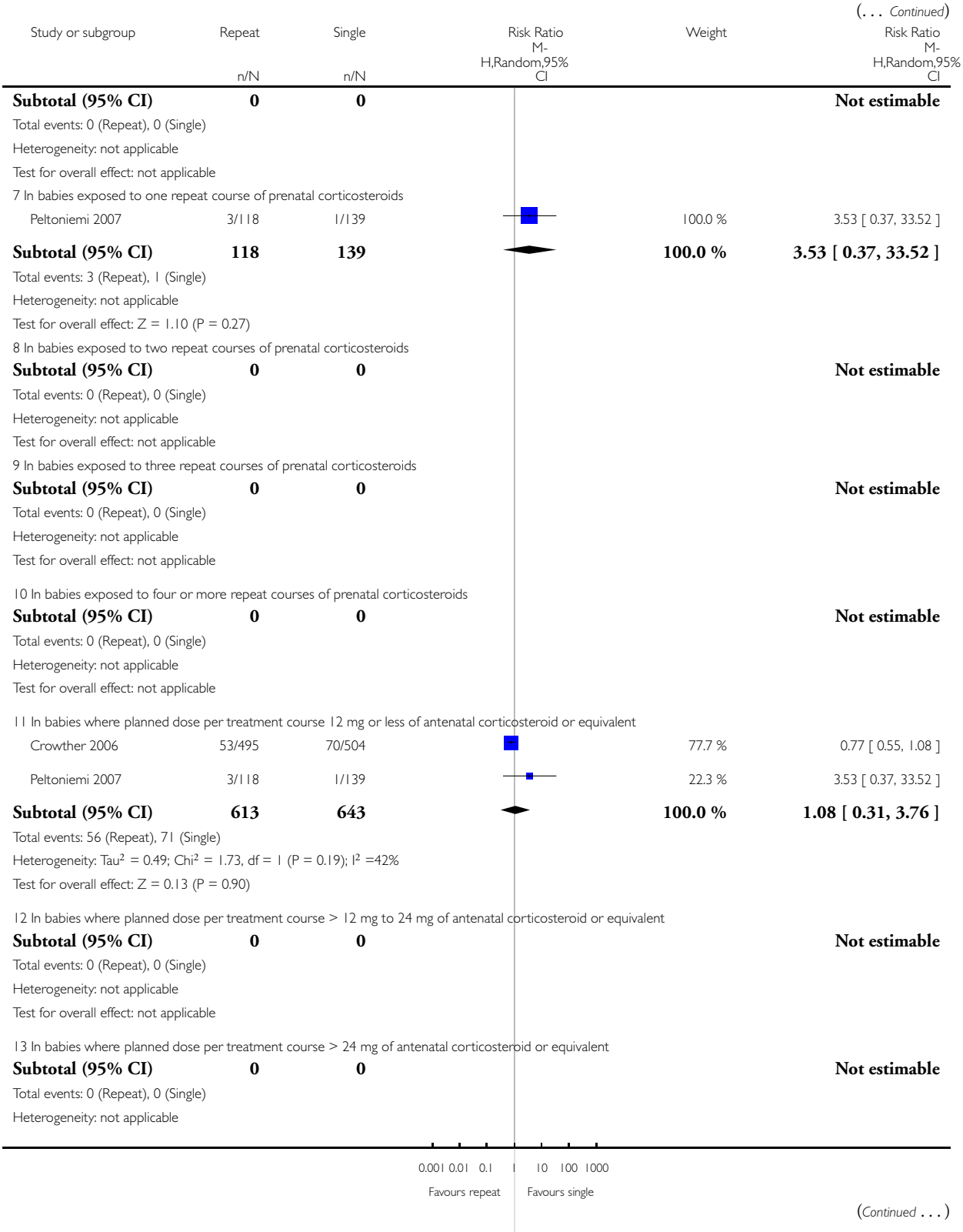

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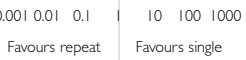
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Random,95% CI	Weight	Risk Ratio M-H,Random,95% CI
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	53/495	70/504		100.0 %	0.77 [0.55, 1.08]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.77 [0.55, 1.08]**
Total events: 53 (Repeat), 70 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 1.52 (P = 0.13)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



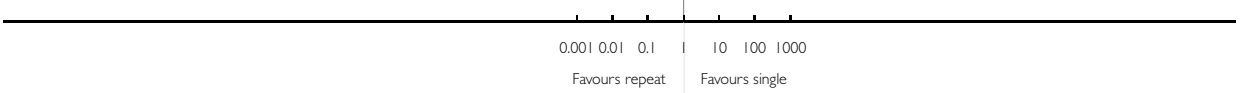
Analysis 1.69. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 69 Disability at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 69 Disability at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	175/495	182/504		100.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.98 [0.83, 1.16]**
Total events: 175 (Repeat), 182 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	175/495	182/504		100.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.98 [0.83, 1.16]**
Total events: 175 (Repeat), 182 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	175/495	182/504		100.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.98 [0.83, 1.16]**
Total events: 175 (Repeat), 182 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
7 In babies exposed to one repeat course of prenatal corticosteroids					



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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	175/495	182/504		100.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.98 [0.83, 1.16]**
Total events: 175 (Repeat), 182 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	175/495	182/504		100.0 %	0.98 [0.83, 1.16]
Subtotal (95% CI)	**495**	**504**		**100.0 %**	**0.98 [0.83, 1.16]**
Total events: 175 (Repeat), 182 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.25 (P = 0.80)					

(*Continued* . . .)

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 1.70. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 70 Composite serious outcome at early childhood follow-up (however defined by authors).

