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

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ABSTRACT

Background
It is not clear whether there is benefit in repeating the dose of prenatal corticosteroids for women who remain at risk of preterm birth after an initial course.

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

Search strategy
We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (February 2007), the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 4), MEDLINE (1965 to November 2006), EMBASE (1988 to November 2006) and Current Contents (1997 to November 2006).

Selection criteria
Randomised controlled trials of women who have already received a single course of corticosteroids seven or more days previously and are still considered to be at risk of preterm birth; outcomes compared for women randomised to receive a repeat dose(s) of prenatal corticosteroids, with women given no further prenatal corticosteroids.

Data collection and analysis
We assessed trial quality and extracted the data independently.

Main results
Five trials, involving over 2000 women between 23 and 33 weeks' gestation, are included. Treatment with repeat dose(s) of corticosteroid was associated with a reduction in occurrence (relative risk (RR) 0.82, 95% confidence interval (CI) 0.72 to 0.93, four trials, 2155 infants) and severity of any neonatal lung disease (RR 0.60, 95% CI 0.48 to 0.75, three trials, 2139 infants) and serious infant morbidity (RR 0.79, 95% CI 0.67 to 0.93, four trials, 2157 infants).

Mean birthweight was not significantly different between treatment groups (weighted mean difference (WMD) -62.07 g, 95% CI -129.10 to 4.96, four trials, 2273 infants), although in one trial, treatment with repeat dose(s) of corticosteroid was associated with a reduction in birthweight Z score (WMD) -0.13, 95% CI -26 to 0.00, 1 trial, 1144 infants), and in two trials, with an increased risk of being small for gestational age at birth (RR 1.63, 95% CI 1.12 to 2.37, two trials, 602 infants).

No statistically significant differences were seen for any of the other primary outcomes that included other measures of respiratory morbidity, fetal and neonatal mortality, periventricular haemorrhage, periventricular leukomalacia and maternal infectious morbidity. Treatment with repeat dose(s) of corticosteroid was associated with a significantly increased risk of caesarean section (RR 1.11, 95% CI 1.01 to 1.22, four trials, 1523 women).

Authors' conclusions

Repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short-term benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth, and there is still insufficient evidence on the longer-term benefits and risks.

PLAIN LANGUAGE SUMMARY

Repeat dose(s) of prenatal corticosteroids given to women who remain at risk of an early birth helps the baby's lungs and reduces serious health problems in the first few weeks of life

Babies born very early are at risk of breathing difficulties (respiratory distress syndrome). A single course of corticosteroids, given to women who may give birth early, helps develop the baby's lungs. However, this benefit does not last beyond seven days. This review of five trials, involving over 2000 women between 23 and 33 weeks' gestation, shows repeat dose(s) of prenatal corticosteroids, given to women who remain at risk of early birth more than seven days after an initial course of corticosteroids, reduces the risk of the baby having breathing difficulties and the baby is less likely to have serious health problems in the first few weeks of life. However, some trials show the baby may be smaller at birth. Further research is needed on other important health outcomes for the woman and baby, which should include child development.

BACKGROUND

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. 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; Soll 2001).

A single course of prenatal corticosteroids reduces the risk of RDS from 26% to 17% (relative risk (RR) 0.66, 95% confidence interval (CI) 0.59 to 0.73, 21 trials, 4038 infants) (Roberts 2006). Other beneficial effects include a reduction in neonatal mortality and a reduced risk of intraventricular haemorrhage (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. 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). The cost benefit of a single course of antenatal steroids is estimated as USD 3000 (NIH 1995). 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 (Soll 2001).

Prenatal corticosteroids have not been shown to be effective in babies who are born more than seven days after treatment (Roberts 2006). Specifically no reduction in the incidence of respiratory distress syndrome 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 Professor Mont Liggins and Associate Professor Howie in the first reported controlled trial of antenatal glucocorticoid treatment for the prevention of respiratory distress syndrome in premature infants (Liggins 1972). Indeed, in some clinical centres this has been standard practice. However, there has been little formal assessment of such a policy, and the effect of this practice on the women and infants is unclear (NIH 2000).

Animal studies have suggested that repeat treatment with prenatal corticosteroids may be more effective than a single course in reducing the risk of respiratory distress syndrome. 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).

However, these potential benefits of repeat prenatal corticosteroid treatment may be balanced by increased maternal risks such as infection and suppression of hypothalamic-pituitary-adrenal function (Ashworth 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 steroids 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 function (Ikegami 1997).

In humans, similar concerns have been raised from non-randomised cohort studies, with adverse effects after repeat doses of steroids 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 steroids are limited to date, have used only non-randomised designs, and have produced conflicting results. Some studies suggest delayed development (Esplin 2000) and adverse effects on childhood behaviour (French 1998), whilst others 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 could program cardiovascular settings in the fetus and lead to adult hypertension (Benediktsson 1993), and insulin resistance leading to diabetes mellitus (Dalziel 2005a).

This review assesses the effectiveness and safety of a repeat dose(s) of prenatal corticosteroids given to women who remain at risk of preterm birth following an initial course of prenatal corticosteroids.

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.

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. Quasi-randomised trials were excluded.

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 at trial entry (eg. 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 intervention

Corticosteroid administered to the women intravenously, intramuscularly or orally, compared with either placebo or no placebo. Trials in which the fetus receives corticosteroids directly were excluded. Predefined subgroups were planned 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.

Primary outcomes

Primary outcomes were chosen to be most representative of the clinically important measures of effectiveness and safety, including serious outcomes, for the women and their infants.

For the infant

Respiratory distress syndrome;
severity of any lung disease (however defined by the authors);
birthweight;
small-for-gestational age;
fetal and neonatal mortality;
fetal, neonatal or infant death;
chronic lung disease (however defined by authors);
periventricular haemorrhage;

periventricular haemorrhage grade 3/4;
periventricular leukomalacia;
composite serious outcome (however defined by authors);
disability at follow up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy);
composite serious outcome (however defined by authors).

For the child
Disability at childhood or adult follow up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy after 18 months of age);
composite serious outcome (however defined by authors).

For the child as an adult
Disability at adult follow up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy);
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;
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;
duration of inotropic support;
use of nitric oxide for respiratory support;
systemic infection in first 48 hours of life;
proven infection while in the neonatal intensive care unit;
admission to neonatal intensive care unit;
air leak syndrome;
necrotising enterocolitis;
patent ductus arteriosus requiring treatment;
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;
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);
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 -2 standard deviations below mean));
developmental delay (however defined by the authors);
intellectual impairment;
motor impairment;
visual impairment;
blindness;
deafness;
hearing impairment;
cerebral palsy;
child behaviour;
child temperament;
learning difficulties;
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);
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 -2 standard deviations below mean));
developmental delay (however defined by the authors);
intellectual impairment;
motor impairment;
visual impairment;
blindness;
deafness;

hearing impairment;
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 (variously 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.

While we sought all the above outcomes from the included trials, only those with data appear in the analysis tables. Outcomes were included in the analysis if reasonable measures were taken to minimise observer bias and data were available for analysis according to original allocation. We reported additional outcomes that appear in individual trials as not prespecified outcomes when included in the review.

SEARCH METHODS FOR IDENTIFICATION OF STUDIES

See: methods used in reviews.

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register by contacting the Trials Search Co-ordinator (February 2007).

The Cochrane Pregnancy and Childbirth Group's Trials Register is maintained by the Trials Search Co-ordinator and contains trials identified from:
(1) quarterly searches of the Cochrane Central Register of Controlled Trials (CENTRAL);
(2) monthly searches of MEDLINE;
(3) handsearches of 30 journals and the proceedings of major conferences;
(4) weekly current awareness search of a further 37 journals.

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

Trials identified through the searching activities described above are given a code (or codes) depending on the topic. The codes are linked to review topics. The Trials Search Co-ordinator searches the register for each review using these codes rather than keywords.

In addition, we searched the Cochrane Central Register of Controlled Trials (*The Cochrane Library* 2006, Issue 4), MEDLINE (1965 to November 2006), EMBASE (1988 to November 2006) and Current Contents (1997 to November 2006), using the search terms: 'repeat' or 'multiple' and 'antenatal' or 'prenatal' and 'corticosteroid*' or 'steroid*' or 'glucocorticoid*' or 'betamethason*' or 'dexamethason*' or 'hydrocortison*'. We manually searched the reference lists of all retrieved articles. We sought unpublished trials and abstracts submitted to major international congresses and contacted expert informants.

We did not apply any language restrictions.

METHODS OF THE REVIEW

Selection of studies
We 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 extracted study data, using a predesigned data form. Philippa Middleton independently extracted data for the ACTORDS trial. We resolved discrepancies through discussion.

When information was unclear, we contacted authors of the original reports to provide further details.

Assessment of methodological quality of included studies

We assessed the validity of each study using the criteria outlined in the Cochrane Handbook for Systematic Reviews of Interventions (Higgins 2005). We described methods used for generation of the randomisation sequence for each trial.

(1) Selection bias (randomisation and allocation concealment)

We assigned codes, using the following criteria:

(A) adequate concealment of allocation: such as telephone randomisation, consecutively-numbered, sealed opaque envelopes;

(B) unclear whether adequate concealment of allocation: such as list or table used, sealed envelopes, or study does not report any concealment approach;

(C) inadequate concealment of allocation: such as open list of random-number tables, use of case record numbers, dates of birth or days of the week.

(2) Attrition bias (loss of participants, eg withdrawals, dropouts, protocol deviations)

We assessed completeness to follow up using the following criteria:

(A) less than 5% loss of participants;

(B) 5% to 9.9% loss of participants;

(C) 10% to 19.9% loss of participants;

(D) more than 20% loss of participants.

(3) Performance bias (blinding of participants, researchers and outcome assessment)

We assessed blinding using the following criteria:

(1) blinding of participants (yes/no/unclear);

(2) blinding of caregiver (yes/no/unclear);

(3) blinding of outcome assessment (yes/no/unclear).

Measures of treatment effect

We performed statistical analyses using the Review Manager software (RevMan 2003). We used fixed-effect meta-analysis for combining data in the absence of significant heterogeneity as the trials were sufficiently similar. In the presence of substantial heterogeneity (I^2 > 40%) we used a random-effects model.

Dichotomous data

For dichotomous data, we presented results as relative risks with 95% confidence intervals.

Continuous data

For continuous data, we used the weighted mean difference with 95% confidence intervals.

Dealing with missing data

We extracted data from the trials on an intention-to-treat basis. Where this was not done in the original report, re-analysis was performed where possible. 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 and was clearly documented. If missing data become available subsequently, they will be included in the analyses.

Assessment of heterogeneity

We applied tests of heterogeneity between trials, using the I^2 statistic. When we identified high levels of heterogeneity among the trials, we explored it by prespecified subgroup analysis and performed sensitivity analysis.

Sensitivity analyses

We planned sensitivity analyses to explore the effect of trial quality assessed by concealment of allocation, by excluding studies with clearly inadequate allocation of concealment (rated C).

Subgroup analyses

We planned subgroup analyses to examine 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 at trial entry, the number of babies in utero (singleton, twins or higher order multiples), the type of corticosteroid given, the planned interval between corticosteroid treatments, the planned number of repeat courses of corticosteroids to be given, the number of repeat courses of corticosteroids actually given postrandomisation, the planned dosage of corticosteroid given per treatment, the planned dose of repeat dose of corticosteroid drug exposure/week, the method of treatment administration, and the gestational age at which the treatment was given.

DESCRIPTION OF STUDIES

Seven trials were identified for consideration for inclusion (Aghajafari 2002; Crowther 2006; Guinn 2002; McEvoy 2002; Mercer 2001; Thorp 2000; Wapner 2006), six 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 five trials met our inclusion criteria (Aghajafari 2002; Crowther 2006; Guinn 2002; McEvoy 2002; Wapner 2006). Two trials were excluded (Mercer 2001; Thorp 2000). One trial was excluded because women recruited to the trial did not have corticosteroids before entry (Mercer 2001). The objective of the trial was to evaluate the need for and benefits of weekly antenatal corticosteroids in women at risk of preterm birth (Mercer 2001). In the other trial, the randomised treatment was not repeat dose(s) of prenatal corticosteroids (Thorp 2000).

A total of 2028 women were recruited into the five trials that met the prespecified criteria for inclusion in this review (12 women in Aghajafari 2002, 502 women in Guinn 2002, 37 women in McEvoy 2002, 982 in Crowther 2006 and 495 in Wapner 2006). Three of the trials were conducted in the United States of America (Guinn 2002; McEvoy 2002; Wapner 2006) and one each in Canada (Aghajafari 2002) and Australia (Crowther 2006).

The gestational age at trial entry varied between the trials being 24 to 30 weeks (Aghajafari 2002), 25 to less than 33 weeks (Guinn 2002), 25 to 33 weeks (McEvoy 2002), less than 32 weeks (Crowther 2006) and 23 to less than 32 weeks (Wapner 2006). 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, defined as two doses of 12 mg/dose intramuscular betamethasone, given at 12 or 24 hourly intervals; or four doses of 5 to 6 mg/dose intramuscular dexamethasone, given at 12 hourly intervals (Aghajafari 2002; Guinn 2002), two doses of 12 mg/dose intramuscular betamethasone (McEvoy 2002) or not defined in Crowther 2006 and Wapner 2006.

The type of corticosteroid given as treatment was betamethasone for all the trials although the gestational age at which treatment could begin or was continued varied slightly between the trials. Four trials gave two doses of 12 mg/dose betamethasone, intramuscularly, at weekly intervals (Aghajafari 2002; Guinn 2002; McEvoy 2002; Wapner 2006). For Aghajafari 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 (Aghajafari 2002). Guinn 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 (Guinn 2002). McEvoy 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 (McEvoy 2002). Wapner 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 6 days (Wapner 2006). Crowther 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 (Crowther 2006).

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. The Guinn 2002 trial had a composite neonatal morbidity primary outcome of any of the following: severe respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge. The primary outcomes for McEvoy 2002 were functional residual capacity and respiratory compliance. For Crowther 2006, the primary outcomes were occurrence of neonatal respiratory distress syndrome, 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. For Wapner 2006 the primary outcome was one of the following: severe respiratory distress syndrome (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 4 intraventricular hemorrhage; 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.

For details of the included and excluded studies, please refer to the 'Characteristics of included studies' and the 'Characteristics of excluded studies' tables.

METHODOLOGICAL QUALITY

Formal randomisation was reported in all five 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; 28 to 30 weeks) and by hospital using block sizes of two. Guinn 2002 used computer-generated randomisation logs prepared centrally, stratified by centre, and distributed to the research pharmacist at each clinical site. Participants were assigned by the pharmacy to treatment group. In the McEvoy 2002 trial group, assignment was via the pharmacy using a random-number table. The study medication was prepared by the pharmacy. No stratification was reported. 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). 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 woman was assigned the next sequentially numbered treatment kit by a centralised research pharmacy.

A placebo was used in all five trials but the preparation used was not stated for Guinn 2002 or Wapner 2006. Aghajafari used normal saline (Aghajafari 2002), McEvoy used 25 mg cortisone acetate, an inactive steroid (McEvoy 2002) and Crowther used normal saline (Crowther 2006).

All five trials attempted to blind participants and caregivers to treatment allocation. In Aghajafari 2002, the pharmacist pre-

pared 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 Guinn 2002, the placebo syringes were indistinguishable from the syringes containing betamethasone. For McEvoy 2002, the placebo was identical in appearance to betamethasone. For Crowther 2006, the treatment packs looked identical and contained an opaque study-labelled syringe. For Wapner 2006, the placebo was identical in appearance to betamethasone.

No losses to follow up were reported for Aghajafari 2002 or McEvoy 2002. In the Guinn 2002 trial, 16 women and one neonate were lost to follow up. Partial data are 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 Crowther 2006, there were no losses to follow-up up to the time of primary hospital discharge. For Wapner 2006, three women were lost to follow up.

Intention-to-treat analyses were conducted for all five trials.

RESULTS

Five trials involving 2028 women were included.

(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 compared with infants exposed to placebo (relative risk (RR) 0.82, 95% confidence interval (CI) 0.72 to 0.93, four trials, 2155 infants).
- Treatment with repeat dose(s) of corticosteroid was associated with a reduction in severe lung disease (RR 0.60, 95% CI 0.48 to 0.75, three trials, 2139 infants).
- Four trials reported a composite outcome for serious infant morbidity. Infants exposed to repeat dose(s) of corticosteroids were significantly less likely to have serious infant morbidity (RR 0.79, 95% CI 0.67 to 0.93, four trials, 2157 infants). The composite outcome of serious infant morbidity was defined by Aghajafari 2002 as one or more of the following: stillborn or neonatal death during the first 28 days of life or before hospital discharge, whichever was sooner; respiratory distress syndrome; bronchopulmonary dysplasia (requiring oxygen at 36 corrected postnatal gestational age); grade 3 or 4 intraventricular haemorrhage and necrotising enterocolitis; Crowther 2006 as one of 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; Guinn 2002 as the presence of any of the following: severe respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge; Wapner 2006 as any one of the following: severe respiratory distress syndrome, 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.

Mean birthweight was not significantly different between treatment groups (weighted mean difference (WMD) -62.07 g, 95% CI -129.10 to 4.96, four trials, 2273 infants), although in one trial, treatment with repeat dose(s) of corticosteroid was associated with a reduction in birthweight Z score (WMD -0.13, 95% CI -0.26 to 0.00, one trial, 1144 infants), and in two trials, with an increased risk of being small-for-gestational age at birth (RR 1.63, 95% CI 1.12 to 2.37, two trials, 602 infants).

No statistically significant differences were seen in infants in the repeat dose(s) of corticosteroids group compared with infants in the placebo group for:

- fetal and neonatal mortality (RR 0.80, 95% CI 0.52 to 1.23, four trials, 2157 infants);
- chronic lung disease (RR 0.95, 95% CI 0.75 to 1.21, four trials, 2155 infants);
- periventricular haemorrhage (RR 0.96, 95% CI 0.71 to 1.29, three trials, 2104 infants);
- periventricular haemorrhage (grade 3 or 4) (RR 1.11, 95% CI 0.24 to 5.24, three trials, 1660 infants);
- periventricular leukomalacia (RR 0.50, 95% CI 0.19 to 1.33, three trials, 1660 infants).

Primary outcomes for the child

No data available for inclusion.

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 for the two outcomes of maternal infectious morbidity;

- chorioamnionitis (RR 1.23, 95% CI 0.95 to 1.59, four trials, 1971 women); and
- puerperal sepsis (RR 0.76, 95% CI 0.42 to 1.36, three trials, 989 women).

Secondary outcomes for the infant

In keeping with the reduction in respiratory morbidity seen, treatment with repeat dose(s) of corticosteroid compared with placebo was associated with a reduction in the use of:

- oxygen (RR 0.89, 95% CI 0.81 to 0.98, one trial, 1144 infants);
- surfactant (RR 0.71, 95% CI 0.61 to 0.83, four trials, 2173 infants); and
- patent ductus arteriosus requiring treatment (RR 0.60, 95% CI 0.43 to 0.84, three trials, 1652 infants).

No statistically significant differences were seen in infants exposed to repeat dose(s) of corticosteroids group compared with infants exposed to placebo for the other secondary respiratory outcomes (including mechanical ventilation, duration of respiratory support, duration of oxygen supplementation, use of inotropic support, use of nitric oxide for respiratory support, use of postnatal corticosteroids), infectious morbidity outcomes (systemic infection in first 48 hours of life, proven infection while in the neonatal intensive care unit), and other neonatal morbidity (including air leak syndrome, necrotising enterocolitis and retinopathy of prematurity).

The mean gestational age at birth (WMD -0.07 weeks, 95% CI -0.39 to 0.26, five trials, 2187 infants) were not significantly different between treatment groups, neither was the proportion of infants born before 37 weeks, 34 weeks or 28 weeks' gestation.

Mean head circumference at birth (WMD -0.17 cm, 95% CI -0.46 to 0.12, four trials, 2271 infants) and mean length at birth (WMD -0.21 cm, 95% CI -0.72 to 0.30, two trials, 1734 infants), were not significantly different between treatment groups, although in one trial treatment with repeat dose(s) of corticosteroid was associated with a reduction in head circumference Z score (WMD -0.16, 95% CI -0.30 to -0.02, 1 trial, 1144 infants) and in another trial significantly lower length multiples of the median at birth (WMD -0.01, 95% CI -0.02 to 0.00, one trial, 590 infants).

In the one trial 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 (WMD -44.90 nmol/L, 95% CI -78.41 to -11.39, one trial, 67 infants).

In the one trial of that reported infant growth assessments at primary hospital discharge no differences were seen between treatment groups for weight, head circumference or length.

Secondary outcomes for the child

No information is currently available for outcomes following primary discharge from hospital.

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

No trial reported any maternal deaths. 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, postpartum haemorrhage or postnatal pyrexia.

Data on mode of birth showed significant heterogeneity for vaginal birth. Using a random-effects model no statistically significant difference was seen between treatment groups (RR 0.90, 95% CI 0.75 to 1.07, four trials, 1523 women). Treatment with repeat dose(s) of corticosteroid was associated with a significantly increased risk of caesarean section (RR 1.11, 95% CI 1.01 to 1.22, four trials, 1523 women).

The two trials that reported on 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 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 (RR 0.49, 95% CI 0.39 to 0.61, one trial, 492 women). Using a random-effects model no statistically significant difference was seen for side-effects of therapy (RR 0.97, 95% CI 0.24 to 3.90, two trials, 1474 women). 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 statistically significant difference was seen using a random-effects model (RR 0.73, 95% CI 0.11 to 5.05, two trials, 1474 women). Wapner 2006 reported a significant reduction in bruising at the site of the injection with treatment with repeat dose(s) of corticosteroid (RR 0.38, 95% CI 0.21 to 0.71, one trial, 492 women). No significant differences were seen for any of the other side-effects of therapy outcomes reported (glucose intolerance and insomnia).

No data have been reported on other secondary outcomes for the women including postnatal depression, parenting stress, breastfeeding after discharge from hospital, satisfaction with the therapy or 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 in the one trial that reported on need for admission to the neonatal intensive care unit. Similarly in the one trial with data no differences were seen between treatment groups for length of postnatal hospitalisation for the women.

(2) Sensitivity analyses based on trial quality

All five trials were rated of high quality for allocation concealment, so sensitivity analyses were not performed based on trial quality.

(3) Planned subgroup analyses

(3.1) Repeat dose(s) of prenatal corticosteroids versus placebo/no treatment by reason for being at risk of preterm birth at trial entry (eg. 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

One trial (Guinn 2002) reported data for the 160 women at risk of preterm birth because of preterm prelabour rupture of membranes. For the infants no statistically significant differences were seen for any of the primary outcomes where data were available, namely respiratory distress syndrome, small-for-gestational age, fetal, neonatal, infant death, chronic lung disease, periventricular haemorrhage grade three or four. For the women, treatment with repeat dose(s) of corticosteroid was associated with an increased risk of chorioamnionitis (RR 1.56, 95% 1.05 to 2.31, one trial, 160 women) although no differences were seen in puerperal sepsis between treatment groups (RR 0.65, 95% CI 0.19 to 2.22, one trial, 160 women).

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 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 subgroups to date.

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

All five trials have used betamethasone so subgroup analyses were not able to be performed 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 8 and 14 days, at a minimum interval greater than 14 days)

All five trials used a minimum interval of seven days or less between corticosteroid treatments so subgroup analyses were not able to be performed.

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

One trial reported data on a subgroup of women given with four or more repeat courses of repeat prenatal corticosteroids (Wapner 2006). Infants exposed to four or more repeat courses of betamethasone had a significantly reduced mean birthweight (WMD -161 g, 95% CI -290.52 to -31.48, one trial, 368 infants), and birthweight multiples of the median (WMD -0.04, 95% CI -0.07 to -0.01, one trial, 368 infants).

(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)

The dose of corticosteroid given per treatment was 12 mg or less of betamethasone for one trial (Crowther 2006) and greater than 12 mg to 24 mg or less of betamethasone for the other four trials (Aghajafari 2002; Guinn 2002; McEvoy 2002; Wapner 2006).

Planned treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone compared with placebo for the infant was associated with a statistically significant reduction in the risk of respiratory distress syndrome (RR 0.79, 95% CI 0.68 to 0.92, one trial, 1144 infants), severe lung disease (RR 0.58, 95% CI 0.44 to 0.77, one trial, 1144 infants), serious neonatal morbidity using a composite outcome (RR 0.77, 95% CI 0.62 to 0.96, one trial, 1144 infants), the use of mechanical ventilation (RR 0.83, 95% CI 0.70 to 0.99, one trial, 1144 infants), the use of oxygen (RR 0.89, 95% CI 0.81 to 0.98, one trial, 1144 infants), use of surfactant (RR 0.76, 95% CI 0.63 to 0.91, one trial, 1144 infants), patent ductus requiring treatment (RR 0.61, 95% CI 0.42 to 0.88, one trial, 1144 infants).

These benefits were associated with a reduction in birthweight Z score (WMD -0.13, 95% CI -0.26 to 0.00, one trial, 1144 infants), reduction in head circumference Z score (WMD -0.16, 95% CI -0.30 to -0.02, one trial, 1144 infants) and significantly lower mean cortisol concentrations at birth in a subgroup of infants (recruited at one of the collaborating hospitals) (WMD -44.90 nmol/L, 95% CI -78.41 to -11.39, one trial, 67 infants).

For the women, treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone compared with placebo was associated with a statistically significant reduction in the chances of having a vaginal birth (RR 0.80, 95% CI 0.68 to 0.94, one trial, 982 women), an increased risk of having a caesarean (RR 1.15, 95% CI 1.04 to 1.26, one trial, 982 women), and a significant increase in having side-effects related to the treatment (RR 1.97, 95% CI 1.23 to 3.18, one trial, 982 women).

No statistically significant differences were seen for any of the other outcomes where data were available.

Planned treatment with repeat dose(s) of corticosteroid of greater than 12 mg to 24 mg or less of betamethasone compared with placebo for

the infant was associated with a statistically significant reduction in the risk of severe lung disease (RR 0.63, 95% CI 0.45 to 0.89, two trials, 995 infants), use of mechanical ventilation (RR 0.58, 95% CI 0.40 to 0.84, one trial, 492 infants) and use of surfactant (RR 0.63, 95% CI 0.48 to 0.83, three trials, 1029 infants).

These benefits were associated with a significantly lower mean birthweight (WMD -113.60, 95% CI -208.14 to -19.05, three trials, 1129 infants), significantly lower length multiples of the median at birth (WMD -0.01, 95% CI -0.02 to 0.00, one trial, 590 infants) and an increased risk of being small-for-gestational age at birth (RR 1.63, 95% CI 1.12 to 2.37, two trials, 602 infants).

For the women treatment with repeat dose(s) of corticosteroid of greater than 12 mg to 24 mg or less of betamethasone compared with placebo was associated with a significant decrease in having any side-effects of treatment (RR 0.49, 95% CI 0.39 to 0.61, one trial, 492 women), a significant reduction in pain at the site of the injection ((RR 0.28, 95% CI 0.19 to 0.41, one trial, 492 women) and a significant reduction in bruising at the site of the injection (RR 0.38, 95% CI 0.21 to 0.71, one trial, 492 women).

No statistically significant differences were seen for any of the other outcomes where data were available.

(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)

The planned repeat drug exposure per week was 12 mg/week or less of betamethasone for one trial (Crowther 2006) and greater than 12 mg to 24 mg or less of betamethasone for the other four trials (Aghajafari 2002; Guinn 2002; McEvoy 2002; Wapner 2006).

Planned treatment with repeat dose(s) of corticosteroid of 12 mg/week or less of betamethasone compared with placebo for the infant was associated with a statistically significant reduction in the risk of respiratory distress syndrome (RR 0.79, 95% CI 0.68 to 0.92, one trial, 1144 infants), severe lung disease (RR 0.58, 95% CI 0.44 to 0.77, one trial, 1144 infants), serious neonatal morbidity using a composite outcome (RR 0.77, 95% CI 0.62 to 0.96, one trial, 1144 infants), use of mechanical ventilation (relative risk (RR) 0.83, 95% CI 0.70 to 0.99, one trial, 1144 infants), the use of oxygen (RR 0.89, 95% CI 0.81 to 0.98, one trial, 1144 infants), the use of surfactant (RR 0.76, 95% CI 0.63 to 0.91, one trial, 1144 infants) and patent ductus requiring treatment (RR 0.61, 95% CI 0.42 to 0.88, one trial, 1144 infants). These benefits were associated with a reduction in birthweight Z score (WMD -0.13, 95% CI -0.26 to 0.00, one trial, 1144 infants), reduction in head circumference Z score (WMD -0.16, 95% CI -0.30 to -0.02, one trial, 1144 infants) and significantly lower mean cortisol concentrations at birth in a subgroup of infants (recruited at one of the collaborating hospitals) (WMD -44.90 nmol/L, 95% CI -78.41 to -11.39, one trial, 67 infants).

For the women, treatment with repeat dose(s) of corticosteroid of 12 mg or less of betamethasone compared with placebo was associated with a statistically significant reduction in the chances of having a vaginal birth (RR 0.80, 95% CI 0.68 to 0.94, one trial, 982 women), an increased risk of having a caesarean (RR 1.15, 95% CI 1.04 to 1.26, one trial, 982 women), and a significant increase in having side-effects related to the treatment (RR 1.97, 95% CI 1.23 to 3.18, one trial, 982 women).

No statistically significant differences were seen for any of the other outcomes where data were available.

Planned treatment with repeat dose(s) of corticosteroid of greater than 12 mg/week to 24 mg/week or less of betamethasone compared with placebo for the infant was associated with a statistically significant reduction in the risk of severe lung disease (RR 0.63, 95% CI 0.45 to 0.89, two trials, 995 infants), use of mechanical ventilation (RR 0.58, 95% CI 0.40 to 0.84, one trial, 492 infants) and use of surfactant (RR 0.63, 95% CI 0.48 to 0.83, three trials, 1029 infants). These benefits were associated with a significantly lower mean birthweight (WMD -113.60, 95% CI -208.14 to -19.05, three trials, 1129 infants), significantly lower length multiples of the median at birth (WMD -0.01, 95% CI -0.02 to 0.00, one trial, 590 infants) and an increased risk of being small-for-gestational age at birth (RR 1.63, 95% CI 1.12 to 2.37, two trials, 602 infants).

For the women treatment with repeat dose(s) of corticosteroid of greater than 12 mg to 24 mg or less of betamethasone compared with placebo was associated with a significant decrease in having any side-effects of treatment (RR 0.49, 95% CI 0.39 to 0.61, one trial, 492 women), a significant reduction in pain at the site of the injection (RR 0.28, 95% CI 0.19 to 0.41, one trial, 492 women) and a significant reduction in bruising at the site of the injection (RR 0.38, 95% CI 0.21 to 0.71, one trial, 492 women).

No statistically significant differences were seen for any of the other outcomes where data were available.

(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.

(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

Since the last update of this review, two further trials have been published adding to the evidence base assessing whether repeat

does(s) of prenatal corticosteroids improve fetal lung maturation, and thereby reduce infant morbidity and mortality. Of the now five included trials, all are recent publications of good methodological quality. All had adequate allocation concealment, used a placebo, and losses to follow up were nil or minimal.

From the available data, there is evidence that repeat doses(s) of prenatal corticosteroids reduce both the occurrence and severity of neonatal lung disease and reduce overall serious neonatal morbidity, all clinically important beneficial effects. In keeping with these benefits, treatment with repeat dose(s) of corticosteroid is associated with less use of mechanical ventilation, oxygen therapy and surfactant and fewer infants have a patent ductus requiring treatment.

In contrast to these clinical benefits, although no overall differences at birth in mean weight, length and head circumference were seen, some trials have reported a increase in the risk of being born small-for-gestational age and a reduction in measures of growth at birth (Z scores for weight and head circumference, length multiples of the median). The data available to date are insufficient to adequately assess any long-term effects the differences observed at birth may have. Only one trial has reported on weight, length and head circumference following birth, at the time of discharge from hospital after birth, and showed no differences in a range of measures of growth.

The few data available on infant cardiovascular outcomes show no differences with repeat dose(s) corticosteroid treatment. Data on longer-term assessment of blood pressure are required.

There was little evidence of either major benefit or harm to the mother from giving repeat dose(s) of prenatal corticosteroids, although women treated with repeat dose(s) of corticosteroid were more likely to give birth by caesarean section. It is unclear why this should be.

There are still no data published on the neurodevelopmental status of the infant or child at follow up or other longer-term outcomes. Such information is needed to assess overall benefits and risks. Several completed trials have ongoing assessment of their children planned (Wapner 2006 24 month postdelivery, Crowther 2006 two years' corrected age and early school-age follow up, MACS 2001 at five years of age).

Planned subgroup analyses were performed where the published data permitted and remain limited to date. Any additional unpublished data will be sought from the trial authors. Currently the data are too few to adequately assess the benefits and harms of repeat dose(s) of corticosteroid treatment by reason for risk of preterm birth at trial entry, plurality of the pregnancy, number of repeat courses planned or given, interval between corticosteroid treatments, planned dose of corticosteroid given per treatment and dose planned per week.

Further information from trials of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth for the prevention of neonatal respiratory disease are required. Trials should be of high quality, be large enough to assess serious morbidity and mortality, compare different corticosteroid preparations and mode of administration, varying times between repeat courses, different amounts of corticosteroid given at each course and provide neurodevelopmental status of the child at follow up and other longer-term outcomes including behaviour, educational achievement, cardiovascular status, bone density, hypothalamo/pituitary/adrenal axis function, glucose intolerance and lung function.

One trial from the US is in progress (Obstetrix 2003). The Canadian MACS trial (MACS 2001) has now finished recruitment and data collection to two years of corrected age is continuing. 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). Another ongoing study was published just as this update was submitted for publication (Peltoniemi 2007). We have therefore added it to the 'Studies awaiting assessment' and will consider it for inclusion in the next update.

AUTHORS' CONCLUSIONS

Implications for practice

Repeat dose(s) of prenatal corticosteroids reduce the occurrence and severity of neonatal lung disease and the risk of serious health problems in the first few weeks of life. These short term benefits for babies support the use of repeat dose(s) of prenatal corticosteroids for women at risk of preterm birth. However, these benefits are associated with a reduction in some measures of weight, and head circumference at birth. and there is still insufficient evidence on the longer-term benefits and risks.

Implications for research

Further information from high-quality trials is required. The trials should be large enough to assess serious morbidity and mortality, compare different corticosteroid preparations, method of administration, dose and timing regimens, and provide neurodevelopmental status of the child at follow up and other longer-term outcomes. Several such trials are in progress.

POTENTIAL CONFLICT OF INTEREST

Both review authors are investigators in the Australasian Collaborative Trial of Repeat Doses of Corticosteroid for the Prevention of Neonatal Respiratory Disease (Crowther 2006).

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* *Indicates the major publication for the study*

TABLES

Characteristics of included studies

Study	Aghajafari 2002
Methods	Type of study: randomised trial. Method of treatment allocation: randomisation was computer-generated and was centrally controlled by one pharmacist at each hospital who kept the randomisation code. The injection of the study treatment was given by a designated research nurse in each hospital who was not caring for the woman. Stratification: by gestational age (24-27 weeks; 28-30 weeks) and by hospital using block sizes of 2. Placebo: yes, normal saline. 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. Sample-size calculation: no. Small pilot study to determine the feasibility of a larger trial. Intention-to-treat analyses: yes. Losses to follow up: none. Funding: support from Canadian Institutes of Health Research Senior Scientist Award.
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 hours 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 one 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; or 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: 12-6 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; bronchopulmonary dysplasia (requiring oxygen at 36 corrected postnatal gestational age); intraventricular haemorrhage (grade 3 or 4; and necrotising enterocolitis.
Notes	
Allocation concealment	A – Adequate

Study	**Crowther 2006**
Methods	Type of study: randomised controlled trial. Method of treatment allocation: central telephone randomisation. Random-number sequence generated by computer with variable block sizes and stratification by centre, gestational age and number of fetuses. Placebo: yes, normal saline. Treatment packs and syringes identical appearance. (opaque study-labelled syringe). Sample-size calculation: yes. Intention-to-treat analyses: yes. Losses to follow up: none. 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.
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 steroid group and 493 women in the placebo group.
Interventions	Repeat steroids: 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	Primary outcomes: frequency and severity of respiratory distress syndrome, weight, length and head circumference at birth and primary discharge from hospital. Secondary outcomes included clinical chorioamnionitis, maternal postpartum pyrexia, any side-effects of the injection for the mother and other measures of neonatal morbidity.
Notes	
Allocation concealment	A – Adequate

Study	**Guinn 2002**
Methods	Type of study: randomised controlled trial. Method of treatment allocation: computer-generated randomisation logs prepared centrally and distributed to the research pharmacist at each clinical site. Participants were assigned by the pharmacy to treatment group. Stratification: by centre. Placebo: yes. Type of placebo not stated. The placebo syringes were indistinguishable from the syringes containing betamethasone. Sample-size calculation: yes. 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 we were able to ascertain the birth date, weight, and health status for the neonate. The denominators presented very slightly from one variable to another because of missing data. 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.
Participants	Location: 13 academic centres in USA. Timeframe: February 1996-April 2000. Eligibility criteria: women 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. In the single-course group: a similarly administered placebo.
Outcomes	Primary outcomes: composite neonatal morbidity defined as presence of any of the following: severe respiratory distress syndrome, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge. Secondary outcomes: frequency and severity of respiratory distress syndrome; need for and duration of oxygen therapy; need for and duration of ventilatory support; bronchopulmonary dysplasia (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 bronchopulmonary dysplasia were used; in the case of neonatal death, bronchopulmonary dysplasia was diagnosed on autopsy findings); severe intraventricular haemorrhage 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, periventricular leukomalacia was defined as the presence of more than 1 obvious hypoechoic cyst in the periventricular white matter; proven necrotising enterocolitis; proven sepsis; perinatal death defined as death of a fetus or neonate at any time between randomisation and nursery discharge.
Notes	Planned sample size was 1000 women. Recruitment was stopped early based on safety concerns.
Allocation concealment	A – Adequate

Study	**McEvoy 2002**
Methods	Type of study: randomised trial. Method of treatment allocation: group assignment done through pharmacy using a random-number table. The study medication was prepared by the pharmacy.