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 70 Composite serious outcome at early childhood follow-up (however defined by authors)

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	204/524	214/536		59.5 %	0.98 [0.84, 1.13]
Murphy 2008	148/1069	142/1035		40.5 %	1.01 [0.81, 1.25]
Subtotal (95% CI)	**1593**	**1571**		**100.0 %**	**0.99 [0.87, 1.12]**
Total events: 352 (Repeat), 356 (Single)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
2 In babies where pregnancy complicated by preterm prelabour rupture of membranes					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					

(*Continued* . . .)

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Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Test for overall effect: not applicable					
3 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	204/524	214/536		59.5 %	0.98 [0.84, 1.13]
Murphy 2008	148/1069	142/1035		40.5 %	1.01 [0.81, 1.25]
Subtotal (95% CI)	**1593**	**1571**		**100.0 %**	**0.99 [0.87, 1.12]**
Total events: 352 (Repeat), 356 (Single)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
4 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	204/524	214/536		100.0 %	0.98 [0.84, 1.13]
Subtotal (95% CI)	**524**	**536**		**100.0 %**	**0.98 [0.84, 1.13]**
Total events: 204 (Repeat), 214 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
5 In babies exposed to repeat corticosteroids at a minimum interval between 8 and <14 days					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
6 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more					
Murphy 2008	148/1069	142/1035		100.0 %	1.01 [0.81, 1.25]
Subtotal (95% CI)	**1069**	**1035**		**100.0 %**	**1.01 [0.81, 1.25]**
Total events: 148 (Repeat), 142 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
7 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
8 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
9 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
10 In babies exposed to four or more repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					

(*Continued* . . .)

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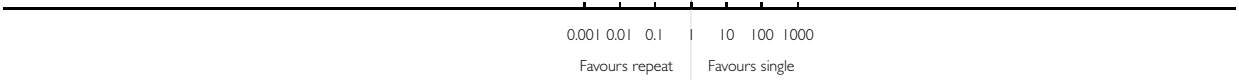
Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
Heterogeneity: not applicable					
Test for overall effect: not applicable					
11 In babies where planned dose per treatment course 12 mg or less of antenatal corticosteroid or equivalent					
Crowther 2006	204/524	214/536		100.0 %	0.98 [0.84, 1.13]
Subtotal (95% CI)	**524**	**536**		**100.0 %**	**0.98 [0.84, 1.13]**
Total events: 204 (Repeat), 214 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.33 (P = 0.74)					
12 In babies where planned dose per treatment course > 12 mg to 24 mg of antenatal corticosteroid or equivalent					
Murphy 2008	148/1069	142/1035		100.0 %	1.01 [0.81, 1.25]
Subtotal (95% CI)	**1069**	**1035**		**100.0 %**	**1.01 [0.81, 1.25]**
Total events: 148 (Repeat), 142 (Single)					
Heterogeneity: not applicable					
Test for overall effect: Z = 0.08 (P = 0.93)					
13 In babies where planned dose per treatment course > 24 mg of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of antenatal corticosteroid or equivalent					
Crowther 2006	204/524	214/536		59.5 %	0.98 [0.84, 1.13]
Murphy 2008	148/1069	142/1035		40.5 %	1.01 [0.81, 1.25]
Subtotal (95% CI)	**1593**	**1571**		**100.0 %**	**0.99 [0.87, 1.12]**
Total events: 352 (Repeat), 356 (Single)					
Heterogeneity: Chi^2 = 0.07, df = 1 (P = 0.79); I^2 =0.0%					
Test for overall effect: Z = 0.18 (P = 0.86)					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of antenatal corticosteroid or equivalent					
Subtotal (95% CI)	**0**	**0**			**Not estimable**
Total events: 0 (Repeat), 0 (Single)					
Heterogeneity: not applicable					
Test for overall effect: not applicable					



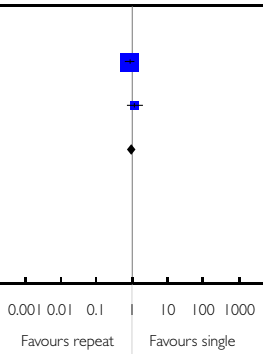
Analysis 1.71. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 71 Weight small for age at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 71 Weight small for age at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	68/520	81/527		77.3 %	0.85 [0.63, 1.15]
Wapner 2006	28/206	23/195		22.7 %	1.15 [0.69, 1.93]
Subtotal (95% CI)	**726**	**722**		**100.0 %**	**0.92 [0.71, 1.19]**
Total events: 96 (Repeat), 104 (Single)					
Heterogeneity: Chi^2 = 1.00, df = 1 (P = 0.32); I^2 =0.0%					
Test for overall effect: Z = 0.64 (P = 0.52)					

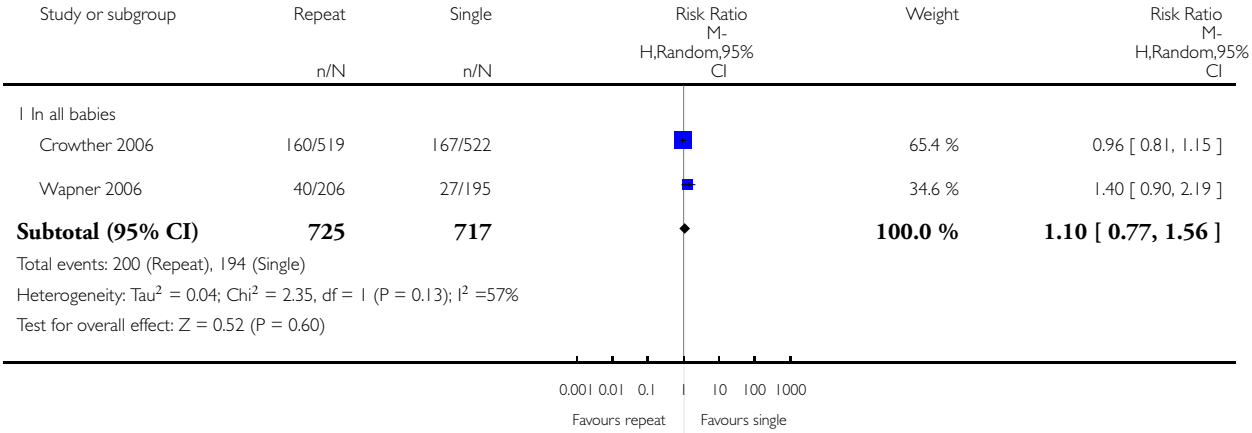


Analysis 1.72. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 72 Head circumference small for age at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 72 Head circumference small for age at early childhood follow-up

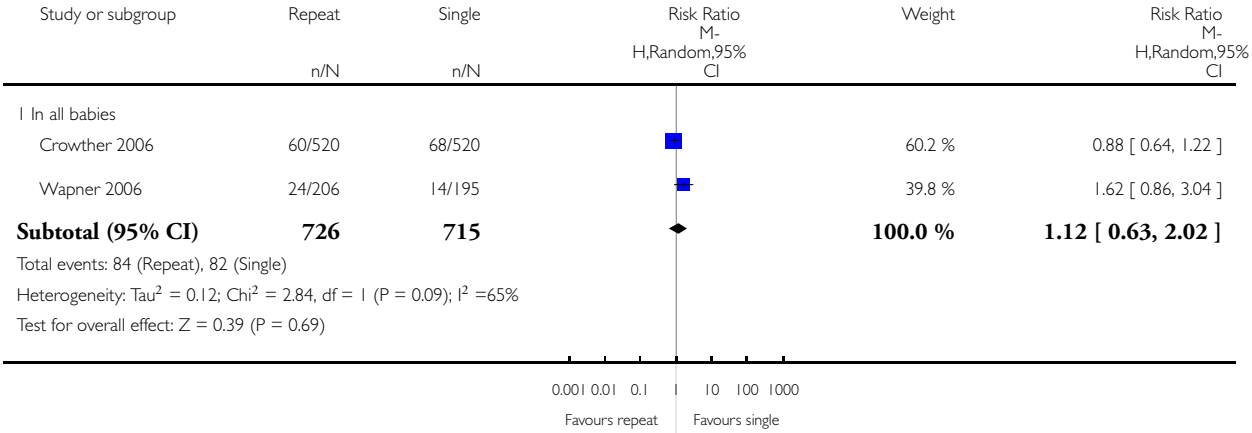


Analysis 1.73. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 73 Height small for age at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 73 Height small for age at early childhood follow-up



Analysis 1.74. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 74 Mean weight at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 74 Mean weight at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	12.6 (1.9)	527	12.6 (1.9)		62.1 %	0.0 [-0.23, 0.23]
Peltoniemi 2007	115	12.1 (1.4)	128	12.1 (1.6)		23.1 %	0.0 [-0.38, 0.38]
Wapner 2006	248	13.5 (2.7)	238	13.7 (2.6)		14.8 %	-0.20 [-0.67, 0.27]
Subtotal (95% CI)	**883**		**893**			**100.0 %**	**-0.03 [-0.21, 0.15]**

Heterogeneity: $Chi^2 = 0.59$, df = 2 (P = 0.74); $I^2 = 0.0\%$

Test for overall effect: Z = 0.32 (P = 0.75)

Test for subgroup differences: Not applicable

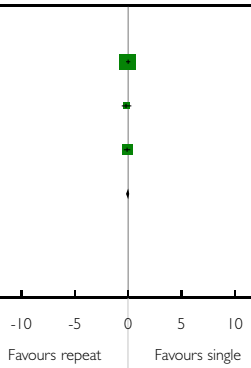
Analysis 1.75. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 75 Mean head circumference at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 75 Mean head circumference at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	48.9 (1.7)	527	48.9 (1.8)		61.0 %	0.0 [-0.21, 0.21]
Peltoniemi 2007	115	49.1 (2)	128	49.3 (1.5)		13.6 %	-0.20 [-0.65, 0.25]
Wapner 2006	248	49 (1.9)	238	49.1 (1.8)		25.4 %	-0.10 [-0.43, 0.23]
Subtotal (95% CI)	**883**		**893**			**100.0 %**	**-0.05 [-0.22, 0.11]**
Heterogeneity: Chi^2 = 0.73, df = 2 (P = 0.69); I^2 =0.0%							
Test for overall effect: Z = 0.62 (P = 0.53)							



Analysis 1.76. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 76 Mean height at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 76 Mean height at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	87.6 (4.6)	527	87.7 (4.7)		57.6 %	-0.10 [-0.66, 0.46]
Peltoniemi 2007	115	87 (3.1)	128	86.9 (3.5)		26.6 %	0.10 [-0.73, 0.93]
Wapner 2006	248	90.5 (6.4)	238	91.1 (5.7)		15.8 %	-0.60 [-1.68, 0.48]
Subtotal (95% CI)	**883**		**893**			**100.0 %**	**-0.13 [-0.55, 0.30]**

Heterogeneity: Chi^2 = 1.04, df = 2 (P = 0.60); I^2 =0.0%

Test for overall effect: Z = 0.58 (P = 0.56)

Test for subgroup differences: Not applicable

Analysis 1.77. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 77 Weight Z score at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 77 Weight Z score at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	-0.04 (1.3)	527	-0.01 (1.29)		100.0 %	-0.03 [-0.19, 0.13]
Subtotal (95% CI)	**520**		**527**			**100.0 %**	**-0.03 [-0.19, 0.13]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.37 (P = 0.71)

Test for subgroup differences: Not applicable

Analysis 1.78. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 78 Head circumference Z score at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 78 Head circumference Z score at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	-0.74 (1.26)	527	-0.76 (1.33)		70.1 %	0.02 [-0.14, 0.18]
Peltoniemi 2007	115	0.1 (1)	128	0 (0.9)		29.9 %	0.10 [-0.14, 0.34]
Subtotal (95% CI)	**635**		**655**			**100.0 %**	**0.04 [-0.09, 0.18]**