Characteristics of included studies (*Continued*)

	Stratification: none stated. Placebo: 25 mg cortisone acetate, an inactive steroid, identical in appearance to betamethasone. 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%). Intention-to-treat analyses: yes. Losses to follow up: none stated. Funding: American Lung Association.
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. 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 delivery or 34 weeks' gestation. In the single-course remote group: weekly courses of placebo intramuscularly, until 34 weeks or delivery.
Outcomes	Primary outcomes: functional residual capacity, respiratory compliance. Secondary outcomes: admission head circumference, surfactant administration, days on oxygen, and mechanical ventilation.
Notes	
Allocation concealment	A – Adequate

Study	**Wapner 2006**
Methods	Type of study: randomised controlled trial. Method of treatment allocation: numbered kits were prepared using randomisation sequences created by an independent data co-ordinating 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. Placebo: yes. Type of placebo not stated. Sample-size calculation: yes. Intention-to-treat analyses: yes. Losses to follow up: 3 women. Funding: National Institute of Child Health and Human Development.
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 steroid arm and 243 to the placebo.
Interventions	Repeat steroid 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	Primary outcome: one of the following: severe respiratory distress syndrome (defined as clinical features of respiratory distress syndrome 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 (FiO2 of at least 60%); grade 3 or 3 intraventricular hemorrhage; 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.
Notes	Planned sample size was 2400 women. Recruitment was stopped early based on safety concerns (because of a tendency towards decreased birthweight in the repeat steroid group without any reduction in the primary morbidity outcome and also because of difficulties in recruitment.
Allocation concealment	A – Adequate

ACTH: adrenocorticotropic hormone
MFMU:
NICHD:

Characteristics of excluded studies

Study	Reason for exclusion
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.
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 ongoing studies

Study	MACS 2001
Trial name or title	Multiple Courses of Antenatal Corticosteroids for Preterm Birth Study.
Participants	NA
Interventions	Betamethasone versus placebo (after a single course of antenatal steroids).
Outcomes	NA

Characteristics of ongoing studies (*Continued*)

Starting date	April 2001.
Contact information	Dr Kellie Murphy: kellie.murphy@utoronto.ca
Notes	ISRCTN 72654148

Study	**Obstetrix 2003**
Trial name or title	A randomised trial comparing the impact of 1 versus 2 courses of antenatal corticosteroids on neonatal outcome.
Participants	434.
Interventions	Second course of antenatal steroids versus placebo.
Outcomes	Composite neonatal morbidity.
Starting date	November 2003. Expected completion: November 2008.
Contact information	Kimberley Maurel, Obstetrix Medical Group, Inc
Notes	NCT00201643

Study	**Sobhrabvand 2001**
Trial name or title	Effects of single versus multiple courses of corticosteroid therapy on pregnancy results in women with PPROM.
Participants	NA
Interventions	NA
Outcomes	NA
Starting date	NA
Contact information	NA
Notes	NA

Study	**TEAMS 1999**
Trial name or title	Trial of the effects of antenatal multiple courses of steroids versus a single course (TEAMS).
Participants	4000 women.
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	ISRCTN 46614711

i.m.: intramuscular
NA: not available
PPROM: preterm prelabour rupture of the membranes

ANALYSES

Comparison 01. Repeat doses of corticosteroids versus single course

Outcome title	No. of studies	No. of participants	Statistical method	Effect size
01 Respiratory distress syndrome			Relative Risk (Fixed) 95% CI	Subtotals only
02 Severe lung disease			Relative Risk (Fixed) 95% CI	Subtotals only
03 Composite serious morbidity (variously defined)			Relative Risk (Fixed) 95% CI	Subtotals only
04 Mean birthweight (g)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
05 Birthweight Z scores			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
06 Birthweight multiples of the median			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
07 Small-for-gestational age at birth			Relative Risk (Fixed) 95% CI	Subtotals only
08 Fetal and neonatal mortality			Relative Risk (Fixed) 95% CI	Subtotals only
09 Fetal death			Relative Risk (Fixed) 95% CI	Subtotals only
10 Neonatal death			Relative Risk (Fixed) 95% CI	Subtotals only
11 Chronic lung disease			Relative Risk (Fixed) 95% CI	Subtotals only
13 Periventricular haemorrhage			Relative Risk (Fixed) 95% CI	Subtotals only
14 Periventricular haemorrhage grade 3/4			Relative Risk (Random) 95% CI	Subtotals only
15 Periventricular leucomalacia			Relative Risk (Fixed) 95% CI	Subtotals only
17 Chorioamnionitis			Relative Risk (Fixed) 95% CI	Subtotals only
18 Puerperal sepsis			Relative Risk (Fixed) 95% CI	Subtotals only
19 Use of mechanical ventilation			Relative Risk (Random) 95% CI	Subtotals only
20 Duration of respiratory support in days			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
21 Use of oxygen supplementation			Relative Risk (Fixed) 95% CI	Subtotals only
22 Duration of oxygen supplementation in days			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
23 Use of surfactant			Relative Risk (Fixed) 95% CI	Subtotals only
24 Patent ductus arteriosus requiring treatment			Relative Risk (Fixed) 95% CI	Subtotals only
25 Use of inotropic support			Relative Risk (Fixed) 95% CI	Subtotals only
26 Use of nitric oxide for respiratory support			Relative Risk (Fixed) 95% CI	Subtotals only
27 Mean gestational age at birth (weeks)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
28 Preterm birth before 37 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
29 Very preterm birth before 34 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
30 Extremely preterm birth before 28 weeks			Relative Risk (Fixed) 95% CI	Subtotals only
31 Mean head circumference at birth (cm)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
32 Head circumference Z scores at birth			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
33 Mean length at birth (cm)			Weighted Mean Difference (Fixed) 95% CI	Subtotals only
34 Length Z scores at birth			Weighted Mean Difference (Fixed) 95% CI	Subtotals only

35 Length multiples of the median at birth	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
36 Apgar score less than 7 at 5 minutes	Relative Risk (Fixed) 95% CI	Subtotals only
37 Systemic infection in the first 48 hours of life (suspected or confirmed)	Relative Risk (Fixed) 95% CI	Subtotals only
38 Proven infection while in the neonatal intensive care unit	Relative Risk (Fixed) 95% CI	Subtotals only
39 Admission to the neonatal intensive care unit	Relative Risk (Fixed) 95% CI	Subtotals only
40 Air leak syndrome	Relative Risk (Random) 95% CI	Subtotals only
41 Necrotising enterocolitis	Relative Risk (Fixed) 95% CI	Subtotals only
42 Retinopathy of prematurity	Relative Risk (Fixed) 95% CI	Subtotals only
43 Use of postnatal steroids	Relative Risk (Fixed) 95% CI	Subtotals only
44 Mean neonatal blood pressure on first day after birth	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
45 Mean neonatal blood pressure 6 weeks after birth	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
46 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd)	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
47 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
48 Mean basal cortisol concentrations (nmol/L) at birth	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
49 Mean weight (g) at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
50 Weight Z scores at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
51 Mean head circumference (cm) at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
52 Head circumference Z scores at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
53 Mean length (cm) at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
54 Length Z score at primary hospital discharge	Weighted Mean Difference (Fixed) 95% CI	Subtotals only
55 Prelabour rupture of membranes after trial entry	Relative Risk (Fixed) 95% CI	Subtotals only
56 Hypertension (variously defined by the authors)	Relative Risk (Fixed) 95% CI	Subtotals only
57 Vaginal birth	Relative Risk (Random) 95% CI	Subtotals only
58 Caesarean section	Relative Risk (Fixed) 95% CI	Subtotals only
59 Postpartum haemorrhage	Relative Risk (Fixed) 95% CI	Subtotals only
60 Postnatal pyrexia (variously defined by authors)	Odds Ratio (Fixed) 95% CI	Subtotals only
61 Length of postnatal hospitalisation (days)	Weighted Mean Difference (Fixed) 95% CI	Subtotals only

62 Any maternal side-effects of therapy	Relative Risk (Random) 95% CI	Subtotals only
63 Maternal hyperglycaemia (variously defined by authors)	Relative Risk (Fixed) 95% CI	Subtotals only
64 Insomnia	Relative Risk (Fixed) 95% CI	Subtotals only
65 Pain at injection site	Relative Risk (Random) 95% CI	Subtotals only
66 Bruising at injection site	Relative Risk (Fixed) 95% CI	Subtotals only

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Pregnancy

COVER SHEET

Title	Repeat doses of prenatal corticosteroids for women at risk of preterm birth for preventing neonatal respiratory disease
Authors	Crowther CA, Harding JE
Contribution of author(s)	Both review authors helped prepare the protocol. Caroline Crowther wrote the draft of the original review and both review authors have commented on subsequent drafts and prepared the updates.
Issue protocol first published	2002/4
Review first published	2003/3
Date of most recent amendment	15 May 2007
Date of most recent SUBSTANTIVE amendment	11 May 2007
What's New	February 2007 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). The review conclusions have not changed.
Date new studies sought but none found	Information not supplied by author
Date new studies found but not yet included/excluded	28 February 2007
Date new studies found and included/excluded	30 November 2006
Date authors' conclusions section amended	24 August 2006
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GRAPHS AND OTHER TABLES

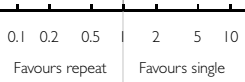
Analysis 01.01. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 01 Respiratory distress syndrome

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 01 Respiratory distress syndrome

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	2/9	2/7		0.7	0.78 [0.14, 4.23]
Crowther 2006	186/567	239/577		69.2	0.79 [0.68, 0.92]
Guinn 2002	69/255	69/245		20.6	0.96 [0.72, 1.28]
Wapner 2006	24/252	32/243		9.5	0.72 [0.44, 1.19]
Subtotal (95% CI)	1083	1072		100.0	0.82 [0.72, 0.93]
Total events: 281 (Repeat), 342 (Single)					
Test for heterogeneity chi-square=1.64 df=3 p=0.65 I^2 =0.0%					
Test for overall effect z=2.99 p=0.003					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Guinn 2002	32/81	36/79		100.0	0.87 [0.60, 1.24]
Subtotal (95% CI)	81	79		100.0	0.87 [0.60, 1.24]
Total events: 32 (Repeat), 36 (Single)					



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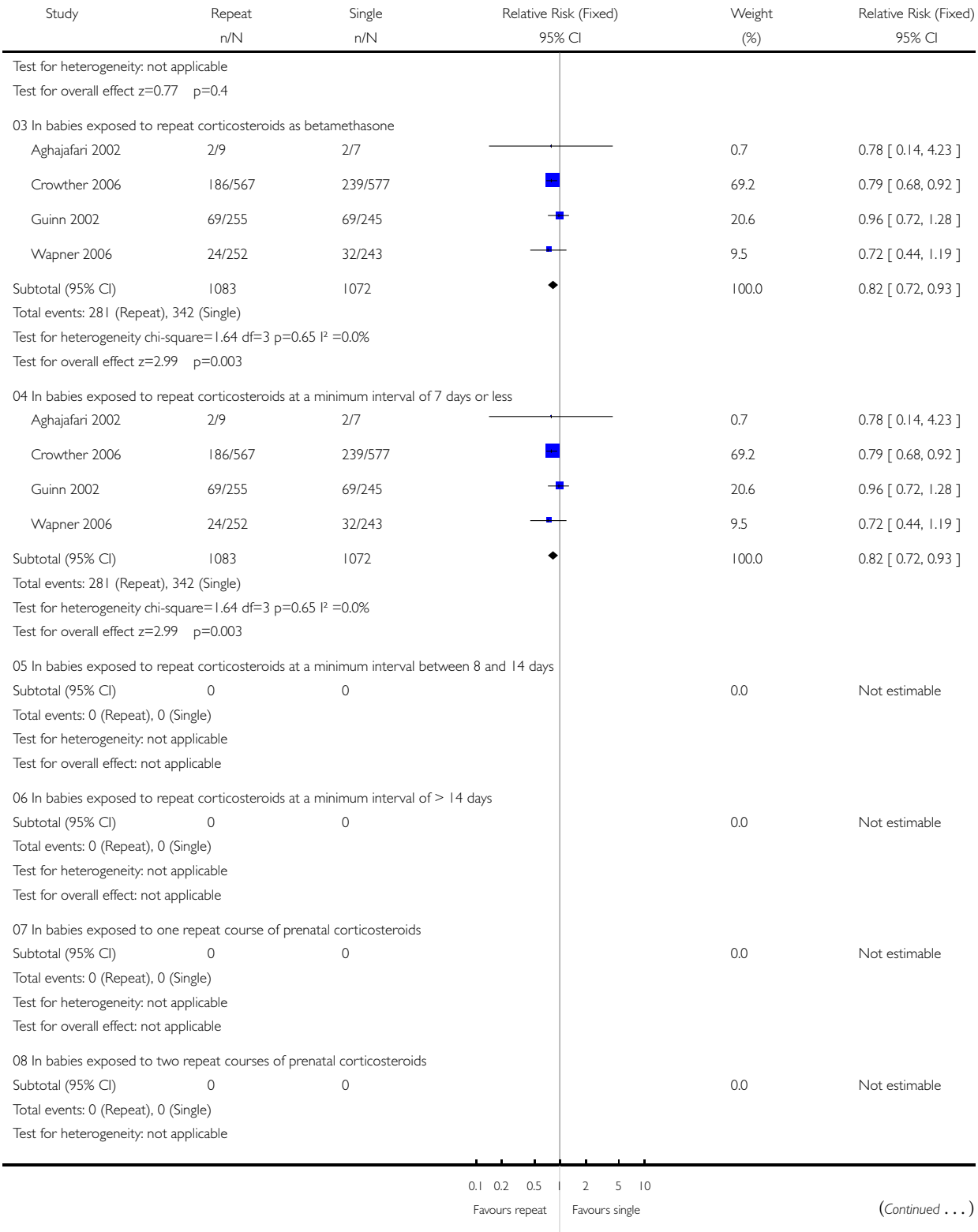

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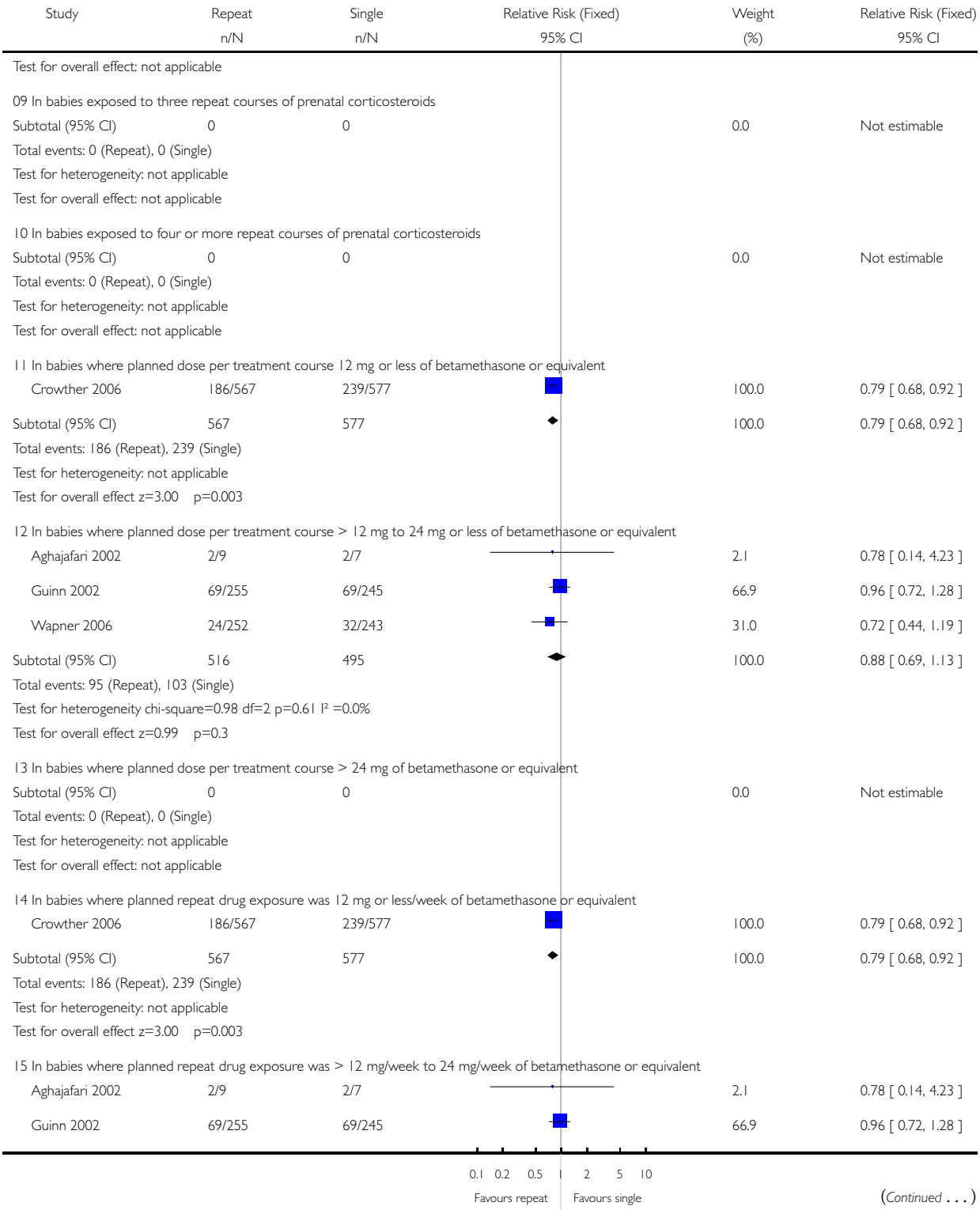

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wapner 2006	24/252	32/243		31.0	0.72 [0.44, 1.19]
Subtotal (95% CI)	516	495		100.0	0.88 [0.69, 1.13]
Total events: 95 (Repeat), 103 (Single)					
Test for heterogeneity chi-square=0.98 df=2 p=0.61 I^2 =0.0%					
Test for overall effect z=0.99 p=0.3					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.02. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 02 Severe lung disease

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 02 Severe lung disease

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	65/567	114/577		62.3	0.58 [0.44, 0.77]
Guinn 2002	38/255	57/245		32.1	0.64 [0.44, 0.93]
Wapner 2006	6/252	10/243		5.6	0.58 [0.21, 1.57]
Subtotal (95% CI)	1074	1065		100.0	0.60 [0.48, 0.75]
Total events: 109 (Repeat), 181 (Single)					
Test for heterogeneity chi-square=0.18 df=2 p=0.91 I^2 =0.0%					
Test for overall effect z=4.58 p<0.00001					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	65/567	114/577		62.3	0.58 [0.44, 0.77]

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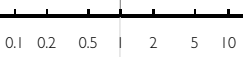
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Guinn 2002	38/255	57/245		32.1	0.64 [0.44, 0.93]
Wapner 2006	6/252	10/243		5.6	0.58 [0.21, 1.57]
Subtotal (95% CI)	1074	1065		100.0	0.60 [0.48, 0.75]
Total events: 109 (Repeat), 181 (Single)					
Test for heterogeneity chi-square=0.18 df=2 p=0.91 I^2 =0.0%					
Test for overall effect z=4.58 p<0.00001					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	65/567	114/577		62.3	0.58 [0.44, 0.77]
Guinn 2002	38/255	57/245		32.1	0.64 [0.44, 0.93]
Wapner 2006	6/252	10/243		5.6	0.58 [0.21, 1.57]
Subtotal (95% CI)	1074	1065		100.0	0.60 [0.48, 0.75]
Total events: 109 (Repeat), 181 (Single)					
Test for heterogeneity chi-square=0.18 df=2 p=0.91 I^2 =0.0%					
Test for overall effect z=4.58 p<0.00001					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	65/567	114/577		100.0	0.58 [0.44, 0.77]
Subtotal (95% CI)	567	577		100.0	0.58 [0.44, 0.77]
Total events: 65 (Repeat), 114 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.79 p=0.0002					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Guinn 2002	38/255	57/245		85.1	0.64 [0.44, 0.93]
Wapner 2006	6/252	10/243		14.9	0.58 [0.21, 1.57]
Subtotal (95% CI)	507	488		100.0	0.63 [0.45, 0.89]
Total events: 44 (Repeat), 67 (Single)					
Test for heterogeneity chi-square=0.04 df=1 p=0.85 I^2 =0.0%					
Test for overall effect z=2.59 p=0.01					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	65/567	114/577		100.0	0.58 [0.44, 0.77]
Subtotal (95% CI)	567	577		100.0	0.58 [0.44, 0.77]
Total events: 65 (Repeat), 114 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.79 p=0.0002					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Guinn 2002	38/255	57/245		85.1	0.64 [0.44, 0.93]
Wapner 2006	6/252	10/243		14.9	0.58 [0.21, 1.57]
Subtotal (95% CI)	507	488		100.0	0.63 [0.45, 0.89]
Total events: 44 (Repeat), 67 (Single)					
Test for heterogeneity chi-square=0.04 df=1 p=0.85 I^2 =0.0%					
Test for overall effect z=2.59 p=0.01					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

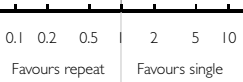
Analysis 01.03. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 03 Composite serious morbidity (variously defined)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 03 Composite serious morbidity (variously defined)

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	4/9	5/7		2.3	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		60.9	0.77 [0.62, 0.96]
Guinn 2002	56/256	66/246		27.6	0.82 [0.60, 1.11]
Wapner 2006	20/252	22/243		9.2	0.88 [0.49, 1.56]
Subtotal (95% CI)	1084	1073		100.0	0.79 [0.67, 0.93]
Total events: 194 (Repeat), 243 (Single)					
Test for heterogeneity chi-square=0.49 df=3 p=0.92 I^2 =0.0%					
Test for overall effect z=2.76 p=0.006					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	4/9	5/7		2.3	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		60.9	0.77 [0.62, 0.96]
Guinn 2002	56/256	66/246		27.6	0.82 [0.60, 1.11]
Wapner 2006	20/252	22/243		9.2	0.88 [0.49, 1.56]
Subtotal (95% CI)	1084	1073		100.0	0.79 [0.67, 0.93]
Total events: 194 (Repeat), 243 (Single)					
Test for heterogeneity chi-square=0.49 df=3 p=0.92 I^2 =0.0%					
Test for overall effect z=2.76 p=0.006					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	4/9	5/7		2.3	0.62 [0.26, 1.48]
Crowther 2006	114/567	150/577		60.9	0.77 [0.62, 0.96]
Guinn 2002	56/256	66/246		27.6	0.82 [0.60, 1.11]
Wapner 2006	20/252	22/243		9.2	0.88 [0.49, 1.56]
Subtotal (95% CI)	1084	1073		100.0	0.79 [0.67, 0.93]
Total events: 194 (Repeat), 243 (Single)					
Test for heterogeneity chi-square=0.49 df=3 p=0.92 I^2 =0.0%					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.76 p=0.006					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	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 (Repeat), 150 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	4/9	5/7		5.9	0.62 [0.26, 1.48]
Guinn 2002	56/256	66/246		70.6	0.82 [0.60, 1.11]

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Wapner 2006	20/252	22/243		23.5	0.88 [0.49, 1.56]
Subtotal (95% CI)	517	496		100.0	0.82 [0.63, 1.07]
Total events: 80 (Repeat), 93 (Single)					
Test for heterogeneity chi-square=0.44 df=2 p=0.80 I^2 =0.0%					
Test for overall effect z=1.49 p=0.1					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	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 (Repeat), 150 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.35 p=0.02					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Aghajafari 2002	4/9	5/7		5.9	0.62 [0.26, 1.48]
Guinn 2002	56/256	66/246		70.6	0.82 [0.60, 1.11]
Wapner 2006	20/252	22/243		23.5	0.88 [0.49, 1.56]
Subtotal (95% CI)	517	496		100.0	0.82 [0.63, 1.07]
Total events: 80 (Repeat), 93 (Single)					
Test for heterogeneity chi-square=0.44 df=2 p=0.80 I^2 =0.0%					
Test for overall effect z=1.49 p=0.1					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

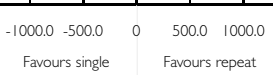
Analysis 01.04. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 04 Mean birthweight (g)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 04 Mean birthweight (g)

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	567	1867.00 (824.00)	577	1877.00 (816.00)		49.7	-10.00 [-105.04, 85.04]
Guinn 2002	256	2009.10 (858.70)	246	2138.80 (875.80)		19.5	-129.70 [-281.50, 22.10]
McEvoy 2002	18	1767.00 (659.00)	19	1975.00 (740.00)		2.2	-208.00 [-659.00, 243.00]
Wapner 2006	296	2194.30 (762.30)	294	2289.60 (791.80)		28.6	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	1137		1136			100.0	-62.07 [-129.10, 4.96]
Test for heterogeneity chi-square=2.59 df=3 p=0.46 I² =0.0%							
Test for overall effect z=1.82 p=0.07							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	1867.00 (824.00)	577	1877.00 (816.00)		49.7	-10.00 [-105.04, 85.04]
Guinn 2002	256	2009.10 (858.70)	246	2138.80 (875.80)		19.5	-129.70 [-281.50, 22.10]
McEvoy 2002	18	1767.00 (659.00)	19	1975.00 (740.00)		2.2	-208.00 [-659.00, 243.00]
Wapner 2006	296	2194.30 (762.30)	294	2289.60 (791.80)		28.6	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	1137		1136			100.0	-62.07 [-129.10, 4.96]
Test for heterogeneity chi-square=2.59 df=3 p=0.46 I² =0.0%							
Test for overall effect z=1.82 p=0.07							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	1867.00 (824.00)	577	1877.00 (816.00)		49.7	-10.00 [-105.04, 85.04]
Guinn 2002	256	2009.10 (858.70)	246	2138.80 (875.80)		19.5	-129.70 [-281.50, 22.10]
McEvoy 2002	18	1767.00 (659.00)	19	1975.00 (740.00)		2.2	-208.00 [-659.00, 243.00]
Wapner 2006	296	2194.30 (762.30)	294	2289.60 (791.80)		28.6	-95.30 [-220.73, 30.13]
Subtotal (95% CI)	1137		1136			100.0	-62.07 [-129.10, 4.96]
Test for heterogeneity chi-square=2.59 df=3 p=0.46 I² =0.0%							
Test for overall effect z=1.82 p=0.07							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable



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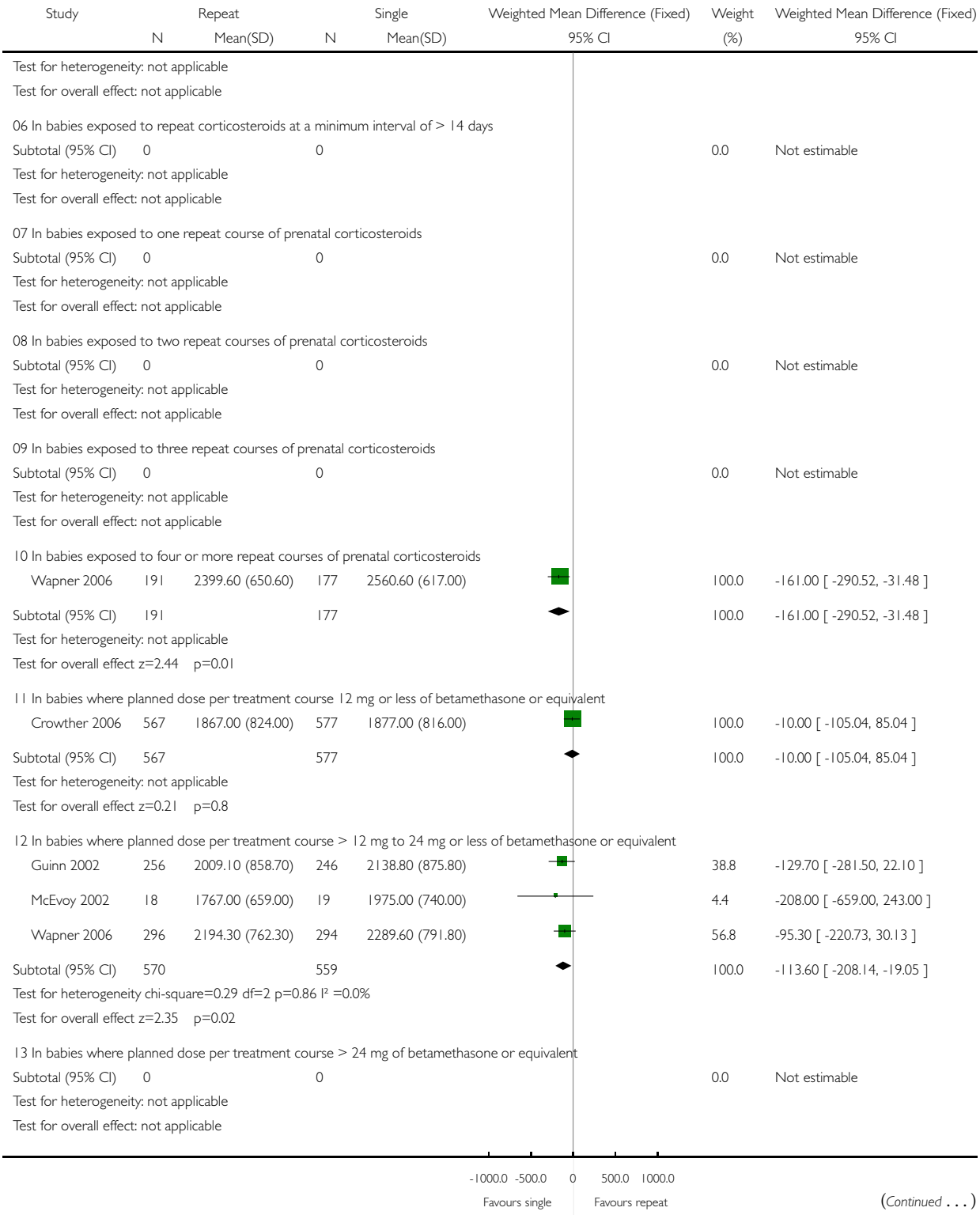

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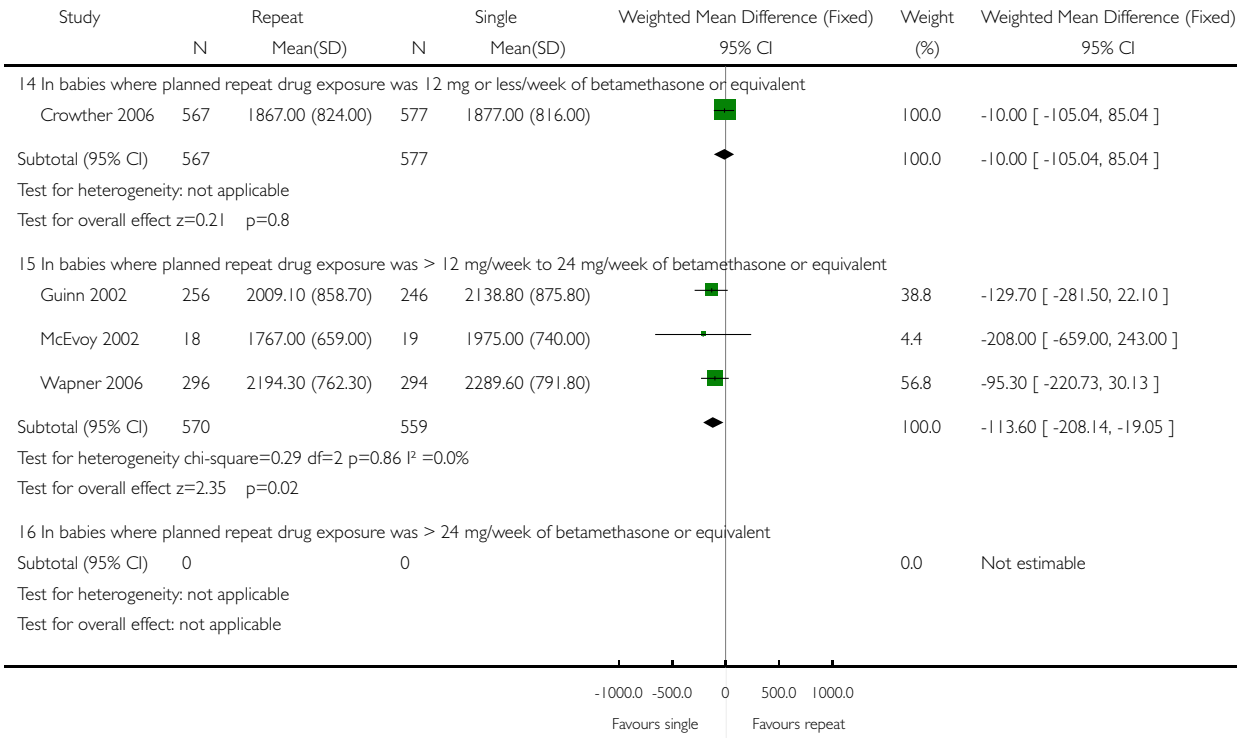


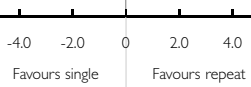
Analysis 01.05. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 05 Birthweight Z scores

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 05 Birthweight Z scores

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	567	-0.40 (1.05)	577	-0.27 (1.14)		100.0	-0.13 [-0.26, 0.00]
Subtotal (95% CI)	567		577			100.0	-0.13 [-0.26, 0.00]
Test for heterogeneity: not applicable							
Test for overall effect z=2.01 p=0.04							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	-0.40 (1.05)	577	-0.27 (1.14)		100.0	-0.13 [-0.26, 0.00]
Subtotal (95% CI)	567		577			100.0	-0.13 [-0.26, 0.00]
Test for heterogeneity: not applicable							
Test for overall effect z=2.01 p=0.04							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	-0.40 (1.05)	577	-0.27 (1.14)		100.0	-0.13 [-0.26, 0.00]
Subtotal (95% CI)	567		577			100.0	-0.13 [-0.26, 0.00]
Test for heterogeneity: not applicable							
Test for overall effect z=2.01 p=0.04							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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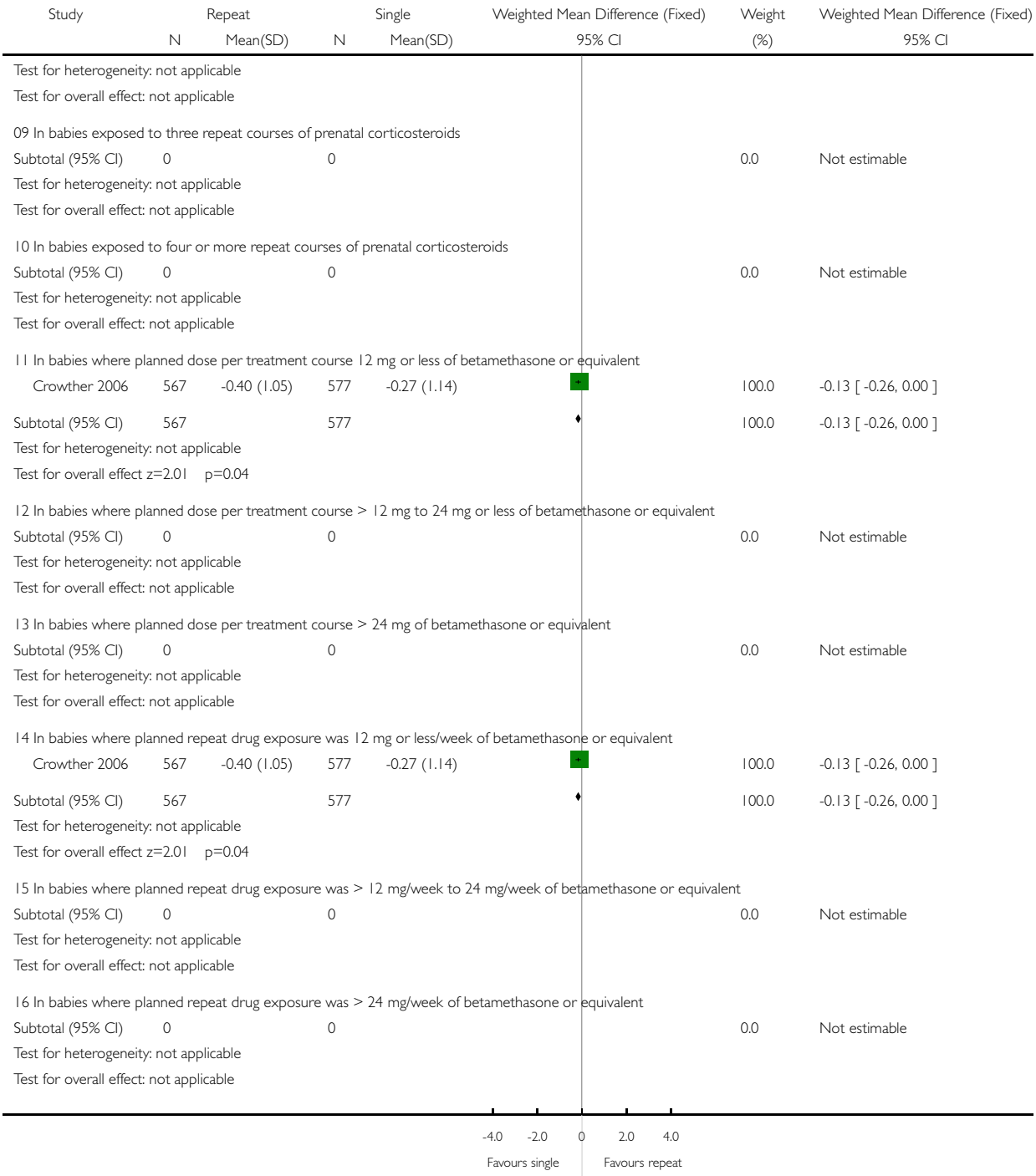


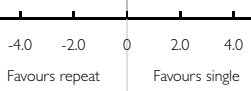
Analysis 01.06. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 06 Birthweight multiples of the median

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 06 Birthweight multiples of the median

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0	0.00 [-0.03, 0.03]
Subtotal (95% CI)	296		294			100.0	0.00 [-0.03, 0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0	0.00 [-0.03, 0.03]
Subtotal (95% CI)	296		294			100.0	0.00 [-0.03, 0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
04 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	0.00 [-0.03, 0.03]
Subtotal (95% CI)	296		294			100.0	0.00 [-0.03, 0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of >14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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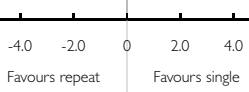
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	0.90 (0.14)		100.0	-0.04 [-0.07, -0.01]
Subtotal (95% CI)	191		177			100.0	-0.04 [-0.07, -0.01]
Test for heterogeneity: not applicable							
Test for overall effect z=2.65 p=0.008							
11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0	0.00 [-0.03, 0.03]
Subtotal (95% CI)	296		294			100.0	0.00 [-0.03, 0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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 betamethasone or equivalent							
Wapner 2006	296	0.88 (0.16)	294	0.88 (0.15)		100.0	0.00 [-0.03, 0.03]
Subtotal (95% CI)	296		294			100.0	0.00 [-0.03, 0.03]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



Analysis 01.07. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 07 Small-for-gestational age at birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 07 Small-for-gestational age at birth

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	2/6	0/6		1.3	5.00 [0.29, 86.43]
Wapner 2006	59/296	37/294		98.7	1.58 [1.09, 2.31]
Subtotal (95% CI)	302	300		100.0	1.63 [1.12, 2.37]
Total events: 61 (Repeat), 37 (Single)					
Test for heterogeneity chi-square=0.62 df=1 p=0.43 I^2 =0.0%					
Test for overall effect z=2.56 p=0.01					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	2/6	0/6		1.3	5.00 [0.29, 86.43]
Wapner 2006	59/296	37/294		98.7	1.58 [1.09, 2.31]
Subtotal (95% CI)	302	300		100.0	1.63 [1.12, 2.37]
Total events: 61 (Repeat), 37 (Single)					
Test for heterogeneity chi-square=0.62 df=1 p=0.43 I^2 =0.0%					
Test for overall effect z=2.56 p=0.01					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	2/6	0/6		1.3	5.00 [0.29, 86.43]
Wapner 2006	59/296	37/294		98.7	1.58 [1.09, 2.31]
Subtotal (95% CI)	302	300		100.0	1.63 [1.12, 2.37]
Total events: 61 (Repeat), 37 (Single)					
Test for heterogeneity chi-square=0.62 df=1 p=0.43 I^2 =0.0%					
Test for overall effect z=2.56 p=0.01					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					

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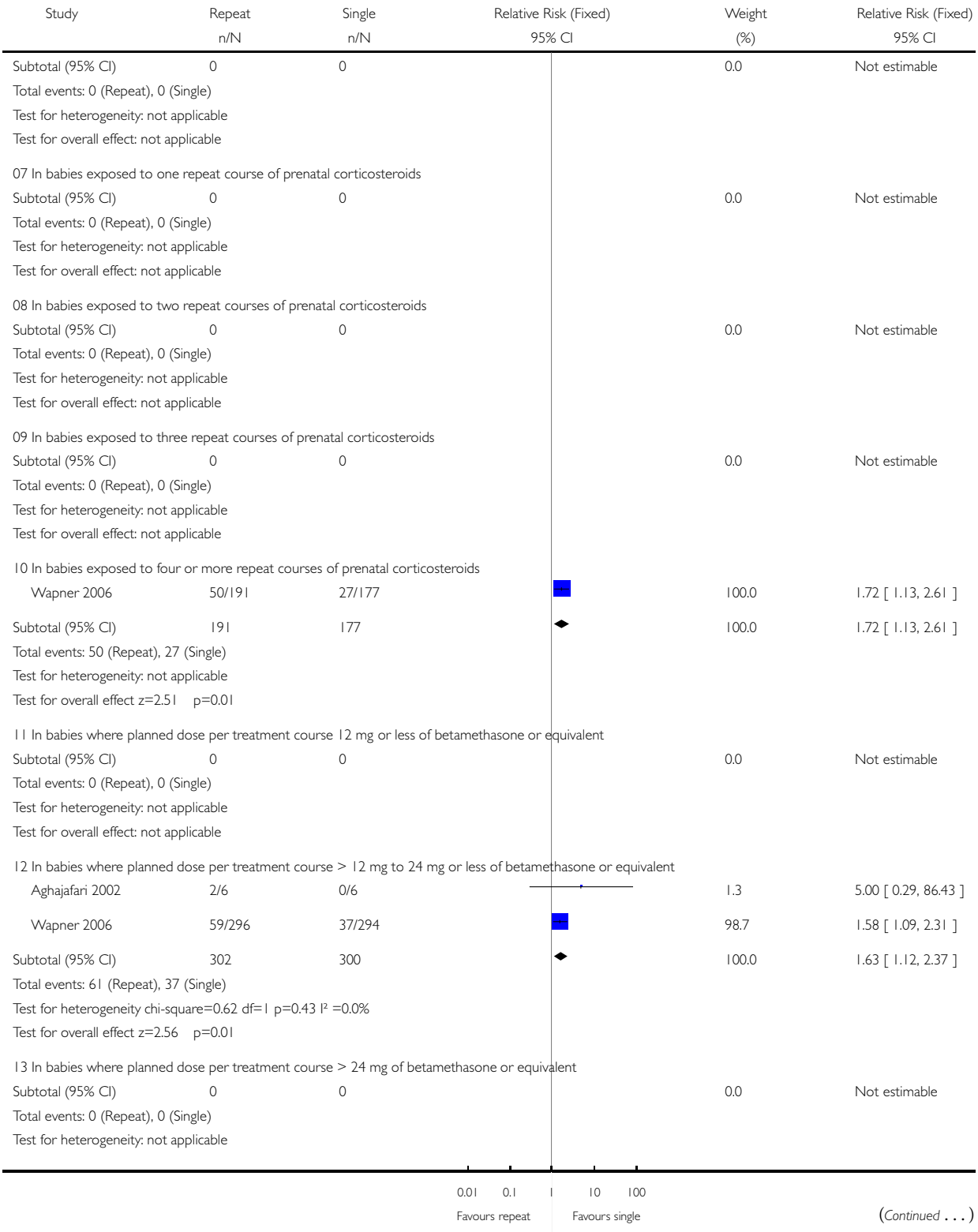