Heterogeneity: Chi^2 = 0.30, df = 1 (P = 0.58); I^2 =0.0%

Test for overall effect: Z = 0.66 (P = 0.51)

Test for subgroup differences: Not applicable

Analysis 1.79. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 79 Height Z score at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

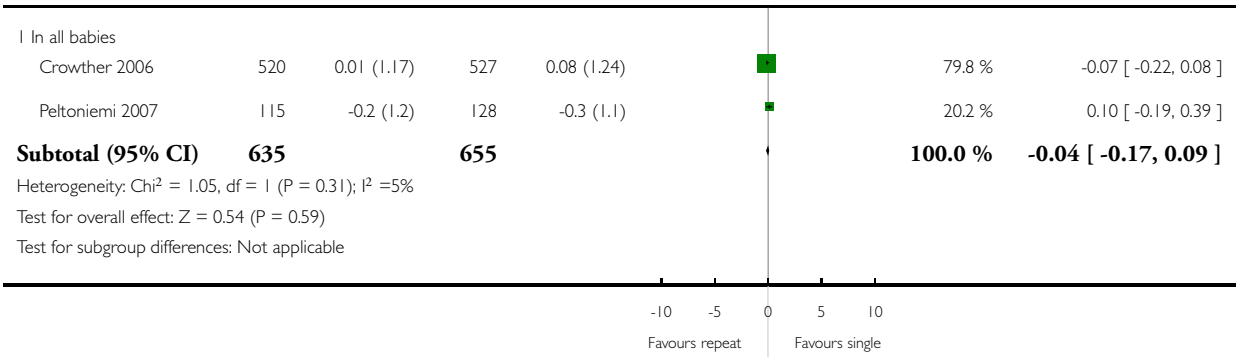
Outcome: 79 Height Z score at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	520	0.01 (1.17)	527	0.08 (1.24)		79.8 %	-0.07 [-0.22, 0.08]
Peltoniemi 2007	115	-0.2 (1.2)	128	-0.3 (1.1)		20.2 %	0.10 [-0.19, 0.39]
Subtotal (95% CI)	**635**		**655**			**100.0 %**	**-0.04 [-0.17, 0.09]**

Heterogeneity: Chi^2 = 1.05, df = 1 (P = 0.31); I^2 =5%

Test for overall effect: Z = 0.54 (P = 0.59)

Test for subgroup differences: Not applicable



Analysis 1.80. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 80 Developmental delay at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 80 Developmental delay at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	168/495	175/504		64.8 %	0.98 [0.82, 1.16]
Murphy 2008	86/1020	84/988		31.9 %	0.99 [0.74, 1.32]
Peltoniemi 2007	6/88	10/107		3.4 %	0.73 [0.28, 1.93]
Subtotal (95% CI)	**1603**	**1599**		**100.0 %**	**0.97 [0.84, 1.13]**
Total events: 260 (Repeat), 269 (Single)					
Heterogeneity: Chi^2 = 0.36, df = 2 (P = 0.84); I^2 =0.0%					
Test for overall effect: Z = 0.36 (P = 0.72)					

Analysis 1.81. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 81 Mental Developmental Index at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

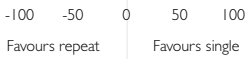
Outcome: 81 Mental Developmental Index at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	474	91.1 (17.1)	493	90.5 (17.7)		73.6 %	0.60 [-1.59, 2.79]
Peltoniemi 2007	88	104 (13)	107	101 (13)		26.4 %	3.00 [-0.67, 6.67]
Total (95% CI)	**562**		**600**			**100.0 %**	**1.23 [-0.65, 3.11]**

Heterogeneity: Chi^2 = 1.21, df = 1 (P = 0.27); I^2 =17%

Test for overall effect: Z = 1.28 (P = 0.20)

Test for subgroup differences: Not applicable



Analysis 1.82. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 82 Psychomotor Developmental Index at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

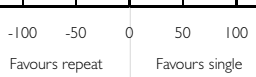
Outcome: 82 Psychomotor Developmental Index at early childhood follow-up

Study or subgroup	Repeat N	Mean(SD)	Single N	Mean(SD)	Mean Difference IV,Fixed,95% CI	Weight	Mean Difference IV,Fixed,95% CI
1 In all babies							
Crowther 2006	472	92.5 (17.3)	486	92.1 (16.7)		100.0 %	0.40 [-1.75, 2.55]
Total (95% CI)	**472**		**486**			**100.0 %**	**0.40 [-1.75, 2.55]**

Heterogeneity: not applicable

Test for overall effect: Z = 0.36 (P = 0.72)

Test for subgroup differences: Not applicable



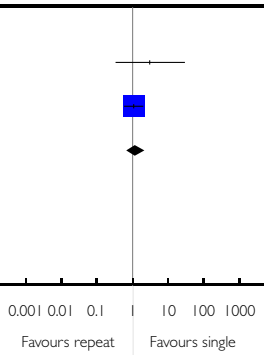
Analysis 1.83. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 83 Bindness at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 83 Bindness at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	3/521	1/526		4.9 %	3.03 [0.32, 29.02]
Murphy 2008	21/1069	19/1035		95.1 %	1.07 [0.58, 1.98]
Subtotal (95% CI)	**1590**	**1561**		**100.0 %**	**1.17 [0.65, 2.10]**
Total events: 24 (Repeat), 20 (Single)					
Heterogeneity: Chi^2 = 0.76, df = 1 (P = 0.38); I^2 =0.0%					
Test for overall effect: Z = 0.51 (P = 0.61)					



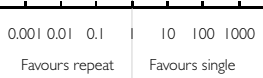
Analysis 1.84. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 84 Deafness at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 84 Deafness at early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	4/521	5/521		71.1 %	0.80 [0.22, 2.96]
Murphy 2008	2/1069	2/1035		28.9 %	0.97 [0.14, 6.86]
Peltoniemi 2007	0/120	0/139			Not estimable
Subtotal (95% CI)	**1710**	**1695**		**100.0 %**	**0.85 [0.29, 2.52]**
Total events: 6 (Repeat), 7 (Single)					
Heterogeneity: Chi^2 = 0.03, df = 1 (P = 0.87); I^2 =0.0%					
Test for overall effect: Z = 0.30 (P = 0.77)					

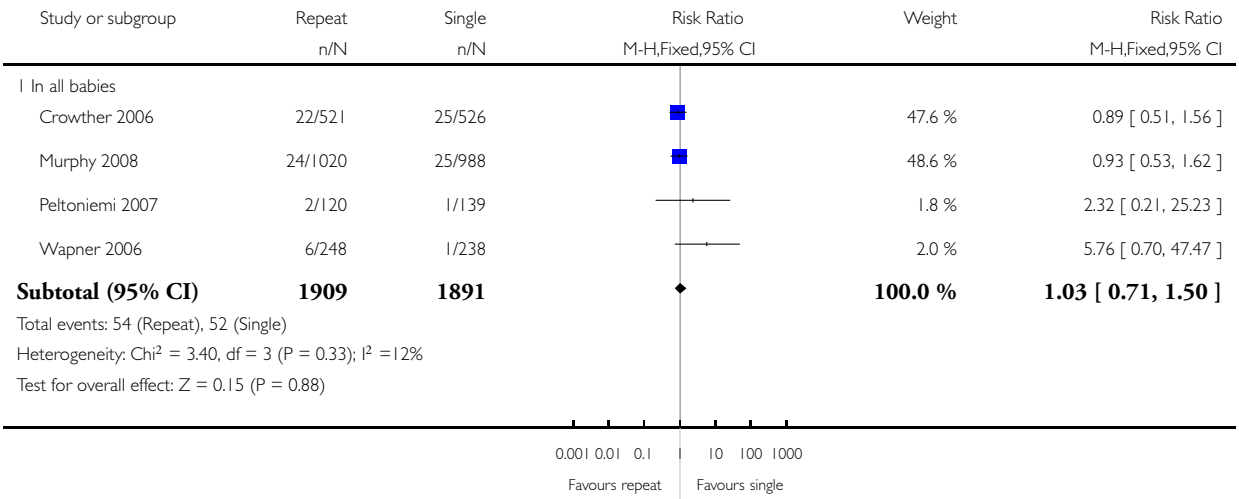


Analysis 1.85. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 85 Cerebral palsy at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 85 Cerebral palsy at early childhood follow-up

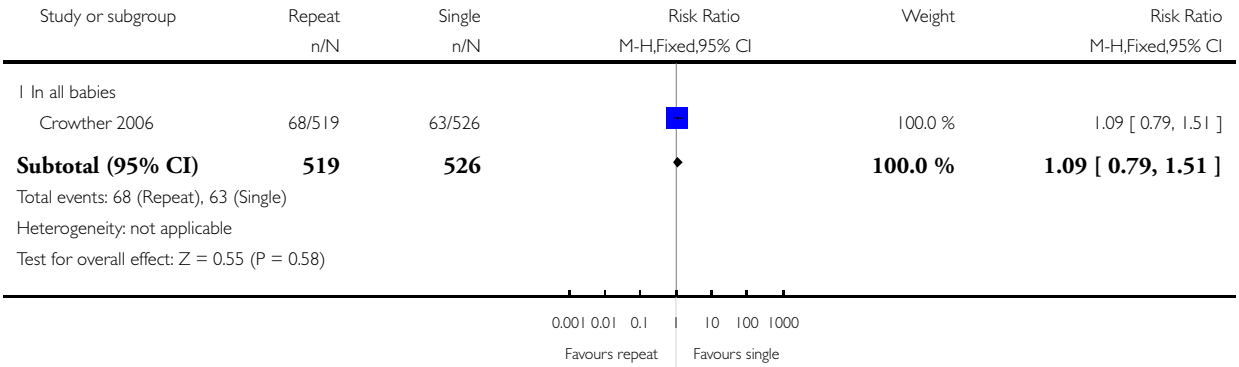


Analysis 1.86. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 86 Behaviour score at early childhood follow-up within clinical range.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 86 Behaviour score at early childhood follow-up within clinical range

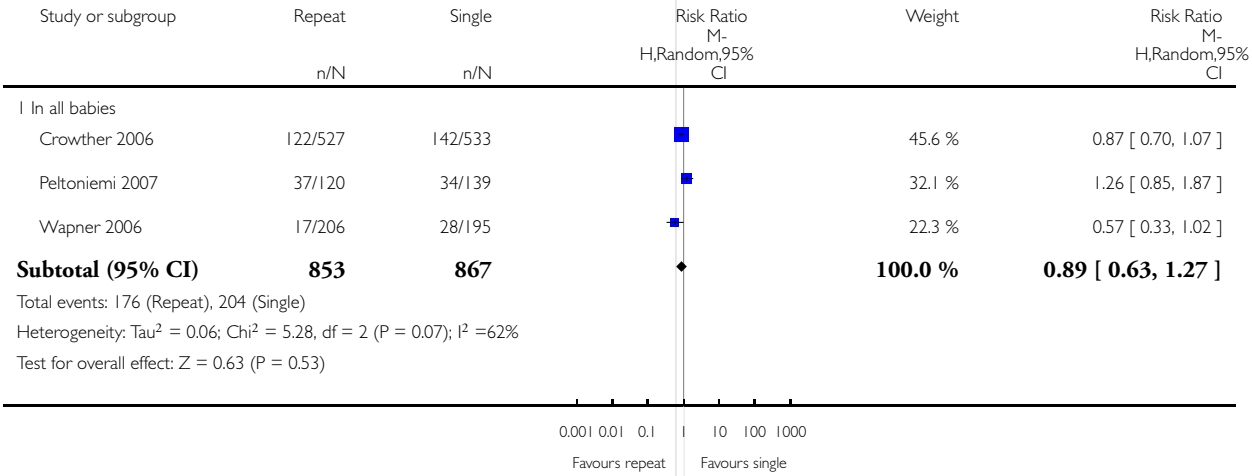


Analysis 1.87. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 87 Asthma/Wheezing at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 87 Asthma/Wheezing at early childhood follow-up