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect: not applicable					
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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 betamethasone or equivalent					
Aghajafari 2002	2/6	0/6		1.3	5.00 [0.29, 86.43]
Wapner 2006	59/296	37/294		98.7	1.58 [1.09, 2.31]
Subtotal (95% CI)	302	300		100.0	1.63 [1.12, 2.37]
Total events: 61 (Repeat), 37 (Single)					
Test for heterogeneity chi-square=0.62 df=1 p=0.43 I^2 =0.0%					
Test for overall effect z=2.56 p=0.01					
16 In babies where planned repeat drug exposure was >24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.08. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 08 Fetal and neonatal mortality

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 08 Fetal and neonatal mortality

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	27/567	29/577		65.3	0.95 [0.57, 1.58]
Guinn 2002	5/256	9/246		20.8	0.53 [0.18, 1.57]
Wapner 2006	3/252	6/243		13.9	0.48 [0.12, 1.91]
Subtotal (95% CI)	1084	1073		100.0	0.80 [0.52, 1.23]
Total events: 35 (Repeat), 44 (Single)					
Test for heterogeneity chi-square=1.48 df=2 p=0.48 I^2 =0.0%					
Test for overall effect z=1.03 p=0.3					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
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 (Repeat), 6 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.04 p=0.3					
03 In babies exposed to repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	27/567	29/577		65.3	0.95 [0.57, 1.58]
Guinn 2002	5/256	9/246		20.8	0.53 [0.18, 1.57]
Wapner 2006	3/252	6/243		13.9	0.48 [0.12, 1.91]
Subtotal (95% CI)	1084	1073		100.0	0.80 [0.52, 1.23]
Total events: 35 (Repeat), 44 (Single)					
Test for heterogeneity chi-square=1.48 df=2 p=0.48 I^2 =0.0%					
Test for overall effect z=1.03 p=0.3					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	27/567	29/577		65.3	0.95 [0.57, 1.58]
Guinn 2002	5/256	9/246		20.8	0.53 [0.18, 1.57]
Wapner 2006	3/252	6/243		13.9	0.48 [0.12, 1.91]
Subtotal (95% CI)	1084	1073		100.0	0.80 [0.52, 1.23]

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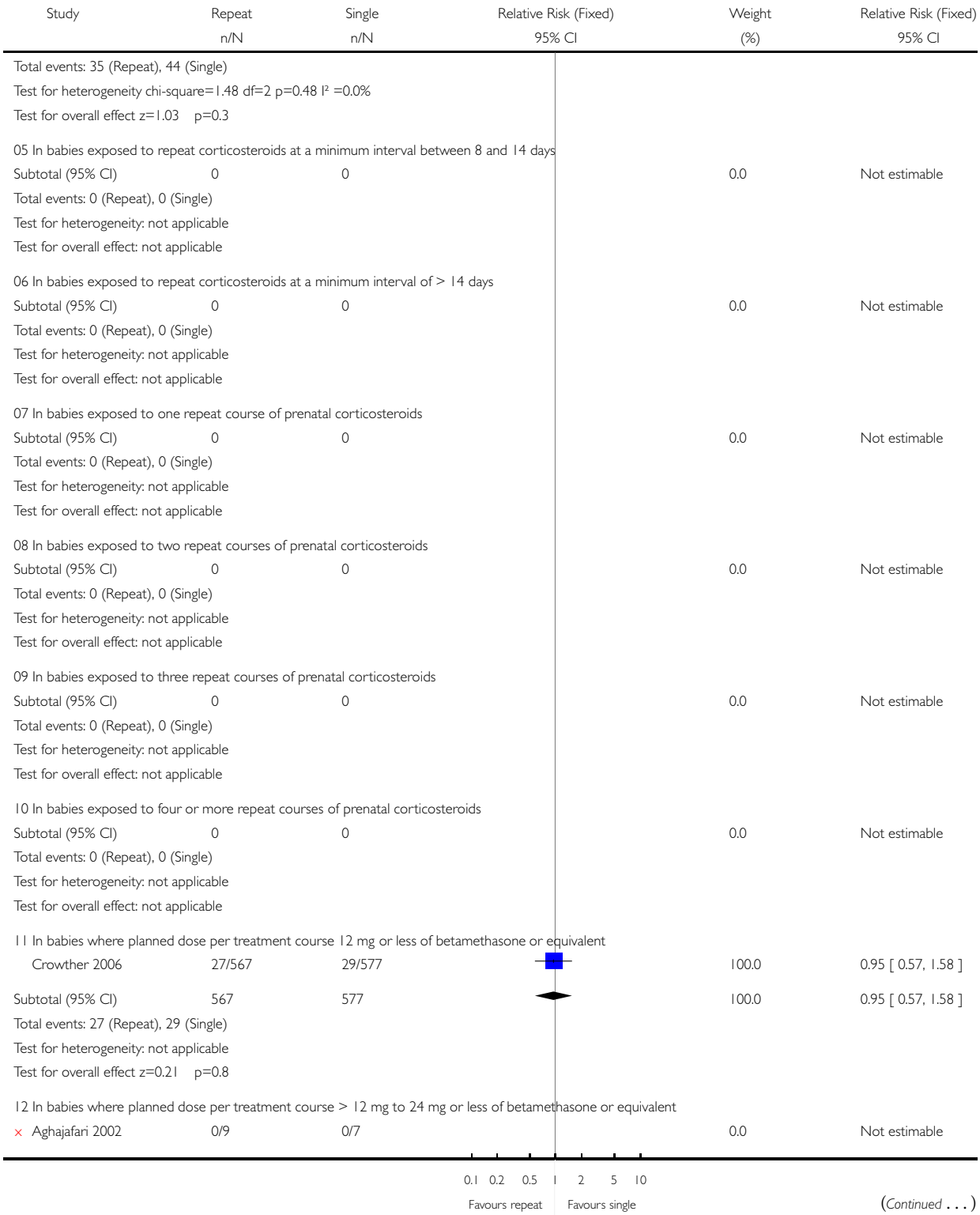

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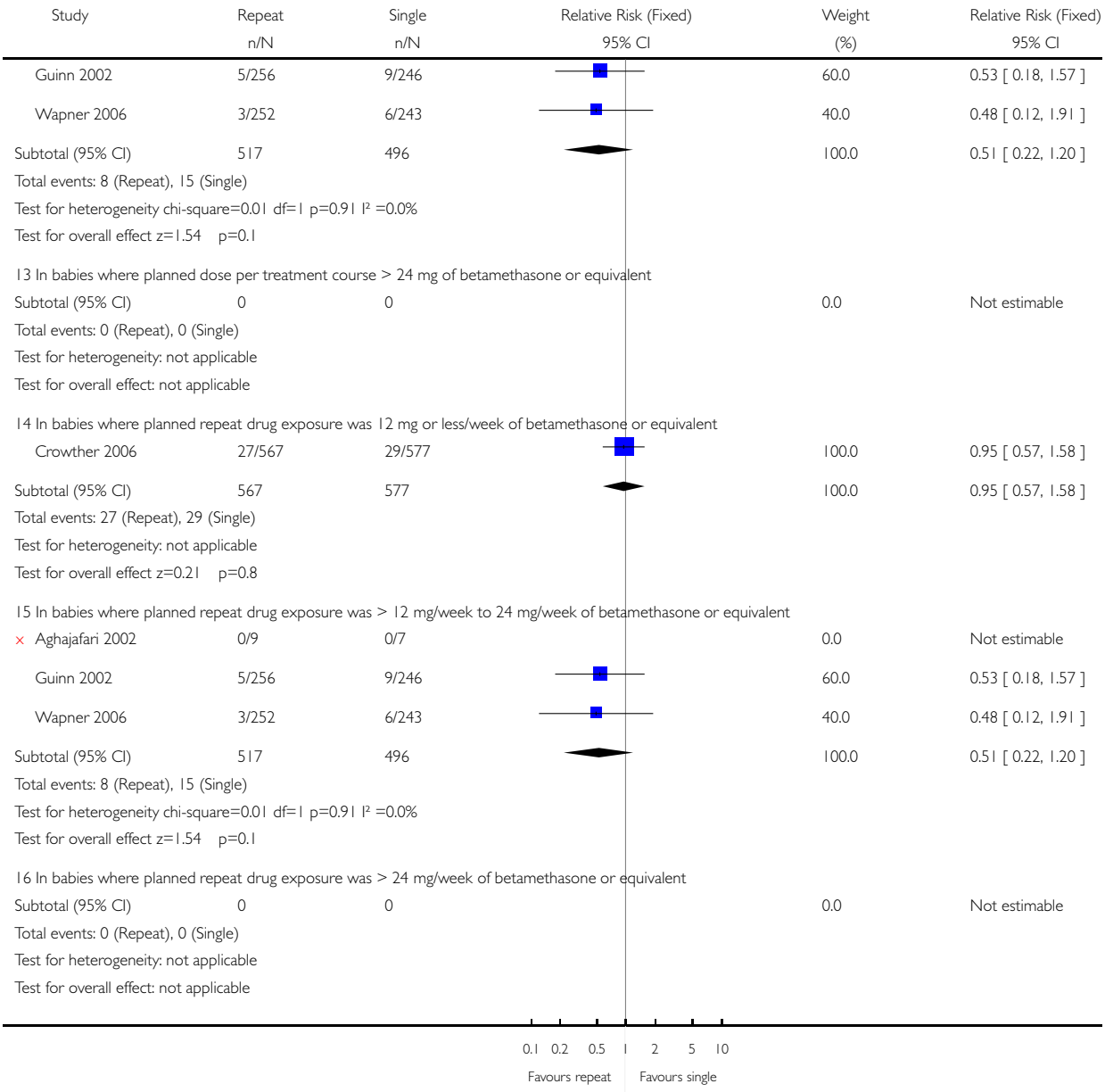

Analysis 01.09. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 09 Fetal death

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 09 Fetal death

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	1/568	1/577		100.0	1.02 [0.06, 16.20]
Subtotal (95% CI)	577	584		100.0	1.02 [0.06, 16.20]
Total events: 1 (Repeat), 1 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	1/568	1/577		100.0	1.02 [0.06, 16.20]
Subtotal (95% CI)	577	584		100.0	1.02 [0.06, 16.20]
Total events: 1 (Repeat), 1 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	1/568	1/577		100.0	1.02 [0.06, 16.20]
Subtotal (95% CI)	577	584		100.0	1.02 [0.06, 16.20]
Total events: 1 (Repeat), 1 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	1/568	1/577		100.0	1.02 [0.06, 16.20]
Subtotal (95% CI)	568	577		100.0	1.02 [0.06, 16.20]
Total events: 1 (Repeat), 1 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Subtotal (95% CI)	9	7		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Crowther 2006	1/568	1/577		100.0	1.02 [0.06, 16.20]
Subtotal (95% CI)	568	577		100.0	1.02 [0.06, 16.20]
Total events: 1 (Repeat), 1 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.01 p=1					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Subtotal (95% CI)	9	7		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.10. Comparison 01 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 preventing neonatal respiratory disease

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 10 Neonatal death

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	26/567	28/577		100.0	0.94 [0.56, 1.59]
Subtotal (95% CI)	576	584		100.0	0.94 [0.56, 1.59]
Total events: 26 (Repeat), 28 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.21 p=0.8					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					

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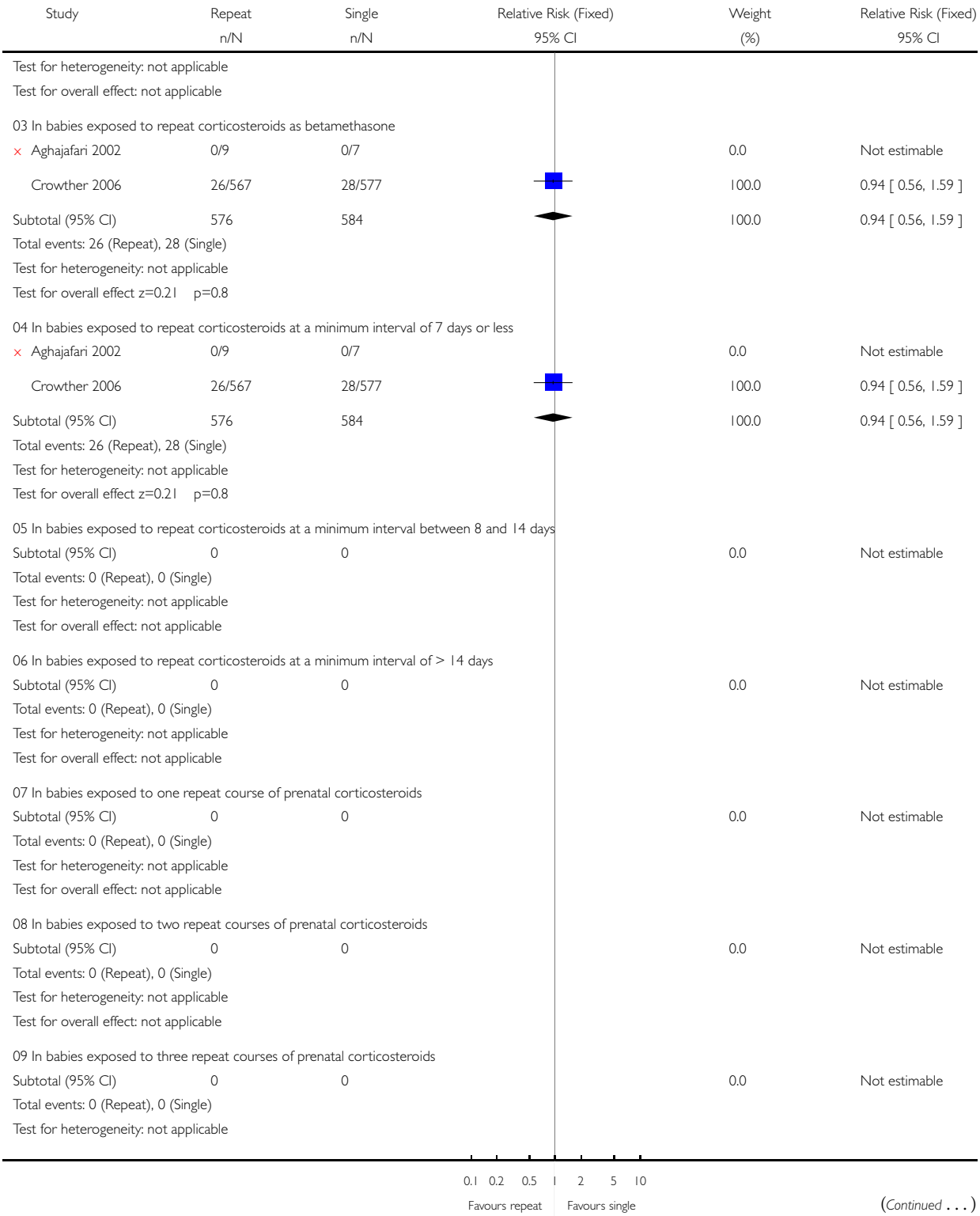

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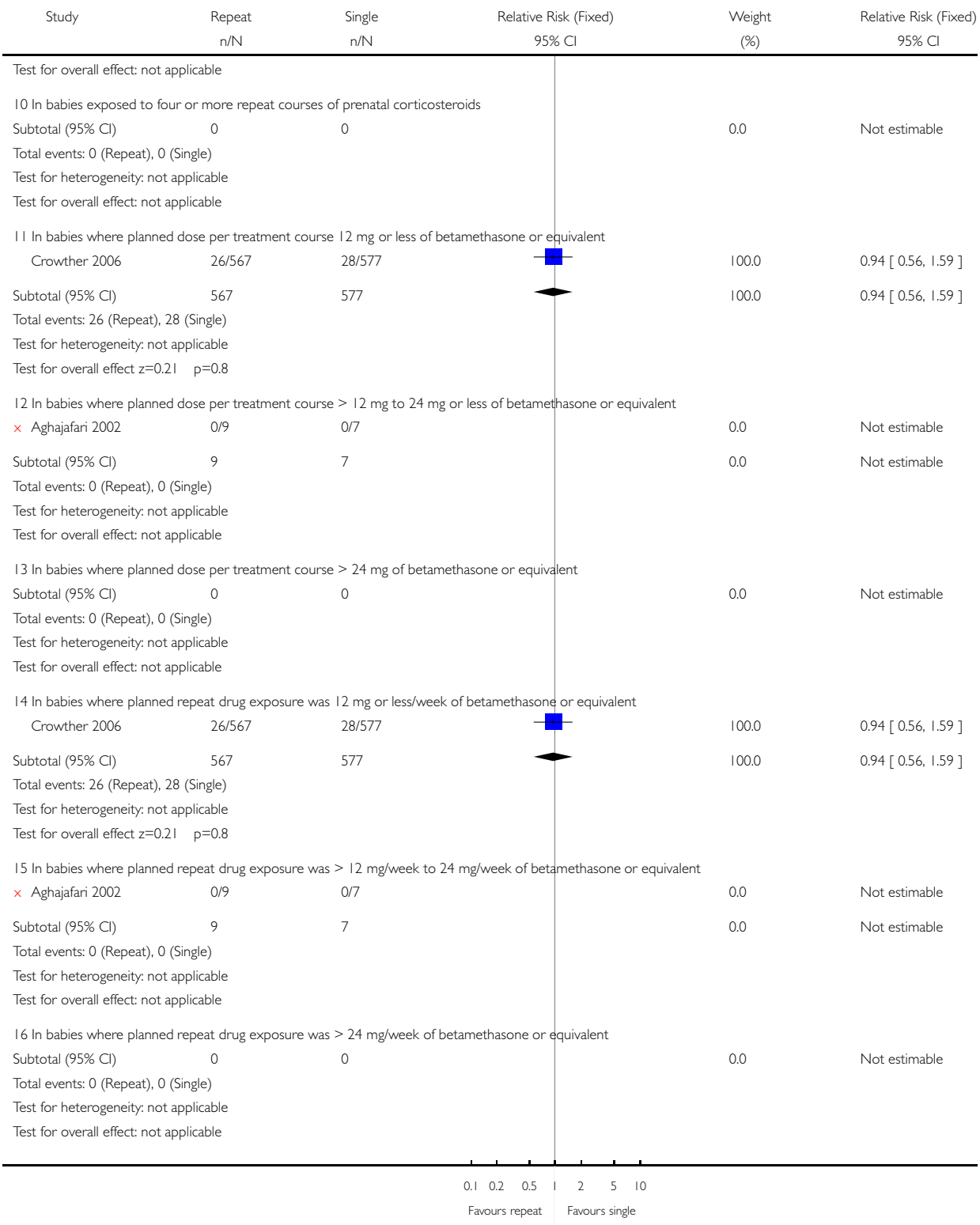

Analysis 01.11. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 11 Chronic lung disease

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 11 Chronic lung disease

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	2/9	2/7		1.8	0.78 [0.14, 4.23]
Crowther 2006	76/567	82/577		64.9	0.94 [0.71, 1.26]
Guinn 2002	28/255	26/245		21.2	1.03 [0.62, 1.71]
Wapner 2006	14/252	15/243		12.2	0.90 [0.44, 1.82]
Subtotal (95% CI)	1083	1072		100.0	0.95 [0.75, 1.21]
Total events: 120 (Repeat), 125 (Single)					
Test for heterogeneity chi-square=0.19 df=3 p=0.98 I^2 =0.0%					
Test for overall effect z=0.39 p=0.7					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
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 (Repeat), 19 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.85 p=0.4					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	2/9	2/7		1.8	0.78 [0.14, 4.23]
Crowther 2006	76/567	82/577		64.9	0.94 [0.71, 1.26]
Guinn 2002	28/255	26/245		21.2	1.03 [0.62, 1.71]
Wapner 2006	14/252	15/243		12.2	0.90 [0.44, 1.82]
Subtotal (95% CI)	1083	1072		100.0	0.95 [0.75, 1.21]
Total events: 120 (Repeat), 125 (Single)					
Test for heterogeneity chi-square=0.19 df=3 p=0.98 I^2 =0.0%					
Test for overall effect z=0.39 p=0.7					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	2/9	2/7		1.8	0.78 [0.14, 4.23]
Crowther 2006	76/567	82/577		64.9	0.94 [0.71, 1.26]
Guinn 2002	28/255	26/245		21.2	1.03 [0.62, 1.71]
Wapner 2006	14/252	15/243		12.2	0.90 [0.44, 1.82]
Subtotal (95% CI)	1083	1072		100.0	0.95 [0.75, 1.21]

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 120 (Repeat), 125 (Single)					
Test for heterogeneity chi-square=0.19 df=3 p=0.98 I^2 =0.0%					
Test for overall effect z=0.39 p=0.7					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		100.0	0.94 [0.71, 1.26]
Subtotal (95% CI)	567	577		100.0	0.94 [0.71, 1.26]
Total events: 76 (Repeat), 82 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.40 p=0.7					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	2/9	2/7		5.1	0.78 [0.14, 4.23]

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Guinn 2002	28/255	26/245		60.2	1.03 [0.62, 1.71]
Wapner 2006	14/252	15/243		34.7	0.90 [0.44, 1.82]
Subtotal (95% CI)	516	495		100.0	0.97 [0.65, 1.45]
Total events: 44 (Repeat), 43 (Single)					
Test for heterogeneity chi-square=0.17 df=2 p=0.92 I^2 =0.0%					
Test for overall effect z=0.13 p=0.9					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		100.0	0.94 [0.71, 1.26]
Subtotal (95% CI)	567	577		100.0	0.94 [0.71, 1.26]
Total events: 76 (Repeat), 82 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.40 p=0.7					
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	28/255	26/245		60.2	1.03 [0.62, 1.71]
Wapner 2006	14/252	15/243		34.7	0.90 [0.44, 1.82]
Subtotal (95% CI)	516	495		100.0	0.97 [0.65, 1.45]
Total events: 44 (Repeat), 43 (Single)					
Test for heterogeneity chi-square=0.17 df=2 p=0.92 I^2 =0.0%					
Test for overall effect z=0.13 p=0.9					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.13. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 13 Periventricular haemorrhage

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 13 Periventricular haemorrhage

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	34/567	39/577		47.1	0.89 [0.57, 1.38]
Guinn 2002	30/255	25/245		31.0	1.15 [0.70, 1.90]
Wapner 2006	15/230	18/230		21.9	0.83 [0.43, 1.61]
Subtotal (95% CI)	1052	1052		100.0	0.96 [0.71, 1.29]
Total events: 79 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.81 df=2 p=0.67 I^2 =0.0%					
Test for overall effect z=0.28 p=0.8					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	34/567	39/577		47.1	0.89 [0.57, 1.38]
Guinn 2002	30/255	25/245		31.0	1.15 [0.70, 1.90]
Wapner 2006	15/230	18/230		21.9	0.83 [0.43, 1.61]
Subtotal (95% CI)	1052	1052		100.0	0.96 [0.71, 1.29]
Total events: 79 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.81 df=2 p=0.67 I^2 =0.0%					
Test for overall effect z=0.28 p=0.8					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	34/567	39/577		47.1	0.89 [0.57, 1.38]
Guinn 2002	30/255	25/245		31.0	1.15 [0.70, 1.90]
Wapner 2006	15/230	18/230		21.9	0.83 [0.43, 1.61]
Subtotal (95% CI)	1052	1052		100.0	0.96 [0.71, 1.29]
Total events: 79 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.81 df=2 p=0.67 I^2 =0.0%					
Test for overall effect z=0.28 p=0.8					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable

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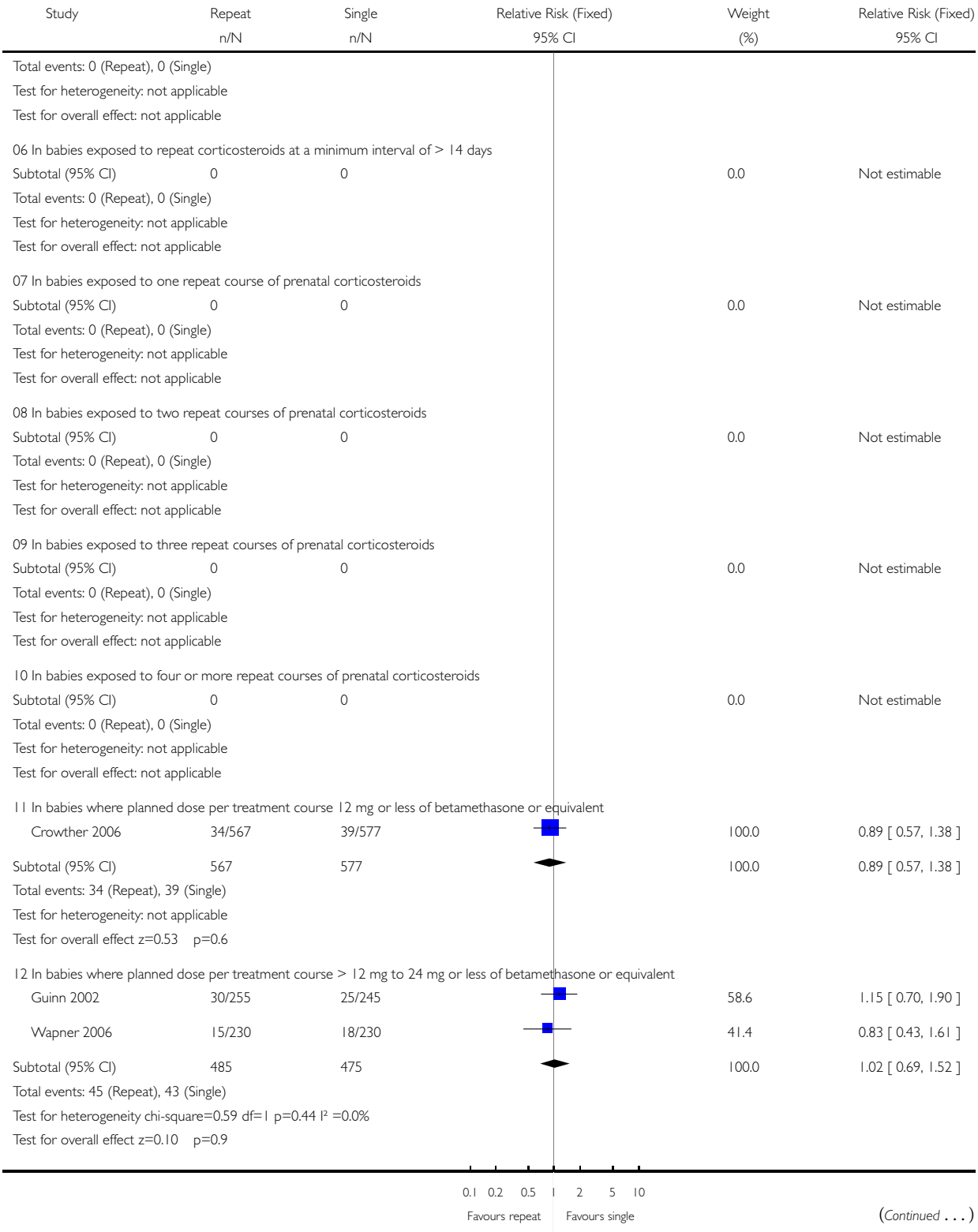

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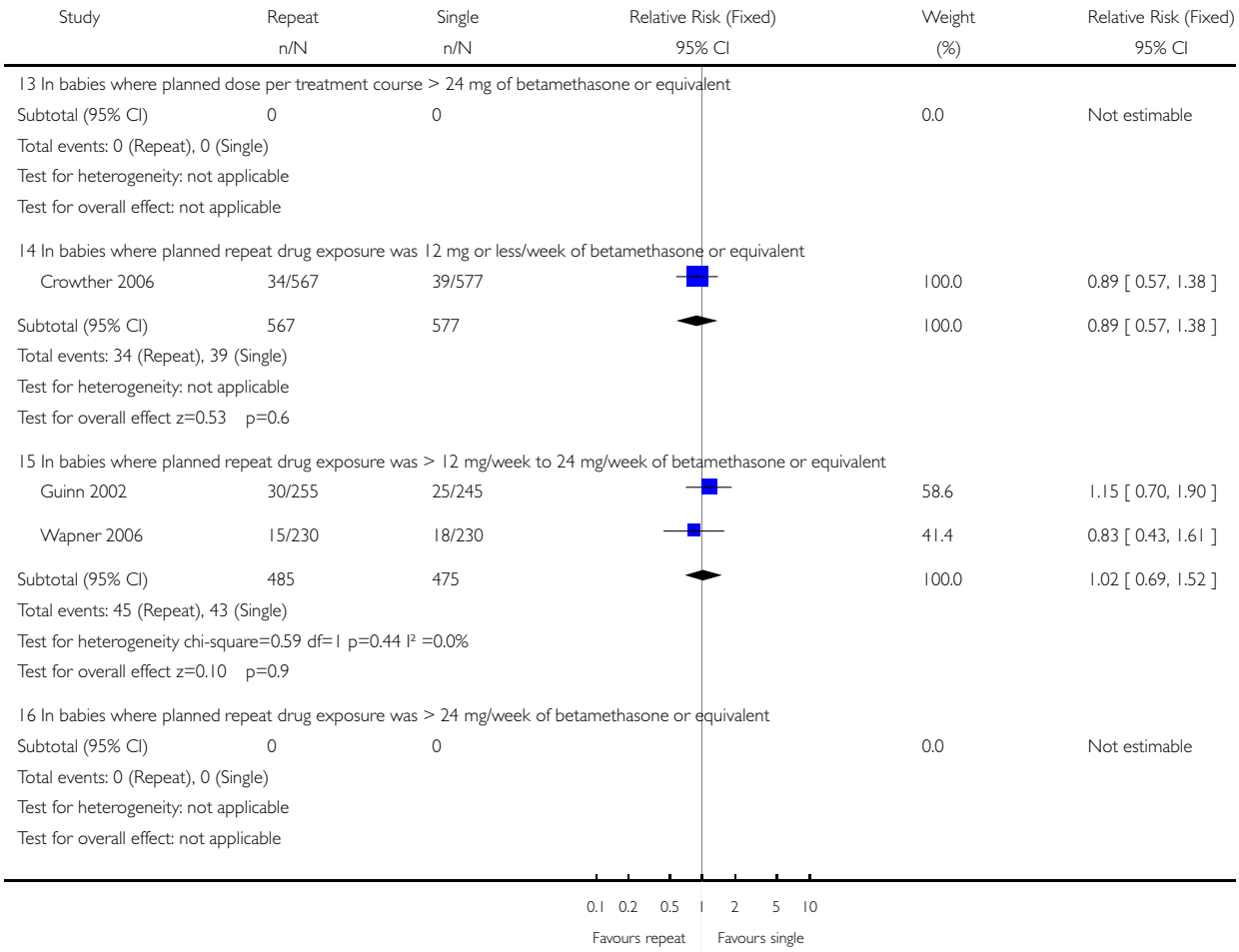
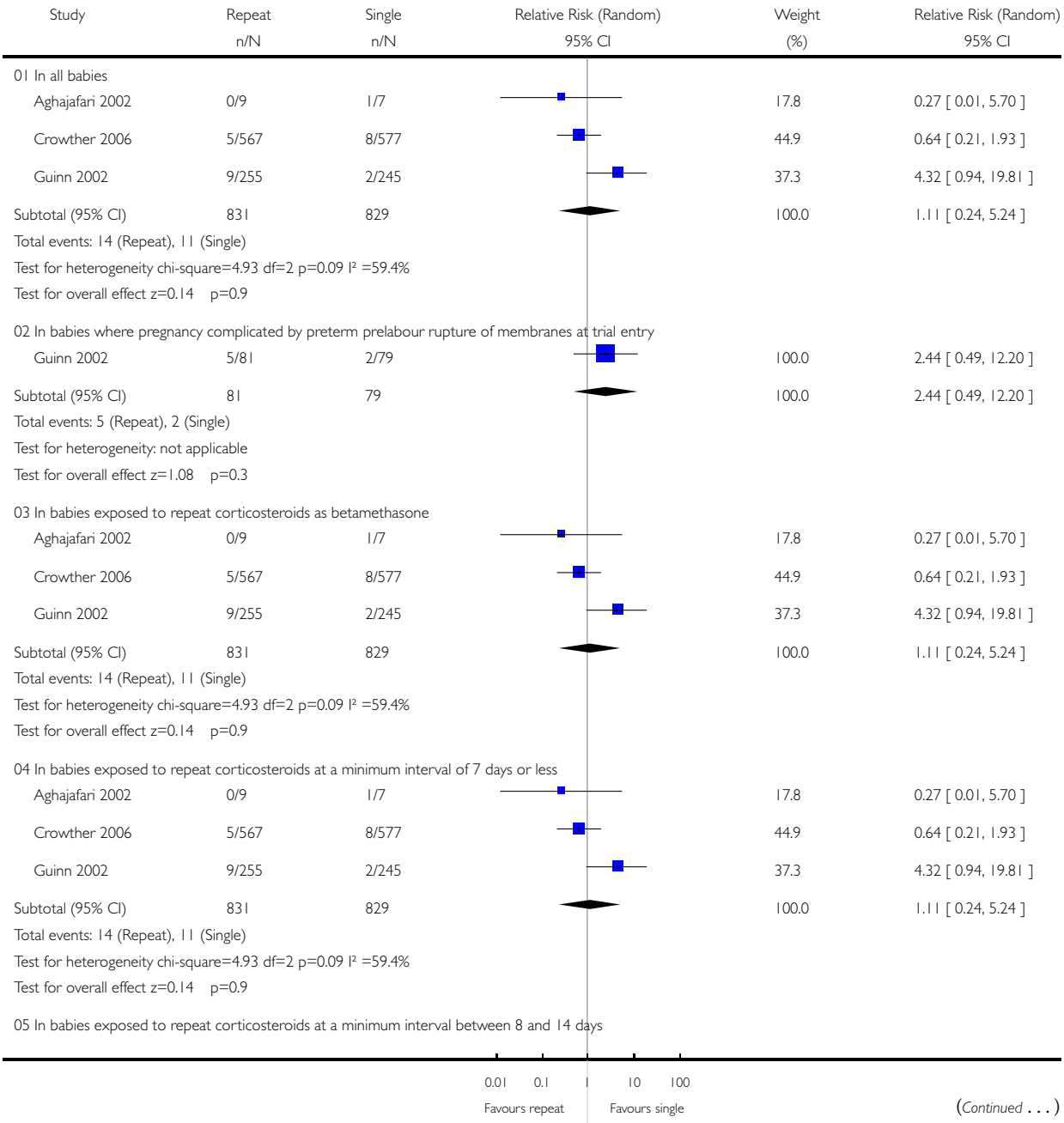


Analysis 01.14. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 14 Periventricular haemorrhage grade 3/4

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 14 Periventricular haemorrhage grade 3/4



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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	5/567	8/577		100.0	0.64 [0.21, 1.93]
Subtotal (95% CI)	567	577		100.0	0.64 [0.21, 1.93]
Total events: 5 (Repeat), 8 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.80 p=0.4					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	0/9	1/7		38.2	0.27 [0.01, 5.70]
Guinn 2002	9/255	2/245		61.8	4.32 [0.94, 19.81]
Subtotal (95% CI)	264	252		100.0	1.49 [0.11, 21.19]
Total events: 9 (Repeat), 3 (Single)					
Test for heterogeneity chi-square=2.55 df=1 p=0.11 I^2 =60.8%					

0.01 0.1 1 10 100

Favours repeat Favours single

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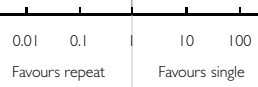
Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for overall effect z=0.30 p=0.8					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	5/567	8/577		100.0	0.64 [0.21, 1.93]
Subtotal (95% CI)	567	577		100.0	0.64 [0.21, 1.93]
Total events: 5 (Repeat), 8 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.80 p=0.4					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Aghajafari 2002	0/9	1/7		38.2	0.27 [0.01, 5.70]
Guinn 2002	9/255	2/245		61.8	4.32 [0.94, 19.81]
Subtotal (95% CI)	264	252		100.0	1.49 [0.11, 21.19]
Total events: 9 (Repeat), 3 (Single)					
Test for heterogeneity chi-square=2.55 df=1 p=0.11 I^2 =60.8%					
Test for overall effect z=0.30 p=0.8					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



Analysis 01.15. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 15 Periventricular leucomalacia

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 15 Periventricular leucomalacia

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	4/567	9/577		74.5	0.45 [0.14, 1.46]
Guinn 2002	2/255	3/245		25.5	0.64 [0.11, 3.80]
Subtotal (95% CI)	831	829		100.0	0.50 [0.19, 1.33]
Total events: 6 (Repeat), 12 (Single)					
Test for heterogeneity chi-square=0.10 df=1 p=0.75 I² =0.0%					
Test for overall effect z=1.39 p=0.2					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	4/567	9/577		74.5	0.45 [0.14, 1.46]
Guinn 2002	2/255	3/245		25.5	0.64 [0.11, 3.80]
Subtotal (95% CI)	831	829		100.0	0.50 [0.19, 1.33]
Total events: 6 (Repeat), 12 (Single)					
Test for heterogeneity chi-square=0.10 df=1 p=0.75 I² =0.0%					
Test for overall effect z=1.39 p=0.2					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	4/567	9/577		74.5	0.45 [0.14, 1.46]
Guinn 2002	2/255	3/245		25.5	0.64 [0.11, 3.80]
Subtotal (95% CI)	831	829		100.0	0.50 [0.19, 1.33]
Total events: 6 (Repeat), 12 (Single)					
Test for heterogeneity chi-square=0.10 df=1 p=0.75 I² =0.0%					
Test for overall effect z=1.39 p=0.2					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable

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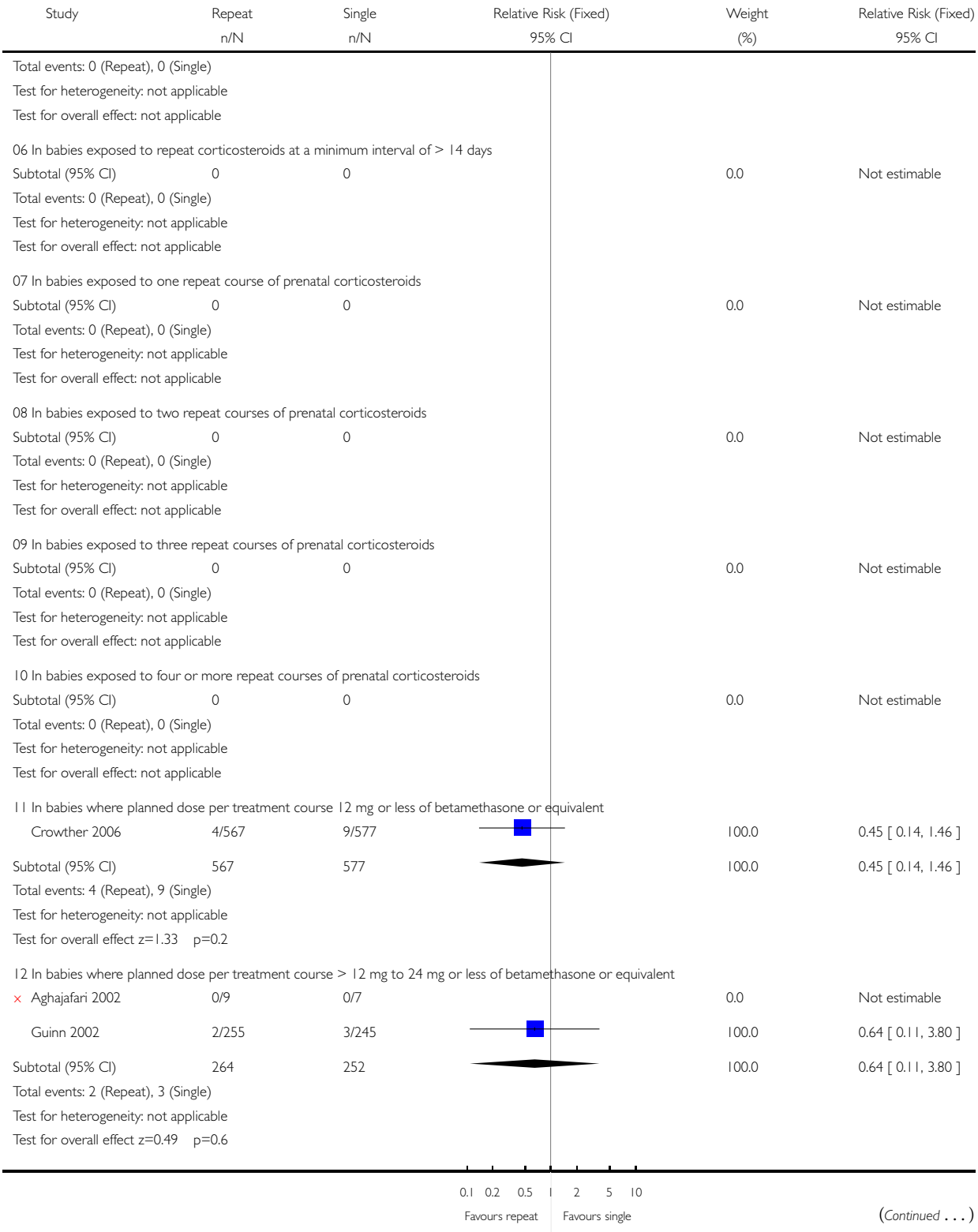