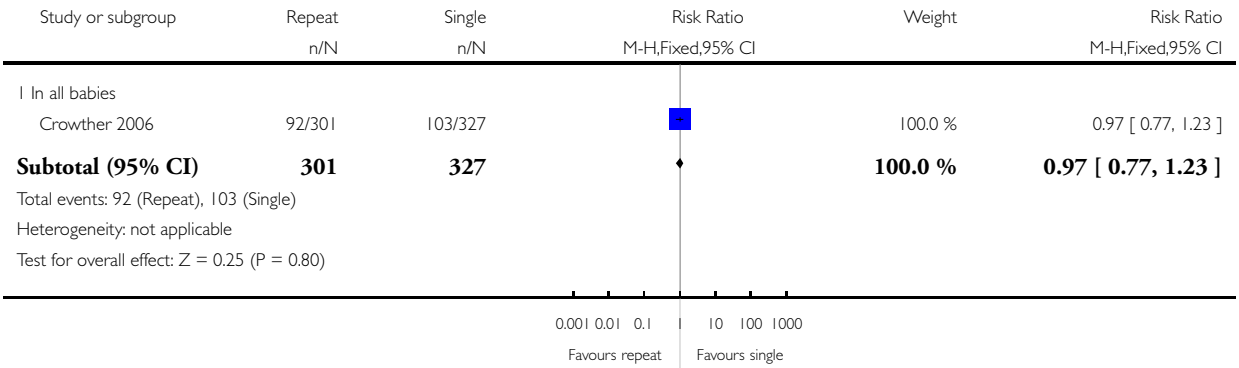


Analysis 1.88. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 88 Hypertensive at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 88 Hypertensive at early childhood follow-up

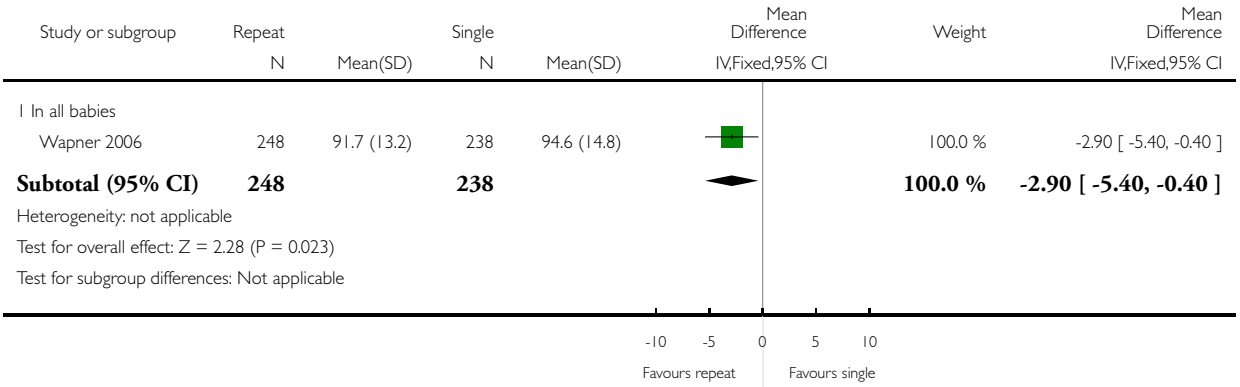


Analysis 1.89. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 89 Mean systolic blood pressure at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 89 Mean systolic blood pressure at early childhood follow-up

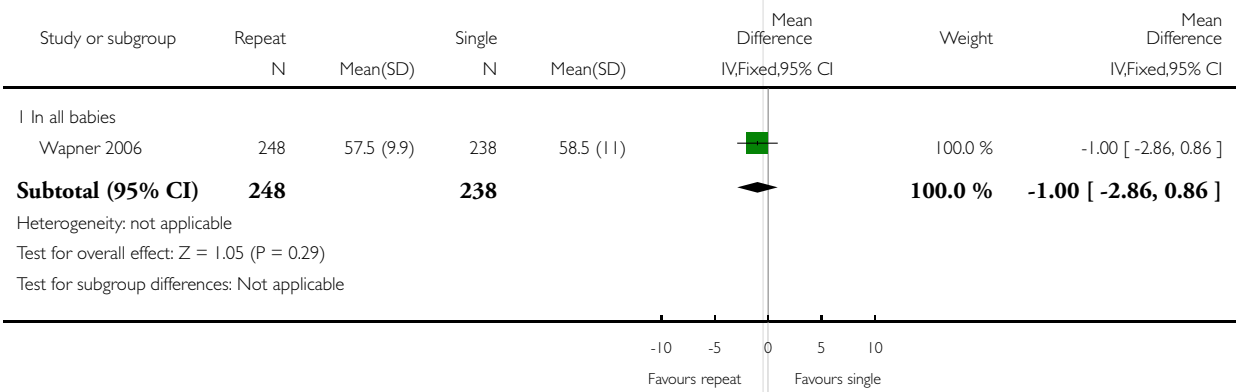


Analysis 1.90. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 90 Mean diasystolic blood pressure at early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 90 Mean diasystolic blood pressure at early childhood follow-up



Analysis 1.91. Comparison 1 Repeat doses of corticosteroids versus single course, Outcome 91 Hospital re-admission by early childhood follow-up.

Review: Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes

Comparison: 1 Repeat doses of corticosteroids versus single course

Outcome: 91 Hospital re-admission by early childhood follow-up

Study or subgroup	Repeat n/N	Single n/N	Risk Ratio M-H,Fixed,95% CI	Weight	Risk Ratio M-H,Fixed,95% CI
1 In all babies					
Crowther 2006	266/527	261/533		39.5 %	1.03 [0.91, 1.16]
Murphy 2008	266/1069	256/1035		39.6 %	1.01 [0.87, 1.17]
Peltoniemi 2007	71/120	70/139		9.9 %	1.17 [0.94, 1.47]
Wapner 2006	65/206	71/195		11.1 %	0.87 [0.66, 1.14]
Subtotal (95% CI)	**1922**	**1902**		**100.0 %**	**1.02 [0.93, 1.11]**
Total events: 668 (Repeat), 658 (Single)					
Heterogeneity: Chi^2 = 3.00, df = 3 (P = 0.39); I^2 =0%					
Test for overall effect: Z = 0.39 (P = 0.70)					

FEEDBACK

Murphy, 5 July 2012

Summary

As the authors of the Multiple courses of Antenatal Corticosteroids for preterm birth Study (MACS), which is one of the trials included in this review, we have a few comments that need to be addressed.

1. In MACS, we collected data on 'severe respiratory distress syndrome (RDS)' rather than 'RDS'. In this review, data from MACS for 'severe RDS' are included in the meta-analysis for 'severe lung disease' but not in the meta-analysis for 'RDS'. As a result, the data from MACS are currently not able to contribute to answering the question as to the effect of multiple courses of antenatal corticosteroids on RDS. Because RDS is defined differently in the various trials we believe it is reasonable that the outcome RDS should include both mild and severe disease. Subgroup analyses could then look at mild RDS and severe RDS separately. Given that MACS is the largest

trial included in the review, it is particularly important that its results should contribute to answering the question about the effect of repeated doses of antenatal corticosteroids on RDS.

2. The review authors have chosen to include data for 'severe RDS' from the various trials in an outcome of 'severe lung disease'. We find the labelling of severe RDS as 'severe lung disease' ambiguous. Severe lung disease could theoretically include meconium aspiration, pneumothorax, group B streptococcal pneumonia and other conditions that are not thought to benefit from antenatal corticosteroids.

3. In the Results text section 'secondary outcomes for the child', the review states that "Data were not able to be included in the meta-analysis for Murphy 2008 for anthropometric assessments expressed as means, as standard deviations were not available in the published report." In our report of the 18-24 month follow-up for MACS (Asztalos 2008[1], not Murphy 2008 as stated in the review) the data are expressed as means, mean differences and confidence intervals. The within-group standard deviations are actually not needed for the meta-analysis, as all that is required is the mean difference (which we reported) and its variance. The variance can be derived by squaring the width of the CI divided by 2*1.96.

That is: Variance of Mean Difference = [(UL - LL)/(2*1.96)]2. In any case, an estimate of the within-group standard deviations can be calculated from the confidence limits and the group sample sizes.
The table below shows the summary statistic for the mean difference in birth weight at early childhood follow-up with and without the MACS data. When MACS data are included, the difference in birth weight between the two groups is statistically significant..

Table Summary statistic for the mean difference in birth weight at early childhood follow-up.

	Mean Difference in Weight	**Variance of Mean Difference**	**Lower Limit**	**Upper Limit**	**P value**
Summary without MACS	-0.0297	0.0086	-0.2114	0.1520	0.7488
Summary with MACS	-0.2003	0.0046	-0.3327	-0.0678	0.0030

The long term impact of weighing less in early childhood is not known. Nevertheless, that repeated doses of antenatal corticosteroids have adverse effects on growth is worrisome in that it signifies the potential for repeated doses to cause harm.
Follow-up studies have thus far been reassuring, demonstrating no difference in death or neurologic impairment in early childhood. However, we should not be falsely reassured by these studies. The long-term follow-up studies have limited power to rule out the effect of repeated doses of antenatal corticosteroids on infrequent adverse events. Thus, finding no difference in long-term outcome does not necessarily prove safety. We are reminded of the RCTs of postnatal corticosteroid treatment which initially demonstrated short term benefits and then over time, with the completion of long-term studies, demonstrated the potential for harm.[2]
4. We believe that the findings of short term neonatal benefits from repeated courses of antenatal corticosteroids are important. However, given the adverse effect of antenatal corticosteroids on birth weight and weight at early childhood follow-up, and the uncertain effect on long term outcomes, we believe that the conclusions and recommendations for clinical practice in this review should be more cautious than they currently are. We would suggest the review authors consider a statement such as "Although the short term neonatal benefits of repeated courses of antenatal corticosteroids support their use, long-term benefits have not been demonstrated and long-term adverse effects have not been ruled out. The adverse effect of repeated doses of antenatal corticosteroids on birth weight and weight at early childhood follow-up is a concern. Caution should therefore be exercised to ensure that only those women who are at particularly high risk of very early preterm birth are offered treatment with repeated courses of antenatal corticosteroids."

References

1. Asztalos EV, Murphy KE, Hannah ME, Willan AR, Matthews SG, Ohlsson A, et al. Multiple courses of antenatal corticosteroids for preterm birth study: 2-year outcomes. *Pediatrics* 2010;**126**:e1045-e1055.
2. Halliday HL, Ehrenkranz RA, Doyle LW. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochran Database of Sys Rev 2010, Issue 5.