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	4/567	9/577		100.0	0.45 [0.14, 1.46]
Subtotal (95% CI)	567	577		100.0	0.45 [0.14, 1.46]
Total events: 4 (Repeat), 9 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.33 p=0.2					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Guinn 2002	2/255	3/245		100.0	0.64 [0.11, 3.80]
Subtotal (95% CI)	264	252		100.0	0.64 [0.11, 3.80]
Total events: 2 (Repeat), 3 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.49 p=0.6					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.17. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 17 Chorioamnionitis

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 17 Chorioamnionitis

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Crowther 2006	44/489	41/493		45.3	1.08 [0.72, 1.62]
Guinn 2002	60/249	42/236		47.9	1.35 [0.95, 1.92]
Wapner 2006	8/250	6/242		6.8	1.29 [0.45, 3.66]
Subtotal (95% CI)	994	977		100.0	1.23 [0.95, 1.59]
Total events: 112 (Repeat), 89 (Single)					
Test for heterogeneity chi-square=0.68 df=2 p=0.71 I^2 =0.0%					
Test for overall effect z=1.55 p=0.1					
02 In women where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Guinn 2002	40/81	25/79		100.0	1.56 [1.05, 2.31]
Subtotal (95% CI)	81	79		100.0	1.56 [1.05, 2.31]
Total events: 40 (Repeat), 25 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.23 p=0.03					
03 In women given repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Crowther 2006	44/489	41/493		45.3	1.08 [0.72, 1.62]
Guinn 2002	60/249	42/236		47.9	1.35 [0.95, 1.92]
Wapner 2006	8/250	6/242		6.8	1.29 [0.45, 3.66]
Subtotal (95% CI)	994	977		100.0	1.23 [0.95, 1.59]
Total events: 112 (Repeat), 89 (Single)					
Test for heterogeneity chi-square=0.68 df=2 p=0.71 I^2 =0.0%					
Test for overall effect z=1.55 p=0.1					
04 In women given repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Crowther 2006	44/489	41/493		45.3	1.08 [0.72, 1.62]
Guinn 2002	60/249	42/236		47.9	1.35 [0.95, 1.92]
Wapner 2006	8/250	6/242		6.8	1.29 [0.45, 3.66]
Subtotal (95% CI)	994	977		100.0	1.23 [0.95, 1.59]

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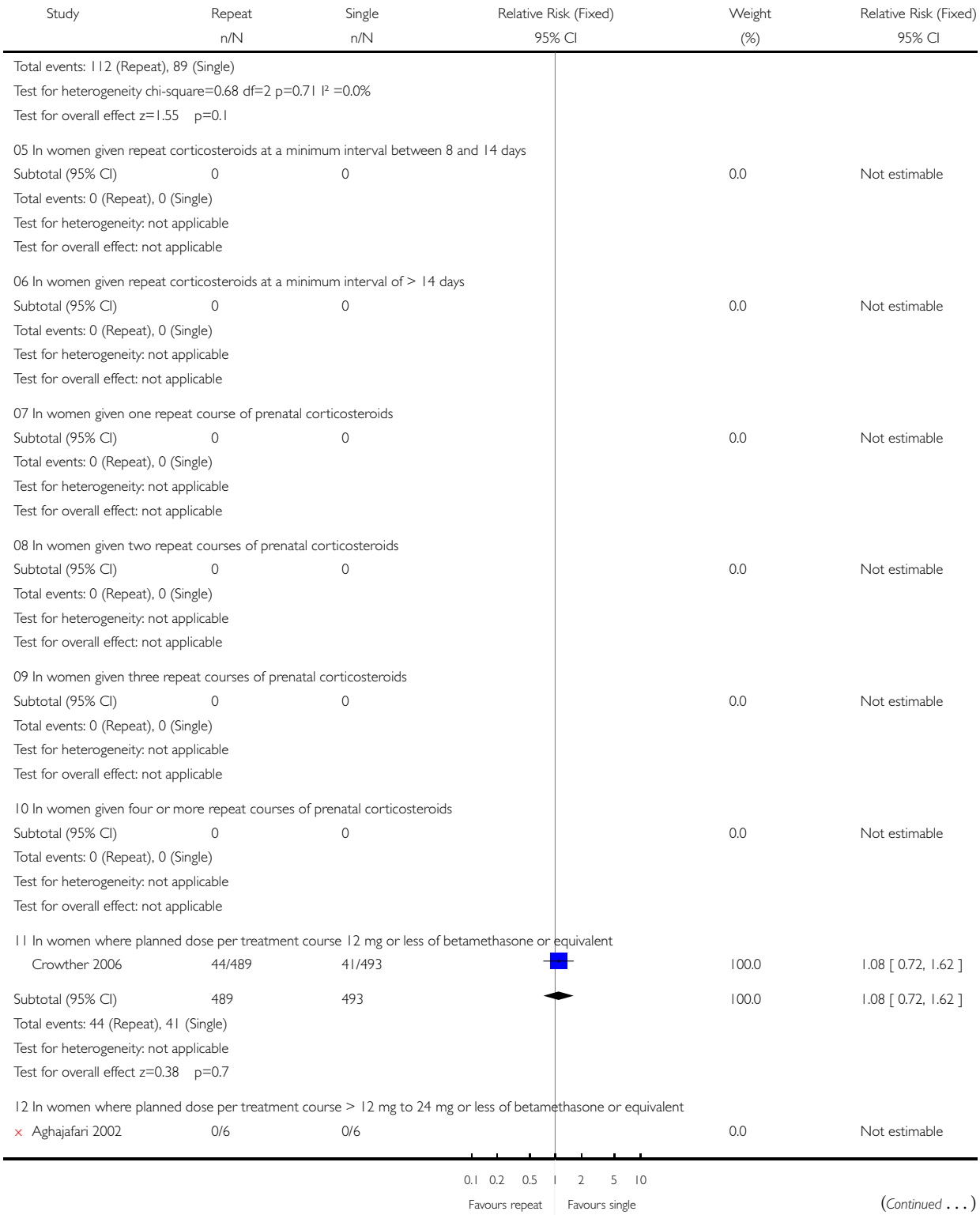

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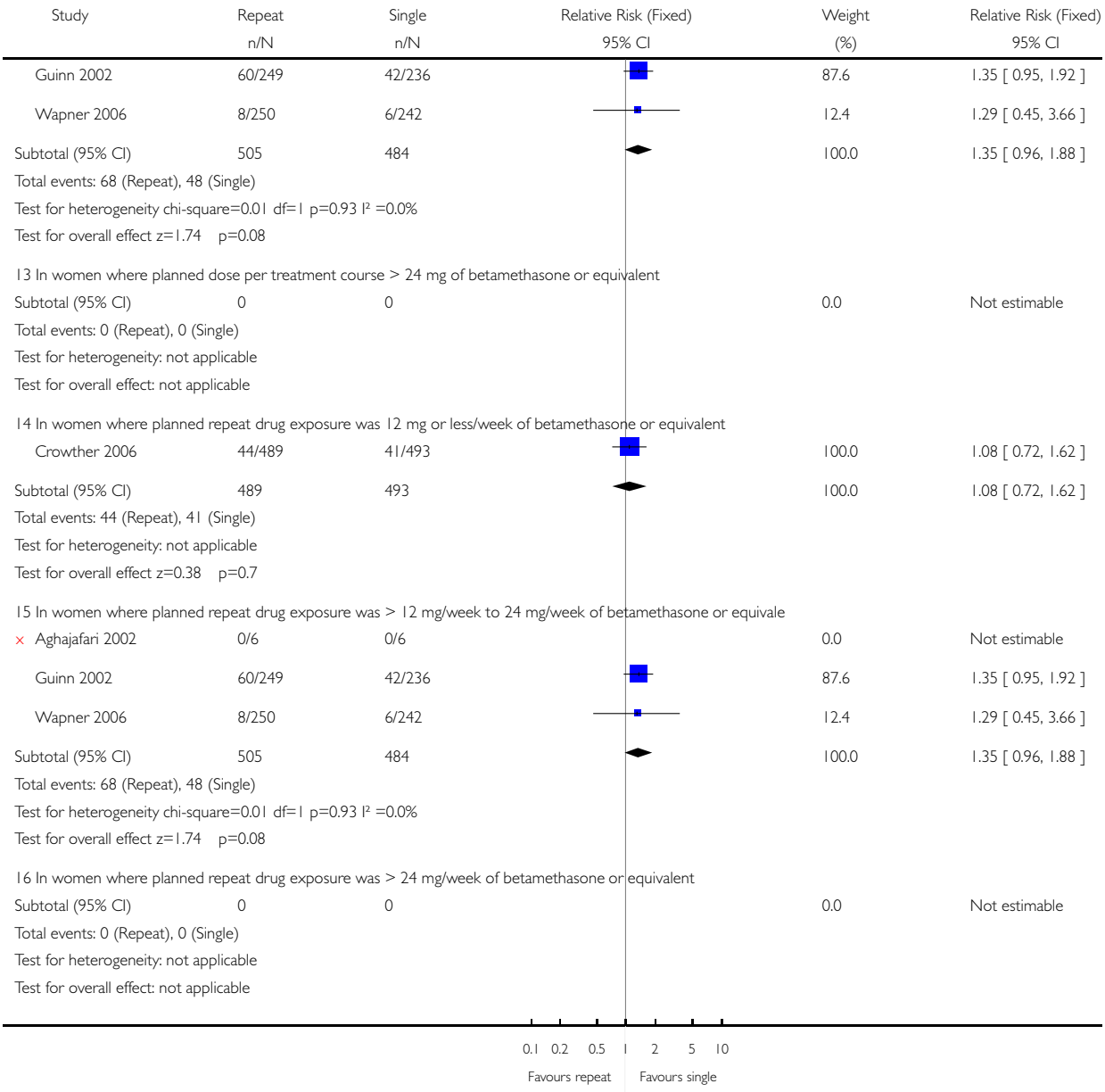


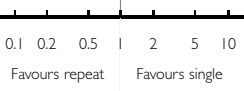
Analysis 01.18. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 18 Puerperal sepsis

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 18 Puerperal sepsis

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Guinn 2002	13/249	14/236		58.6	0.88 [0.42, 1.83]
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)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.93 p=0.4					
02 In women where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.69 p=0.5					
03 In women given repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Guinn 2002	13/249	14/236		58.6	0.88 [0.42, 1.83]
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)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.93 p=0.4					
04 In women given repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Guinn 2002	13/249	14/236		58.6	0.88 [0.42, 1.83]
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)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.93 p=0.4					
05 In women given repeat corticosteroids at a minimum interval between 8 and 14 days					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In women given repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In women given one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In women given two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In women given three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
12 In women where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalen					
× Aghajafari 2002	0/6	0/6		0.0	Not estimable
Guinn 2002	13/249	14/236		58.6	0.88 [0.42, 1.83]
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)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					

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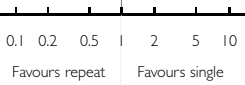
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=0.93 p=0.4					
13 In women where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
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		0.0	Not estimable
Guinn 2002	13/249	14/236		58.6	0.88 [0.42, 1.83]
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)					
Test for heterogeneity chi-square=0.43 df=1 p=0.51 I^2 =0.0%					
Test for overall effect z=0.93 p=0.4					
16 In women where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



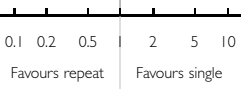
Analysis 01.19. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 19 Use of mechanical ventilation

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 19 Use of mechanical ventilation

Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 In all babies					
Crowther 2006	167/567	204/577		61.0	0.83 [0.70, 0.99]
Wapner 2006	36/250	60/242		39.0	0.58 [0.40, 0.84]
Subtotal (95% CI)	817	819		100.0	0.72 [0.51, 1.02]
Total events: 203 (Repeat), 264 (Single)					
Test for heterogeneity chi-square=3.00 df=1 p=0.08 I^2 =66.7%					
Test for overall effect z=1.83 p=0.07					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	167/567	204/577		61.0	0.83 [0.70, 0.99]
Wapner 2006	36/250	60/242		39.0	0.58 [0.40, 0.84]
Subtotal (95% CI)	817	819		100.0	0.72 [0.51, 1.02]
Total events: 203 (Repeat), 264 (Single)					
Test for heterogeneity chi-square=3.00 df=1 p=0.08 I^2 =66.7%					
Test for overall effect z=1.83 p=0.07					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	167/567	204/577		61.0	0.83 [0.70, 0.99]
Wapner 2006	36/250	60/242		39.0	0.58 [0.40, 0.84]
Subtotal (95% CI)	817	819		100.0	0.72 [0.51, 1.02]
Total events: 203 (Repeat), 264 (Single)					
Test for heterogeneity chi-square=3.00 df=1 p=0.08 I^2 =66.7%					
Test for overall effect z=1.83 p=0.07					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					



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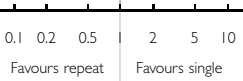
Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	167/567	204/577		100.0	0.83 [0.70, 0.99]
Subtotal (95% CI)	567	577		100.0	0.83 [0.70, 0.99]
Total events: 167 (Repeat), 204 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.12 p=0.03					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Wapner 2006	36/250	60/242		100.0	0.58 [0.40, 0.84]
Subtotal (95% CI)	250	242		100.0	0.58 [0.40, 0.84]
Total events: 36 (Repeat), 60 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.85 p=0.004					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	167/567	204/577		100.0	0.83 [0.70, 0.99]
Subtotal (95% CI)	567	577		100.0	0.83 [0.70, 0.99]
Total events: 167 (Repeat), 204 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.12 p=0.03					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Wapner 2006	36/250	60/242		100.0	0.58 [0.40, 0.84]
Subtotal (95% CI)	250	242		100.0	0.58 [0.40, 0.84]
Total events: 36 (Repeat), 60 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.85 p=0.004					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

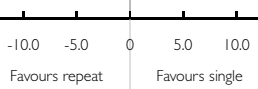
Analysis 01.20. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 20 Duration of respiratory support in days

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 20 Duration of respiratory support in days

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
McEvoy 2002	18	0.80 (2.40)	19	0.50 (1.00)		100.0	0.30 [-0.90, 1.50]
Subtotal (95% CI)	18		19			100.0	0.30 [-0.90, 1.50]
Test for heterogeneity: not applicable							
Test for overall effect z=0.49 p=0.6							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
McEvoy 2002	18	0.80 (2.40)	19	0.50 (1.00)		100.0	0.30 [-0.90, 1.50]
Subtotal (95% CI)	18		19			100.0	0.30 [-0.90, 1.50]
Test for heterogeneity: not applicable							
Test for overall effect z=0.49 p=0.6							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
McEvoy 2002	18	0.80 (2.40)	19	0.50 (1.00)		100.0	0.30 [-0.90, 1.50]
Subtotal (95% CI)	18		19			100.0	0.30 [-0.90, 1.50]
Test for heterogeneity: not applicable							
Test for overall effect z=0.49 p=0.6							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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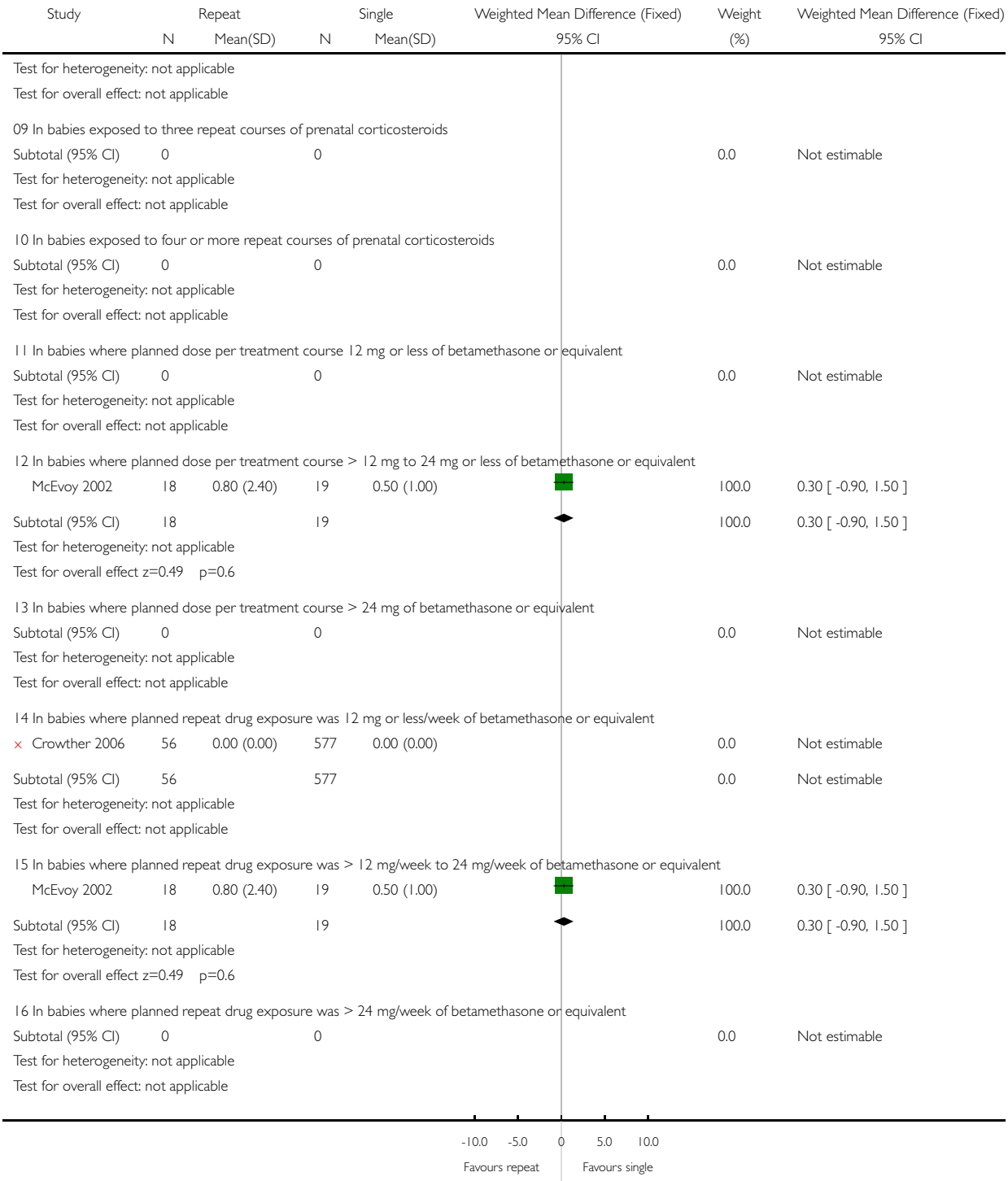

Analysis 01.21. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 21 Use of oxygen supplementation

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 21 Use of oxygen supplementation

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	317/567	361/577		100.0	0.89 [0.81, 0.98]
Subtotal (95% CI)	567	577		100.0	0.89 [0.81, 0.98]
Total events: 317 (Repeat), 361 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.28 p=0.02					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	317/567	361/577		100.0	0.89 [0.81, 0.98]
Subtotal (95% CI)	567	577		100.0	0.89 [0.81, 0.98]
Total events: 317 (Repeat), 361 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.28 p=0.02					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	317/567	361/577		100.0	0.89 [0.81, 0.98]
Subtotal (95% CI)	567	577		100.0	0.89 [0.81, 0.98]
Total events: 317 (Repeat), 361 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.28 p=0.02					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	317/567	361/577		100.0	0.89 [0.81, 0.98]
Subtotal (95% CI)	567	577		100.0	0.89 [0.81, 0.98]
Total events: 317 (Repeat), 361 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.28 p=0.02					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	317/567	361/577		100.0	0.89 [0.81, 0.98]
Subtotal (95% CI)	567	577		100.0	0.89 [0.81, 0.98]
Total events: 317 (Repeat), 361 (Single)					
Test for heterogeneity: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.28 p=0.02					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

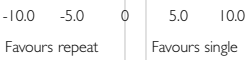
Analysis 01.22. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 22 Duration of oxygen supplementation in days

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 22 Duration of oxygen supplementation in days

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
McEvoy 2002	18	4.00 (12.00)	19	0.70 (1.90)		100.0	3.30 [-2.31, 8.91]
Subtotal (95% CI)	18		19			100.0	3.30 [-2.31, 8.91]
Test for heterogeneity: not applicable							
Test for overall effect z=1.15 p=0.2							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Subtotal (95% CI)	0		0			0.0	Not estimable



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							

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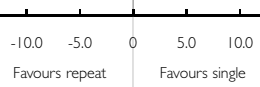
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for overall effect: not applicable							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



Analysis 01.23. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 23 Use of surfactant

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 23 Use of surfactant

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	138/567	186/577		62.3	0.76 [0.63, 0.91]
Guinn 2002	40/255	59/245		20.3	0.65 [0.45, 0.93]
McEvoy 2002	3/18	5/19		1.6	0.63 [0.18, 2.27]
Wapner 2006	29/250	46/242		15.8	0.61 [0.40, 0.94]
Subtotal (95% CI)	1090	1083		100.0	0.71 [0.61, 0.83]
Total events: 210 (Repeat), 296 (Single)					
Test for heterogeneity chi-square=1.14 df=3 p=0.77 I^2 =0.0%					
Test for overall effect z=4.37 p=0.00001					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	138/567	186/577		62.3	0.76 [0.63, 0.91]

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Guinn 2002	40/255	59/245		20.3	0.65 [0.45, 0.93]
McEvoy 2002	3/18	5/19		1.6	0.63 [0.18, 2.27]
Wapner 2006	29/250	46/242		15.8	0.61 [0.40, 0.94]
Subtotal (95% CI)	1090	1083		100.0	0.71 [0.61, 0.83]
Total events: 210 (Repeat), 296 (Single)					
Test for heterogeneity chi-square=1.14 df=3 p=0.77 I^2 =0.0%					
Test for overall effect z=4.37 p=0.00001					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	138/567	186/577		62.3	0.76 [0.63, 0.91]
Guinn 2002	40/255	59/245		20.3	0.65 [0.45, 0.93]
McEvoy 2002	3/18	5/19		1.6	0.63 [0.18, 2.27]
Wapner 2006	29/250	46/242		15.8	0.61 [0.40, 0.94]
Subtotal (95% CI)	1090	1083		100.0	0.71 [0.61, 0.83]
Total events: 210 (Repeat), 296 (Single)					
Test for heterogeneity chi-square=1.14 df=3 p=0.77 I^2 =0.0%					
Test for overall effect z=4.37 p=0.00001					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					

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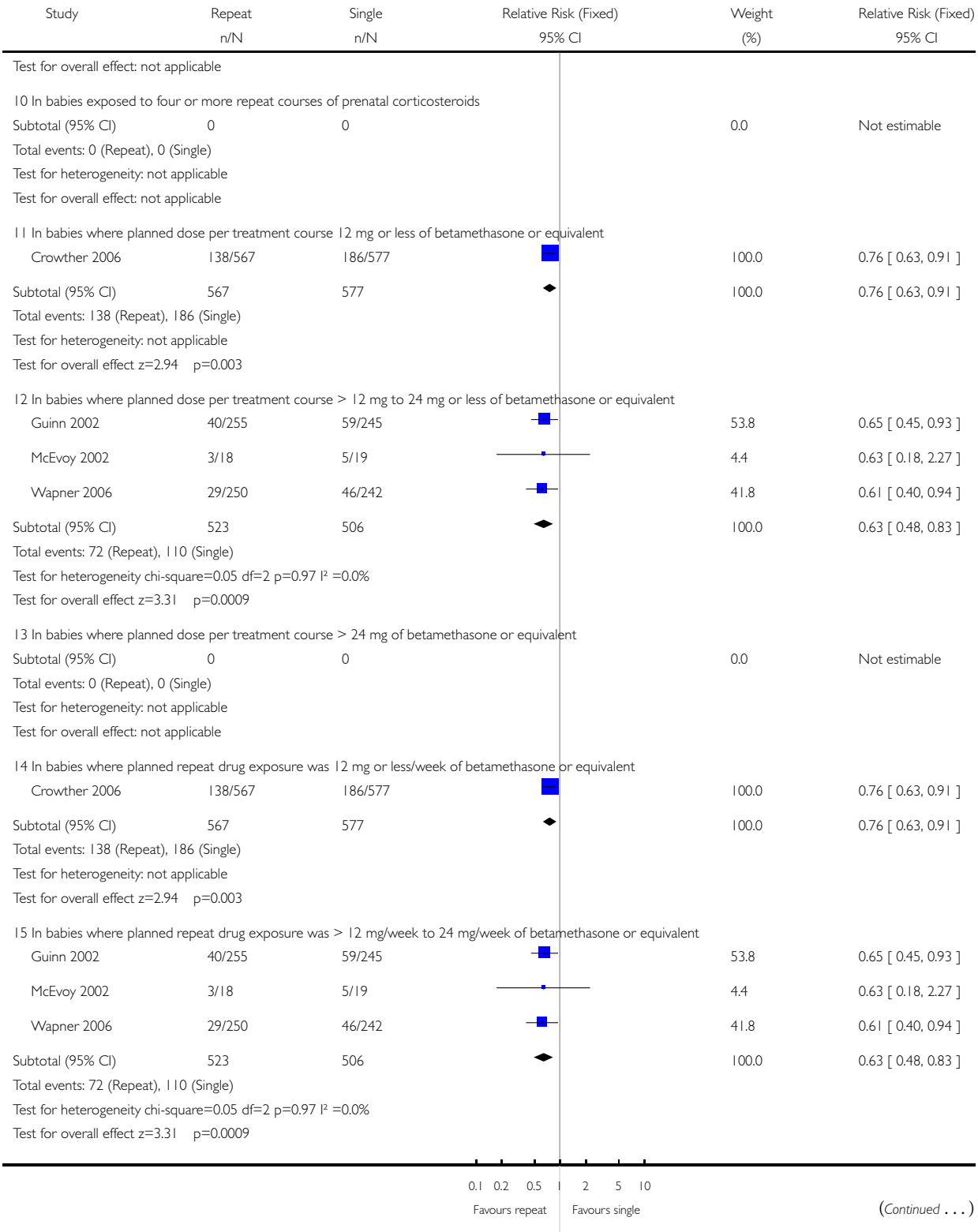

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.24. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 24 Patent ductus arteriosus requiring treatment

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 24 Patent ductus arteriosus requiring treatment

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	2/9	1/7		1.4	1.56 [0.17, 13.87]
Crowther 2006	40/567	67/577		81.2	0.61 [0.42, 0.88]
Wapner 2006	7/250	14/242		17.4	0.48 [0.20, 1.18]
Subtotal (95% CI)	826	826		100.0	0.60 [0.43, 0.84]
Total events: 49 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.96 df=2 p=0.62 I^2 =0.0%					
Test for overall effect z=2.96 p=0.003					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	2/9	1/7		1.4	1.56 [0.17, 13.87]
Crowther 2006	40/567	67/577		81.2	0.61 [0.42, 0.88]
Wapner 2006	7/250	14/242		17.4	0.48 [0.20, 1.18]
Subtotal (95% CI)	826	826		100.0	0.60 [0.43, 0.84]
Total events: 49 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.96 df=2 p=0.62 I^2 =0.0%					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.96 p=0.003					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	2/9	1/7		1.4	1.56 [0.17, 13.87]
Crowther 2006	40/567	67/577		81.2	0.61 [0.42, 0.88]
Wapner 2006	7/250	14/242		17.4	0.48 [0.20, 1.18]
Subtotal (95% CI)	826	826		100.0	0.60 [0.43, 0.84]
Total events: 49 (Repeat), 82 (Single)					
Test for heterogeneity chi-square=0.96 df=2 p=0.62 I^2 =0.0%					
Test for overall effect z=2.96 p=0.003					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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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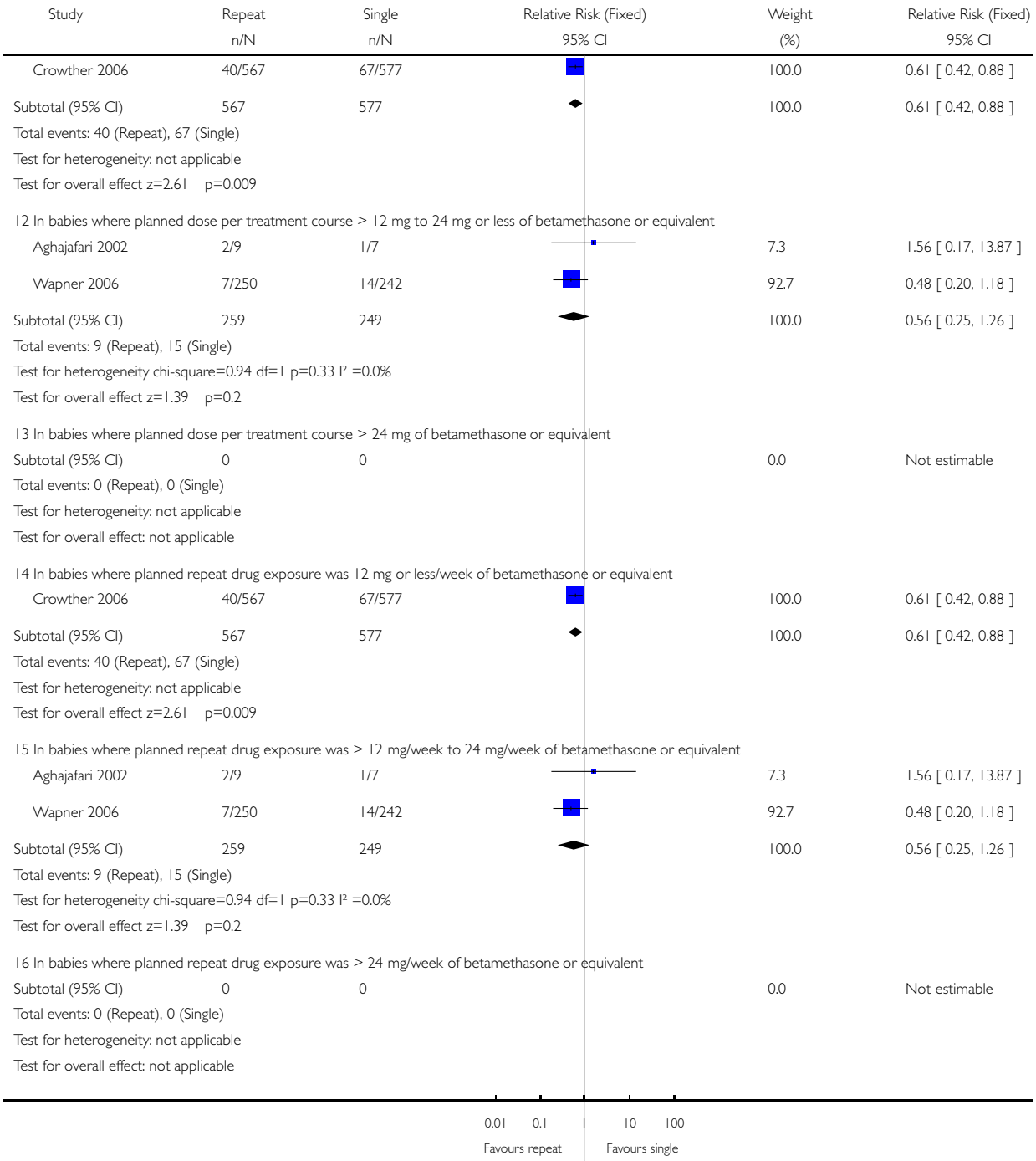

Analysis 01.25. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 25 Use of inotropic support

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 25 Use of inotropic support

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	64/567	87/577		100.0	0.75 [0.55, 1.01]
Subtotal (95% CI)	567	577		100.0	0.75 [0.55, 1.01]
Total events: 64 (Repeat), 87 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.88 p=0.06					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	64/567	87/577		100.0	0.75 [0.55, 1.01]
Subtotal (95% CI)	567	577		100.0	0.75 [0.55, 1.01]
Total events: 64 (Repeat), 87 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.88 p=0.06					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	64/567	87/577		100.0	0.75 [0.55, 1.01]
Subtotal (95% CI)	567	577		100.0	0.75 [0.55, 1.01]
Total events: 64 (Repeat), 87 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.88 p=0.06					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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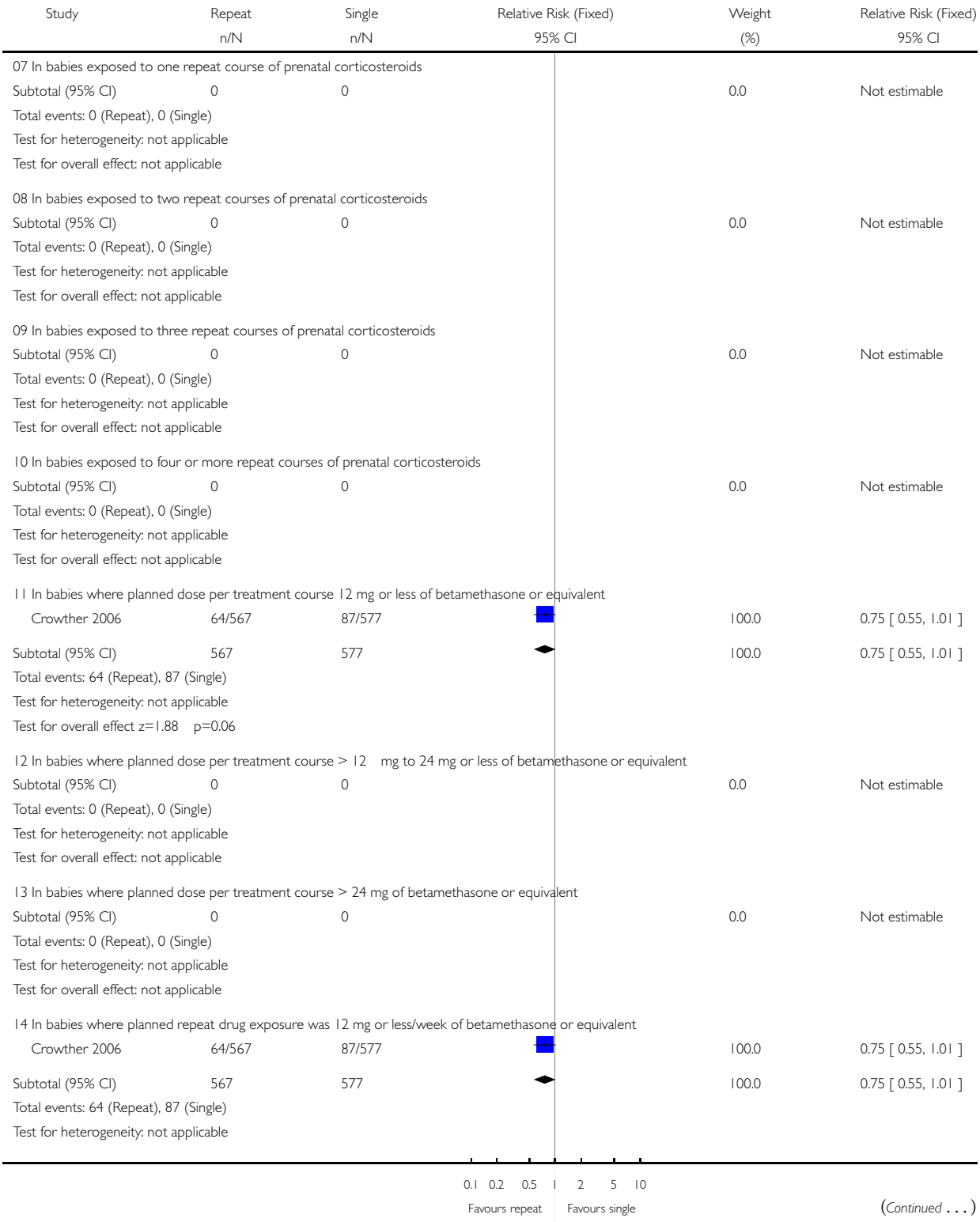

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.88 p=0.06					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.26. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 26 Use of nitric oxide for respiratory support

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 26 Use of nitric oxide for respiratory support

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	12/567	21/577		100.0	0.58 [0.29, 1.17]
Subtotal (95% CI)	567	577		100.0	0.58 [0.29, 1.17]
Total events: 12 (Repeat), 21 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	12/567	21/577		100.0	0.58 [0.29, 1.17]
Subtotal (95% CI)	567	577		100.0	0.58 [0.29, 1.17]
Total events: 12 (Repeat), 21 (Single)					

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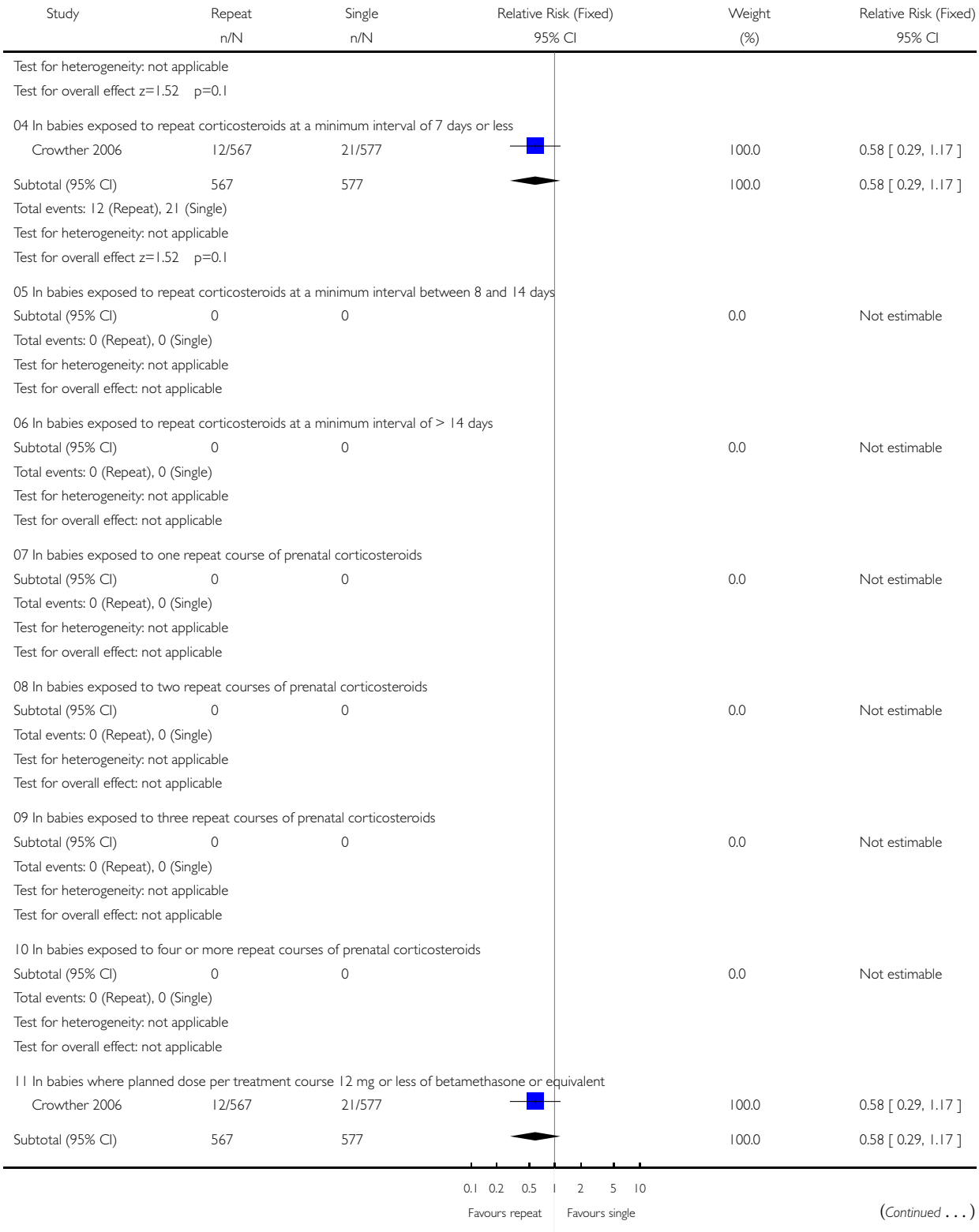

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 12 (Repeat), 21 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	12/567	21/577		100.0	0.58 [0.29, 1.17]
Subtotal (95% CI)	567	577		100.0	0.58 [0.29, 1.17]
Total events: 12 (Repeat), 21 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.52 p=0.1					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

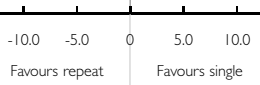
Analysis 01.27. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 27 Mean gestational age at birth (weeks)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 27 Mean gestational age at birth (weeks)

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 In all babies							
Aghajafari 2002	6	31.00 (4.00)	6	35.00 (5.00)		0.4	-4.00 [-9.12, 1.12]
Crowther 2006	567	32.50 (3.90)	577	32.40 (3.90)		52.1	0.10 [-0.35, 0.55]
Guinn 2002	256	33.10 (4.00)	246	33.50 (4.00)		21.7	-0.40 [-1.10, 0.30]
McEvoy 2002	18	32.20 (3.30)	19	32.80 (2.70)		2.8	-0.60 [-2.55, 1.35]
Wapner 2006	250	34.80 (3.80)	242	34.80 (3.90)		23.0	0.00 [-0.68, 0.68]
Subtotal (95% CI)	1097		1090			100.0	-0.07 [-0.39, 0.26]
Test for heterogeneity chi-square=3.98 df=4 p=0.41 I² =0.0%							
Test for overall effect z=0.41 p=0.7							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Aghajafari 2002	6	31.00 (4.00)	6	35.00 (5.00)		0.4	-4.00 [-9.12, 1.12]
Crowther 2006	567	32.50 (3.90)	577	32.40 (3.90)		52.1	0.10 [-0.35, 0.55]
Guinn 2002	256	33.10 (4.00)	246	33.50 (4.00)		21.7	-0.40 [-1.10, 0.30]
McEvoy 2002	18	32.20 (3.30)	19	32.80 (2.70)		2.8	-0.60 [-2.55, 1.35]
Wapner 2006	250	34.80 (3.80)	242	34.80 (3.90)		23.0	0.00 [-0.68, 0.68]
Subtotal (95% CI)	1097		1090			100.0	-0.07 [-0.39, 0.26]
Test for heterogeneity chi-square=3.98 df=4 p=0.41 I² =0.0%							
Test for overall effect z=0.41 p=0.7							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Aghajafari 2002	6	31.00 (4.00)	6	35.00 (5.00)		0.4	-4.00 [-9.12, 1.12]
Crowther 2006	567	32.50 (3.90)	577	32.40 (3.90)		52.1	0.10 [-0.35, 0.55]
Guinn 2002	256	33.10 (4.00)	246	33.50 (4.00)		21.7	-0.40 [-1.10, 0.30]
McEvoy 2002	18	32.20 (3.30)	19	32.80 (2.70)		2.8	-0.60 [-2.55, 1.35]
Wapner 2006	250	34.80 (3.80)	242	34.80 (3.90)		23.0	0.00 [-0.68, 0.68]
Subtotal (95% CI)	1097		1090			100.0	-0.07 [-0.39, 0.26]



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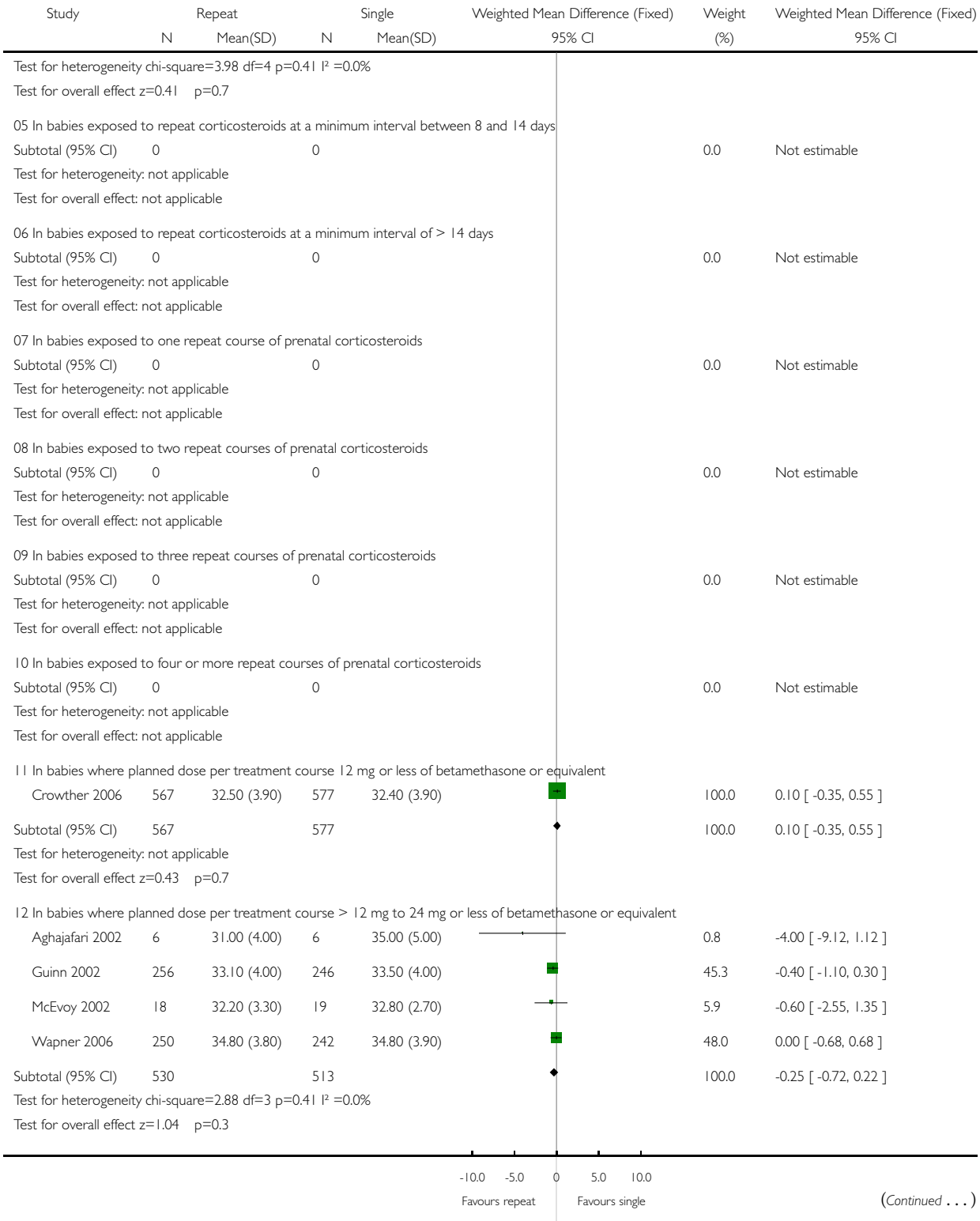

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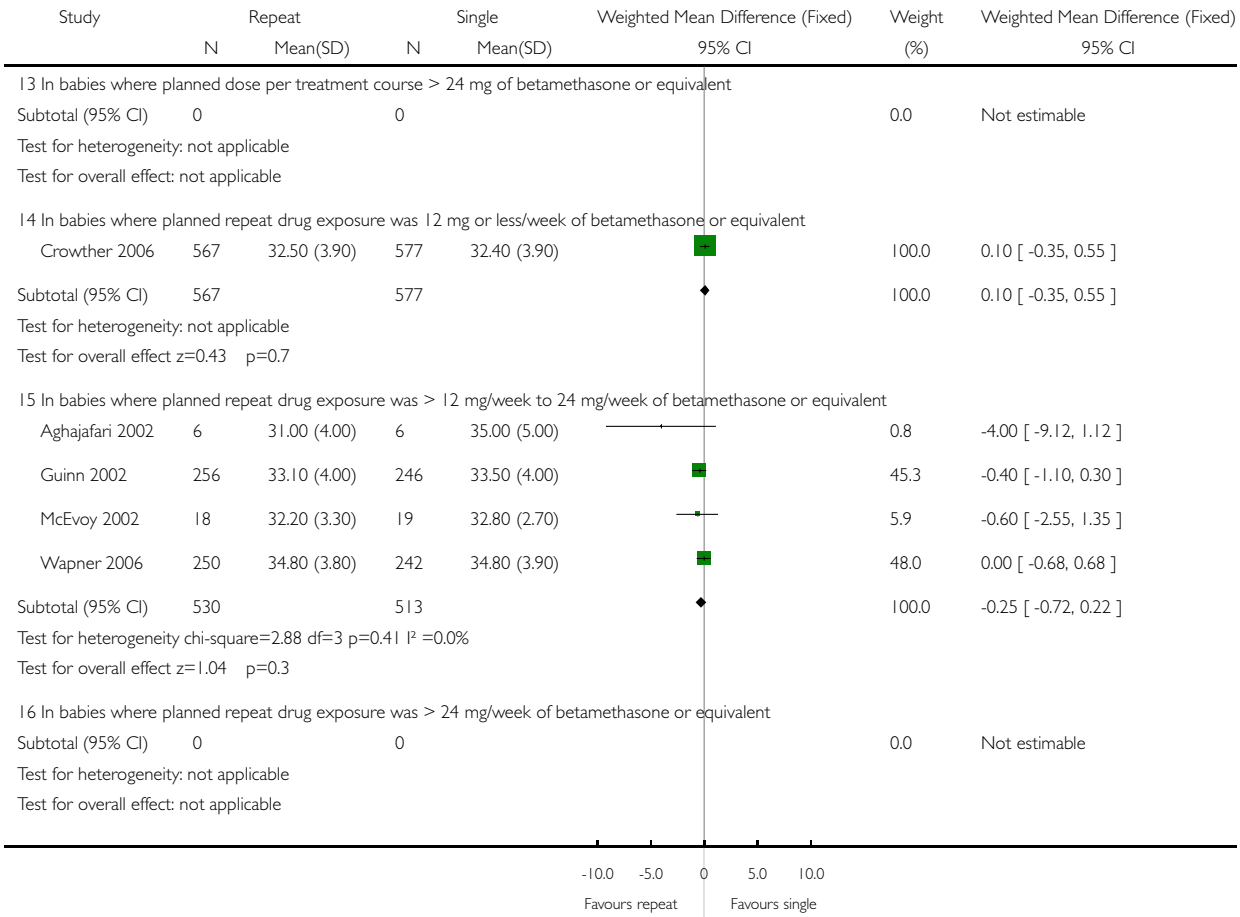


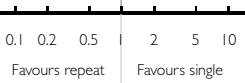
Analysis 01.28. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 28 Preterm birth before 37 weeks

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 28 Preterm birth before 37 weeks

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	6/6	3/6		0.5	2.00 [0.90, 4.45]
Crowther 2006	458/567	483/577		74.0	0.96 [0.91, 1.02]
McEvoy 2002	5/18	6/19		0.9	0.88 [0.32, 2.38]
Wapner 2006	157/250	157/242		24.7	0.97 [0.85, 1.11]
Subtotal (95% CI)	841	844		100.0	0.97 [0.92, 1.02]
Total events: 626 (Repeat), 649 (Single)					
Test for heterogeneity chi-square=3.21 df=3 p=0.36 I^2 =6.6%					
Test for overall effect z=1.15 p=0.3					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	6/6	3/6		0.5	2.00 [0.90, 4.45]
Crowther 2006	458/567	483/577		74.0	0.96 [0.91, 1.02]
McEvoy 2002	5/18	6/19		0.9	0.88 [0.32, 2.38]
Wapner 2006	157/250	157/242		24.7	0.97 [0.85, 1.11]
Subtotal (95% CI)	841	844		100.0	0.97 [0.92, 1.02]
Total events: 626 (Repeat), 649 (Single)					
Test for heterogeneity chi-square=3.21 df=3 p=0.36 I^2 =6.6%					
Test for overall effect z=1.15 p=0.3					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	6/6	3/6		0.5	2.00 [0.90, 4.45]
Crowther 2006	458/567	483/577		74.0	0.96 [0.91, 1.02]
McEvoy 2002	5/18	6/19		0.9	0.88 [0.32, 2.38]
Wapner 2006	157/250	157/242		24.7	0.97 [0.85, 1.11]
Subtotal (95% CI)	841	844		100.0	0.97 [0.92, 1.02]
Total events: 626 (Repeat), 649 (Single)					
Test for heterogeneity chi-square=3.21 df=3 p=0.36 I^2 =6.6%					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=1.15 p=0.3					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	458/567	483/577		100.0	0.96 [0.91, 1.02]
Subtotal (95% CI)	567	577		100.0	0.96 [0.91, 1.02]
Total events: 458 (Repeat), 483 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.30 p=0.2					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	6/6	3/6		1.8	2.00 [0.90, 4.45]
McEvoy 2002	5/18	6/19		3.5	0.88 [0.32, 2.38]

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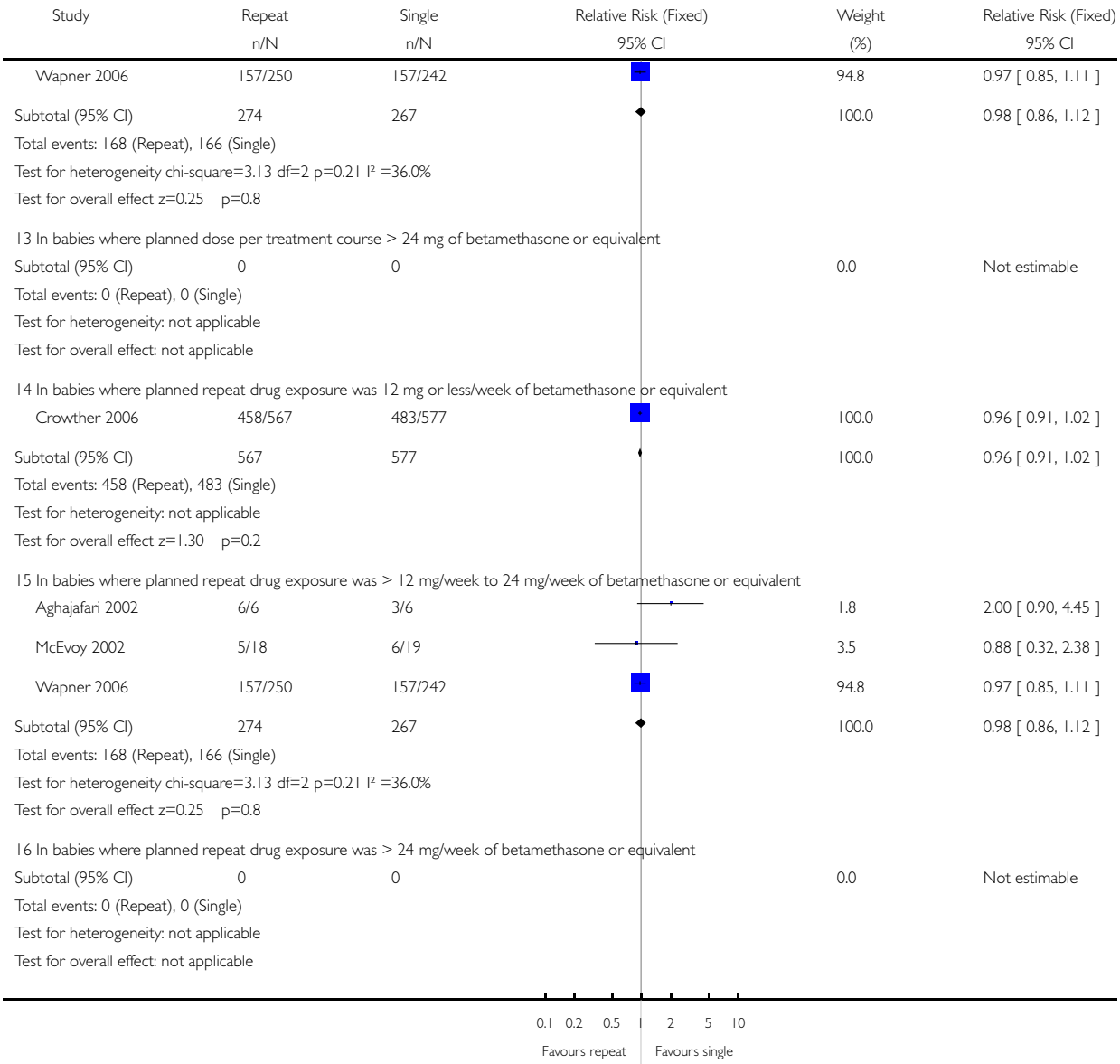

Analysis 01.29. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 29 Very preterm birth before 34 weeks

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 29 Very preterm birth before 34 weeks

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	4/6	3/6		0.6	1.33 [0.50, 3.55]
Crowther 2006	362/567	373/577		70.8	0.99 [0.91, 1.08]
Guinn 2002	167/251	145/237		28.6	1.09 [0.95, 1.24]
Subtotal (95% CI)	824	820		100.0	1.02 [0.95, 1.09]
Total events: 533 (Repeat), 521 (Single)					
Test for heterogeneity chi-square=1.69 df=2 p=0.43 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	4/6	3/6		0.6	1.33 [0.50, 3.55]
Crowther 2006	362/567	373/577		70.8	0.99 [0.91, 1.08]
Guinn 2002	167/251	145/237		28.6	1.09 [0.95, 1.24]
Subtotal (95% CI)	824	820		100.0	1.02 [0.95, 1.09]
Total events: 533 (Repeat), 521 (Single)					
Test for heterogeneity chi-square=1.69 df=2 p=0.43 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	4/6	3/6		0.6	1.33 [0.50, 3.55]
Crowther 2006	362/567	373/577		70.8	0.99 [0.91, 1.08]
Guinn 2002	167/251	145/237		28.6	1.09 [0.95, 1.24]
Subtotal (95% CI)	824	820		100.0	1.02 [0.95, 1.09]
Total events: 533 (Repeat), 521 (Single)					
Test for heterogeneity chi-square=1.69 df=2 p=0.43 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable

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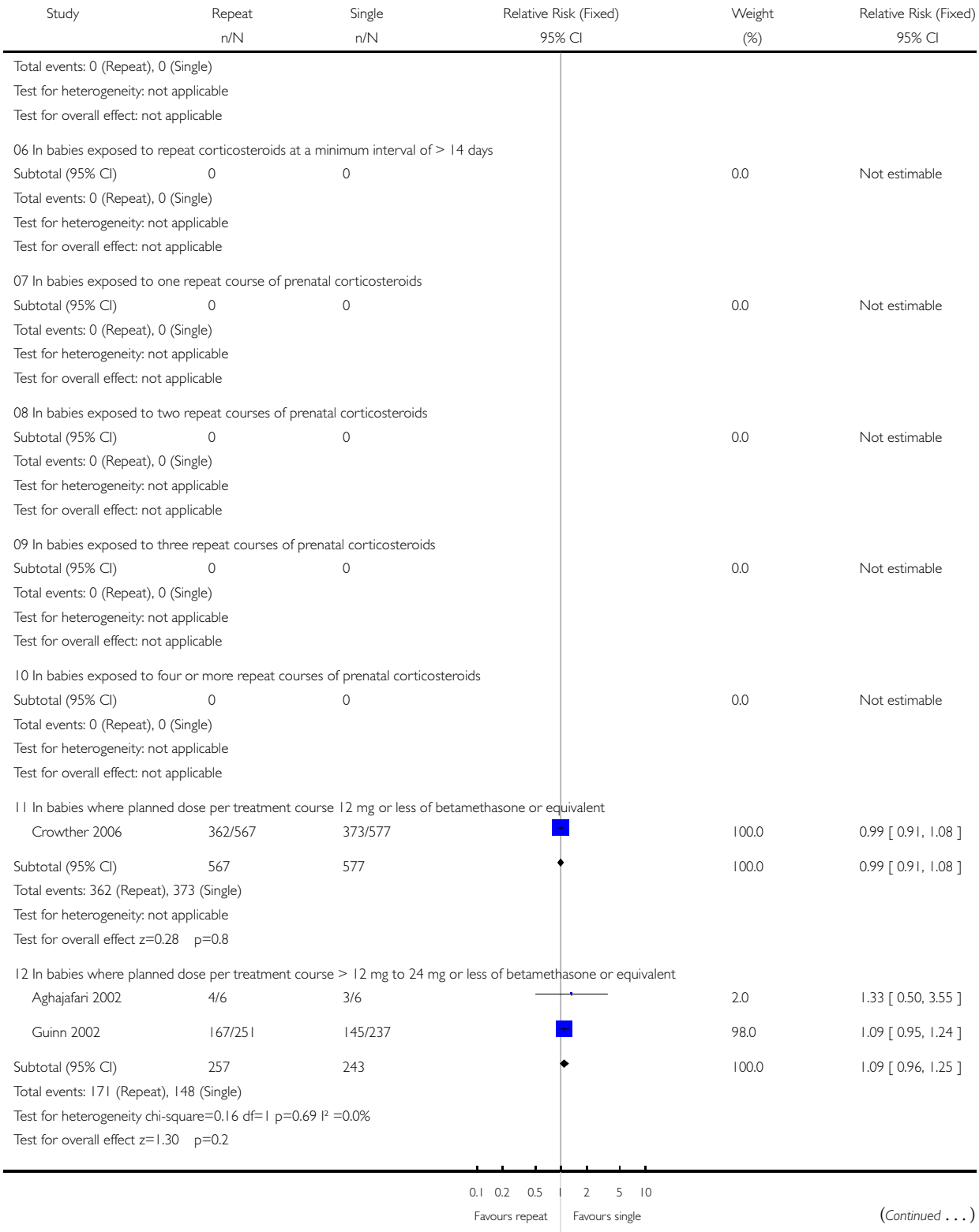

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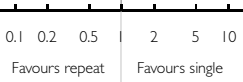
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: 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	362/567	373/577		100.0	0.99 [0.91, 1.08]
Subtotal (95% CI)	567	577		100.0	0.99 [0.91, 1.08]
Total events: 362 (Repeat), 373 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.28 p=0.8					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Aghajafari 2002	4/6	3/6		2.0	1.33 [0.50, 3.55]
Guinn 2002	167/251	145/237		98.0	1.09 [0.95, 1.24]
Subtotal (95% CI)	257	243		100.0	1.09 [0.96, 1.25]
Total events: 171 (Repeat), 148 (Single)					
Test for heterogeneity chi-square=0.16 df=1 p=0.69 I^2 =0.0%					
Test for overall effect z=1.30 p=0.2					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



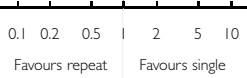
Analysis 01.30. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 30 Extremely preterm birth before 28 weeks

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 30 Extremely preterm birth before 28 weeks

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	74/567	71/577		71.0	1.06 [0.78, 1.44]
Guinn 2002	32/251	28/237		29.0	1.08 [0.67, 1.74]
Subtotal (95% CI)	818	814		100.0	1.07 [0.83, 1.38]
Total events: 106 (Repeat), 99 (Single)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	74/567	71/577		71.0	1.06 [0.78, 1.44]
Guinn 2002	32/251	28/237		29.0	1.08 [0.67, 1.74]
Subtotal (95% CI)	818	814		100.0	1.07 [0.83, 1.38]
Total events: 106 (Repeat), 99 (Single)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	74/567	71/577		71.0	1.06 [0.78, 1.44]
Guinn 2002	32/251	28/237		29.0	1.08 [0.67, 1.74]
Subtotal (95% CI)	818	814		100.0	1.07 [0.83, 1.38]
Total events: 106 (Repeat), 99 (Single)					
Test for heterogeneity chi-square=0.00 df=1 p=0.95 I^2 =0.0%					
Test for overall effect z=0.49 p=0.6					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					



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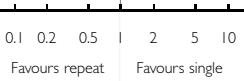
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	74/567	71/577		100.0	1.06 [0.78, 1.44]
Subtotal (95% CI)	567	577		100.0	1.06 [0.78, 1.44]
Total events: 74 (Repeat), 71 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.38 p=0.7					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Guinn 2002	32/251	28/237		100.0	1.08 [0.67, 1.74]
Subtotal (95% CI)	251	237		100.0	1.08 [0.67, 1.74]
Total events: 32 (Repeat), 28 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.31 p=0.8					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	74/567	71/577		100.0	1.06 [0.78, 1.44]
Subtotal (95% CI)	567	577		100.0	1.06 [0.78, 1.44]
Total events: 74 (Repeat), 71 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.38 p=0.7					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Guinn 2002	32/251	28/237		100.0	1.08 [0.67, 1.74]
Subtotal (95% CI)	251	237		100.0	1.08 [0.67, 1.74]
Total events: 32 (Repeat), 28 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.31 p=0.8					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.31. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 31 Mean head circumference at birth (cm)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 31 Mean head circumference at birth (cm)

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 In all babies							
Crowther 2006	567	29.60 (3.70)	577	29.70 (3.60)		46.6	-0.10 [-0.52, 0.32]
Guinn 2002	255	29.10 (4.00)	245	29.40 (3.40)		19.7	-0.30 [-0.95, 0.35]
McEvoy 2002	18	29.40 (3.00)	19	29.60 (2.70)		2.5	-0.20 [-2.04, 1.64]
Wapner 2006	296	30.60 (3.10)	294	30.80 (3.30)		31.2	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	1136		1135			100.0	-0.17 [-0.46, 0.12]
Test for heterogeneity chi-square=0.27 df=3 p=0.97 I² =0.0%							
Test for overall effect z=1.18 p=0.2							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	29.60 (3.70)	577	29.70 (3.60)		46.6	-0.10 [-0.52, 0.32]
Guinn 2002	255	29.10 (4.00)	245	29.40 (3.40)		19.7	-0.30 [-0.95, 0.35]
McEvoy 2002	18	29.40 (3.00)	19	29.60 (2.70)		2.5	-0.20 [-2.04, 1.64]
Wapner 2006	296	30.60 (3.10)	294	30.80 (3.30)		31.2	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	1136		1135			100.0	-0.17 [-0.46, 0.12]
Test for heterogeneity chi-square=0.27 df=3 p=0.97 I² =0.0%							
Test for overall effect z=1.18 p=0.2							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	29.60 (3.70)	577	29.70 (3.60)		46.6	-0.10 [-0.52, 0.32]
Guinn 2002	255	29.10 (4.00)	245	29.40 (3.40)		19.7	-0.30 [-0.95, 0.35]
McEvoy 2002	18	29.40 (3.00)	19	29.60 (2.70)		2.5	-0.20 [-2.04, 1.64]
Wapner 2006	296	30.60 (3.10)	294	30.80 (3.30)		31.2	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	1136		1135			100.0	-0.17 [-0.46, 0.12]
Test for heterogeneity chi-square=0.27 df=3 p=0.97 I² =0.0%							
Test for overall effect z=1.18 p=0.2							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable

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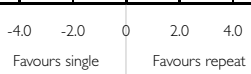
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	567	29.60 (3.70)	577	29.70 (3.60)		100.0	-0.10 [-0.52, 0.32]
Subtotal (95% CI)	567		577			100.0	-0.10 [-0.52, 0.32]
Test for heterogeneity: not applicable							
Test for overall effect z=0.46 p=0.6							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Guinn 2002	255	29.10 (4.00)	245	29.40 (3.40)		37.0	-0.30 [-0.95, 0.35]
McEvoy 2002	18	29.40 (3.00)	19	29.60 (2.70)		4.6	-0.20 [-2.04, 1.64]
Wapner 2006	296	30.60 (3.10)	294	30.80 (3.30)		58.4	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	569		558			100.0	-0.24 [-0.63, 0.16]
Test for heterogeneity chi-square=0.06 df=2 p=0.97 I^2 =0.0%							
Test for overall effect z=1.18 p=0.2							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	567	29.60 (3.70)	577	29.70 (3.60)		100.0	-0.10 [-0.52, 0.32]



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Subtotal (95% CI)	567		577			100.0	-0.10 [-0.52, 0.32]
Test for heterogeneity: not applicable							
Test for overall effect z=0.46 p=0.6							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Guinn 2002	255	29.10 (4.00)	245	29.40 (3.40)		37.0	-0.30 [-0.95, 0.35]
McEvoy 2002	18	29.40 (3.00)	19	29.60 (2.70)		4.6	-0.20 [-2.04, 1.64]
Wapner 2006	296	30.60 (3.10)	294	30.80 (3.30)		58.4	-0.20 [-0.72, 0.32]
Subtotal (95% CI)	569		558			100.0	-0.24 [-0.63, 0.16]
Test for heterogeneity chi-square=0.06 df=2 p=0.97 I^2 =0.0%							
Test for overall effect z=1.18 p=0.2							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 01.32. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 32 Head circumference Z scores at birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 32 Head circumference Z scores at birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	567	-0.30 (1.22)	577	-0.14 (1.28)		100.0	-0.16 [-0.30, -0.02]
Subtotal (95% CI)	567		577			100.0	-0.16 [-0.30, -0.02]
Test for heterogeneity: not applicable							
Test for overall effect z=2.16 p=0.03							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	-0.30 (1.22)	577	-0.14 (1.28)		100.0	-0.16 [-0.30, -0.02]

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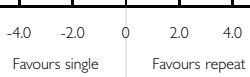
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Subtotal (95% CI)	567		577			100.0	-0.16 [-0.30, -0.02]
Test for heterogeneity: not applicable							
Test for overall effect z=2.16 p=0.03							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	-0.30 (1.22)	577	-0.14 (1.28)		100.0	-0.16 [-0.30, -0.02]
Subtotal (95% CI)	567		577			100.0	-0.16 [-0.30, -0.02]
Test for heterogeneity: not applicable							
Test for overall effect z=2.16 p=0.03							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	567	-0.30 (1.22)	577	-0.14 (1.28)		100.0	-0.16 [-0.30, -0.02]
Subtotal (95% CI)	567		577			100.0	-0.16 [-0.30, -0.02]
Test for heterogeneity: not applicable							
Test for overall effect z=2.16 p=0.03							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	567	-0.30 (1.22)	577	-0.14 (1.28)		100.0	-0.16 [-0.30, -0.02]
Subtotal (95% CI)	567		577			100.0	-0.16 [-0.30, -0.02]
Test for heterogeneity: not applicable							
Test for overall effect z=2.16 p=0.03							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

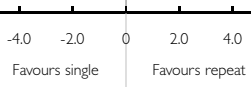
Analysis 01.33. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 33 Mean length at birth (cm)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 33 Mean length at birth (cm)

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	567	42.10 (5.90)	577	42.10 (5.60)		58.0	0.00 [-0.67, 0.67]
Wapner 2006	296	44.20 (4.60)	294	44.70 (5.10)		42.0	-0.50 [-1.28, 0.28]
Subtotal (95% CI)	863		871			100.0	-0.21 [-0.72, 0.30]
Test for heterogeneity chi-square=0.91 df=1 p=0.34 I² =0.0%							
Test for overall effect z=0.81 p=0.4							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	42.10 (5.90)	577	42.10 (5.60)		58.0	0.00 [-0.67, 0.67]
Wapner 2006	296	44.20 (4.60)	294	44.70 (5.10)		42.0	-0.50 [-1.28, 0.28]
Subtotal (95% CI)	863		871			100.0	-0.21 [-0.72, 0.30]
Test for heterogeneity chi-square=0.91 df=1 p=0.34 I² =0.0%							
Test for overall effect z=0.81 p=0.4							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	42.10 (5.90)	577	42.10 (5.60)		58.0	0.00 [-0.67, 0.67]
Wapner 2006	296	44.20 (4.60)	294	44.70 (5.10)		42.0	-0.50 [-1.28, 0.28]
Subtotal (95% CI)	863		871			100.0	-0.21 [-0.72, 0.30]
Test for heterogeneity chi-square=0.91 df=1 p=0.34 I² =0.0%							
Test for overall effect z=0.81 p=0.4							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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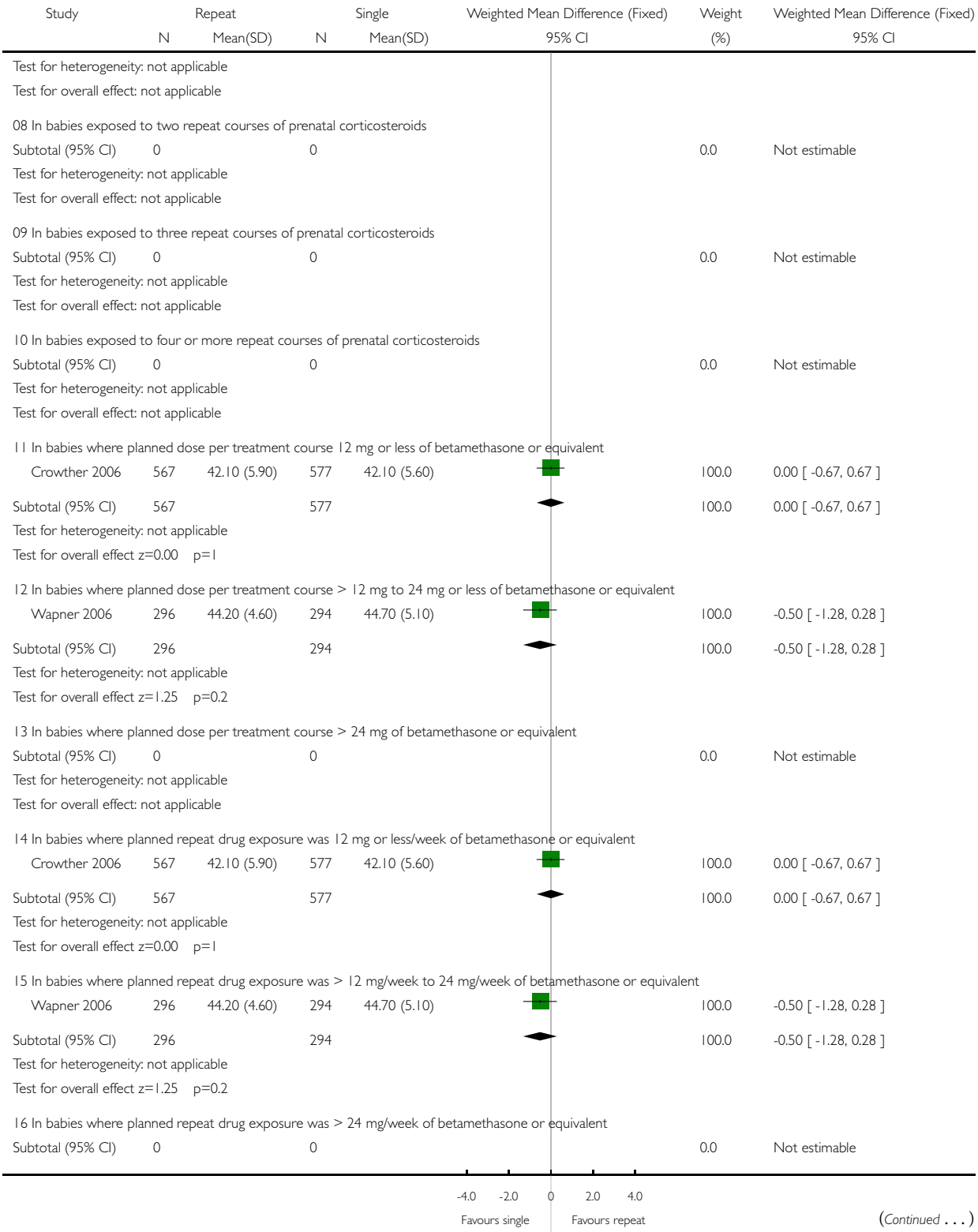

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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 01.34. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 34 Length Z scores at birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 34 Length Z scores at birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	567	-0.53 (1.31)	577	-0.48 (1.22)		100.0	-0.05 [-0.20, 0.10]
Subtotal (95% CI)	567		577			100.0	-0.05 [-0.20, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	567	-0.53 (1.31)	577	-0.48 (1.22)		100.0	-0.05 [-0.20, 0.10]
Subtotal (95% CI)	567		577			100.0	-0.05 [-0.20, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	567	-0.53 (1.31)	577	-0.48 (1.22)		100.0	-0.05 [-0.20, 0.10]
Subtotal (95% CI)	567		577			100.0	-0.05 [-0.20, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

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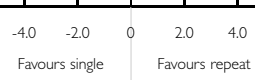
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	567	-0.53 (1.31)	577	-0.48 (1.22)		100.0	-0.05 [-0.20, 0.10]
Subtotal (95% CI)	567		577			100.0	-0.05 [-0.20, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	567	-0.53 (1.31)	577	-0.48 (1.22)		100.0	-0.05 [-0.20, 0.10]
Subtotal (95% CI)	567		577			100.0	-0.05 [-0.20, 0.10]
Test for heterogeneity: not applicable							
Test for overall effect z=0.67 p=0.5							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

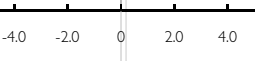
Analysis 01.35. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 35 Length multiples of the median at birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 35 Length multiples of the median at birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 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]
Test for heterogeneity: not applicable							
Test for overall effect z=2.20 p=0.03							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=2.20 p=0.03							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=2.20 p=0.03							



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	0.97 (0.05)	177	0.99 (0.06)		100.0	-0.02 [-0.03, -0.01]
Subtotal (95% CI)	191		177			100.0	-0.02 [-0.03, -0.01]
Test for heterogeneity: not applicable							
Test for overall effect z=3.46 p=0.0005							
11 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=2.20 p=0.03							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable

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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for 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 betamethasone or equivalent							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=2.20 p=0.03							
16 In babies where planned repeat drug exposure was > 24mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

Analysis 01.36. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 36 Apgar score less than 7 at 5 minutes

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 36 Apgar score less than 7 at 5 minutes

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	34/567	38/577		100.0	0.91 [0.58, 1.43]
Subtotal (95% CI)	567	577		100.0	0.91 [0.58, 1.43]
Total events: 34 (Repeat), 38 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.41 p=0.7					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	34/567	38/577		100.0	0.91 [0.58, 1.43]
Subtotal (95% CI)	567	577		100.0	0.91 [0.58, 1.43]
Total events: 34 (Repeat), 38 (Single)					

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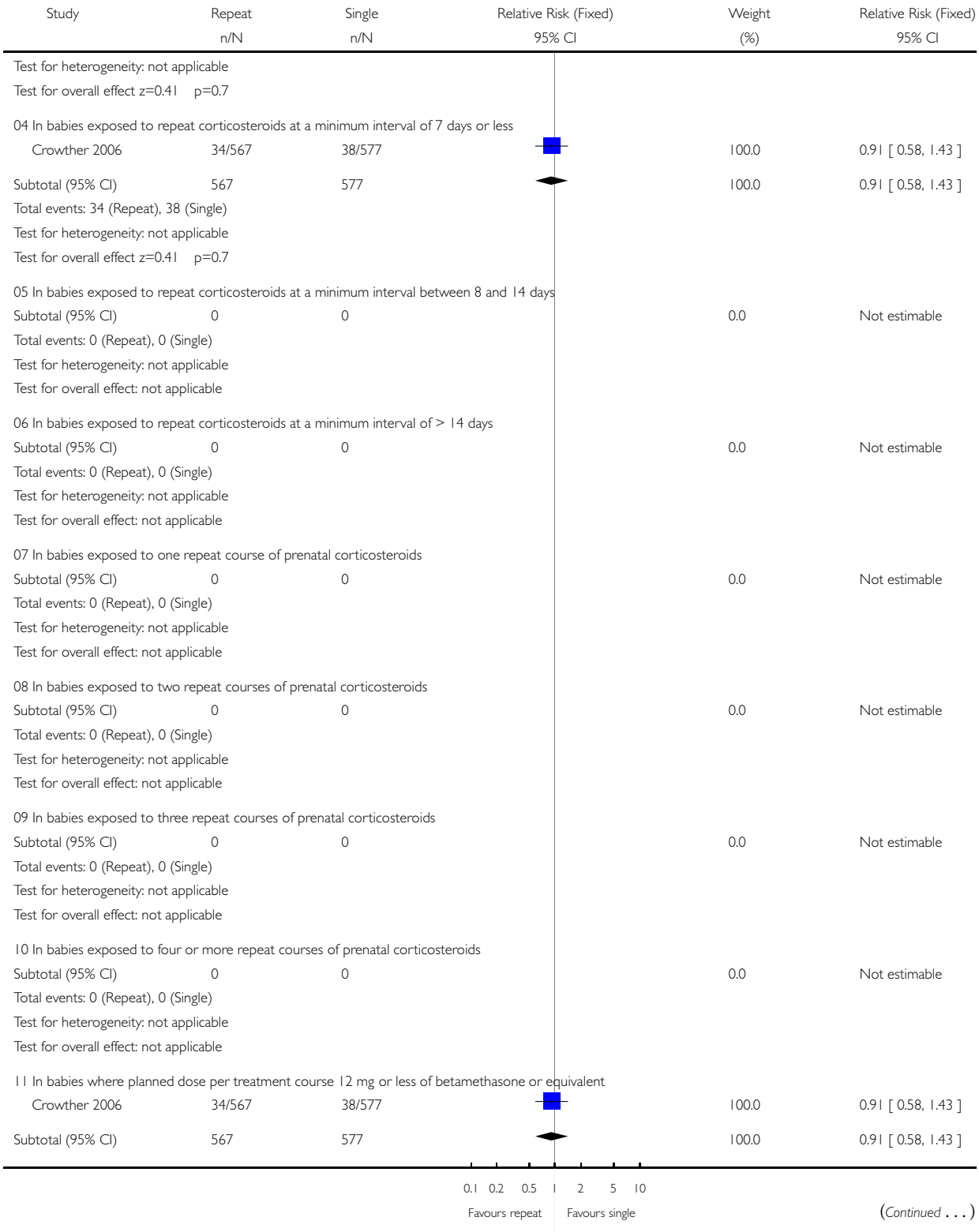

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 34 (Repeat), 38 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.41 p=0.7					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	38/577		100.0	0.91 [0.58, 1.43]
Subtotal (95% CI)	567	577		100.0	0.91 [0.58, 1.43]
Total events: 34 (Repeat), 38 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.41 p=0.7					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.37. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 37 Systemic infection in the first 48 hours of life (suspected or confirmed)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 37 Systemic infection in the first 48 hours of life (suspected or confirmed)

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	173/567	188/577		100.0	0.94 [0.79, 1.11]
Subtotal (95% CI)	567	577		100.0	0.94 [0.79, 1.11]
Total events: 173 (Repeat), 188 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	173/567	188/577		100.0	0.94 [0.79, 1.11]
Subtotal (95% CI)	567	577		100.0	0.94 [0.79, 1.11]
Total events: 173 (Repeat), 188 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	173/567	188/577		100.0	0.94 [0.79, 1.11]
Subtotal (95% CI)	567	577		100.0	0.94 [0.79, 1.11]
Total events: 173 (Repeat), 188 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.75 p=0.5					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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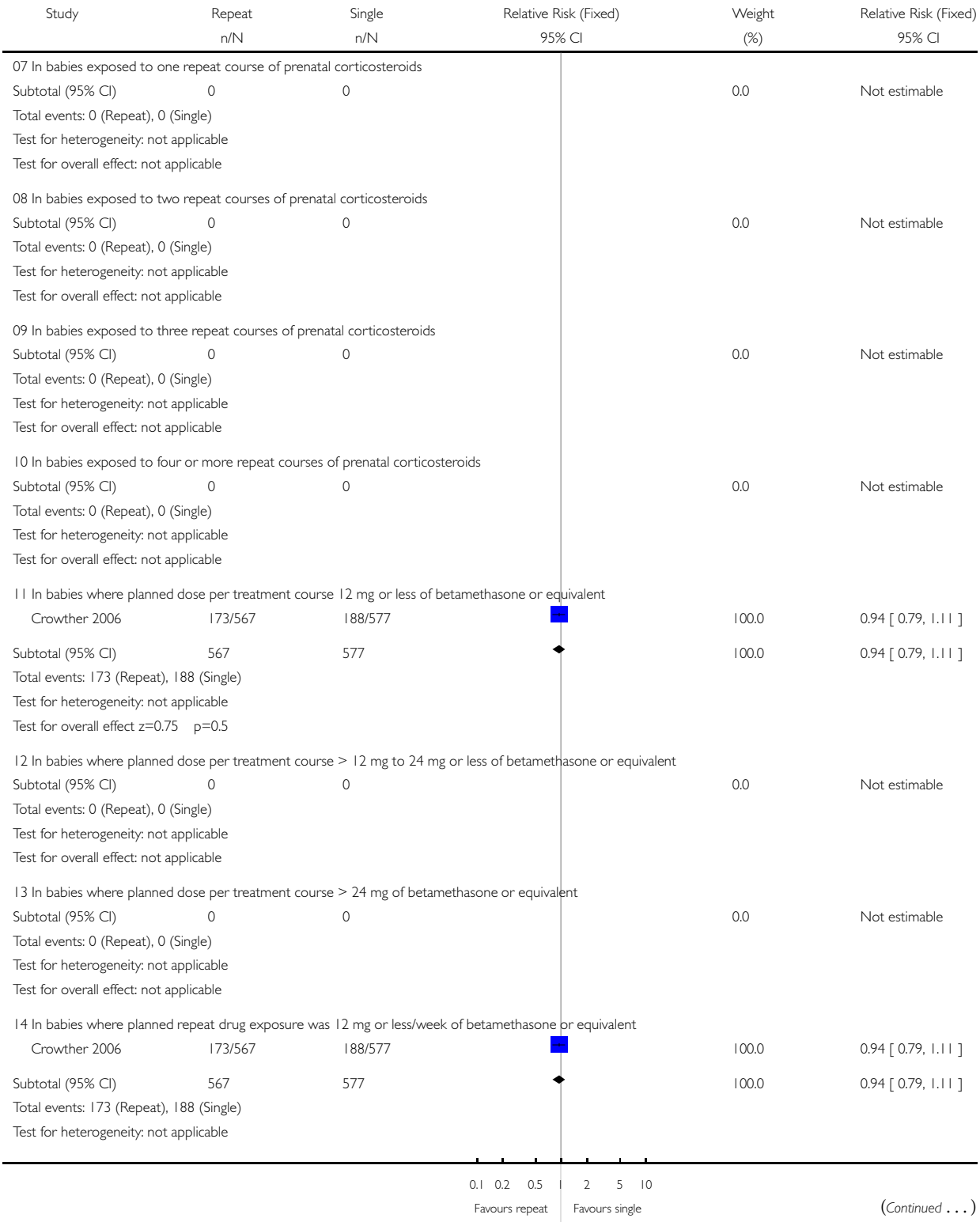

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=0.75 p=0.5					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.38. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 38 Proven infection while in the neonatal intensive care unit

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 38 Proven infection while in the neonatal intensive care unit

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	1/9	2/7		2.2	0.39 [0.04, 3.47]
Crowther 2006	70/567	72/577		69.9	0.99 [0.73, 1.35]
Guinn 2002	13/255	10/245		10.0	1.25 [0.56, 2.80]
Wapner 2006	11/250	18/242		17.9	0.59 [0.29, 1.23]
Subtotal (95% CI)	1081	1071		100.0	0.93 [0.71, 1.21]
Total events: 95 (Repeat), 102 (Single)					
Test for heterogeneity chi-square=2.76 df=3 p=0.43 I^2 =0.0%					
Test for overall effect z=0.53 p=0.6					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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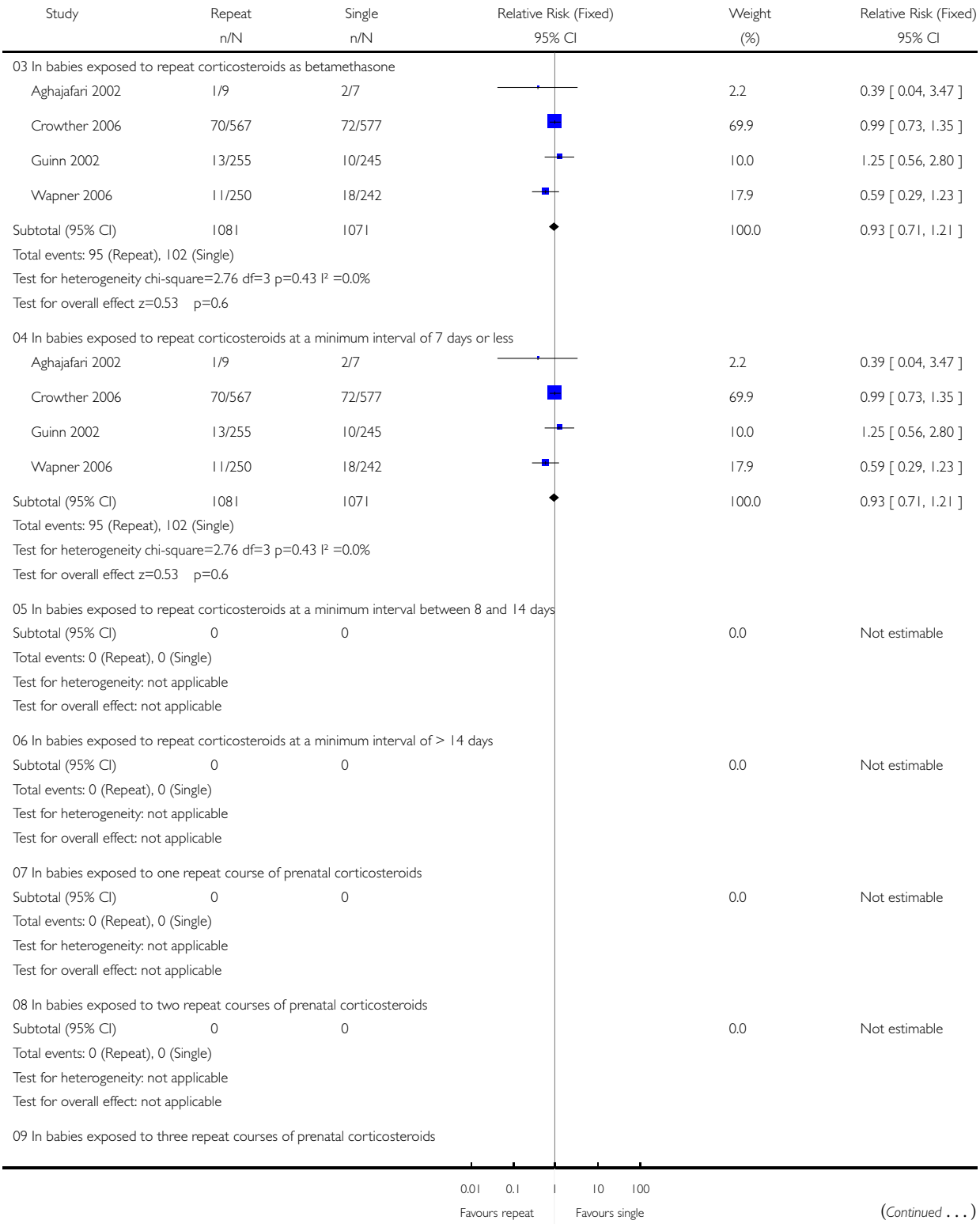

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	1/9	2/7		2.2	0.39 [0.04, 3.47]
Crowther 2006	70/567	72/577		69.9	0.99 [0.73, 1.35]
Guinn 2002	13/255	10/245		10.0	1.25 [0.56, 2.80]
Wapner 2006	11/250	18/242		17.9	0.59 [0.29, 1.23]
Subtotal (95% CI)	1081	1071		100.0	0.93 [0.71, 1.21]
Total events: 95 (Repeat), 102 (Single)					
Test for heterogeneity chi-square=2.76 df=3 p=0.43 I^2 =0.0%					
Test for overall effect z=0.53 p=0.6					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	1/9	2/7		2.2	0.39 [0.04, 3.47]
Crowther 2006	70/567	72/577		69.9	0.99 [0.73, 1.35]
Guinn 2002	13/255	10/245		10.0	1.25 [0.56, 2.80]
Wapner 2006	11/250	18/242		17.9	0.59 [0.29, 1.23]
Subtotal (95% CI)	1081	1071		100.0	0.93 [0.71, 1.21]
Total events: 95 (Repeat), 102 (Single)					
Test for heterogeneity chi-square=2.76 df=3 p=0.43 I^2 =0.0%					
Test for overall effect z=0.53 p=0.6					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					

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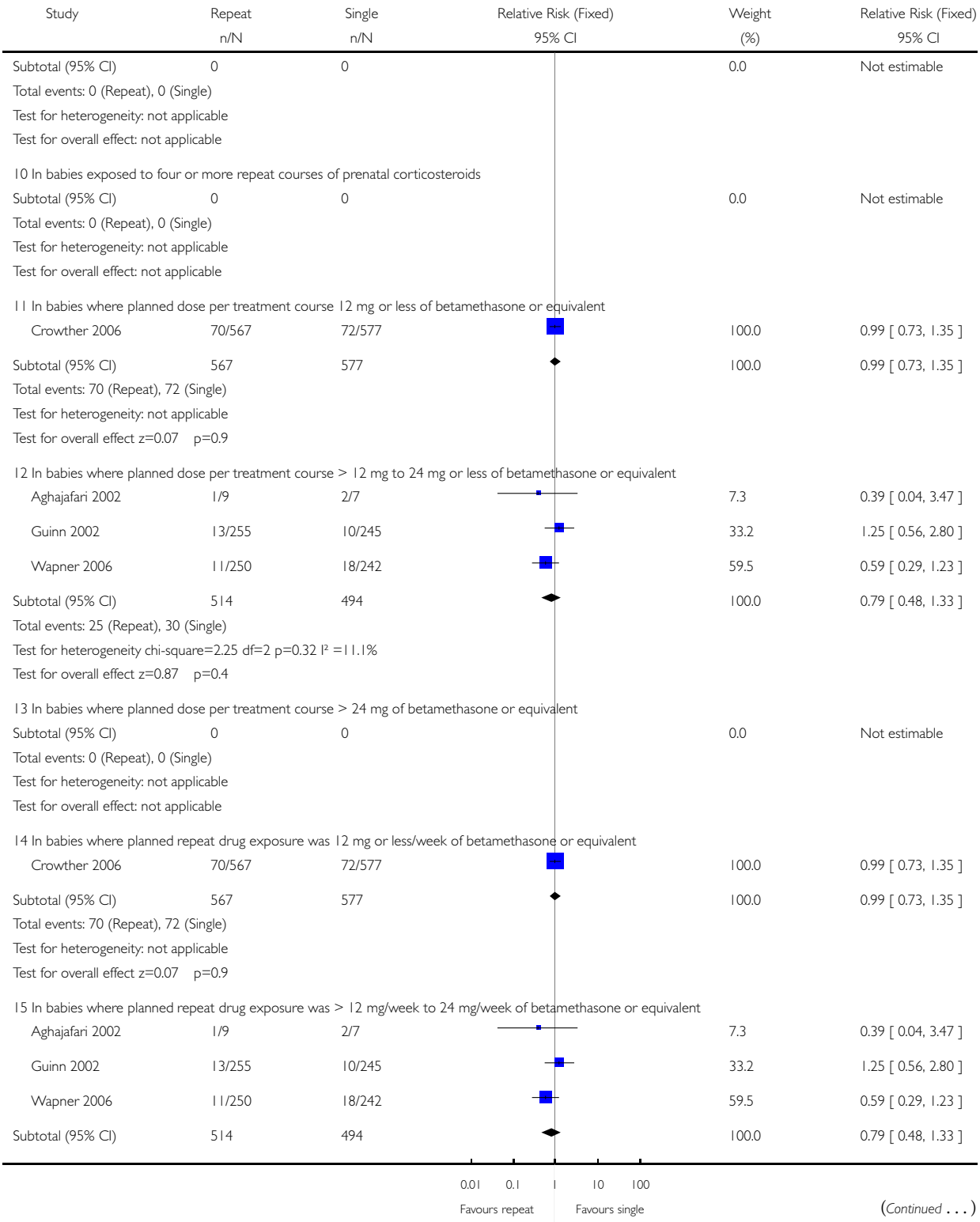

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Total events: 25 (Repeat), 30 (Single)					
Test for heterogeneity chi-square=2.25 df=2 p=0.32 I^2 =11.1%					
Test for overall effect z=0.87 p=0.4					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

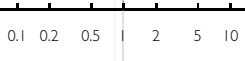
Analysis 01.39. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 39 Admission to the neonatal intensive care unit

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 39 Admission to the neonatal intensive care unit

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	407/567	399/577		100.0	1.04 [0.96, 1.12]
Subtotal (95% CI)	567	577		100.0	1.04 [0.96, 1.12]
Total events: 407 (Repeat), 399 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	407/567	399/577		100.0	1.04 [0.96, 1.12]
Subtotal (95% CI)	567	577		100.0	1.04 [0.96, 1.12]
Total events: 407 (Repeat), 399 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					



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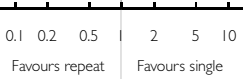
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Crowther 2006	407/567	399/577		100.0	1.04 [0.96, 1.12]
Subtotal (95% CI)	567	577		100.0	1.04 [0.96, 1.12]
Total events: 407 (Repeat), 399 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	407/567	399/577		100.0	1.04 [0.96, 1.12]
Subtotal (95% CI)	567	577		100.0	1.04 [0.96, 1.12]
Total events: 407 (Repeat), 399 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	407/567	399/577		100.0	1.04 [0.96, 1.12]
Subtotal (95% CI)	567	577		100.0	1.04 [0.96, 1.12]
Total events: 407 (Repeat), 399 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.97 p=0.3					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.40. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 40 Air leak syndrome

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 40 Air leak syndrome

Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 In all babies					
Crowther 2006	19/567	18/577		61.8	1.07 [0.57, 2.03]
Wapner 2006	1/250	7/242		38.2	0.14 [0.02, 1.12]
Subtotal (95% CI)	817	819		100.0	0.49 [0.07, 3.59]
Total events: 20 (Repeat), 25 (Single)					
Test for heterogeneity chi-square=3.52 df=1 p=0.06 I^2 =71.6%					
Test for overall effect z=0.70 p=0.5					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	19/567	18/577		61.8	1.07 [0.57, 2.03]
Wapner 2006	1/250	7/242		38.2	0.14 [0.02, 1.12]
Subtotal (95% CI)	817	819		100.0	0.49 [0.07, 3.59]
Total events: 20 (Repeat), 25 (Single)					
Test for heterogeneity chi-square=3.52 df=1 p=0.06 I^2 =71.6%					
Test for overall effect z=0.70 p=0.5					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	19/567	18/577		61.8	1.07 [0.57, 2.03]
Wapner 2006	1/250	7/242		38.2	0.14 [0.02, 1.12]
Subtotal (95% CI)	817	819		100.0	0.49 [0.07, 3.59]
Total events: 20 (Repeat), 25 (Single)					
Test for heterogeneity chi-square=3.52 df=1 p=0.06 I^2 =71.6%					
Test for overall effect z=0.70 p=0.5					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					

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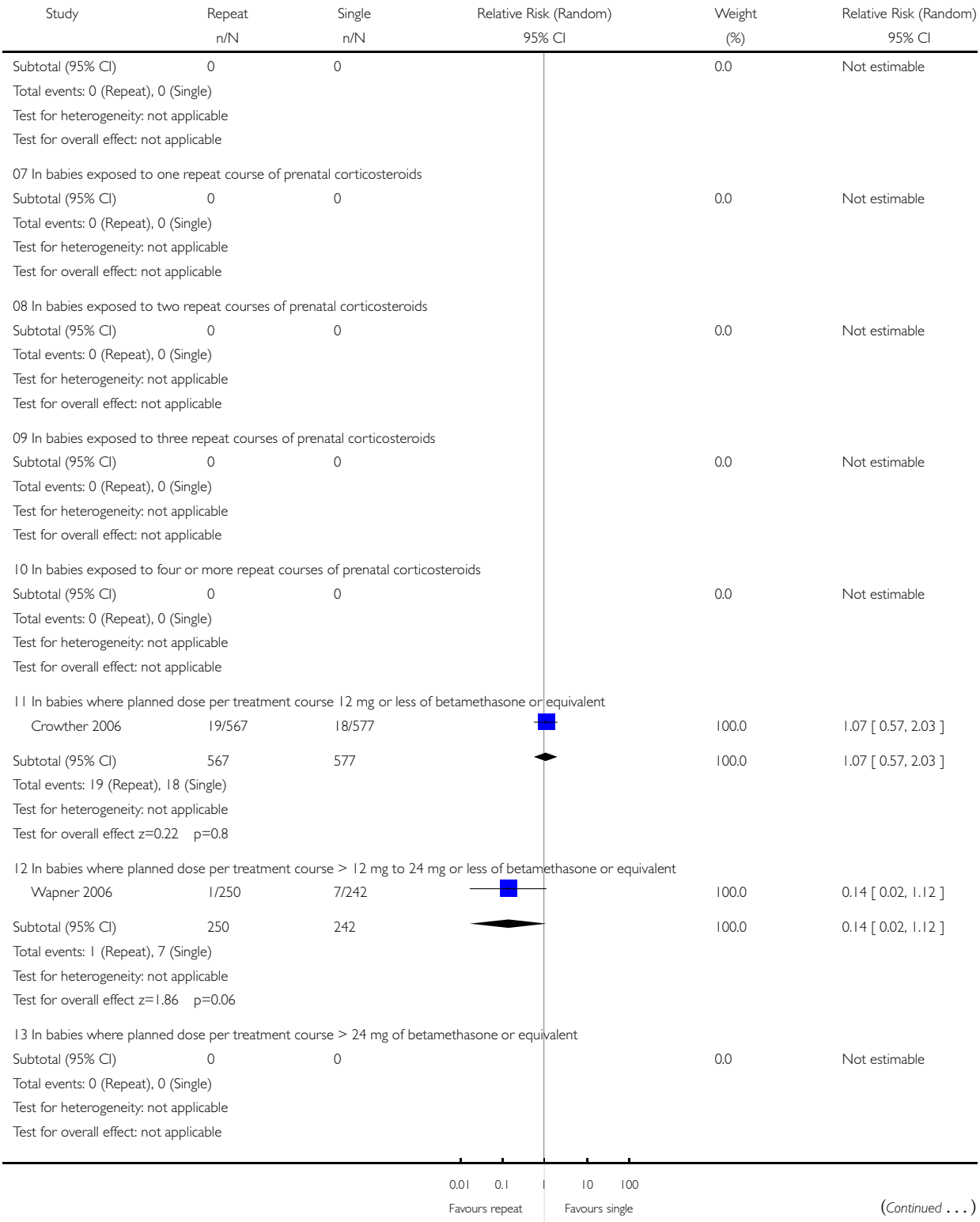

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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	19/567	18/577		100.0	1.07 [0.57, 2.03]
Subtotal (95% CI)	567	577		100.0	1.07 [0.57, 2.03]
Total events: 19 (Repeat), 18 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.22 p=0.8					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Wapner 2006	1/250	7/242		100.0	0.14 [0.02, 1.12]
Subtotal (95% CI)	250	242		100.0	0.14 [0.02, 1.12]
Total events: 1 (Repeat), 7 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.86 p=0.06					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

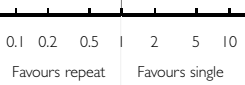
Analysis 01.41. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 41 Necrotising enterocolitis

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 41 Necrotising enterocolitis

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	5/567	11/577		34.9	0.46 [0.16, 1.32]
Guinn 2002	10/255	9/245		29.4	1.07 [0.44, 2.58]
Wapner 2006	10/250	11/242		35.8	0.88 [0.38, 2.03]
Subtotal (95% CI)	1081	1071		100.0	0.79 [0.47, 1.33]
Total events: 25 (Repeat), 31 (Single)					
Test for heterogeneity chi-square=1.51 df=2 p=0.47 I² =0.0%					
Test for overall effect z=0.89 p=0.4					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	5/567	11/577		34.9	0.46 [0.16, 1.32]
Guinn 2002	10/255	9/245		29.4	1.07 [0.44, 2.58]
Wapner 2006	10/250	11/242		35.8	0.88 [0.38, 2.03]
Subtotal (95% CI)	1081	1071		100.0	0.79 [0.47, 1.33]
Total events: 25 (Repeat), 31 (Single)					
Test for heterogeneity chi-square=1.51 df=2 p=0.47 I² =0.0%					
Test for overall effect z=0.89 p=0.4					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
× Aghajafari 2002	0/9	0/7		0.0	Not estimable
Crowther 2006	5/567	11/577		34.9	0.46 [0.16, 1.32]
Guinn 2002	10/255	9/245		29.4	1.07 [0.44, 2.58]
Wapner 2006	10/250	11/242		35.8	0.88 [0.38, 2.03]
Subtotal (95% CI)	1081	1071		100.0	0.79 [0.47, 1.33]
Total events: 25 (Repeat), 31 (Single)					
Test for heterogeneity chi-square=1.51 df=2 p=0.47 I² =0.0%					



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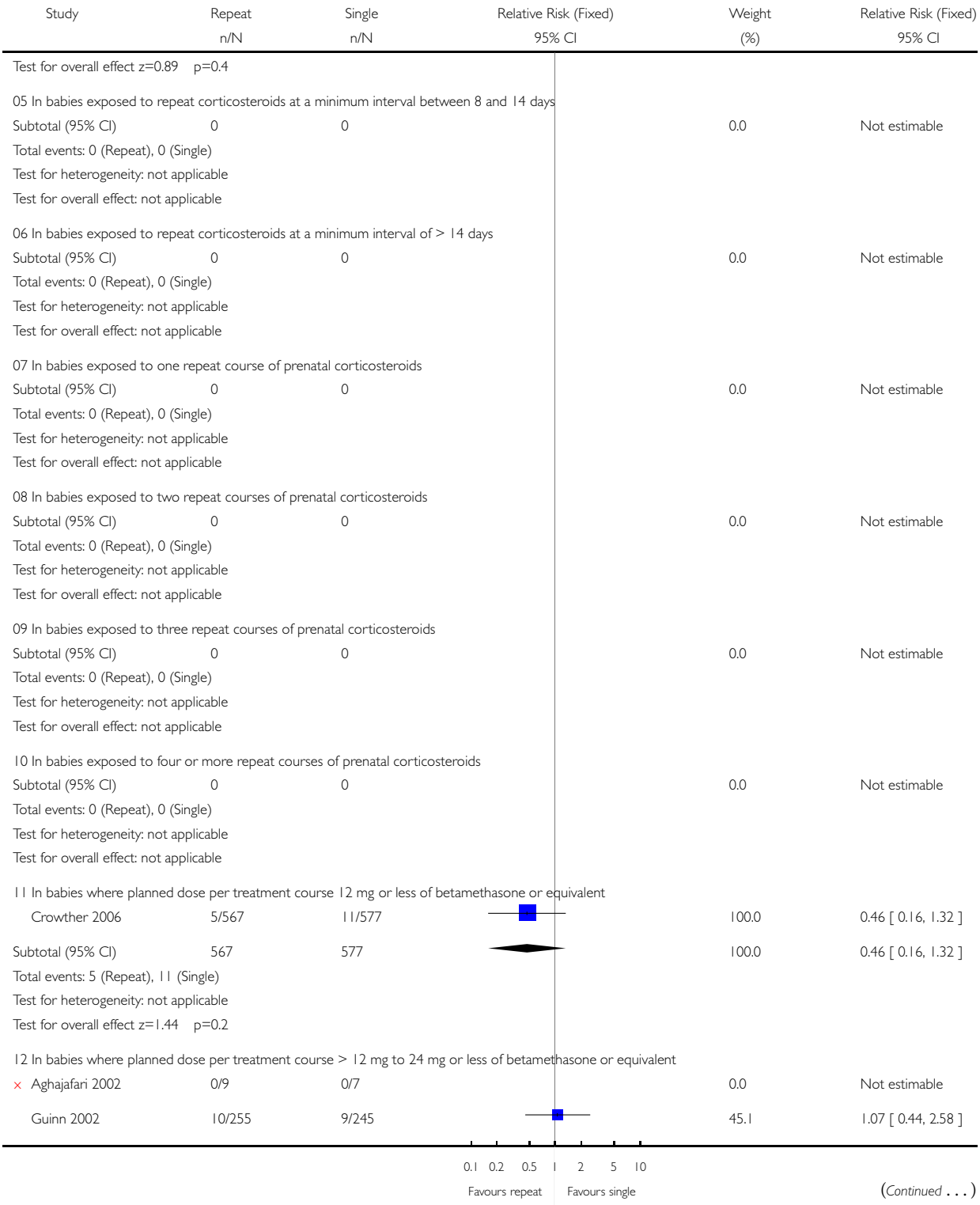

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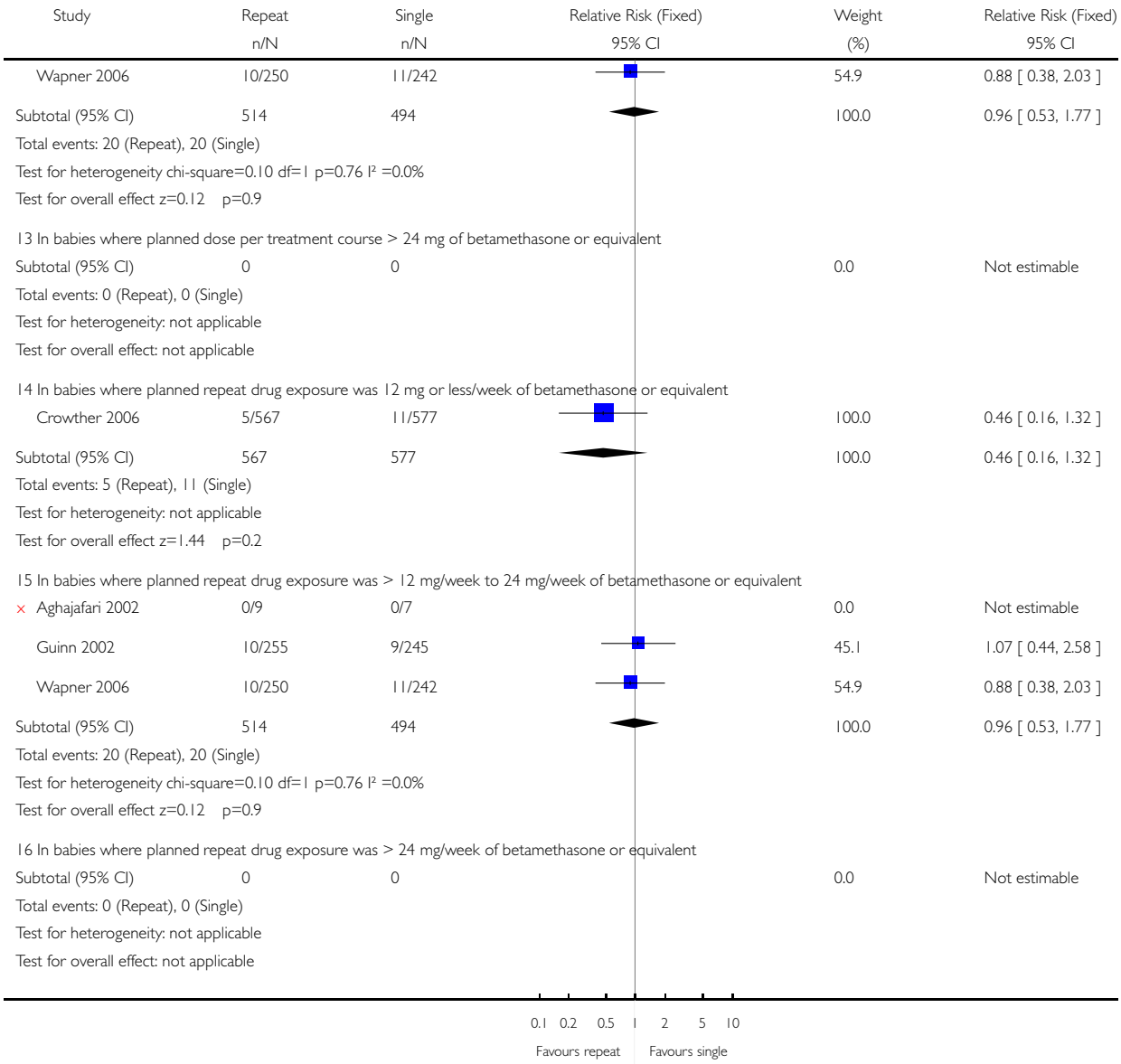

Analysis 01.42. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 42 Retinopathy of prematurity

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 42 Retinopathy of prematurity

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Aghajafari 2002	3/9	3/7		5.1	0.78 [0.22, 2.74]
Crowther 2006	40/567	43/577		64.3	0.95 [0.63, 1.43]
Wapner 2006	15/250	20/242		30.6	0.73 [0.38, 1.38]
Subtotal (95% CI)	826	826		100.0	0.87 [0.62, 1.22]
Total events: 58 (Repeat), 66 (Single)					
Test for heterogeneity chi-square=0.49 df=2 p=0.78 I^2 =0.0%					
Test for overall effect z=0.81 p=0.4					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	3/9	3/7		5.1	0.78 [0.22, 2.74]
Crowther 2006	40/567	43/577		64.3	0.95 [0.63, 1.43]
Wapner 2006	15/250	20/242		30.6	0.73 [0.38, 1.38]
Subtotal (95% CI)	826	826		100.0	0.87 [0.62, 1.22]
Total events: 58 (Repeat), 66 (Single)					
Test for heterogeneity chi-square=0.49 df=2 p=0.78 I^2 =0.0%					
Test for overall effect z=0.81 p=0.4					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	3/9	3/7		5.1	0.78 [0.22, 2.74]
Crowther 2006	40/567	43/577		64.3	0.95 [0.63, 1.43]
Wapner 2006	15/250	20/242		30.6	0.73 [0.38, 1.38]
Subtotal (95% CI)	826	826		100.0	0.87 [0.62, 1.22]
Total events: 58 (Repeat), 66 (Single)					
Test for heterogeneity chi-square=0.49 df=2 p=0.78 I^2 =0.0%					
Test for overall effect z=0.81 p=0.4					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable

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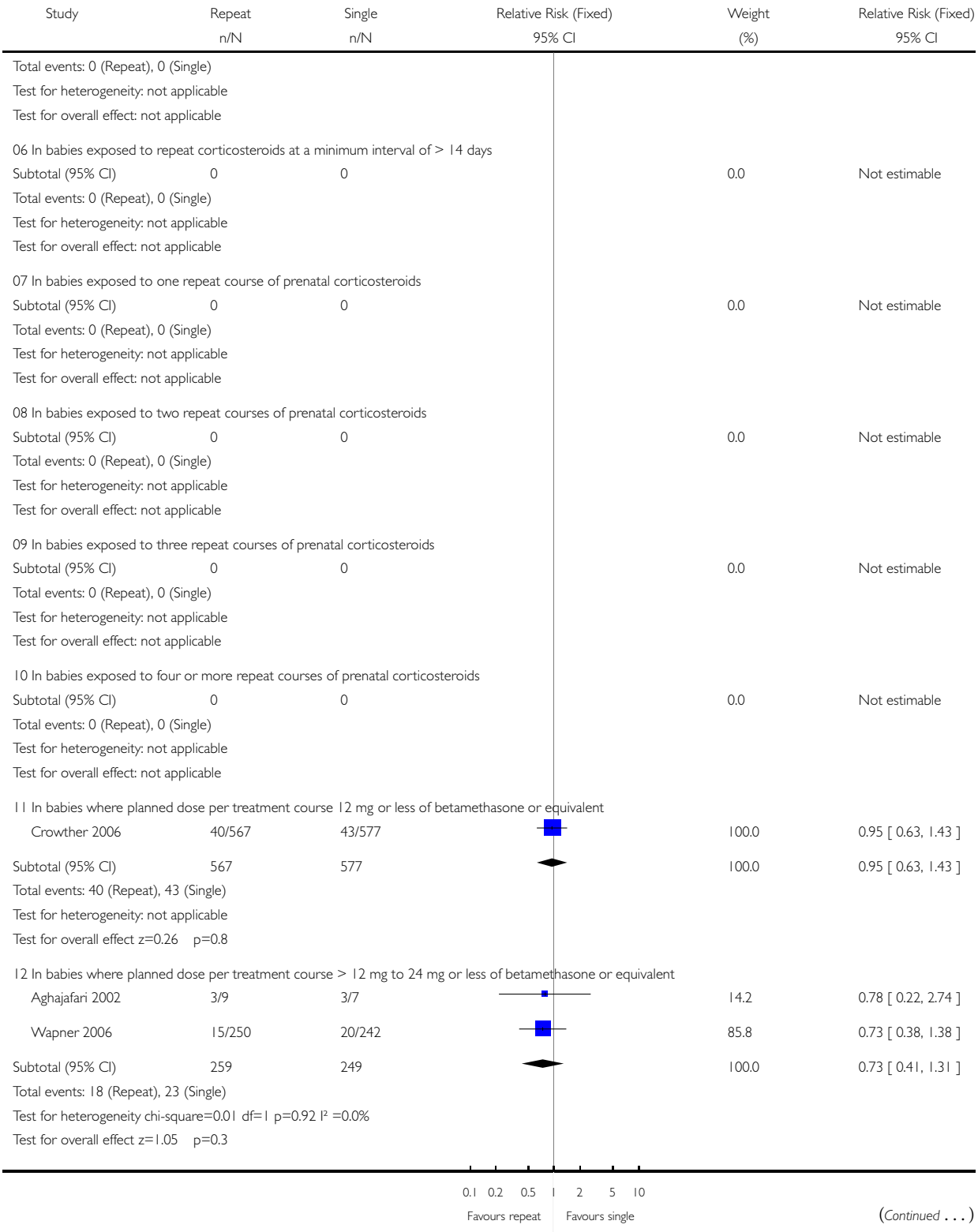

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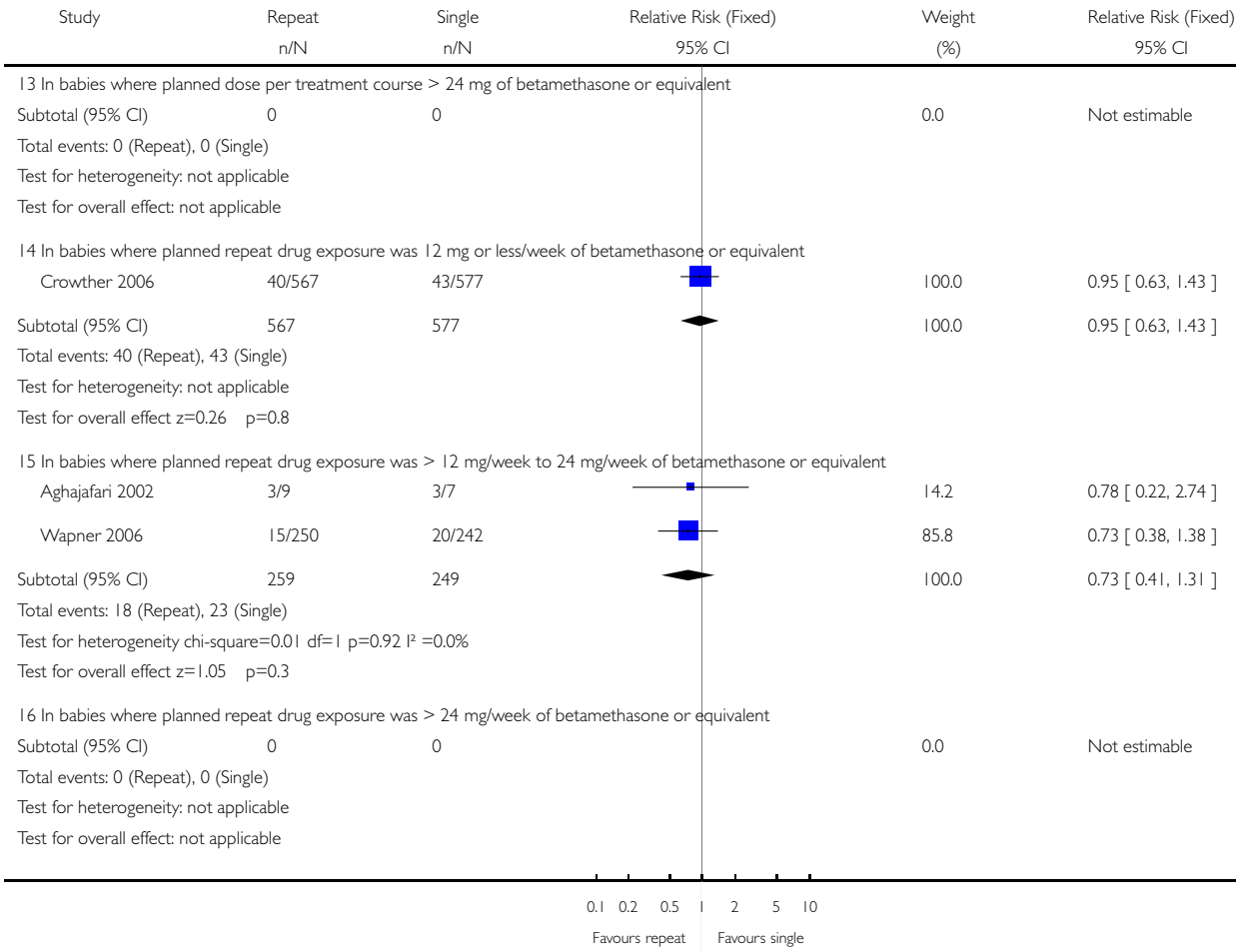


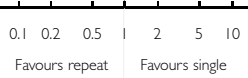
Analysis 01.43. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 43 Use of postnatal steroids

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 43 Use of postnatal steroids

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all babies					
Crowther 2006	43/567	31/577		63.9	1.41 [0.90, 2.21]
Guinn 2002	20/255	17/245		36.1	1.13 [0.61, 2.11]
Subtotal (95% CI)	822	822		100.0	1.31 [0.91, 1.88]
Total events: 63 (Repeat), 48 (Single)					
Test for heterogeneity chi-square=0.32 df=1 p=0.57 I^2 =0.0%					
Test for overall effect z=1.46 p=0.1					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	43/567	31/577		63.9	1.41 [0.90, 2.21]
Guinn 2002	20/255	17/245		36.1	1.13 [0.61, 2.11]
Subtotal (95% CI)	822	822		100.0	1.31 [0.91, 1.88]
Total events: 63 (Repeat), 48 (Single)					
Test for heterogeneity chi-square=0.32 df=1 p=0.57 I^2 =0.0%					
Test for overall effect z=1.46 p=0.1					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	43/567	31/577		63.9	1.41 [0.90, 2.21]
Guinn 2002	20/255	17/245		36.1	1.13 [0.61, 2.11]
Subtotal (95% CI)	822	822		100.0	1.31 [0.91, 1.88]
Total events: 63 (Repeat), 48 (Single)					
Test for heterogeneity chi-square=0.32 df=1 p=0.57 I^2 =0.0%					
Test for overall effect z=1.46 p=0.1					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	43/567	31/577		100.0	1.41 [0.90, 2.21]
Subtotal (95% CI)	567	577		100.0	1.41 [0.90, 2.21]
Total events: 43 (Repeat), 31 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.51 p=0.1					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Guinn 2002	20/255	17/245		100.0	1.13 [0.61, 2.11]
Subtotal (95% CI)	255	245		100.0	1.13 [0.61, 2.11]
Total events: 20 (Repeat), 17 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.39 p=0.7					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	43/567	31/577		100.0	1.41 [0.90, 2.21]
Subtotal (95% CI)	567	577		100.0	1.41 [0.90, 2.21]
Total events: 43 (Repeat), 31 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.51 p=0.1					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Guinn 2002	20/255	17/245		100.0	1.13 [0.61, 2.11]
Subtotal (95% CI)	255	245		100.0	1.13 [0.61, 2.11]
Total events: 20 (Repeat), 17 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.39 p=0.7					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

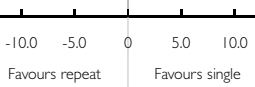
Analysis 01.44. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 44 Mean neonatal blood pressure on first day after birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 44 Mean neonatal blood pressure on first day after birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	85	38.00 (10.80)	90	37.30 (10.60)		100.0	0.70 [-2.47, 3.87]
Subtotal (95% CI)	85		90			100.0	0.70 [-2.47, 3.87]
Test for heterogeneity: not applicable							
Test for overall effect z=0.43 p=0.7							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	85	38.00 (10.80)	90	37.30 (10.60)		100.0	0.70 [-2.47, 3.87]
Subtotal (95% CI)	85		90			100.0	0.70 [-2.47, 3.87]
Test for heterogeneity: not applicable							
Test for overall effect z=0.43 p=0.7							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	85	38.00 (10.80)	90	37.30 (10.60)		100.0	0.70 [-2.47, 3.87]
Subtotal (95% CI)	85		90			100.0	0.70 [-2.47, 3.87]
Test for heterogeneity: not applicable							
Test for overall effect z=0.43 p=0.7							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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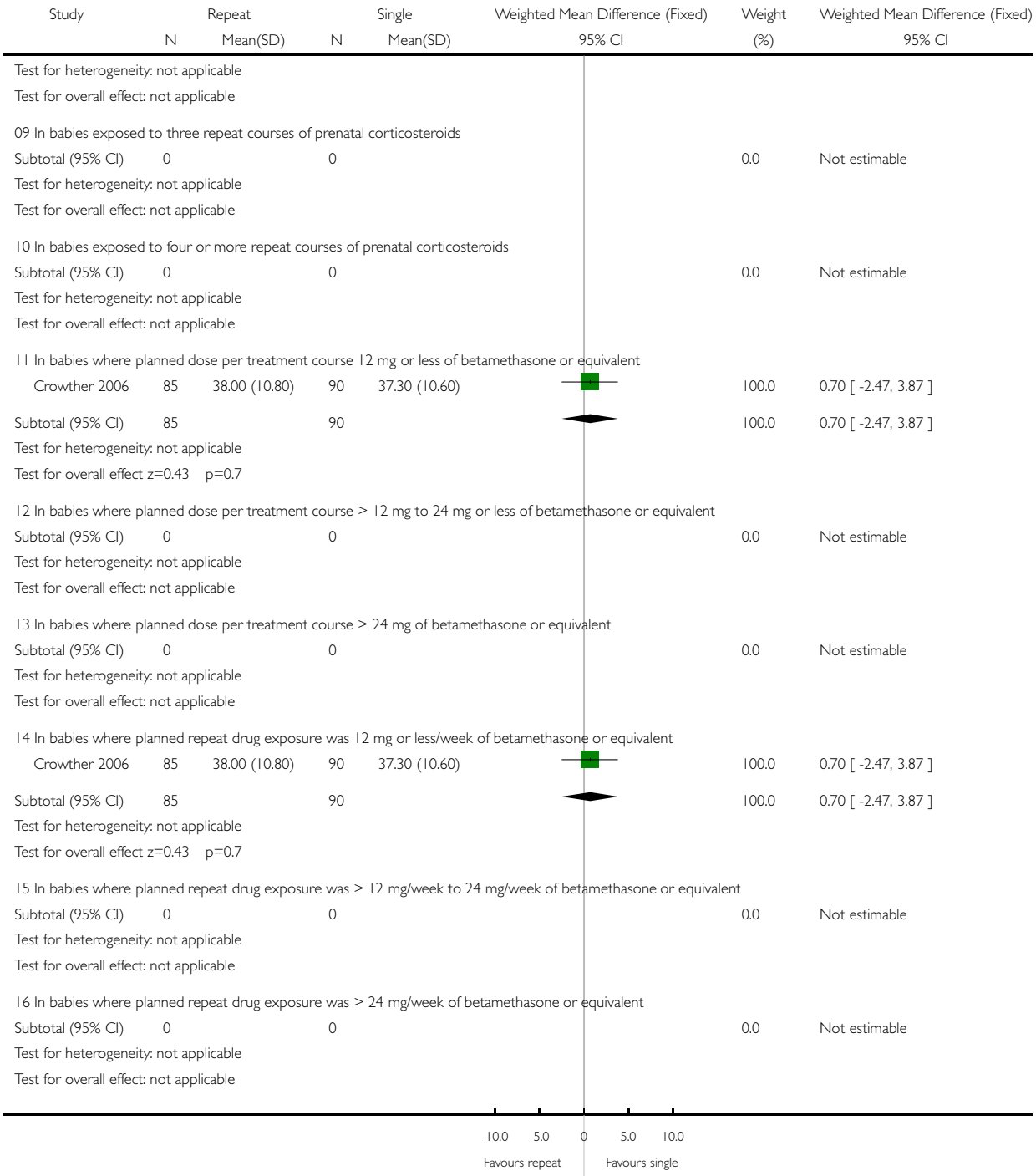


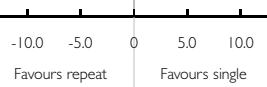
Analysis 01.45. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 45 Mean neonatal blood pressure 6 weeks after birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 45 Mean neonatal blood pressure 6 weeks after birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	85	54.40 (13.40)	90	55.80 (11.10)		100.0	-1.40 [-5.06, 2.26]
Subtotal (95% CI)	85		90			100.0	-1.40 [-5.06, 2.26]
Test for heterogeneity: not applicable							
Test for overall effect z=0.75 p=0.5							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	85	54.40 (13.40)	90	55.80 (11.10)		100.0	-1.40 [-5.06, 2.26]
Subtotal (95% CI)	85		90			100.0	-1.40 [-5.06, 2.26]
Test for heterogeneity: not applicable							
Test for overall effect z=0.75 p=0.5							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	85	54.40 (13.40)	90	55.80 (11.10)		100.0	-1.40 [-5.06, 2.26]
Subtotal (95% CI)	85		90			100.0	-1.40 [-5.06, 2.26]
Test for heterogeneity: not applicable							
Test for overall effect z=0.75 p=0.5							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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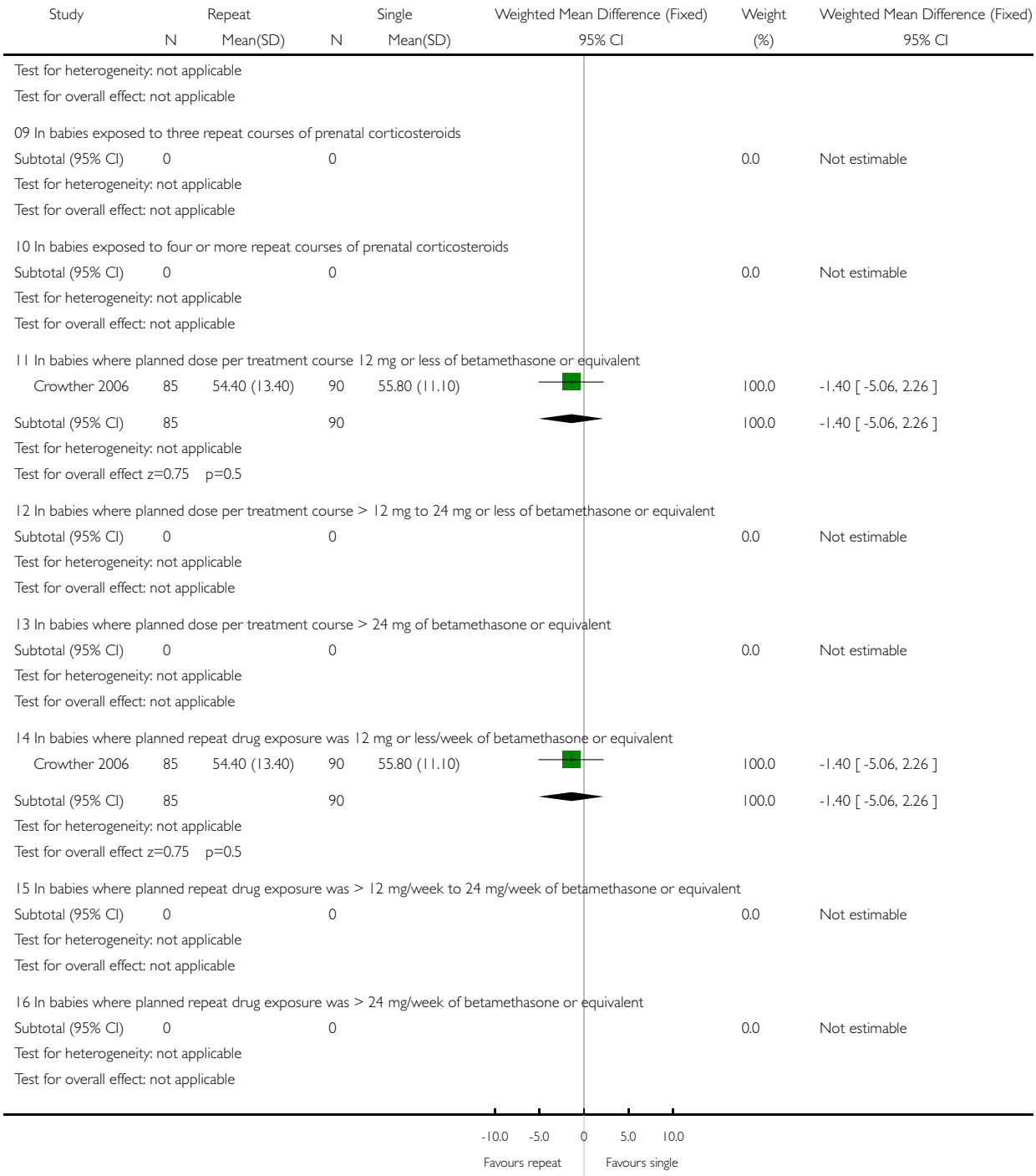


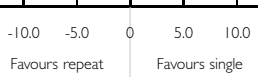
Analysis 01.46. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 46 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 46 Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVSd)

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 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]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
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]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	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]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	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]
Test for heterogeneity: not applicable							
Test for overall effect z=0.08 p=0.9							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

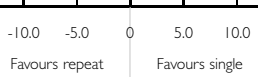
Analysis 01.47. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 47 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 47 Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 In all babies							
Crowther 2006	85	3.02 (0.86)	90	3.06 (0.71)		100.0	-0.04 [-0.27, 0.19]
Subtotal (95% CI)	85		90			100.0	-0.04 [-0.27, 0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	85	3.02 (0.86)	90	3.06 (0.71)		100.0	-0.04 [-0.27, 0.19]
Subtotal (95% CI)	85		90			100.0	-0.04 [-0.27, 0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	85	3.02 (0.86)	90	3.06 (0.71)		100.0	-0.04 [-0.27, 0.19]
Subtotal (95% CI)	85		90			100.0	-0.04 [-0.27, 0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	85	3.02 (0.86)	90	3.06 (0.71)		100.0	-0.04 [-0.27, 0.19]
Subtotal (95% CI)	85		90			100.0	-0.04 [-0.27, 0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	85	3.02 (0.86)	90	3.06 (0.71)		100.0	-0.04 [-0.27, 0.19]
Subtotal (95% CI)	85		90			100.0	-0.04 [-0.27, 0.19]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

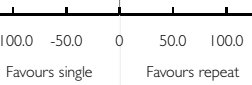
Analysis 01.48. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 48 Mean basal cortisol concentrations (nmol/L) at birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 48 Mean basal cortisol concentrations (nmol/L) at birth

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	34	60.10 (43.00)	33	105.00 (88.60)		100.0	-44.90 [-78.41, -11.39]
Subtotal (95% CI)	34		33			100.0	-44.90 [-78.41, -11.39]
Test for heterogeneity: not applicable							
Test for overall effect z=2.63 p=0.009							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	34	60.10 (43.00)	33	105.00 (88.60)		100.0	-44.90 [-78.41, -11.39]
Subtotal (95% CI)	34		33			100.0	-44.90 [-78.41, -11.39]
Test for heterogeneity: not applicable							
Test for overall effect z=2.63 p=0.009							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	34	60.10 (43.00)	33	105.00 (88.60)		100.0	-44.90 [-78.41, -11.39]
Subtotal (95% CI)	34		33			100.0	-44.90 [-78.41, -11.39]
Test for heterogeneity: not applicable							
Test for overall effect z=2.63 p=0.009							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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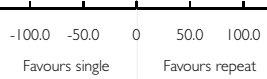
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	34	60.10 (43.00)	33	105.00 (88.60)		100.0	-44.90 [-78.41, -11.39]
Subtotal (95% CI)	34		33			100.0	-44.90 [-78.41, -11.39]
Test for heterogeneity: not applicable							
Test for overall effect z=2.63 p=0.009							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	60.10 (43.00)	33	105.00 (88.60)		100.0	-44.90 [-78.41, -11.39]
Subtotal (95% CI)	34		33			100.0	-44.90 [-78.41, -11.39]
Test for heterogeneity: not applicable							
Test for overall effect z=2.63 p=0.009							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



Analysis 01.49. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 49 Mean weight (g) at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 49 Mean weight (g) at primary hospital discharge

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	541	2692.00 (726.00)	549	2693.00 (542.00)		100.0	-1.00 [-77.15, 75.15]
Subtotal (95% CI)	541		549			100.0	-1.00 [-77.15, 75.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.03 p=1							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	2692.00 (726.00)	549	2693.00 (542.00)		100.0	-1.00 [-77.15, 75.15]
Subtotal (95% CI)	541		549			100.0	-1.00 [-77.15, 75.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.03 p=1							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	2692.00 (726.00)	549	2693.00 (542.00)		100.0	-1.00 [-77.15, 75.15]
Subtotal (95% CI)	541		549			100.0	-1.00 [-77.15, 75.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.03 p=1							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable

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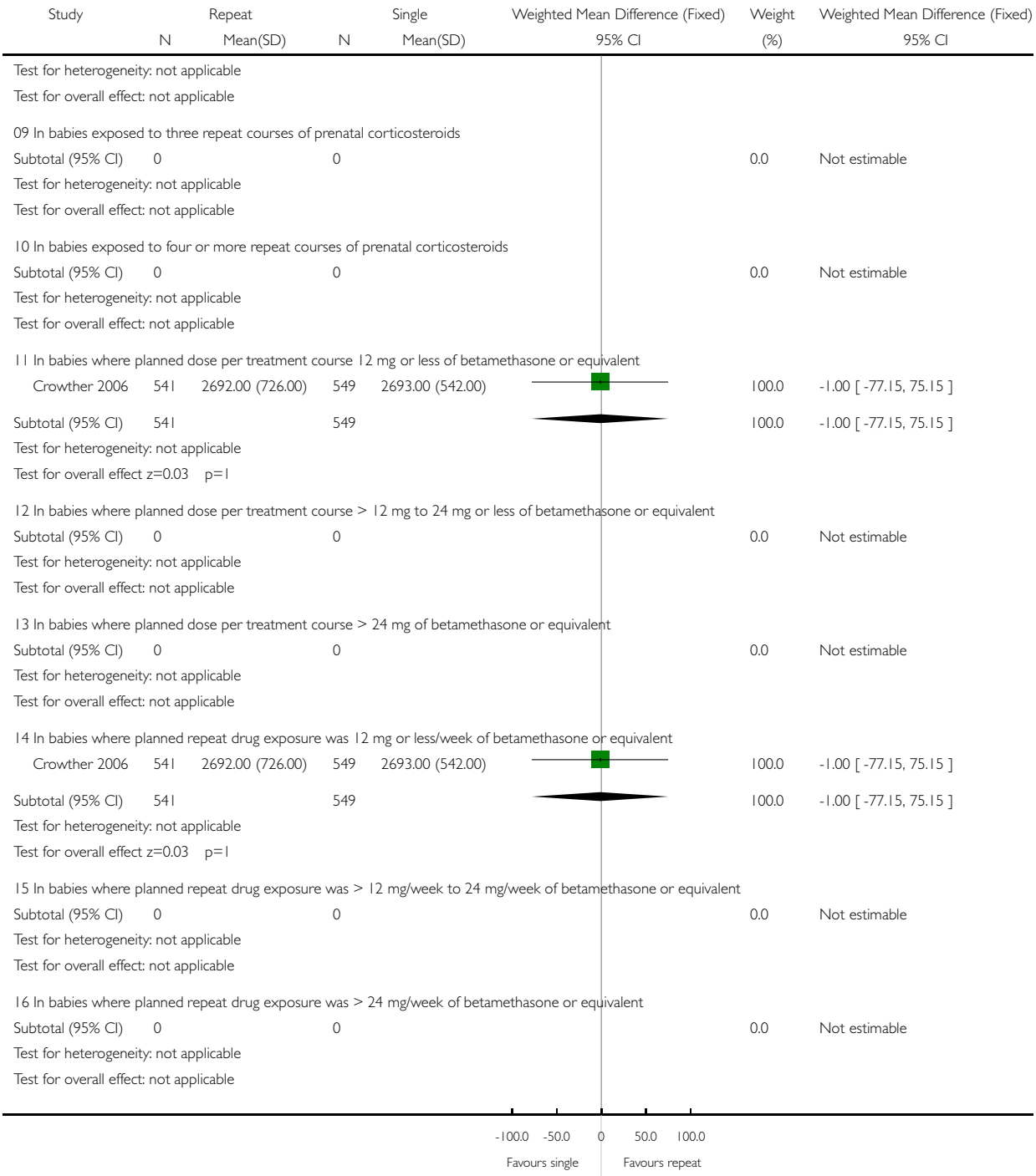


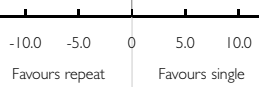
Analysis 01.50. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 50 Weight Z scores at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 50 Weight Z scores at primary hospital discharge

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	541	-1.07 (0.98)	549	-1.02 (0.93)		100.0	-0.05 [-0.16, 0.06]
Subtotal (95% CI)	541		549			100.0	-0.05 [-0.16, 0.06]
Test for heterogeneity: not applicable							
Test for overall effect z=0.86 p=0.4							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	-1.07 (0.98)	549	-1.02 (0.93)		100.0	-0.05 [-0.16, 0.06]
Subtotal (95% CI)	541		549			100.0	-0.05 [-0.16, 0.06]
Test for heterogeneity: not applicable							
Test for overall effect z=0.86 p=0.4							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	-1.07 (0.98)	549	-1.02 (0.93)		100.0	-0.05 [-0.16, 0.06]
Subtotal (95% CI)	541		549			100.0	-0.05 [-0.16, 0.06]
Test for heterogeneity: not applicable							
Test for overall effect z=0.86 p=0.4							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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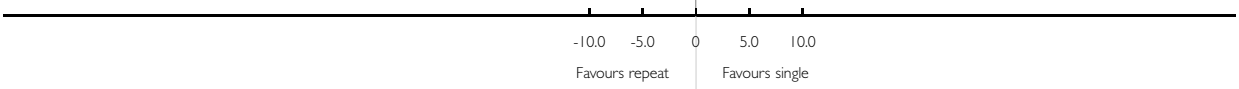
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	541	-1.07 (0.98)	549	-1.02 (0.93)		100.0	-0.05 [-0.16, 0.06]
Subtotal (95% CI)	541		549			100.0	-0.05 [-0.16, 0.06]
Test for heterogeneity: not applicable							
Test for overall effect z=0.86 p=0.4							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	541	-1.07 (0.98)	549	-1.02 (0.93)		100.0	-0.05 [-0.16, 0.06]
Subtotal (95% CI)	541		549			100.0	-0.05 [-0.16, 0.06]
Test for heterogeneity: not applicable							
Test for overall effect z=0.86 p=0.4							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



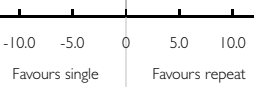
Analysis 01.51. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 51 Mean head circumference (cm) at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 51 Mean head circumference (cm) at primary hospital discharge

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	541	33.70 (2.10)	549	33.60 (1.90)		100.0	0.10 [-0.14, 0.34]
Subtotal (95% CI)	541		549			100.0	0.10 [-0.14, 0.34]
Test for heterogeneity: not applicable							
Test for overall effect z=0.82 p=0.4							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	33.70 (2.10)	549	33.60 (1.90)		100.0	0.10 [-0.14, 0.34]
Subtotal (95% CI)	541		549			100.0	0.10 [-0.14, 0.34]
Test for heterogeneity: not applicable							
Test for overall effect z=0.82 p=0.4							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	33.70 (2.10)	549	33.60 (1.90)		100.0	0.10 [-0.14, 0.34]
Subtotal (95% CI)	541		549			100.0	0.10 [-0.14, 0.34]
Test for heterogeneity: not applicable							
Test for overall effect z=0.82 p=0.4							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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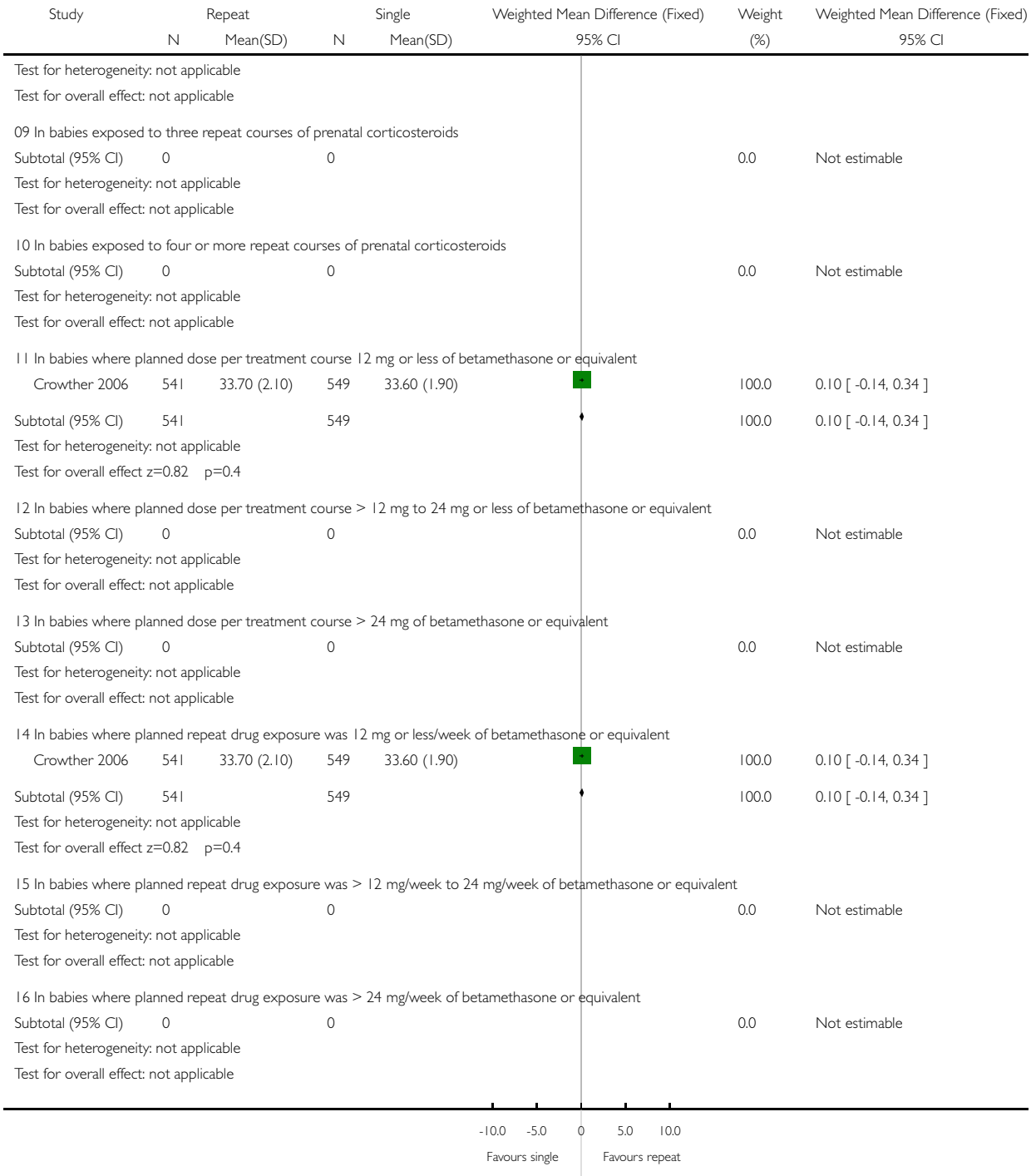


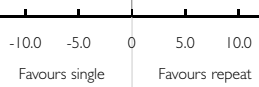
Analysis 01.52. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 52 Head circumference Z scores at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 52 Head circumference Z scores at primary hospital discharge

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	541	-0.19 (1.12)	549	-0.15 (1.06)		100.0	-0.04 [-0.17, 0.09]
Subtotal (95% CI)	541		549			100.0	-0.04 [-0.17, 0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	-0.19 (1.12)	549	-0.15 (1.06)		100.0	-0.04 [-0.17, 0.09]
Subtotal (95% CI)	541		549			100.0	-0.04 [-0.17, 0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	-0.19 (1.12)	549	-0.15 (1.06)		100.0	-0.04 [-0.17, 0.09]
Subtotal (95% CI)	541		549			100.0	-0.04 [-0.17, 0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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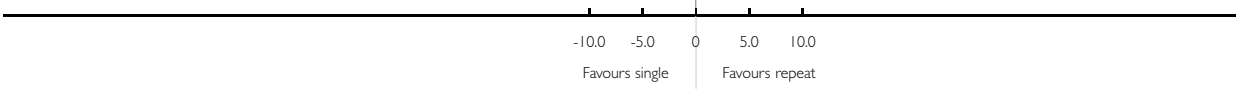
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	541	-0.19 (1.12)	549	-0.15 (1.06)		100.0	-0.04 [-0.17, 0.09]
Subtotal (95% CI)	541		549			100.0	-0.04 [-0.17, 0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	541	-0.19 (1.12)	549	-0.15 (1.06)		100.0	-0.04 [-0.17, 0.09]
Subtotal (95% CI)	541		549			100.0	-0.04 [-0.17, 0.09]
Test for heterogeneity: not applicable							
Test for overall effect z=0.61 p=0.5							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



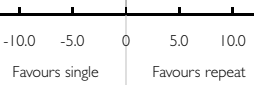
Analysis 01.53. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 53 Mean length (cm) at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 53 Mean length (cm) at primary hospital discharge

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 In all babies							
Crowther 2006	541	47.40 (4.30)	549	47.40 (4.00)		100.0	0.00 [-0.49, 0.49]
Subtotal (95% CI)	541		549			100.0	0.00 [-0.49, 0.49]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	47.40 (4.30)	549	47.40 (4.00)		100.0	0.00 [-0.49, 0.49]
Subtotal (95% CI)	541		549			100.0	0.00 [-0.49, 0.49]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	47.40 (4.30)	549	47.40 (4.00)		100.0	0.00 [-0.49, 0.49]
Subtotal (95% CI)	541		549			100.0	0.00 [-0.49, 0.49]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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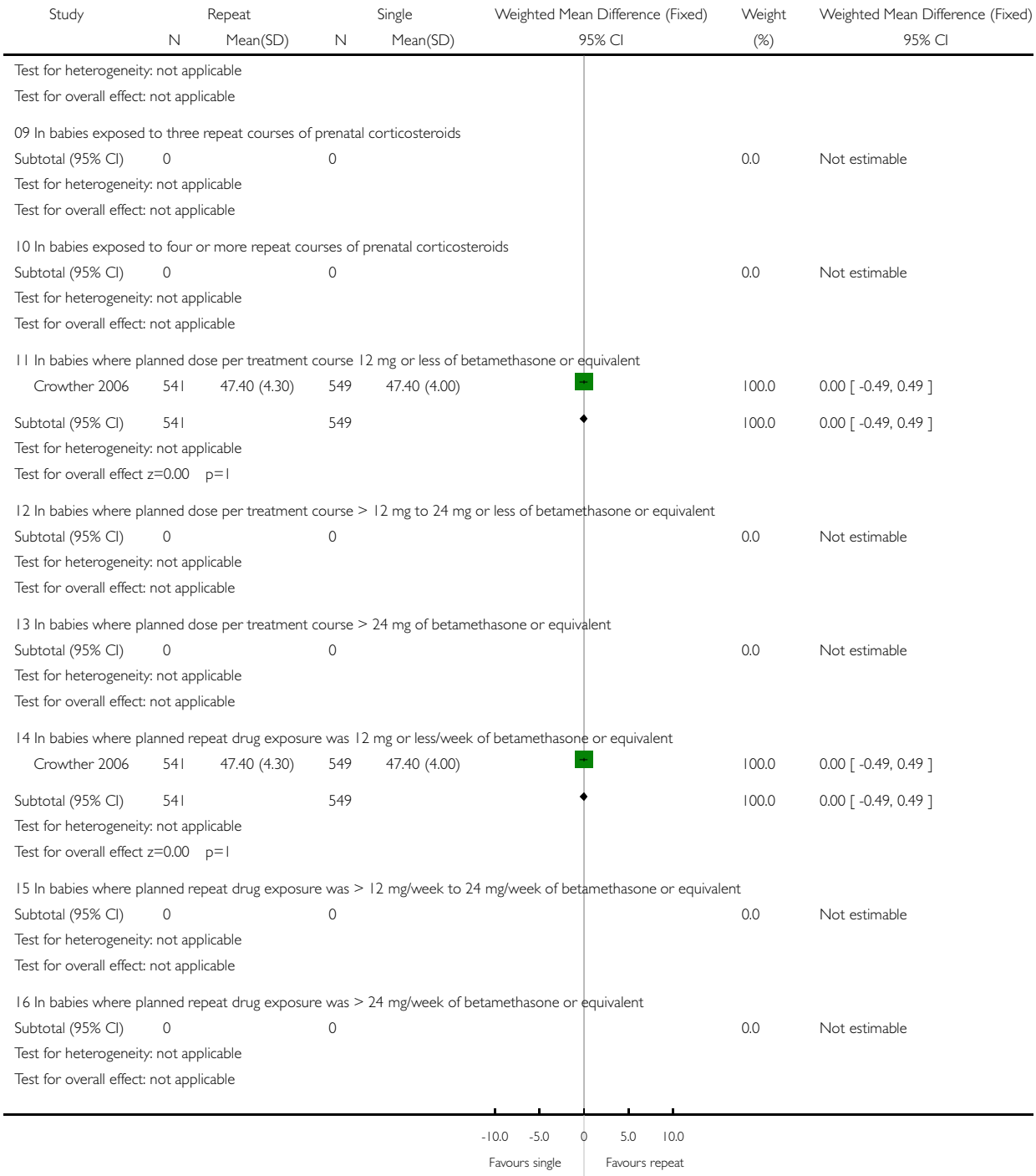


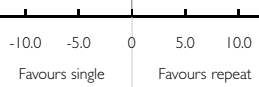
Analysis 01.54. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 54 Length Z score at primary hospital discharge

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 54 Length Z score at primary hospital discharge

Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
01 In all babies							
Crowther 2006	541	-1.11 (1.47)	549	-1.08 (1.55)		100.0	-0.03 [-0.21, 0.15]
Subtotal (95% CI)	541		549			100.0	-0.03 [-0.21, 0.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In babies exposed to repeat corticosteroids as betamethasone							
Crowther 2006	541	-1.11 (1.47)	549	-1.08 (1.55)		100.0	-0.03 [-0.21, 0.15]
Subtotal (95% CI)	541		549			100.0	-0.03 [-0.21, 0.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less							
Crowther 2006	541	-1.11 (1.47)	549	-1.08 (1.55)		100.0	-0.03 [-0.21, 0.15]
Subtotal (95% CI)	541		549			100.0	-0.03 [-0.21, 0.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In babies exposed to one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In babies exposed to two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In babies exposed to three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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	541	-1.11 (1.47)	549	-1.08 (1.55)		100.0	-0.03 [-0.21, 0.15]
Subtotal (95% CI)	541		549			100.0	-0.03 [-0.21, 0.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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	541	-1.11 (1.47)	549	-1.08 (1.55)		100.0	-0.03 [-0.21, 0.15]
Subtotal (95% CI)	541		549			100.0	-0.03 [-0.21, 0.15]
Test for heterogeneity: not applicable							
Test for overall effect z=0.33 p=0.7							
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
16 In babies where planned repeat drug exposure was > 24mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							

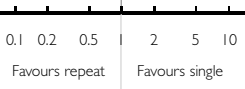
Analysis 01.55. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 55 Prelabour rupture of membranes after trial entry

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 55 Prelabour rupture of membranes after trial entry

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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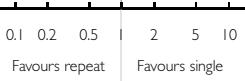
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.11 p=0.9					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.56. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 56 Hypertension (variously defined by the authors)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 56 Hypertension (variously defined by the authors)

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
Crowther 2006	62/489	67/493		89.1	0.93 [0.68, 1.29]
Wapner 2006	15/250	8/242		10.9	1.82 [0.78, 4.20]
Subtotal (95% CI)	739	735		100.0	1.03 [0.76, 1.39]
Total events: 77 (Repeat), 75 (Single)					
Test for heterogeneity chi-square=2.11 df=1 p=0.15 I^2 =52.6%					
Test for overall effect z=0.19 p=0.9					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	62/489	67/493		89.1	0.93 [0.68, 1.29]
Wapner 2006	15/250	8/242		10.9	1.82 [0.78, 4.20]

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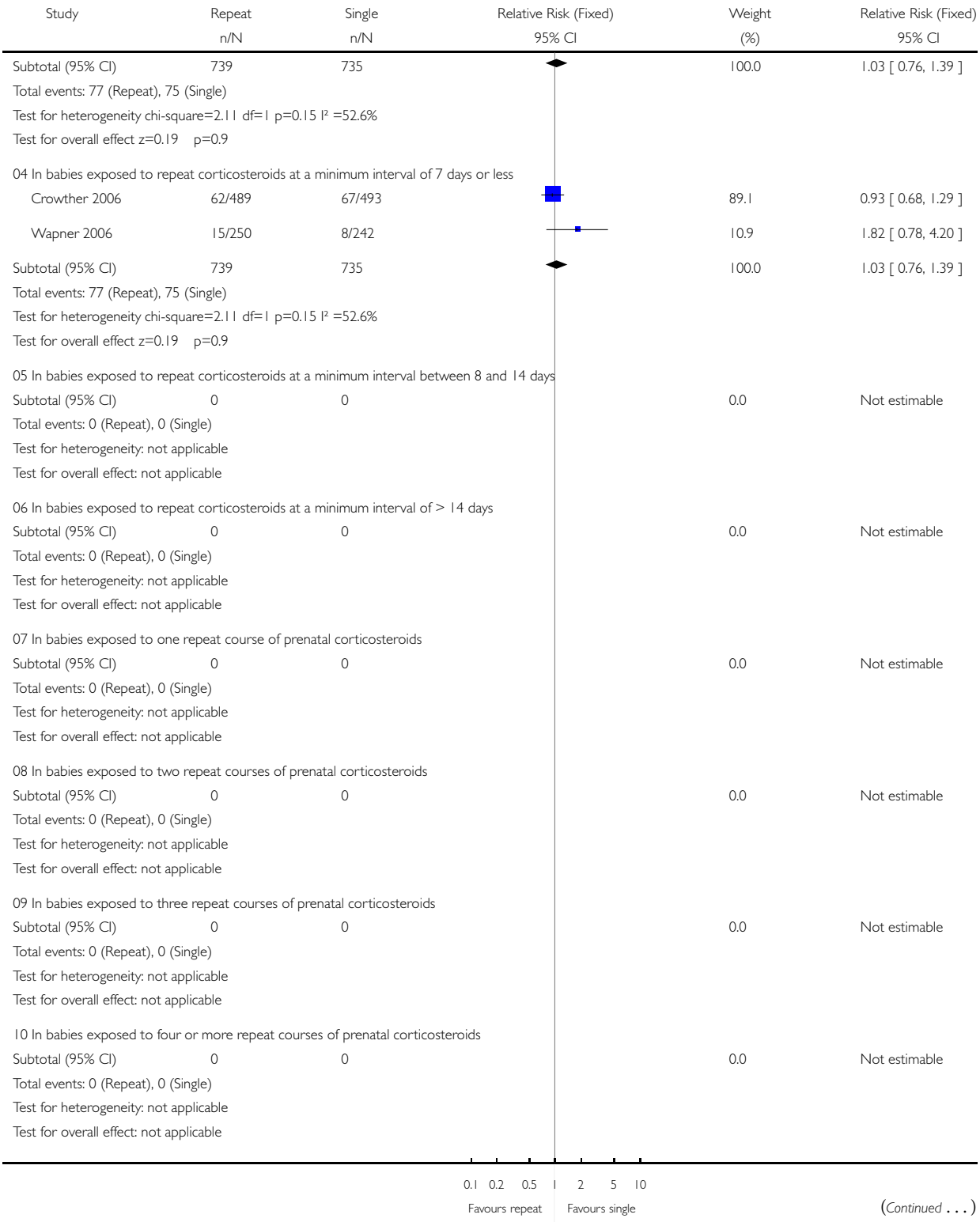

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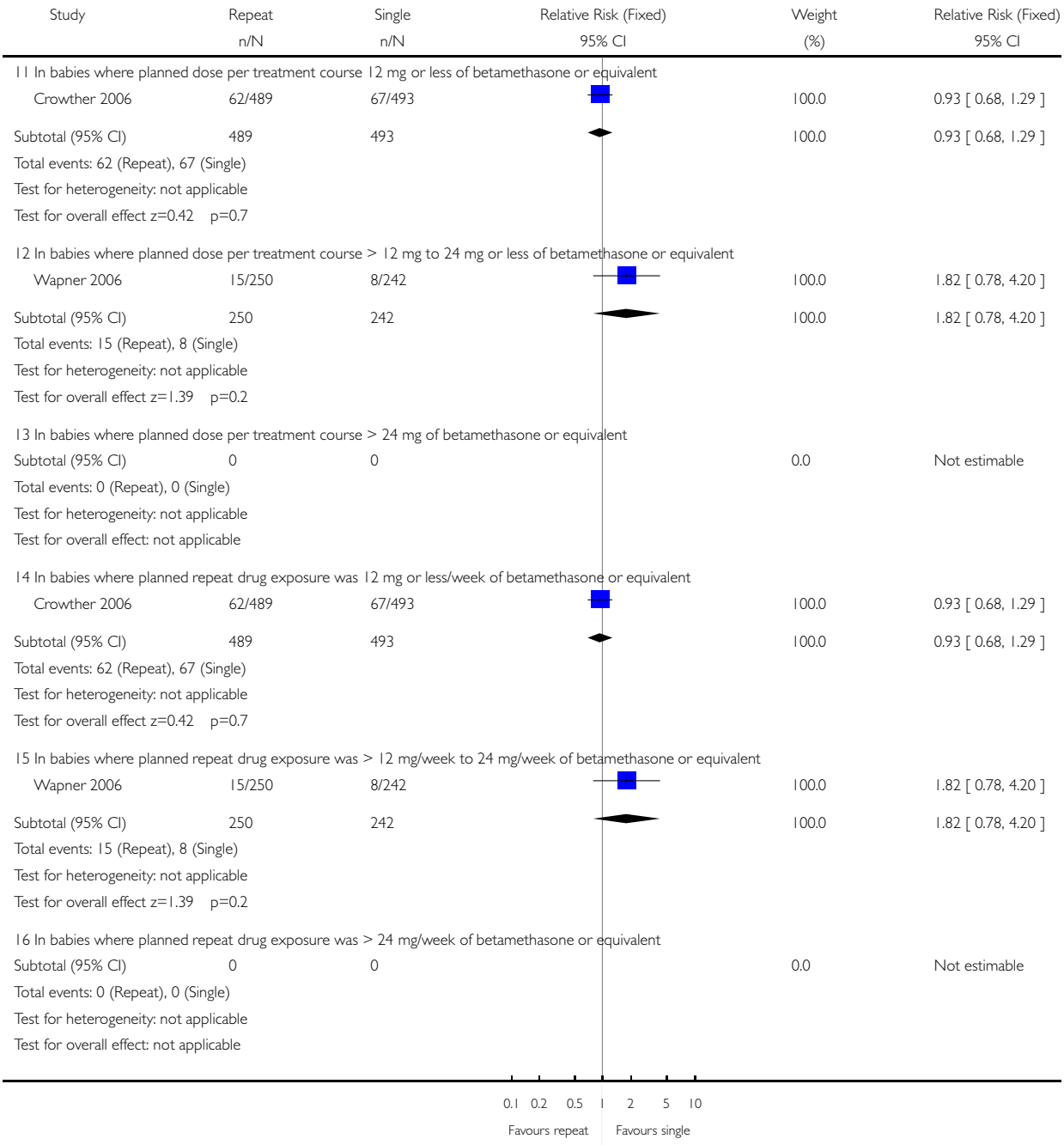

Analysis 01.57. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 57 Vaginal birth

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 57 Vaginal birth

Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 In all women					
Aghajafari 2002	1/6	2/6		0.7	0.50 [0.06, 4.15]
Crowther 2006	163/489	206/493		43.2	0.80 [0.68, 0.94]
McEvoy 2002	9/18	11/19		7.8	0.86 [0.47, 1.57]
Wapner 2006	157/250	151/242		48.4	1.01 [0.88, 1.15]
Subtotal (95% CI)	763	760		100.0	0.90 [0.75, 1.07]
Total events: 330 (Repeat), 370 (Single)					
Test for heterogeneity chi-square=5.27 df=3 p=0.15 I^2 =43.0%					
Test for overall effect z=1.22 p=0.2					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	1/6	2/6		0.7	0.50 [0.06, 4.15]
Crowther 2006	163/489	206/493		43.2	0.80 [0.68, 0.94]
McEvoy 2002	9/18	11/19		7.8	0.86 [0.47, 1.57]
Wapner 2006	157/250	151/242		48.4	1.01 [0.88, 1.15]
Subtotal (95% CI)	763	760		100.0	0.90 [0.75, 1.07]
Total events: 330 (Repeat), 370 (Single)					
Test for heterogeneity chi-square=5.27 df=3 p=0.15 I^2 =43.0%					
Test for overall effect z=1.22 p=0.2					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	1/6	2/6		0.7	0.50 [0.06, 4.15]
Crowther 2006	163/489	206/493		43.2	0.80 [0.68, 0.94]
McEvoy 2002	9/18	11/19		7.8	0.86 [0.47, 1.57]
Wapner 2006	157/250	151/242		48.4	1.01 [0.88, 1.15]
Subtotal (95% CI)	763	760		100.0	0.90 [0.75, 1.07]
Total events: 330 (Repeat), 370 (Single)					
Test for heterogeneity chi-square=5.27 df=3 p=0.15 I^2 =43.0%					

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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Test for overall effect z=1.22 p=0.2					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	163/489	206/493		100.0	0.80 [0.68, 0.94]
Subtotal (95% CI)	489	493		100.0	0.80 [0.68, 0.94]
Total events: 163 (Repeat), 206 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.72 p=0.007					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	1/6	2/6		0.4	0.50 [0.06, 4.15]
McEvoy 2002	9/18	11/19		4.9	0.86 [0.47, 1.57]

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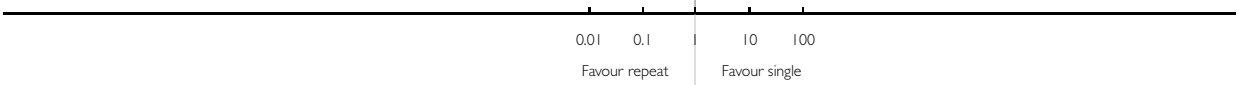
Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Wapner 2006	157/250	151/242		94.7	1.01 [0.88, 1.15]
Subtotal (95% CI)	274	267		100.0	1.00 [0.87, 1.14]
Total events: 167 (Repeat), 164 (Single)					
Test for heterogeneity chi-square=0.65 df=2 p=0.72 I^2 =0.0%					
Test for overall effect z=0.06 p=1					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	163/489	206/493		100.0	0.80 [0.68, 0.94]
Subtotal (95% CI)	489	493		100.0	0.80 [0.68, 0.94]
Total events: 163 (Repeat), 206 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.72 p=0.007					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Aghajafari 2002	1/6	2/6		0.4	0.50 [0.06, 4.15]
McEvoy 2002	9/18	11/19		4.9	0.86 [0.47, 1.57]
Wapner 2006	157/250	151/242		94.7	1.01 [0.88, 1.15]
Subtotal (95% CI)	274	267		100.0	1.00 [0.87, 1.14]
Total events: 167 (Repeat), 164 (Single)					
Test for heterogeneity chi-square=0.65 df=2 p=0.72 I^2 =0.0%					
Test for overall effect z=0.06 p=1					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



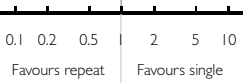
Analysis 01.58. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 58 Caesarean section

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 58 Caesarean section

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
Aghajafari 2002	5/6	4/6		1.0	1.25 [0.64, 2.44]
Crowther 2006	326/489	287/493		73.3	1.15 [1.04, 1.26]
McEvoy 2002	9/18	8/19		2.0	1.19 [0.59, 2.39]
Wapner 2006	93/250	91/242		23.7	0.99 [0.79, 1.24]
Subtotal (95% CI)	763	760		100.0	1.11 [1.01, 1.22]
Total events: 433 (Repeat), 390 (Single)					
Test for heterogeneity chi-square=1.52 df=3 p=0.68 I^2 =0.0%					
Test for overall effect z=2.27 p=0.02					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Aghajafari 2002	5/6	4/6		1.0	1.25 [0.64, 2.44]
Crowther 2006	326/489	287/493		73.3	1.15 [1.04, 1.26]
McEvoy 2002	9/18	8/19		2.0	1.19 [0.59, 2.39]
Wapner 2006	93/250	91/242		23.7	0.99 [0.79, 1.24]
Subtotal (95% CI)	763	760		100.0	1.11 [1.01, 1.22]
Total events: 433 (Repeat), 390 (Single)					
Test for heterogeneity chi-square=1.52 df=3 p=0.68 I^2 =0.0%					
Test for overall effect z=2.27 p=0.02					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Aghajafari 2002	5/6	4/6		1.0	1.25 [0.64, 2.44]
Crowther 2006	326/489	287/493		73.3	1.15 [1.04, 1.26]
McEvoy 2002	9/18	8/19		2.0	1.19 [0.59, 2.39]
Wapner 2006	93/250	91/242		23.7	0.99 [0.79, 1.24]
Subtotal (95% CI)	763	760		100.0	1.11 [1.01, 1.22]
Total events: 433 (Repeat), 390 (Single)					
Test for heterogeneity chi-square=1.52 df=3 p=0.68 I^2 =0.0%					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
Test for overall effect z=2.27 p=0.02					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	326/489	287/493		100.0	1.15 [1.04, 1.26]
Subtotal (95% CI)	489	493		100.0	1.15 [1.04, 1.26]
Total events: 326 (Repeat), 287 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.72 p=0.006					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Aghajafari 2002	5/6	4/6		3.8	1.25 [0.64, 2.44]
McEvoy 2002	9/18	8/19		7.5	1.19 [0.59, 2.39]

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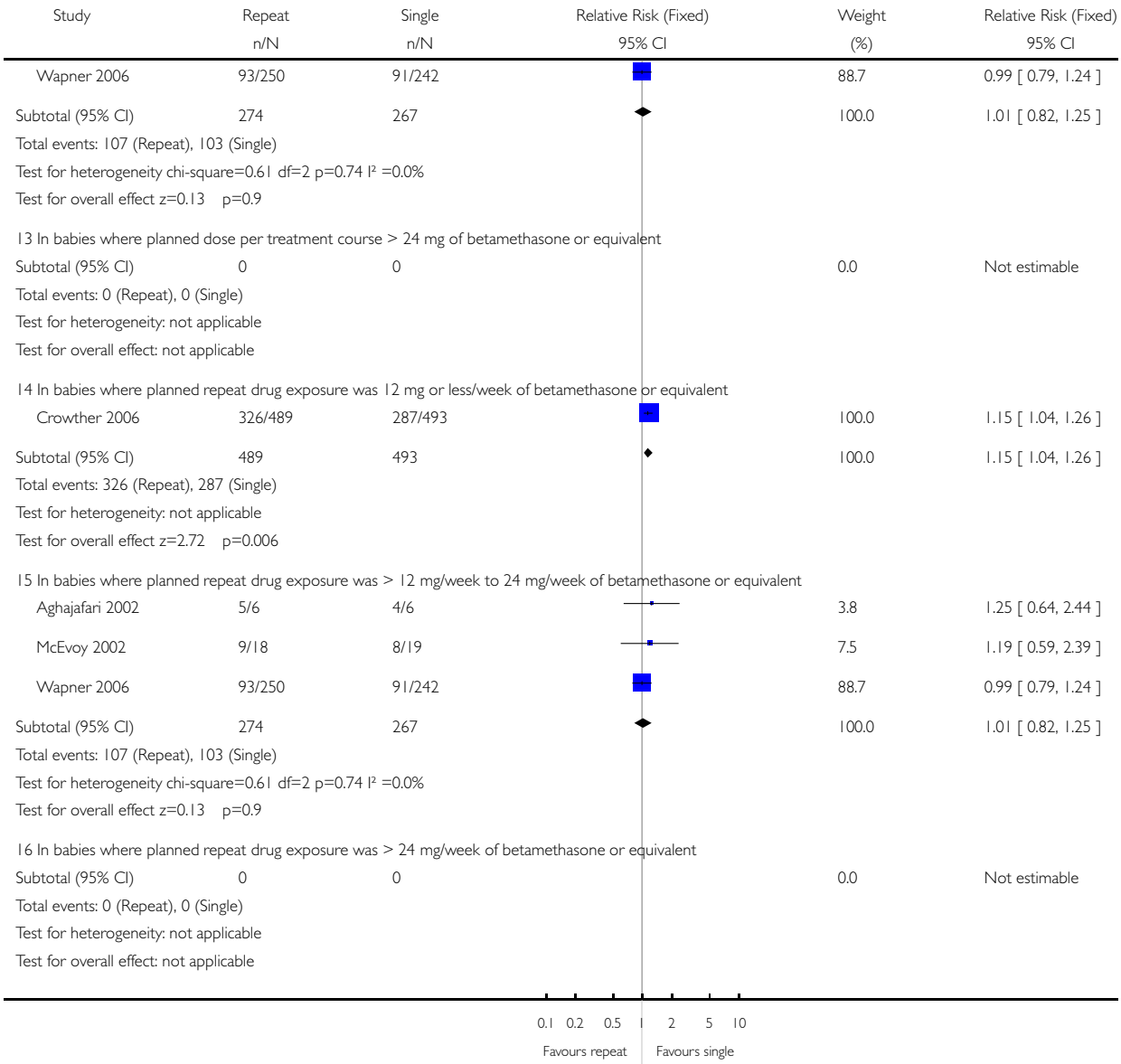


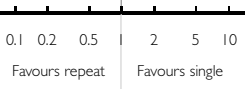
Analysis 01.59. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 59 Postpartum haemorrhage

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 59 Postpartum haemorrhage

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
Guinn 2002	17/249	27/236		100.0	0.60 [0.33, 1.07]
Subtotal (95% CI)	249	236		100.0	0.60 [0.33, 1.07]
Total events: 17 (Repeat), 27 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Guinn 2002	17/249	27/236		100.0	0.60 [0.33, 1.07]
Subtotal (95% CI)	249	236		100.0	0.60 [0.33, 1.07]
Total events: 17 (Repeat), 27 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Guinn 2002	17/249	27/236		100.0	0.60 [0.33, 1.07]
Subtotal (95% CI)	249	236		100.0	0.60 [0.33, 1.07]
Total events: 17 (Repeat), 27 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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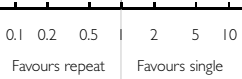
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Guinn 2002	17/249	27/236		100.0	0.60 [0.33, 1.07]
Subtotal (95% CI)	249	236		100.0	0.60 [0.33, 1.07]
Total events: 17 (Repeat), 27 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Guinn 2002	17/249	27/236		100.0	0.60 [0.33, 1.07]
Subtotal (95% CI)	249	236		100.0	0.60 [0.33, 1.07]
Total events: 17 (Repeat), 27 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.74 p=0.08					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.60. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 60 Postnatal pyrexia (variously defined by authors)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 60 Postnatal pyrexia (variously defined by authors)

Study	Repeat n/N	Single n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
01 In all women					
Crowther 2006	32/489	37/493		100.0	0.86 [0.53, 1.41]
Subtotal (95% CI)	489	493		100.0	0.86 [0.53, 1.41]
Total events: 32 (Repeat), 37 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	32/489	37/493		100.0	0.86 [0.53, 1.41]
Subtotal (95% CI)	489	493		100.0	0.86 [0.53, 1.41]
Total events: 32 (Repeat), 37 (Single)					

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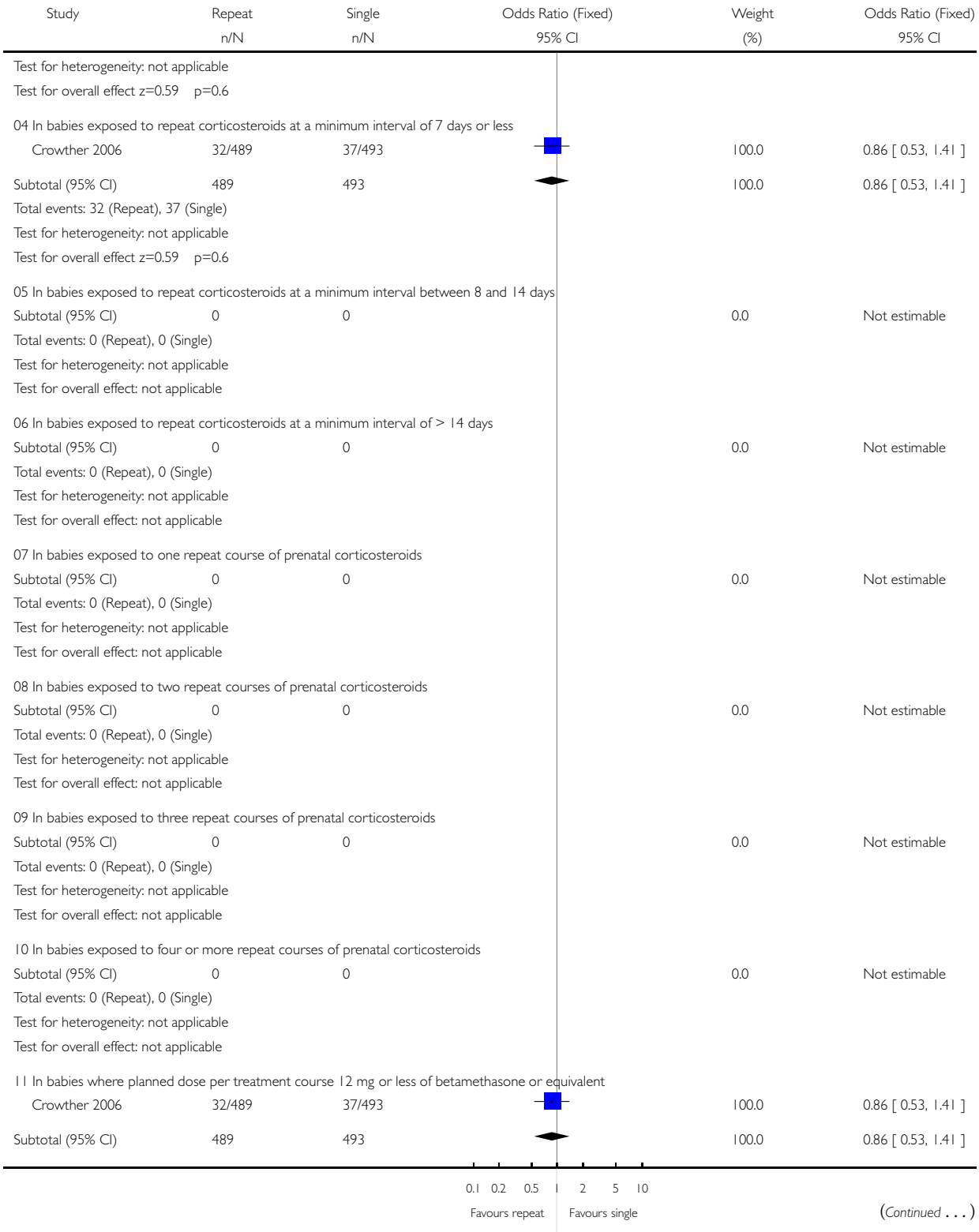

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Study	Repeat n/N	Single n/N	Odds Ratio (Fixed) 95% CI	Weight (%)	Odds Ratio (Fixed) 95% CI
Total events: 32 (Repeat), 37 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	32/489	37/493		100.0	0.86 [0.53, 1.41]
Subtotal (95% CI)	489	493		100.0	0.86 [0.53, 1.41]
Total events: 32 (Repeat), 37 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=0.59 p=0.6					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

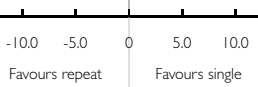
Analysis 01.61. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 61 Length of postnatal hospitalisation (days)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 61 Length of postnatal hospitalisation (days)

Study	Repeat		Single		Weighted Mean Difference (Fixed)	Weight	Weighted Mean Difference (Fixed)
	N	Mean(SD)	N	Mean(SD)	95% CI	(%)	95% CI
01 In all women							
Guinn 2002	249	2.60 (1.20)	236	2.60 (1.30)		100.0	0.00 [-0.22, 0.22]
Subtotal (95% CI)	249		236			100.0	0.00 [-0.22, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
02 In women where pregnancy complicated by preterm prelabour rupture of membranes at trial entry							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
03 In women given repeat corticosteroids as betamethasone							
Guinn 2002	249	2.60 (1.20)	236	2.60 (1.30)		100.0	0.00 [-0.22, 0.22]
Subtotal (95% CI)	249		236			100.0	0.00 [-0.22, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
04 In women given repeat corticosteroids at a minimum interval of 7 days or less							
Guinn 2002	249	2.60 (1.20)	236	2.60 (1.30)		100.0	0.00 [-0.22, 0.22]
Subtotal (95% CI)	249		236			100.0	0.00 [-0.22, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
05 In women given repeat corticosteroids at a minimum interval between 8 and 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
06 In women given repeat corticosteroids at a minimum interval of > 14 days							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
07 In women given one repeat course of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
08 In women given two repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable



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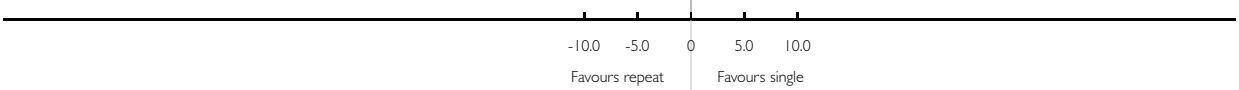
Study	Repeat N	Repeat Mean(SD)	Single N	Single Mean(SD)	Weighted Mean Difference (Fixed) 95% CI	Weight (%)	Weighted Mean Difference (Fixed) 95% CI
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
09 In women given three repeat courses of prenatal corticosteroids							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
12 In women where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent							
Guinn 2002	249	2.60 (1.20)	236	2.60 (1.30)		100.0	0.00 [-0.22, 0.22]
Subtotal (95% CI)	249		236			100.0	0.00 [-0.22, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
13 In women where planned dose per treatment course > 24 mg of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for 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							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							
15 In women where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent							
Guinn 2002	249	2.60 (1.20)	236	2.60 (1.30)		100.0	0.00 [-0.22, 0.22]
Subtotal (95% CI)	249		236			100.0	0.00 [-0.22, 0.22]
Test for heterogeneity: not applicable							
Test for overall effect z=0.00 p=1							
16 In women where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent							
Subtotal (95% CI)	0		0			0.0	Not estimable
Test for heterogeneity: not applicable							
Test for overall effect: not applicable							



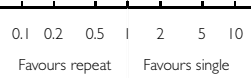
Analysis 01.62. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 62 Any maternal side-effects of therapy

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 62 Any maternal side-effects of therapy

Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 In all women					
Crowther 2006	47/489	24/493		48.9	1.97 [1.23, 3.18]
Wapner 2006	68/250	135/242		51.1	0.49 [0.39, 0.61]
Subtotal (95% CI)	739	735		100.0	0.97 [0.24, 3.90]
Total events: 115 (Repeat), 159 (Single)					
Test for heterogeneity chi-square=27.82 df=1 p=<0.0001 I^2 =96.4%					
Test for overall effect z=0.05 p=1					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	47/489	24/493		48.9	1.97 [1.23, 3.18]
Wapner 2006	68/250	135/242		51.1	0.49 [0.39, 0.61]
Subtotal (95% CI)	739	735		100.0	0.97 [0.24, 3.90]
Total events: 115 (Repeat), 159 (Single)					
Test for heterogeneity chi-square=27.82 df=1 p=<0.0001 I^2 =96.4%					
Test for overall effect z=0.05 p=1					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	47/489	24/493		48.9	1.97 [1.23, 3.18]
Wapner 2006	68/250	135/242		51.1	0.49 [0.39, 0.61]
Subtotal (95% CI)	739	735		100.0	0.97 [0.24, 3.90]
Total events: 115 (Repeat), 159 (Single)					
Test for heterogeneity chi-square=27.82 df=1 p=<0.0001 I^2 =96.4%					
Test for overall effect z=0.05 p=1					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					



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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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	47/489	24/493		100.0	1.97 [1.23, 3.18]
Subtotal (95% CI)	489	493		100.0	1.97 [1.23, 3.18]
Total events: 47 (Repeat), 24 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.80 p=0.005					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Wapner 2006	68/250	135/242		100.0	0.49 [0.39, 0.61]
Subtotal (95% CI)	250	242		100.0	0.49 [0.39, 0.61]
Total events: 68 (Repeat), 135 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=6.07 p<0.00001					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	47/489	24/493		100.0	1.97 [1.23, 3.18]
Subtotal (95% CI)	489	493		100.0	1.97 [1.23, 3.18]
Total events: 47 (Repeat), 24 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=2.80 p=0.005					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Wapner 2006	68/250	135/242		100.0	0.49 [0.39, 0.61]
Subtotal (95% CI)	250	242		100.0	0.49 [0.39, 0.61]
Total events: 68 (Repeat), 135 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=6.07 p<0.00001					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.63. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 63 Maternal hyperglycaemia (variously defined by authors)

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 63 Maternal hyperglycaemia (variously defined by authors)

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 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)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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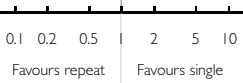
Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					



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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
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)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.36 p=0.2					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.64. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 64 Insomnia

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 64 Insomnia

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
Crowther 2006	3/489	0/493		8.9	7.06 [0.37, 136.26]
Wapner 2006	11/250	5/242		91.1	2.13 [0.75, 6.04]
Subtotal (95% CI)	739	735		100.0	2.57 [0.98, 6.77]
Total events: 14 (Repeat), 5 (Single)					
Test for heterogeneity chi-square=0.57 df=1 p=0.45 I^2 =0.0%					
Test for overall effect z=1.91 p=0.06					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	3/489	0/493		8.9	7.06 [0.37, 136.26]
Wapner 2006	11/250	5/242		91.1	2.13 [0.75, 6.04]

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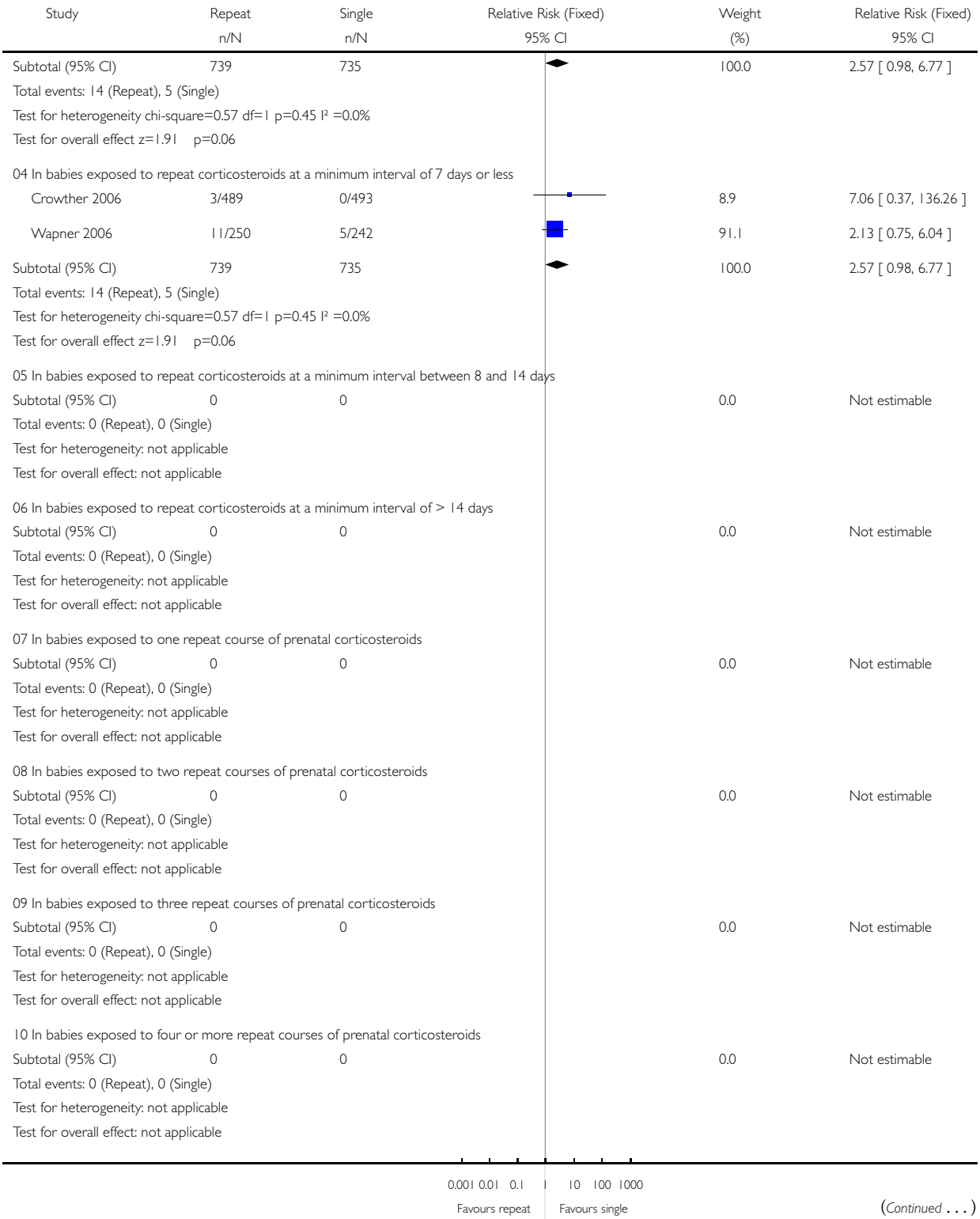

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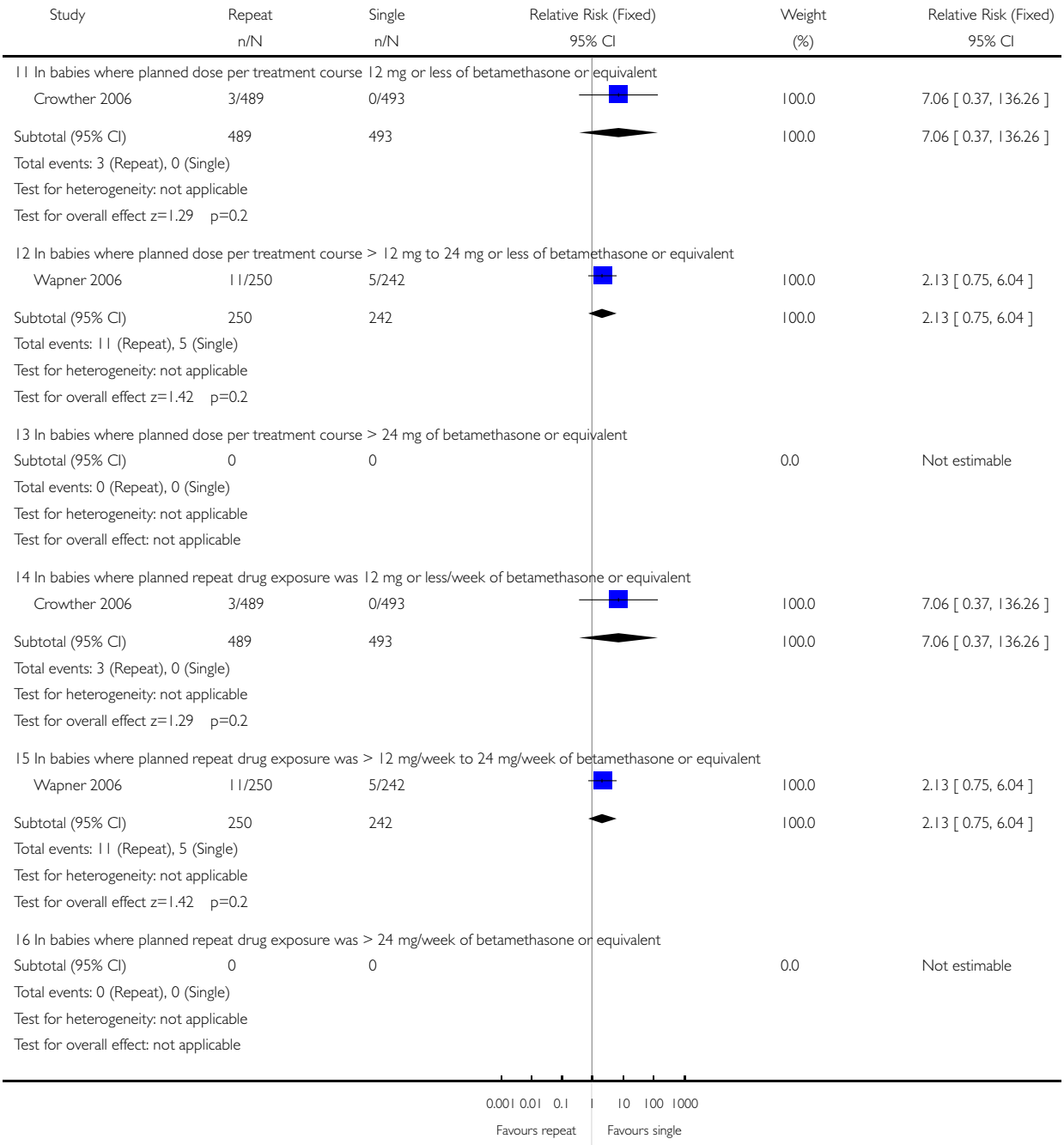


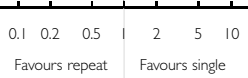
Analysis 01.65. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 65 Pain at injection site

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 65 Pain at injection site

Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
01 In all women					
Crowther 2006	20/489	10/493		48.6	2.02 [0.95, 4.26]
Wapner 2006	28/250	96/242		51.4	0.28 [0.19, 0.41]
Subtotal (95% CI)	739	735		100.0	0.73 [0.11, 5.05]
Total events: 48 (Repeat), 106 (Single)					
Test for heterogeneity chi-square=21.08 df=1 p=<0.0001 I² =95.3%					
Test for overall effect z=0.31 p=0.8					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Crowther 2006	20/489	10/493		48.6	2.02 [0.95, 4.26]
Wapner 2006	28/250	96/242		51.4	0.28 [0.19, 0.41]
Subtotal (95% CI)	739	735		100.0	0.73 [0.11, 5.05]
Total events: 48 (Repeat), 106 (Single)					
Test for heterogeneity chi-square=21.08 df=1 p=<0.0001 I² =95.3%					
Test for overall effect z=0.31 p=0.8					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Crowther 2006	20/489	10/493		48.6	2.02 [0.95, 4.26]
Wapner 2006	28/250	96/242		51.4	0.28 [0.19, 0.41]
Subtotal (95% CI)	739	735		100.0	0.73 [0.11, 5.05]
Total events: 48 (Repeat), 106 (Single)					
Test for heterogeneity chi-square=21.08 df=1 p=<0.0001 I² =95.3%					
Test for overall effect z=0.31 p=0.8					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					



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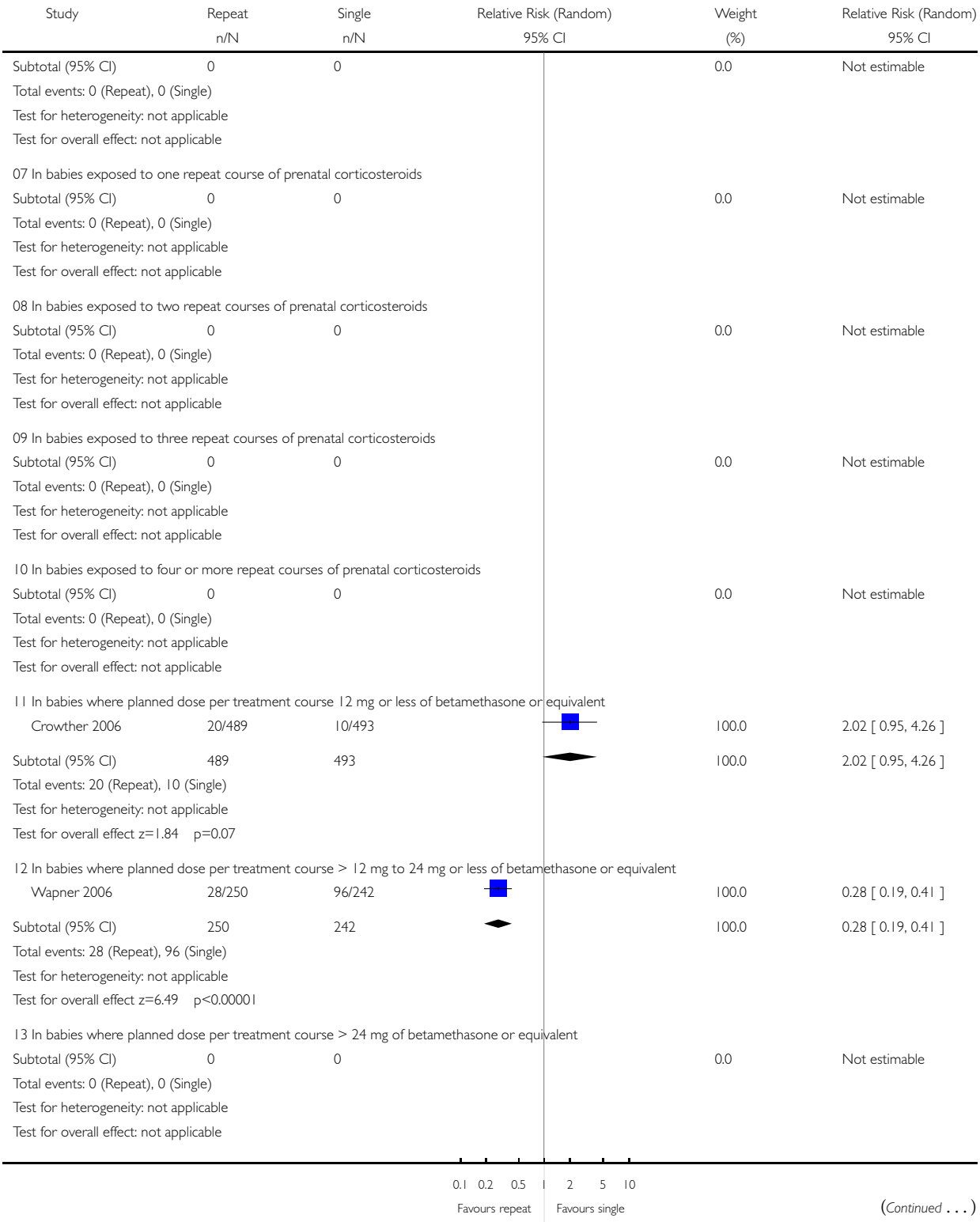

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Study	Repeat n/N	Single n/N	Relative Risk (Random) 95% CI	Weight (%)	Relative Risk (Random) 95% CI
14 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent					
Crowther 2006	20/489	10/493		100.0	2.02 [0.95, 4.26]
Subtotal (95% CI)	489	493		100.0	2.02 [0.95, 4.26]
Total events: 20 (Repeat), 10 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=1.84 p=0.07					
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Wapner 2006	28/250	96/242		100.0	0.28 [0.19, 0.41]
Subtotal (95% CI)	250	242		100.0	0.28 [0.19, 0.41]
Total events: 28 (Repeat), 96 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=6.49 p<0.00001					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

Analysis 01.66. Comparison 01 Repeat doses of corticosteroids versus single course, Outcome 66 Bruising at injection site

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

Comparison: 01 Repeat doses of corticosteroids versus single course

Outcome: 66 Bruising at injection site

Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
01 In all women					
Wapner 2006	13/250	33/242		100.0	0.38 [0.21, 0.71]
Subtotal (95% CI)	250	242		100.0	0.38 [0.21, 0.71]
Total events: 13 (Repeat), 33 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.06 p=0.002					
02 In babies where pregnancy complicated by preterm prelabour rupture of membranes at trial entry					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
03 In babies exposed to repeat corticosteroids as betamethasone					
Wapner 2006	13/250	33/242		100.0	0.38 [0.21, 0.71]
Subtotal (95% CI)	250	242		100.0	0.38 [0.21, 0.71]
Total events: 13 (Repeat), 33 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.06 p=0.002					
04 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less					
Wapner 2006	13/250	33/242		100.0	0.38 [0.21, 0.71]
Subtotal (95% CI)	250	242		100.0	0.38 [0.21, 0.71]
Total events: 13 (Repeat), 33 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.06 p=0.002					
05 In babies exposed to repeat corticosteroids at a minimum interval between 8 and 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
06 In babies exposed to repeat corticosteroids at a minimum interval of > 14 days					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
07 In babies exposed to one repeat course of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
08 In babies exposed to two repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
09 In babies exposed to three repeat courses of prenatal corticosteroids					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					
12 In babies where planned dose per treatment course > 12 mg to 24 mg or less of betamethasone or equivalent					
Wapner 2006	13/250	33/242		100.0	0.38 [0.21, 0.71]
Subtotal (95% CI)	250	242		100.0	0.38 [0.21, 0.71]
Total events: 13 (Repeat), 33 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.06 p=0.002					
13 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for 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					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable					

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Study	Repeat n/N	Single n/N	Relative Risk (Fixed) 95% CI	Weight (%)	Relative Risk (Fixed) 95% CI
15 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent					
Wapner 2006	13/250	33/242		100.0	0.38 [0.21, 0.71]
Subtotal (95% CI)	250	242		100.0	0.38 [0.21, 0.71]
Total events: 13 (Repeat), 33 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect z=3.06 p=0.002					
16 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent					
Subtotal (95% CI)	0	0		0.0	Not estimable
Total events: 0 (Repeat), 0 (Single)					
Test for heterogeneity: not applicable					
Test for overall effect: not applicable