Kellie E. Murphy, Andrew R Willan, Mary E. Hannah, Elizabeth Asztalos, Arne Ohlsson, Edmond N Kelly, Stephen G Matthews, Saroj Saigal, Susan Ross, Marie-France Delisle, Kofi Amankwah, Patricia Guselle, Amiram Gafni, Shoo K Lee, B Anthony Armson, for the MACS Collaborative Group. July 2012
[Feedback received from Kellie E Murphy, 5 July 2012]

Reply

Many thanks to the authors of the Multiple courses of Antenatal Corticosteroids for preterm birth Study (MACS).
1. The MACS trial reported on the outcome of 'severe respiratory distress syndrome'. The authors query why the data from MACS were only included in the outcome for 'severe lung disease' rather than RDS (any).
We do not feel that it would be appropriate to combine data from trials reporting respiratory distress syndrome (mild or severe) with severe RDS. This is likely to result in significant heterogeneity and therefore we chose to report data for RDS and severe lung disease as separate outcomes. If the authors of the MACS trial can provide data for RDS (any) we would certainly be willing to add it to the appropriate analysis.
2. The authors of the MACS trial query the labelling of the outcome 'severe lung disease'.
This outcome was selected by the review authors and is defined in the review protocol.
3. The authors of the MACS trial query why their data for anthropometric assessments at 18 to 24 months were not included in the meta-analysis.
Data were not included as SD's were not available in the trial report. We acknowledge that the author of this report was Asztalos 2008, however Cochrane methodology requires that it is the primary trial that is cited in the text. The reference to Asztalos can be found in the reference section of this review. In order to enter data in to the statistical programme we require mean values for each group with the associated standard deviation or standard error. If the authors of the MACS trial can provide us with the mean and standard deviations for the treatment and the control groups with the numbers of children in each group we will certainly be willing to add these data to the appropriate analyses.
4. The authors of the MACS trial query the conclusions of the review.
The review authors consider the conclusions and both the clinical and research recommendations to be appropriate summaries of the available evidence.

Contributors

Caroline Crowther

WHAT'S NEW

Last assessed as up-to-date: 20 January 2015.

Date	Event	Description
5 January 2015	New citation required but conclusions have not changed	There are no changes to the conclusions of this review.
5 January 2015	New search has been performed	Search updated and two new trials excluded (Bontis 2011; Romejko-Wolniewicz 2013).

HISTORY

Protocol first published: Issue 4, 2002

Review first published: Issue 3, 2003

Date	Event	Description
24 July 2012	Feedback has been incorporated	Comments from Kellie Murphy added - see Feedback 1.
18 July 2011	Amended	Corrected reference error - Ashworth 2006 amended to read Ashwood 2006.
18 April 2011	New citation required and conclusions have changed	Conclusions are now stronger; early benefit now without evidence of longer term harm Two additional authors joined the review team (C McKinlay and P Middleton)
31 March 2011	New search has been performed	Search updated in March 2011 and data from five new trials added (Garite 2009; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007). Published longer term follow-up in early childhood now included for four trials (Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006) and information on follow up for one further trial added (Mazumder 2008). Acknowledgement of unpublished information provided on caesarean section by Emeritus Professor Thomas Garite for the Garite 2009 trial.
20 September 2008	Amended	Converted to new review format.
11 May 2007	New search has been performed	Search updated in November 2006 and data from two trials now published added (Crowther 2006; Wapner 2006). We updated the search just before submission for publication and identified the published report for the previously listed Peltoniemi ongoing study. We have added it to the ' Studies awaiting assessment' section and will consider it for inclusion in the next update (Peltoniemi 2007)

CONTRIBUTIONS OF AUTHORS

CAC and JEH prepared the original protocol, CAC wrote the draft of the original review, and both CAC and JEH commented on subsequent draft and prepared the previous updates. For the 2011 update, CAC prepared the first draft; CAC, CM and PM prepared the 'Risk of bias' tables, CAC and CM assessed identified studies for eligibility and CAC, CM and PM extracted data for the included trials. All authors commented on subsequent drafts and approved the final version.

All authors (CAC, CM, PM, JEH) commented on subsequent drafts and approved the final version.

DECLARATIONS OF INTEREST

CAC and JEH are investigators in the Australasian Collaborative Trial of Repeat Doses of Corticosteroid for the Prevention of Neonatal Respiratory Disease (Crowther 2006).

SOURCES OF SUPPORT

Internal sources

- Discipline of Obstetrics and Gynaecology, The University of Adelaide, Australia.
- Liggins Institute, University of Auckland, New Zealand.

External sources

- Australian Department of Health and Ageing, Australia.
- National Institute for Health Research, UK.

NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS: 10/4001/02

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Amendments made to the protocol for the 2011 update that clarify the longer-term health outcomes: total deaths added under outcomes for the child and the child as an adult; survival free of any disability and survival free of major disability added under primary outcomes for the child and for the child as an adult.

In addition: periventricular haemorrhage changed to intraventricular haemorrhage; small-for-gestational age, intraventricular haemorrhage, intraventricular haemorrhage grade 3/4 and periventricular leukomalacia moved to secondary outcomes for the infant; "However defined by authors" has been added to the definitions of the following outcomes: necrotising enterocolitis; patent ductus arteriosus; retinopathy of prematurity; and early systemic neonatal infection.

Methods updated according to the current Cochrane Pregnancy and Childbirth Group standard methods text (2015). In the 2015 update the prespecified groups for subgroup analysis were edited to describe specific populations of interest .

INDEX TERMS

Medical Subject Headings (MeSH)

*Obstetric Labor, Premature; Adrenal Cortex Hormones [*administration & dosage; adverse effects]; Betamethasone [*administration & dosage; adverse effects]; Infant, Premature; Randomized Controlled Trials as Topic; Respiratory Distress Syndrome, Newborn [*prevention & control]; Retreatment [adverse effects]

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy