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

Walters A, McKinlay C, Middleton P, Harding JE, Crowther CA

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Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes.
Cochrane Database of Systematic Reviews 2022, Issue 4. Art. No.: CD003935.
DOI: 10.1002/14651858.CD003935.pub5.

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mother and her baby, and reduce the baby's growth. It is, therefore, important that both the benefits and potential negative effects of repeat courses of corticosteroids are understood to allow the best treatment decisions to be made in clinical practice.

What evidence did we find?

We searched for evidence on 27 January 2021 and identified 11 randomised controlled trials (clinical studies where people are randomly put into one of two or more treatment groups), involving 4895 women and their 5975 babies who remained at risk of early birth more than seven days after an initial course of corticosteroids between 23 and 34 weeks' gestation at trial enrolment.

Overall, these trials showed that repeat dose(s) of prenatal corticosteroids reduced the risk of the baby having breathing difficulties, including severe difficulties, and serious health problems in the first few weeks after birth (moderate to high quality and low risk of bias evidence). There was probably no effect on chronic lung disease (usually defined by persistent breathing difficulty and need for oxygen treatment at the age they would have reached 36 weeks of pregnancy). The data available could not confirm if there was an increase, decrease or no change in the combination of fetal or newborn or infant death under one year of age, severe bleeding in the brain or severe bowel inflammation.

For the women, there was no increase in the likelihood of a caesarean birth but it was uncertain if there was an increase or decrease in maternal death, maternal infection, risk of maternal side effects or the need to stop treatment due to side effects. No trials reported data for breastfeeding at the time of leaving hospital or risk of the woman being admitted to the intensive care unit.

In five trials that follow the babies up to early childhood, there were no long-term benefits or harms on later development. Similarly, the two trials that follow children up to mid-childhood (five years in one trial and six to eight years in another trial) found no long-term benefits or harms to development. For early and mid-childhood follow-up it was unclear if the total deaths after randomisation up to the time of follow-up were increased, decreased or the same.

The evidence on which these statements were based was generally of moderate or high quality. Most results were based on information with low risk of bias or some concerns of risk of bias.

What does this mean?

This review shows that a repeat dose of prenatal corticosteroids given to women who remain at risk of an early birth after an initial course of prenatal corticosteroids helps the baby's lungs and reduces serious health problems in the first few weeks of life without harm on health or development up to mid-childhood. Further research is needed on the long-term benefits or harms for the baby into adulthood.

[Intervention Review]

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

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Editorial group: Cochrane Pregnancy and Childbirth Group.
Publication status and date: New search for studies and content updated (conclusions changed), published in Issue 4, 2022.

Citation: Walters A, McKinlay C, Middleton P, Harding JE, Crowther CA.Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving neonatal health outcomes. *Cochrane Database of Systematic Reviews* 2022, Issue 4. Art. No.: CD003935. DOI: 10.1002/14651858.CD003935.pub5.

ABSTRACT

Background

Infants born preterm (before 37 weeks' gestation) are at risk of respiratory distress syndrome (RDS) and need for respiratory support due to lung immaturity. One course of prenatal corticosteroids, administered to women at risk of preterm birth, reduces the risk of respiratory morbidity and improves survival of their infants, but these benefits do not extend beyond seven days. Repeat doses of prenatal corticosteroids have been used for women at ongoing risk of preterm birth more than seven days after their first course of corticosteroids, with improvements in respiratory outcomes, but uncertainty remains about any long-term benefits and harms. This is an update of a review last published in 2015.

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 and neonatal mortality and morbidity.

Search methods

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register, ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP), and reference lists of retrieved studies.

Selection criteria

Randomised controlled trials, including cluster-randomised trials, of women who had already received one course of corticosteroids seven or more days previously and were still at risk of preterm birth, randomised to further dose(s) or no repeat doses, with or without placebo. Quasi-randomised trials were excluded. Abstracts were accepted if they met specific criteria. All trials had to meet criteria for trustworthiness, including a search of the Retraction Watch database for retractions or expressions of concern about the trials or their publications.

Data collection and analysis

We used standard Cochrane Pregnancy and Childbirth methods. Two review authors independently selected trials, extracted data, and assessed trial quality and scientific integrity. We chose primary outcomes based on clinical importance as measures of effectiveness and safety, including serious outcomes, for the women and their fetuses/infants, infants in early childhood (age two to less than five years), the infant in mid- to late childhood (age five to less than 18 years) and the infant as an adult. We assessed risk of bias at the outcome level using the RoB 2 tool and assessed certainty of evidence using GRADE.

Main results

We included 11 trials (4895 women and 5975 babies). High-certainty evidence from these trials indicated that treatment of women who remain at risk of preterm birth seven or more days after an initial course of prenatal corticosteroids with repeat dose(s) of corticosteroids, compared with no repeat corticosteroid treatment, reduced the risk of their infants experiencing the primary infant outcome of RDS (risk ratio (RR) 0.82, 95% confidence interval (CI) 0.74 to 0.90; 3540 babies; number needed to treat for an additional beneficial outcome (NNTB) 16, 95% CI 11 to 29) and had little or no effect on chronic lung disease (RR 1.00, 95% CI 0.83 to 1.22; 5661 babies). Moderate-certainty evidence indicated that the composite of serious infant outcomes was probably reduced with repeat dose(s) of corticosteroids (RR 0.88, 95% CI 0.80 to 0.97; 9 trials, 5736 babies; NNTB 39, 95% CI 24 to 158), as was severe lung disease (RR 0.83, 95% CI 0.72 to 0.97; NNTB 45, 95% CI 27 to 256; 4955 babies). Moderate-certainty evidence could not exclude benefit or harm for fetal or neonatal or infant death less than one year of age (RR 0.95, 95% CI 0.73 to 1.24; 5849 babies), severe intraventricular haemorrhage (RR 1.13, 95% CI 0.69 to 1.86; 5066 babies) and necrotising enterocolitis (RR 0.84, 95% CI 0.59 to 1.22; 5736 babies).

In women, moderate-certainty evidence found little or no effect on the likelihood of a caesarean birth (RR 1.03, 95% CI 0.98 to 1.09; 4266 mothers). Benefit or harm could not be excluded for maternal death (RR 0.32, 95% 0.01 to 7.81; 437 women) and maternal sepsis (RR 1.13, 95% CI 0.93 to 1.39; 4666 mothers). The evidence was unclear for risk of adverse effects and discontinuation of therapy due to maternal adverse effects. No trials reported breastfeeding status at hospital discharge or risk of admission to the intensive care unit.

At early childhood follow-up, moderate- to high-certainty evidence identified little or no effect of exposure to repeat prenatal corticosteroids compared with no repeat corticosteroids for primary outcomes relating to neurodevelopment (neurodevelopmental impairment: RR 0.97, 95% CI 0.85 to 1.10; 3616 children), survival without neurodevelopmental impairment (RR 1.01, 95% CI 0.98 to 1.04; 3845 children) and survival without major neurodevelopmental impairment (RR 1.02, 95% CI 0.98 to 1.05; 1816 children). An increase or decrease in the risk of death since randomisation could not be excluded (RR 1.06, 95% CI 0.81 to 1.40; 5 trials, 4565 babies randomised).

At mid-childhood follow-up, moderate-certainty evidence identified little or no effect of exposure to repeat prenatal corticosteroids compared with no repeat corticosteroids on survival free of neurocognitive impairment (RR 1.01, 95% CI 0.95 to 1.08; 963 children) or survival free of major neurocognitive impairment (RR 1.00, 95% CI 0.97 to 1.04; 2682 children). Benefit or harm could not be excluded for death since randomisation (RR 0.93, 95% CI 0.69 to 1.26; 2874 babies randomised) and any neurocognitive impairment (RR 0.96, 95% CI 0.72 to 1.29; 897 children).

No trials reported data for follow-up into adolescence or adulthood.

Risk of bias across outcomes was generally low although there were some concerns of bias. For childhood follow-up, most outcomes had some concerns of risk of bias due to missing data from loss to follow-up.

Authors' conclusions

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

Further research is needed on the long-term benefits and risks for the baby into adulthood.

PLAIN LANGUAGE SUMMARY

Repeat doses of prenatal corticosteroids for women at risk of preterm birth for improving health outcomes in their babies

What is the issue?

Infants born preterm (before 37 weeks' of pregnancy) are at risk of difficulty breathing and lung disease because their lungs are not fully developed. One course of prenatal (administered during pregnancy) corticosteroids, given to women who may give birth early, helps develop the baby's lungs and improves survival. This benefit does not last beyond seven days so those babies born preterm more than seven days after the course of corticosteroid are still at risk of difficulty breathing and lung disease. This review details the evidence available for the benefits and harms of giving a further course(s) of corticosteroids with the aim of extending the benefits on lung development and breathing.

Why is this important?

Preterm birth is common, affecting approximately one in nine babies worldwide. In addition to breathing difficulties after birth, preterm babies who survive the early weeks after birth are at risk of long-term disabilities such as delays in their development, epilepsy (fits) and cerebral palsy (weakness and problems in the muscles that affects movement and co-ordination).

Corticosteroid medications are anti-inflammatory and suppress growth and the production of cortisol (stress hormone) from the adrenal gland. As a result, repeat prenatal corticosteroid treatment could increase the risk of infection and suppress production of cortisol for the

Summary of findings 1. Summary of findings table - Repeat dose(s) of prenatal corticosteroid compared to single course for the fetus/neonate/infant

Repeat dose(s) of prenatal corticosteroid compared to single course for the fetus/neonate/infant

Patient or population: the fetus/neonate/infant
Setting: hospitals in low-, middle- and high-resource countries
Intervention: repeat dose(s)
Comparison: single course

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with single course	Risk with repeat dose(s)				
A1: Fetal or neonatal or infant death (< 1 year of age) – all fetuses randomised	37 per 1000	**35 per 1000** (27 to 46)	**RR 0.95** (0.73 to 1.24)	5849 (10 RCTs)	⊕⊕⊕⊖ Moderate[a]	For fetal or neonatal or infant death (< 1 year of age), benefit or harm with repeat dose(s) of corticosteroids compared with placebo or standard care could not be excluded.
A5: Respiratory distress syndrome – all fetuses randomised	340 per 1000	**279 per 1000** (252 to 306)	**RR 0.82** (0.74 to 0.90)	3540 (9 RCTs)	⊕⊕⊕⊕ High	Repeat dose(s) of prenatal corticosteroid reduces respiratory distress syndrome.
A7: Severe lung disease – all fetuses randomised	130 per 1000	**108 per 1000** (94 to 126)	**RR 0.83** (0.72 to 0.97)	4955 (6 RCTs)	⊕⊕⊕⊖ Moderate[b]	Repeat dose(s) of prenatal corticosteroids probably results in a slight reduction in severe lung disease.
A8: Chronic lung disease – all fetuses randomised	66 per 1000	**66 per 1000** (54 to 80)	**RR 1.00** (0.83 to 1.22)	5661 (9 RCTs)	⊕⊕⊕⊕ High	Repeat dose(s) of prenatal corticosteroid results in little to no difference in chronic lung disease.
A9: Severe intraventricular haemorrhage (grade 3 or 4) – all fetuses randomised	11 per 1000	**13 per 1000** (8 to 21)	**RR 1.13** (0.69 to 1.86)	5066 (7 RCTs)	⊕⊕⊕⊖ Moderate[c]	For severe intraventricular haemorrhage (grade 3 or 4), benefit or harm with repeat dose(s) of prenatal corticosteroid could not be excluded.
A11: Necrotising enterocolitis – all fetuses randomised	21 per 1000	**18 per 1000** (13 to 26)	**RR 0.84** (0.59 to 1.22)	5736 (9 RCTs)	⊕⊕⊕⊖ Moderate[d]	For necrotising enterocolitis, benefit or harm with repeat dose(s) of prenatal corticosteroid could not be excluded.

A12: Composite of serious outcomes– all fetuses randomised	211 per 1000	**185 per 1000** (169 to 204)	**RR 0.88** (0.80 to 0.97)	5736 (9 RCTs)	⊕⊕⊕⊖ Moderate[e]	Repeat dose(s) of prenatal corticosteroids probably reduces the composite of serious outcomes.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low certainty: our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.
Very low certainty: we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect.

See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427554148264309002.

[a] Downgraded one level due to imprecision as the 95% confidence interval included both benefit and harm.
[b] Downgraded one level due to inconsistency as evidenced by significant statistical heterogeneity, likely due to variation in the definition of serious lung disease.
[c] Downgraded one level due to imprecision as the 95% confidence interval included both marked benefit and marked harm.
[d] Downgraded one level due to imprecision as the 95% confidence interval included both marked benefit and harm.
[e] Downgraded one level due to inconsistency as evidenced by significant statistical heterogeneity, likely due to variation in the definition of the composite serious outcome.

Summary of findings 2. Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the woman

Repeat dose(s) of prenatal corticosteroids compared to single course for the woman

Patient or population: the woman
Setting: hospitals in low-, middle- and high-resource countries
Intervention: repeat dose(s)
Comparison: single course

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with single course	Risk with repeat dose(s)				
B1: Maternal death – all women	5 per 1000	**1 per 1000** (0 to 36)	**RR 0.32** (0.01 to 7.81)	437 (1 RCT)	⊕⊕⊖⊖ Low[a]	For maternal death, benefit or harm with repeat dose(s) of prenatal corticosteroids compared with placebo/standard care could not be excluded.

B2: Maternal sepsis – an all women	67 per 1000	**76 per 1000** (62 to 93)	**RR 1.13** (0.93 to 1.39)	4666 (8 RCTs)	⊕⊕⊕⊖ Moderate[b]	For maternal sepsis, benefit or harm with repeat dose(s) of prenatal corticosteroids compared with placebo/standard care could not be excluded.
B3: Caesarean section – an all women	559 per 1000	**576 per 1000** (548 to 609)	**RR 1.03** (0.98 to 1.09)	4266 (8 RCTs)	⊕⊕⊕⊖ Moderate[c]	Repeat doses of prenatal corticosteroids likely results in little to no difference in the risk of caesarean section.
B4: Discontinuation of therapy due to maternal adverse effects – an all women	Not pooled	Not pooled	Not pooled	485 (1 RCT)	⊕⊕⊖⊖ Low[d]	It was unclear if repeat dose prenatal corticosteroid had an effect on discontinuation of therapy due to maternal adverse effects as only 1 trial reported this outcome and the outcome occurred in 0 women.
Adverse effects of corticosteroids	Not pooled	Not pooled	Not pooled	1477 (2 RCTs)	⊕⊕⊖⊖ Low[e]	It was unclear if repeat dose(s) of prenatal corticosteroids had an effect on the risk of adverse effects. Meta-analysis was not performed as it was not considered appropriate to combine the results due to a marked differences in event rates and direction of effect.
Admission to the intensive care unit - not reported	-	-	-	-	-	No trials reported data for this outcome.
Breastfeeding at hospital discharge - not reported	-	-	-	-	-	No trials reported data for this outcome.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427567765501157336.

[a] Downgraded two levels due to imprecision given there was only one event and a wide 95% confidence interval included both significant benefit and significant harm.

[b] Downgraded one level for imprecision as the 95% confidence interval included possible benefit and possible harm.
[c] Downgraded one level for inconsistency as evidenced by statistical heterogeneity.
[d] Downgraded two levels due to imprecision as there were no events recorded making it impossible to provide a relative effect estimate.
[e] Downgraded two levels for marked inconsistency of effect as evidenced by very serious heterogeneity.

Summary of findings 3. Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the child aged 2 to < 5 years

Repeat dose(s) of prenatal corticosteroids compared to single course for the child aged 2 to < 5 years

Patient or population: the child
Setting: outpatient settings in high-resource countries
Intervention: repeat dose(s)
Comparison: single course

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with single course	Risk with repeat dose(s)				
C1: Total deaths (after randomisation) up to early childhood follow-up - In all children follow-up: range 2 years to 3 years	42 per 1000	**44 per 1000** (34 to 58)	**RR 1.06** (0.81 to 1.40)	4565 (5 RCTs)	⊕⊕⊕⊖ Moderate[a]	For the risk of death after randomisation up to early childhood follow-up, benefit or harm could not be excluded for repeat dose(s) of corticosteroids.
C2: Neurodevelopmental impairment at early childhood follow-up - In all children follow-up: range 2 years to 3 years	187 per 1000	**181 per 1000** (159 to 205)	**RR 0.97** (0.85 to 1.10)	3616 (4 RCTs)	⊕⊕⊕⊕ High	Repeat dose(s) of prenatal corticosteroids results in little to no difference in neurodevelopmental impairment at early childhood follow-up.
C3: Survival free of neurodevelopmental impairment at early childhood follow-up - In all children follow-up: range 2 years to 3 years	777 per 1000	**785 per 1000** (761 to 808)	**RR 1.01** (0.98 to 1.04)	3845 (4 RCTs)	⊕⊕⊕⊕ High	Repeat dose(s) of prenatal corticosteroids results in little to no difference in survival free of neurodevelopmental impairment at early childhood follow-up.
C4: Survival free of major neurodevelopmental impairment atearly childhood follow-up - In all children	856 per 1000	**873 per 1000** (839 to 899)	**RR 1.02** (0.98 to 1.05)	1816 (3 RCTs)	⊕⊕⊕⊖ Moderate[b]	Repeat dose(s) of prenatal corticosteroids probably results in little to no difference in survival free of major

follow-up: range 2 years to 3 years						neurodevelopmental impairment at early childhood follow-up.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427569318660056467.

[a] Downgraded one level due to imprecision as the 95% confidence interval included possible benefit and harm.
[b] Downgraded one level due to inconsistency as evidenced by marked statistical heterogeneity.

Summary of findings 4. Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the child in mid- to late childhood (5 to < 18 years of age)

Repeat dose(s) of prenatal corticosteroids compared to single course for the child in mid- to late childhood (5 to < 18 years of age)

Patient or population: the child
Setting: outpatient settings in high-resource countries
Intervention: repeat dose(s)
Comparison: single course

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	№ of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with single course	Risk with repeat dose(s)				
D1: Total deaths (after randomisation) up to mid- to later childhood follow-up - In all children follow-up: range 5 years to 8 years	57 per 1000	**53 per 1000** (39 to 72)	**RR 0.93** (0.69 to 1.26)	2874 (2 RCTs)	⊕⊕⊕⊖ Moderate[a]	For total deaths after randomisation up to mid-childhood follow-up, benefit or harm could not be excluded for repeat dose(s) of corticosteroids.

D2: Neurocognitive impairment atmid- to later childhood follow-up - In all children follow-up: range 5 years to 8 years	167 per 1000	**160 per 1000** (120 to 215)	**RR 0.96** (0.72 to 1.29)	897 (1 RCT)	⊕⊕⊖⊖ Low[b,c]	For neurocognitive impairment at mid-childhood follow-up, benefit or harm could not be excluded for repeat dose(s) of corticosteroids.
D3: Survival free of neurocognitive impairment atmid- to later childhood follow-up - In all children follow-up: range 5 years to 8 years	773 per 1000	**780 per 1000** (734 to 835)	**RR 1.01** (0.95 to 1.08)	963 (1 RCT)	⊕⊕⊕⊖ Moderate[d]	Repeat dose(s) of prenatal corticosteroids likely results in little to no difference in survival free of neurocognitive impairment at mid-childhood follow-up.
D4: Survival free of major neurocognitive impairment atmid- to later childhood follow-up - In all children follow-up: range 5 years to 8 years	807 per 1000	**807 per 1000** (783 to 839)	**RR 1.00** (0.97 to 1.04)	2682 (2 RCTs)	⊕⊕⊕⊖ Moderate[b]	Repeat dose(s) of prenatal corticosteroids likely results in little to no difference in survival free of major neurocognitive impairment at mid-childhood follow-up.

*__The risk in the intervention group__ (and its 95% confidence interval) is based on the assumed risk in the comparison group and the __relative effect__ of the intervention (and its 95% CI).

CI: confidence interval; **RR:** risk ratio

GRADE Working Group grades of evidence
High certainty: we are very confident that the true effect lies close to that of the estimate of the effect.
Moderate certainty: we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
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See interactive version of this table: https://gdt.gradepro.org/presentations/#/isof/isof_question_revman_web_427569595635902654.

[a] Downgraded one level for imprecision due to a wide 95% confidence interval that included benefit and possible harm.
[b] Downgraded one level due to risk of bias as the included trials were judged to have some concerns of risk of bias due to missing outcome data.
[c] Downgraded one level for imprecision as the 95% confidence interval included possible benefit and harm.
[d] Downgraded one level due to risk of bias as the single included trial was judged to have some concerns of risk of bias due to missing outcome data.

BACKGROUND

Description of the condition

Infants born preterm (before 37 weeks' gestation) are at high risk of neonatal lung disease and its sequelae. Worldwide in 2010, an estimated 11.1% of all live births were preterm (Blencowe 2013). The more preterm the baby, the greater are the risks, especially when birth occurs before 32 weeks' gestation. In Australia, in 2018, 1.6% of all births were before 32 weeks' gestation (AIHW 2020). 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 after birth are at risk of long-term neurological disability (Cheong 2017). 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 (McGoldrick 2020; Rojas-Reyes 2012).

A single course of prenatal corticosteroids reduces the risk of RDS from 14.8% to 10.5% (risk ratio (RR) 0.71, 95% confidence interval (CI) 0.65 to 0.78; 26 trials, 11,183 infants) (McGoldrick 2020). Other beneficial effects include a reduced risk of neonatal death, intraventricular haemorrhage, necrotising enterocolitis and childhood developmental delay (McGoldrick 2020). Prenatal corticosteroids enhance the benefits of postnatal surfactant therapy (Jobe 1994), and reduce the need for blood pressure support (Moise 1995). Overall, there is a reduction in the cost and duration of neonatal care. The cost-benefit of a single course of prenatal corticosteroids is estimated as USD 3000 (NIH 1995). Long-term follow-up into adulthood of infants exposed to prenatal corticosteroids in the first (New Zealand) trial (Liggins 1972), have shown no adverse clinical outcomes (Dalziel 2005a; Dalziel 2005b). However, even though prenatal corticosteroids remain the most effective known strategy for reducing the adverse consequences of preterm birth, and despite postnatal intensive care and exogenous surfactant, there is still significant neonatal morbidity (Rojas-Reyes 2012).

Description of the intervention

Prenatal corticosteroid treatment compared with no prenatal corticosteroid treatment has been shown to be ineffective if babies are born more than seven days after the corticosteroid treatment has been given (Roberts 2006). Specifically, there is no reduction in the incidence of RDS or neonatal mortality (McLaughlin 2003; Roberts 2006). There may be benefit in repeating the dose of prenatal corticosteroids to women who remain at risk of preterm birth more than seven days after the initial course. This was suggested by Liggins and Howie in the first reported controlled trial of prenatal glucocorticoid treatment for the prevention of RDS in premature infants (Liggins 1972). Indeed, in some clinical centres this has become standard practice and has been incorporated into clinical guidelines (Antenatal Corticosteroids CPG Panel 2015).

How the intervention might work

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

Why it is important to do this review

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

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

Other animal studies have shown that repeat doses of corticosteroids may have harmful effects on neuronal myelination, the development of insulation for nerve fibres, affecting nerve conduction (Dunlop 1997); the development of the alveolar septa (the sites of gas exchange in the lung) leaving 'emphysematous'-like alveoli (Tschanz 1995) and HPA axis function (Ikegami 1997). Effects on the HPA axis can persist into adulthood.

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

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

This is an update of a review first published in 2000 and updated in 2007, 2011 and 2015.

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 and neonatal morbidity and mortality.

METHODS

Criteria for considering studies for this review

Types of studies

All published, unpublished and ongoing randomised trials with reported data that compared outcomes for women at risk of preterm birth randomised to receive a repeat dose(s) of prenatal corticosteroids with outcomes in controls given a single course of prenatal corticosteroids, with or without additional placebo administration. Trials must have used some form of random allocation. Quasi-randomised trials and cross-over trials were not eligible for inclusion. Cluster-randomised trials were eligible for inclusion. Trials published as abstracts were included if they met the criteria discussed in 'Selection of studies: Abstracts'.

Types of participants

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

Types of interventions

Corticosteroid administered to the women intravenously, intramuscularly or orally, compared with either placebo or no placebo. Both groups must have received their initial course of corticosteroids seven or more days earlier. We excluded trials in which the fetus received corticosteroids directly as these are included in another Cochrane Review ("Transplacental versus direct fetal corticosteroid treatment for accelerating fetal lung maturation where there is a risk of preterm birth"; Utama 2018).

Types of outcome measures

We prespecified outcomes for the review after each outcome was independently ranked for clinical importance by each review author using the scale described in Chapter 3 of the GRADE Handbook (gdt.gradepro.org/app/handbook/handbook.html). This scale uses scores from 1 to 9 to divide outcomes into those of *critical importance*, *important but not critical* and *of limited importance* to clinical decision-making. Outcomes of critical importance to clinical decision-making were included as primary outcomes for the review. Those outcomes classified as important but not critical were included as secondary outcomes.

Primary outcomes

We chose primary outcomes to be most representative of the clinically important measures of effectiveness and safety, including serious outcomes, for the women and their fetuses/infants, the infant in early childhood (age two to less than five years), the infant in mid- to late childhood (age five to less than 18 years) and the infant as an adult. These outcomes were changed from the previous version of the review after first identifying outcomes considered of clinical importance by the review authors, refining their definitions by discussion among the review authors, and ranking their importance using the criteria described in the GRADE handbook in Types of outcome measures. The changes to outcome descriptions are summarised in the Differences between protocol and review section.

For the fetus/neonate/infant

- Fetal or neonatal or infant death (less than one year of age).
- Fetal death.
- Neonatal death.
- Infant death (less than one year of age).
- Respiratory distress syndrome (however defined by authors).
- Severe respiratory distress syndrome (however defined by authors).
- Severe lung disease (however defined by authors).
- Chronic lung disease (however defined by authors).
- Severe intraventricular haemorrhage (grade 3 or 4).
- Intraventricular haemorrhage (any grade).
- Necrotising enterocolitis (however defined by authors).
- Composite serious outcome (however defined by authors).

For the woman

- Maternal death.
- Maternal sepsis (any of chorioamnionitis during labour, endometritis, pyrexia after trial entry requiring the use of antibiotics, puerperal sepsis, intrapartum fever requiring the use of antibiotics, postnatal pyrexia or however defined by authors).
- Caesarean section.
- Discontinuation of therapy because of maternal side effects.
- Adverse effects of corticosteroids (including gastrointestinal upset, insomnia, local injection site adverse effects (pain, bruising, haematoma or infection at the injection site)).
- Admission to the intensive care unit.
- Breastfeeding at hospital discharge.

For the child in early childhood (aged two to less than five years)

- Total deaths (after randomisation).
- Neurodevelopmental impairment at age two to less than five years (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one standard deviation (SD) below the mean), motor impairment (mild or major impairment by appropriate mode of assessment), or cerebral palsy, or however defined by authors).
- Survival free of neurodevelopmental impairment at age two to less than five years (none of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), motor impairment (mild or major impairment by appropriate mode of assessment), cerebral palsy or however defined by authors).
- Survival free of major neurodevelopmental impairment at age two to less than five years (none of: moderate or severe intellectual impairment (developmental quotient or intelligence quotient more than two SDs below the mean), moderate or severe cerebral palsy, major motor impairment, blindness (corrected visual acuity worse than 6/60 in the better eye) or

deafness (hearing loss requiring amplification or worse), or however defined by authors).
- Cerebral palsy (categorised as nil, mild, moderate or severe, however defined by authors).
- Developmental delay or intellectual impairment at age two to less than five years (categorised as mild (one SD below the mean), moderate (two SDs below the mean) or severe (three SDs below the mean) by an appropriate rating scale, or however defined by authors).

For the child in mid- to late childhood (aged five to less than 18 years)

- Total deaths (after randomisation).
- Neurocognitive impairment at age five to less than 18 years (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment), or cerebral palsy, or however defined by authors).
- Survival free of neurocognitive impairment at age five to less than 18 (none of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment) cerebral palsy, or however defined by authors).
- Survival free of major neurocognitive impairment at age five to less than 18 years (none of: moderate or severe intellectual impairment (developmental quotient or intelligence quotient more than two SD below the mean), major motor impairment, moderate or severe cerebral palsy, blindness (corrected visual acuity worse than 6/60 in the better eye) or deafness (hearing loss requiring amplification or worse), or however defined by authors).
- Motor impairment at age five to less than 18 years (categorised as nil, mild impairment, major impairment by appropriate mode of assessment or however defined by authors).
- Cognitive impairment at age five to less than 18 years (categorised as mild (one SD below the mean), moderate (two SDs below the mean) or severe (three SDs below the mean) by an appropriate rating scale, or however defined by authors).
- Educational achievement (however defined by authors).
- Cerebral palsy (categorised as nil, mild, moderate or severe by an appropriate rating scale or however defined by authors).
- Hypertension (however defined by authors).

For the child as an adult (aged 18 years or greater)

- Total deaths (after randomisation).
- Neurodevelopmental disability at age 18 years or greater (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), cerebral palsy, or however defined by authors).
- Cardiovascular disease (including diagnosis of ischaemic heart disease, cerebrovascular disease, heart failure or however defined by authors).
- Cardiovascular death (ischaemic heart disease, stroke, arrhythmia or heart failure as cause of death or however defined by authors).
- Type 2 diabetes mellitus (however defined by authors).
- Glucose intolerance (however defined by authors).
- Obesity/overweight (however defined by authors).
- Hypertension (however defined by authors).

Secondary outcomes

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

For the fetus/neonate/infant

- Birthweight (including weight for gestation if reported).
- Small-for-gestational age (however defined by authors).
- Length at birth (including length for gestation if reported).
- Head circumference at birth (including head circumference for gestation if reported).
- Growth assessments at primary hospital discharge (weight, head circumference and length including measurements standardised for postmenstrual age if reported).
- Growth assessments at infant follow-up (weight, head circumference, length, including measurements standardised for postmenstrual age if reported).
- Gestational age at birth (term birth 37 weeks or greater, preterm birth less than 37 weeks, very preterm birth less than 34 weeks, extremely preterm birth less than 28 weeks and mean gestational age).
- Interval between trial entry and birth.
- Admission to the neonatal intensive care unit (NICU).
- Proven neonatal infection while in the NICU.
- Early systemic neonatal infection (less than 48 hours after birth or however defined by authors).
- Late systemic neonatal infection (48 hours or greater after birth or however defined by authors).
- Retinopathy of prematurity (however defined by authors).
- Periventricular leukomalacia (however defined by authors).
- Neonatal encephalopathy (however defined by authors).
- Patent ductus arteriosus.
- Use of respiratory support (any respiratory support including invasive (via an endotracheal tube) or non-invasive modalities or however defined by authors).
- Duration of respiratory support (any respiratory support, including any invasive (via an endotracheal tube) and non-invasive modalities or however defined by authors).
- Use of invasive respiratory support (any respiratory support via an endotracheal tube or however defined by authors).
- Duration of invasive respiratory support (any respiratory support via an endotracheal tube or however defined by authors).
- Use of non-invasive respiratory support (any form of respiratory support that does not require an endotracheal tube including any non-invasive ventilation, continuous positive airway pressure (CPAP), high or low flow gases or however defined by authors).
- Duration of non-invasive respiratory support (any form of respiratory support that does not require an endotracheal tube including any non-invasive ventilation, CPAP and high or low flow gases or however defined by authors).
- Use of oxygen supplementation.

- Duration of oxygen supplementation.
- Use of surfactant.
- Use of postnatal corticosteroids.
- Use of nitric oxide for respiratory support.
- Pulmonary hypertension (however defined by authors).
- Use of inotropic support.
- Duration of inotropic support.
- Air leak syndrome.
- Measures of renal function (however reported by authors).
- Feed tolerance (time to full feed tolerance, number of feed interruptions or however defined by authors).
- Apgar score less than 7 at five minutes.
- Cardiac hypertrophy (however defined by authors).
- Measures of HPA function (however assessed by authors).

For the woman

- Puerperal sepsis (aged 18 years or greater).
- Chorioamnionitis during labour (however defined by authors).
- Endometritis (however defined by authors).
- Pyrexia after trial entry requiring the use of antibiotics.
- Intrapartum fever requiring the use of antibiotics.
- Postpartum haemorrhage.
- Postnatal pyrexia (however defined by authors).
- Preterm prelabour rupture of the membranes after trial entry.
- Mode of birth.
- Hypertension (however defined by authors).
- Pulmonary oedema.
- Glucose intolerance (however defined by authors).
- Postnatal depression (however defined by authors).
- Local injection site adverse effects (pain, bruising, haematoma or infection at the injection site).
- Insomnia after treatment (however defined by authors).
- Gastrointestinal adverse effects of treatment (however defined by authors).
- Satisfaction with the therapy.
- Quality of life.

For the child aged two to less than five years

- Child behaviour (measured by an appropriate mode of behavioural assessment or however defined by authors).
- Motor impairment at age two to less than five years (categorised as nil, mild impairment, major impairment by appropriate mode of assessment or however defined by authors).
- Deafness/hearing impairment (however defined by authors).
- Blindness/visual impairment (however defined by authors).
- Growth assessments (weight, head circumference, height and assessments for age if available).
- Body mass index (BMI).
- Obesity/overweight.
- Blood pressure (systolic, diastolic, mean arterial).
- Hypertension (however defined by authors).
- Measures of lung function (however defined by authors).
- Chronic lung disease of infancy (however defined by authors).
- Asthma or recurrent wheeze (however defined by authors).
- Any respiratory disease (however defined by authors).
- Measures of insulin and glucose homeostasis (however defined by authors).
- Measures of lipid profile (however defined by authors).
- Measures of HPA axis function (however assessed by authors).
- Body composition (lean body mass corrected for height, fat mass corrected for height or however defined by authors).
- Bone density (however assessed by authors).

For the child aged five to less than 18 years

- Child behaviour (however defined by authors).
- Deafness/hearing impairment (however defined by authors).
- Blindness/visual impairment (however defined by authors).
- Growth assessments (weight, head circumference, height and assessments for age if available).
- BMI.
- Obesity/overweight.
- Blood pressure (systolic, diastolic, mean arterial).
- Measures of lung function (however defined by authors).
- Asthma or recurrent wheeze (however defined by authors).
- Respiratory disease (however defined by authors).
- Measure of insulin and glucose homeostasis (however defined by authors).
- Lipid profile (however reported by authors).
- Measures of HPA axis function (however defined by authors).
- Bone density (however assessed by authors).
- Body composition (lean body mass (fat free mass) for height, fat mass for height or however defined by authors).

For the child as an adult (aged 18 years or greater)

- Educational achievement (however defined by authors).
- Prediabetes (however defined by authors).
- Mental health disorders (however defined by authors).
- Diagnosis of depression (however defined by authors).
- Diagnosis of bipolar affective disorder (however defined by authors).
- Diagnosis of anxiety disorder (however defined by authors).
- Ischaemic heart disease (however defined by authors).
- Stroke (however defined by authors).
- Heart failure.
- Blindness/visual impairment (however defined by authors).
- Deafness/hearing impairment (however defined by authors).
- Measures of insulin and glucose homeostasis (however defined by authors).

Use of health services

- Length of prenatal hospitalisation for the woman.
- Length of postnatal hospitalisation for the woman.
- Maternal admission to the intensive care unit.
- Admission to and length of stay in NICU.
- Length of infant hospitalisation.
- Costs of maternal care.
- Costs of neonatal care.
- Hospital re-admission at childhood follow-up.

While we sought all the above outcomes from the included trials, only those with data appear in the analysis tables. We included outcomes in the analyses if data were available for analysis according to original allocation.

Search methods for identification of studies

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

Electronic searches

For this update, we searched Cochrane Pregnancy and Childbirth's Trials Register by contacting their Information Specialist (27 January 2021).

The Register is a database containing over 27,000 reports of controlled trials in the field of pregnancy and childbirth. It represents over 30 years of searching. For full current search methods used to populate Pregnancy and Childbirth's Trials Register including the detailed search strategies for the Cochrane Central Register of Controlled Trials (CENTRAL), MEDLINE, Embase and CINAHL; the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service, see pregnancy.cochrane.org/pregnancy-and-childbirth-groups-trials-register.

Briefly, Cochrane Pregnancy and Childbirth's Trials Register is maintained by their Information Specialist and contains trials identified from:

- monthly searches of CENTRAL;
- weekly searches of MEDLINE (Ovid);
- weekly searches of Embase (Ovid);
- monthly searches of CINAHL (EBSCO);
- handsearches of 30 journals and the proceedings of major conferences;
- weekly current awareness alerts for a further 44 journals plus monthly BioMed Central email alerts.

Search results are screened by two people and the full text of all relevant trial reports identified through the searching activities described above is reviewed. Based on the intervention described, each trial report is assigned a number that corresponds to a specific Pregnancy and Childbirth review topic (or topics), and is then added to the Register. The Information Specialist searches the Register for each review using this topic number rather than keywords. This results in a more specific search set that has been fully accounted for in the relevant review sections (Included studies; Excluded studies; Studies awaiting classification; Ongoing studies).

In addition, we searched ClinicalTrials.gov and the World Health Organization (WHO) International Clinical Trials Registry Platform (ICTRP; trialsearch.who.int/) (27 January 2021) for unpublished, planned and ongoing trial reports using the search methods detailed in Appendix 1.

Searching other resources

We searched reference lists of trials and other review articles. We attempted to contact authors of two studies listed under 'ongoing studies' in the previous version of the review and two newly identified trials that are ongoing for further information for this update.

We applied no language restrictions.

Data collection and analysis

For methods used in the previous version of this review, see Crowther 2015.

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

Selection of studies

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

Two review authors assessed the trials for eligibility and trustworthiness. Trials were not assessed blind, as we knew the author's names, institution and the source of publication. We resolved any disagreement by discussion until we reached consensus.

Screening eligible studies for scientific integrity/trustworthiness

All studies meeting our inclusion criteria were also evaluated by two review authors against predefined criteria to select studies that, based on available information, were deemed sufficiently trustworthy to be included in the analysis. Studies were considered at high risk for untrustworthiness if one or more of the following criteria were met.

Research governance

- Are there any retraction notices or expressions of concern listed on the Retraction Watch Database relating to this study (retractiondatabase.org/RetractionSearch.aspx?)?
- No prospective trial registration for studies published after 2010 without plausible explanation.
- When requested, trial authors refused to provide/share the protocol or ethics approval letter, or both.
- Trial authors refused to engage in communication with the Cochrane editorial group.
- Trial authors refused to provide individual participant data upon request with no justifiable reason.

Baseline characteristics

- Characteristics of the study participants being too similar (distribution of mean (SD) excessively narrow or excessively wide, as noted by Carlisle 2017).

Feasibility

- Implausible numbers (e.g. 500 women with severe cholestasis of pregnancy recruited in 12 months).
- (Close to) zero losses to follow-up without plausible explanation.

Results

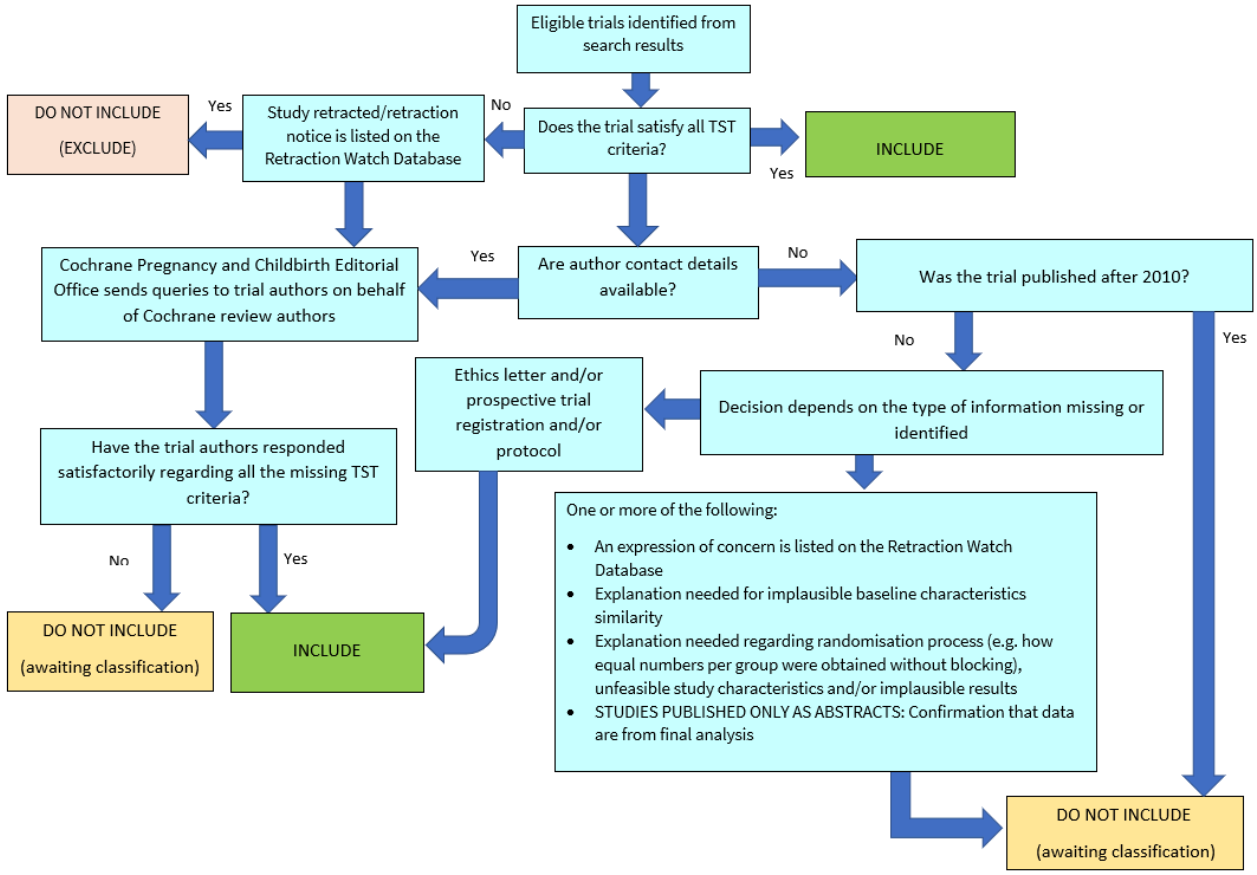
- Implausible results (e.g. massive risk reduction for main outcomes with small sample size).

- Concerns about the methods of randomisation such as unexpectedly even numbers of women 'randomised' including a mismatch between the numbers and the methods (e.g. if the authors say 'no blocking was used' but still have equal numbers, or if the authors say they used 'blocks of four' but the final numbers differ by six).

Studies assessed as being potentially 'high risk' were not included in the review. Where a study was classified as 'high risk' for one or more of the above criteria we attempted to contact the study authors to address any possible lack of information/concerns. If adequate information remained unavailable, the study remained in 'awaiting classification' and the reasons and communications with the author (or lack of) described in detail.

The process is described in full in Figure 1.

Figure 1. Applying the Cochrane Pregnancy and Childbirth Trustworthiness Screening Tool.



Abstracts

Data from abstracts were only included if, in addition to the trustworthiness assessment, the study authors confirmed in writing that the data to be included in the review had come from the final analysis and will not change. If such information was not available/provided, the study remained as 'awaiting classification' (as above).

Data extraction and management

Two review authors independently extracted study data, using a predesigned data form. Two review authors (AW and PM) independently extracted data for the ACTORDS (Australasian Collaborative Trial of Repeat Doses of Steroids) trial (Crowther 2006). We resolved discrepancies through discussion. When information was unclear, we attempted to contact authors of the original reports to request further details. We entered data into Review Manager software (RevMan Web 2021) and checked them for accuracy.

Assessment of risk of bias in included studies

Two review authors independently assessed risk of bias for each outcome for each study using the RoB 2 tool (accessed 30 June 2021, available from: sites.google.com/site/riskofbiastool/welcome/rob-2-0-tool), as detailed in Chapter 8 of the *Cochrane Handbook for Systematic Reviews of Interventions* (Higgins 2019). All primary and secondary outcomes were assessed (by outcome measure and time point of assessment where relevant) for risk of bias using the ROB 2 tool. Three review authors (CC, JH and CM) had authored publications for Crowther 2006 or its follow-up studies and, therefore, they were not involved in risk of bias assessment related to this trial and its outcomes. Two review authors (AW and PM) assessed risk of bias for Crowther 2006 and its follow-up studies. We resolved disagreements by

discussion. The effect of interest was the effect of assignment to the intervention (intention-to-treat effect). The risk of bias assessments were recorded alongside forest plots for meta-analyses. We used the RoB 2 Excel tool for managing assessments of risk of bias.

The assessments involved assessing five domains in which risk of bias may arise.

- Bias arising from the randomisation process.
- Bias due to deviations from intended interventions.
- Bias due to missing outcome data.
- Bias in measurement of the outcome.
- Bias in selection of the reported result.

For each domain, signalling questions follow decision algorithms to arrive at a judgement of the risk of bias as described in the ROB 2 detailed guidance (Higgins 2019). For each signalling question the possible responses are 'yes', 'probably yes', 'probably no', 'no' or 'no information'. Supporting information was provided for answers to signalling questions and judgements of risk of bias. Risk of bias in each domain was determined to be low risk of bias, high risk of bias or some concerns. Based on the bias in each domain, an overall risk of bias was formulated using the same categories of low risk of bias, high risk of bias or some concerns. If any domain had a high risk of bias, then the outcome was considered to have a high risk of bias. If the risk of bias was assessed as some concerns in multiple domains of relevance to the outcome then the overall risk of bias was considered high.

When assessing risk of bias for outcomes from cluster-randomised trials using the RoB 2 tool we included an additional domain 1b: bias arising from the timing of identification and recruitment of participants, as described in the ROB 2 guidance on additional considerations for cluster-randomised trials (Eldridge 2021).

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratios (RRs) with 95% confidence intervals (CI). We calculated number needed to treat for an additional beneficial outcome (NNTB) or harmful outcome (NNTH) from the summary risk differences and their 95% confidence limits (Higgins 2021).

Continuous data

For continuous data, we used the mean difference (MD) with 95% CIs. If median and interquartile range were reported, we estimated mean values and SDs to calculate MDs (Wan 2014).

Where studies used different instruments, we used the standardised mean difference (SMD) with 95% CI with the following interpretations:

- SMD 0.8 or greater = large effect;
- SMD greater than 0.49 and less than 0.8 = medium effect;
- SMD greater than 0.19 and less than 0.5 = small effect;
- SMD less than 0.2 = trivial or no effect.

Unit of analysis issues

Unit of analysis

The unit of analysis for maternal outcomes was the individual woman. To account for multiple pregnancies, the unit of analysis for outcomes in infants or children was the fetus alive at randomisation. In accordance with the Pregnancy and Childbirth Cochrane Group guidelines, for neonatal outcomes the number of fetuses alive at the point of randomisation was used as the denominator for analysis. This avoids bias by ensuring analysis is based on the total group of women and their fetuses initially randomised but may bias the analysis by underestimating the occurrence of neonatal morbidity, as the most unwell fetuses may die in utero or soon after birth and contribute to the denominator but not to measures of neonatal morbidity.

Cluster-randomised trials

Cluster-randomised trials were eligible for inclusion, but we did not identify any. Should we encounter cluster-randomised trials subsequently, we will include them in the analyses along with individually randomised trials. We will adjust their sample sizes using the methods described in the *Cochrane Handbook for Systematic Reviews of Interventions* using an estimate of the intracluster correlation coefficient (ICC) derived from the trial (if possible), or from another source (Chapter 23.1.4; Higgins 2021). If ICCs from other sources are used, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify both cluster-randomised trials and individually randomised trials, we plan to synthesise the relevant information. We consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and an interaction between the effect of intervention and the choice of randomisation unit is considered unlikely. We will also acknowledge heterogeneity in the randomisation unit and perform a separate meta-analysis.

When assessing risk of bias for outcomes from cluster-randomised trials using the RoB 2 tool we will include an additional Domain 1b: bias arising from the timing of identification and recruitment of participants, as described in the ROB 2 guidance on additional considerations for cluster-randomised trials (Eldridge 2021).

Cross-over trials

Cross-over trials were not eligible for inclusion.

Dealing with missing data

For included studies, we noted levels of attrition. Bias associated with missing outcome data was assessed using the Risk of Bias 2 Tool in Domain 3: bias due to missing outcome data.

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

Assessment of heterogeneity

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

Assessment of reporting biases

Where we identified high risk or some concerns for reporting bias (assessed in Domain 5: bias in selection of the reported result) we explored the impact of including such studies in the overall assessment of results by a sensitivity analysis.

Where there were 10 or more studies in the meta-analysis, we investigated reporting biases (such as publication bias) using funnel plots. We assessed funnel plot asymmetry visually.

Data synthesis

We carried out statistical analysis using Review Manager software (RevMan Web 2021). We used fixed-effect meta-analysis for combining data because it was reasonable to assume that studies were estimating the same underlying treatment effect (i.e. where trials were examining the same intervention, and the trials' populations and methods were judged sufficiently similar).

Subgroup analysis and investigation of heterogeneity

Clinical subgroups

We prespecified secondary analyses of the primary outcomes for the infant, woman, child and adult to explore clinical diversity by examining interactions between the effect of repeat dose(s) of prenatal corticosteroids compared with women receiving no repeat prenatal corticosteroids/placebo and the following variables:

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

Sensitivity analysis

We carried out sensitivity analyses to explore the effect of risk of bias on outcomes of critical importance in the review (using the primary outcomes for each of the epochs). Where overall risk of bias was assessed as 'high risk' or 'some concerns' for a study outcome, we explored this by sensitivity analysis excluding these studies.

Sensitivity analysis was also performed to examine the effect of substantial levels of heterogeneity. We regarded heterogeneity as substantial if the I^2 statistic was greater than 30% or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Summary of findings and assessment of the certainty of the evidence

For this update, we assessed the certainty of the evidence using the GRADE approach as outlined in the GRADE handbook) for the following outcomes (gdt.gradepro.org/app/handbook/handbook.html; Schünemann 2013).

Outcomes for the fetus/neonate/infant

- Fetal or neonatal or infant death.
- Respiratory distress syndrome (however defined by authors).
- Severe lung disease (however defined by authors).
- Chronic lung disease (however defined by authors).
- Severe intraventricular haemorrhage (grade 3 or 4).
- Necrotising enterocolitis (however defined by authors).
- Composite serious outcome (however defined by authors).

Outcomes for the woman

- Maternal death.
- Maternal sepsis (any of chorioamnionitis during labour, endometritis, pyrexia after trial entry requiring the use of antibiotics, puerperal sepsis, intrapartum fever requiring the use of antibiotics, postnatal pyrexia or however defined by authors).
- Caesarean section.
- Discontinuation of therapy because of maternal side effects.
- Adverse effects of corticosteroids (including gastrointestinal upset, insomnia, local injection site adverse effects (pain, bruising, haematoma or infection at the injection site)).
- Admission to the intensive care unit.
- Breastfeeding at hospital discharge.

For the child in early childhood (aged two to less than five years)

- Total deaths (after randomisation).
- Neurodevelopmental impairment at age two to less than five years (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), motor impairment (mild or major impairment by appropriate mode of assessment), or cerebral palsy, or however defined by authors).
- Survival free of neurodevelopmental impairment at age two to less than five years (none of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), motor impairment (mild or major impairment by appropriate mode of assessment), cerebral palsy or however defined by authors).

- Survival free of major neurodevelopmental impairment at age two to less than five years (none of: moderate or severe intellectual impairment (developmental quotient or intelligence quotient more than two SDs below the mean), moderate or severe cerebral palsy, major motor impairment, blindness (corrected visual acuity worse than 6/60 in the better eye) or deafness (hearing loss requiring amplification or worse), or however defined by authors).

For the child in mid- to late childhood (aged five to less than 18 years)

- Total deaths (after randomisation).
- Neurocognitive impairment at age five to less than 18 years (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment), or cerebral palsy, or however defined by authors).
- Survival free of neurocognitive impairment at age five to less than 18 years (none of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment) cerebral palsy, or however defined by authors).
- Survival free of major neurocognitive impairment at age five to less than 18 years (none of: moderate or severe intellectual impairment (developmental quotient or intelligence quotient more than two SD below the mean), major motor impairment, moderate or severe cerebral palsy, blindness (corrected visual acuity worse than 6/60 in the better eye) or deafness (hearing loss requiring amplification or worse), or however defined by authors).

For the child as an adult (aged 18 years or greater)

- Total deaths (after randomisation).
- Neurodevelopmental disability at age 18 years or greater (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), cerebral palsy, or however defined by authors).
- Cardiovascular disease (including diagnosis of ischaemic heart disease, cerebrovascular disease, heart failure or however defined by authors).
- Type 2 diabetes mellitus (however defined by authors).
- Glucose intolerance (however defined by authors).
- Obesity/overweight (however defined by authors).
- Hypertension (however defined by authors).

We used GRADEpro GDT (GRADEpro GDT) to import data from Review Manager Web (RevMan Web 2021) to create summary of findings tables. We produced a summary of the intervention effect and a measure of certainty for each of the above outcomes using the GRADE approach. The GRADE approach uses five considerations (risk of bias, inconsistency of results, imprecision, indirectness of evidence and publication bias) to assess the certainty of the body of evidence. The evidence can be downgraded from 'high certainty' by one level for serious (or by two levels for very serious) limitations in any of the five considerations.

We used the GRADE approach to assess the evidence available for all secondary outcomes, with the level of certainty and individual domain judgements described in Table 1; Table 2; Table 3; Table 4; and Table 5.

RESULTS

Description of studies

Results of the search

See: Figure 2.

Figure 2. Study flow diagram.

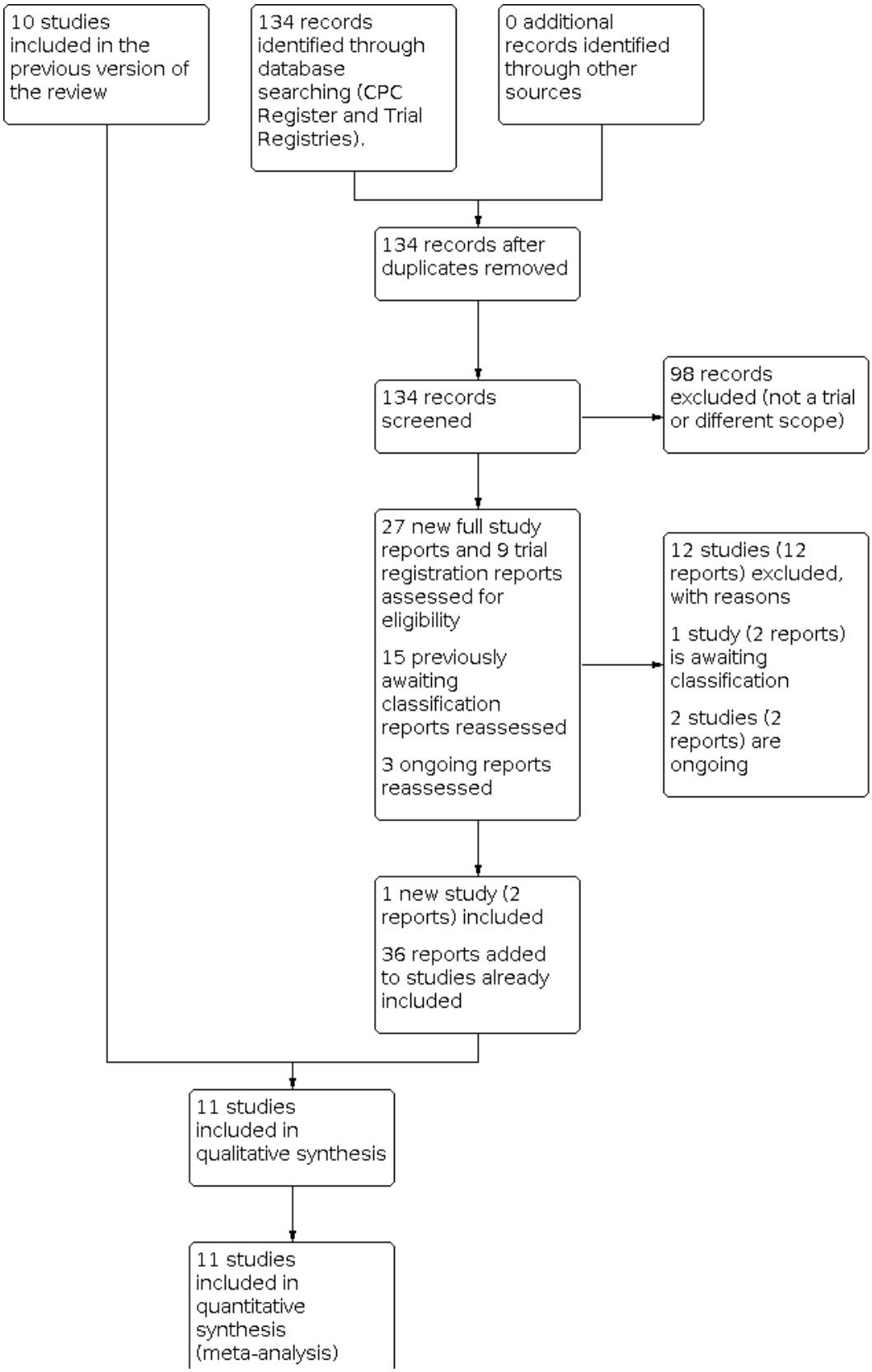
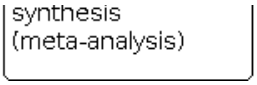


Figure 2. (Continued)



The updated search identified 36 new study reports to assess in full. We also reassessed the three studies (15 reports) awaiting classification in the previous version of the review and the two ongoing trials (three reports). We included one new study (two reports) and excluded 12 new studies (12 reports). One study is awaiting classification (two reports), and two are ongoing. The remaining 36 were additional reports of studies already included and have been added under the main study report.

Screening eligible studies for trustworthiness

One study that was awaiting classification in the previous version of this review met our inclusion criteria, but we judged that it did not meet our criteria for trustworthiness due to concerns about randomisation processes as identical numbers were randomised to each group despite using a randomisation table for 1348 participants (Atarod 2014). There was also no explanation for the exclusion of 104 women after randomisation (Atarod 2014). We attempted to contact the authors, but we received no response to our queries; therefore, it remains as awaiting classification (see Studies awaiting classification).

Included studies

See Characteristics of included studies table for full details.

The 11 included trials randomised 4895 women (5975 babies) (Aghajafari 2002: 12 women, 16 fetuses; Crowther 2006: 982 women, 1146 fetuses; Garite 2009: 437 women, 577 fetuses; Guinn 2001: 502 women, 589 fetuses; Mazumder 2008: 76 women, 76 fetuses; McEvoy 2002: 37 women, 37 fetuses; McEvoy 2010: 85 women, 113 fetuses; Murphy 2008: 1858 women, 2309 fetuses; Peltoniemi 2007: 249 women, 328 fetuses; TEAMS 1999: 162 women, 188 fetuses; Wapner 2006: 495 women, 594 fetuses).

Five trials were conducted in the US (Garite 2009; Guinn 2001; McEvoy 2002; McEvoy 2010; Wapner 2006); one each in Canada (Aghajafari 2002), India (Mazumder 2008), the UK (TEAMS 1999), and Finland (Peltoniemi 2007); one in Australia and New Zealand (Crowther 2006); and one involved 20 countries (Murphy 2008).

Gestational age at trial entry varied between trials: 24 to 30 weeks in Aghajafari 2002; 25 to 32 weeks in Murphy 2008; 25 to less than 33 weeks in Guinn 2001 and Garite 2009; 26 to 33 weeks in Mazumder 2008 and McEvoy 2010; 25 to 33 weeks in McEvoy 2002; 23 to less than 32 weeks in Wapner 2006; less than 32 weeks in Crowther 2006 and TEAMS 1999; and less than 34 weeks in Peltoniemi 2007. All women were at increased risk of preterm birth and had received a single course of prenatal corticosteroids one week or more before trial entry. The type, amount and timing regimen for administration of the corticosteroid given for the pretrial course of prenatal corticosteroids varied between trials.

In seven trials, women were eligible for inclusion seven or more days after a pretrial course (Aghajafari 2002; Crowther 2006; Guinn 2001; Mazumder 2008; McEvoy 2002; TEAMS 1999; Peltoniemi 2007); in one trial between seven and 10 days after a pretrial course (Wapner 2006); in two trials 14 or more days after a pretrial course (Garite 2009: McEvoy 2010); and in one trial between 14 and 21 days after a pretrial course (Murphy 2008).

All trials started recruitment between 1996 and 2004. Four trials started recruitment prior to 2000 and seven trials started recruitment after 2000. All trials completed recruitment between 1999 and 2008.

Four trials were terminated early (Guinn 2001; McEvoy 2002; TEAMS 1999; Wapner 2006). Guinn 2001 and McEvoy 2002 were terminated early based on concern from reports in the literature of potential harm from repeat courses of prenatal corticosteroids and interim analyses suggesting that they were unlikely to detect a difference between groups for the primary outcomes. Wapner 2006 was terminated early due to a trend towards reduced birthweight in the repeat prenatal corticosteroids group without any suggestion of benefit for the primary outcome.

Exclusion criteria for recruitment to the included trials

Aghajafari 2002: chronic doses of corticosteroids secondary to medical conditions, contraindication to corticosteroids, clinical evidence of chorioamnionitis or fetus(es) had a known lethal congenital anomaly.

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

Garite 2009: major fetal anomaly, cervical dilation 5 cm or more, multiple pregnancy of higher order than twins, ruptured membranes, documented lung maturity, receiving corticosteroids for other indications, HIV infection or active tuberculosis.

Guinn 2001: required immediate delivery, fetal anomalies incompatible with life, documented fetal lung maturity, maternal active tuberculosis or HIV infection.

Mazumder 2008: unreliable gestational age, frank chorioamnionitis, major fetal malformation or unavailable for follow-up.

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

McEvoy 2010: insulin-dependent diabetes, major documented fetal or chromosomal abnormality, multiple pregnancy of higher order than twins, clinical chorioamnionitis, first course of prenatal corticosteroids given before 24 weeks' gestation or chronic steroid use during pregnancy for clinical care.

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

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

TEAMS 1999: maternal long-term systemic corticosteroid therapy (not including inhaled or topical therapy).

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

Interventions

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

In six trials, a planned treatment course was two doses of betamethasone 12 mg/dose, intramuscularly, at weekly intervals (Aghajafari 2002; Guinn 2001; Mazumder 2008; McEvoy 2002; TEAMS 1999; Wapner 2006).

- Aghajafari 2002 gave a weekly course of betamethasone (two doses of 12 mg/dose (Celestone Soluspan; Schering Canada Inc.) intramuscularly, 24 hours apart) until 33 weeks or birth if the woman remained at increased risk of preterm birth.
- Guinn 2001 used a weekly course of betamethasone (two doses of 12 mg/dose, intramuscularly 24 hours apart) until 34 weeks or birth, whichever came first.
- Mazumder 2008 used betamethasone 12 mg intramuscularly, two doses, 24 hours apart until the end of the 33rd week of gestation.
- McEvoy 2002 used a weekly course of betamethasone (two doses of 12 mg/dose (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey)), intramuscularly, until 34 weeks or birth.
- TEAMS 1999 used a weekly course of betamethasone (two doses of 12 mg given 12 or 24 hours apart) but allowed for a dosing interval of up to 14 days depending on local protocols.
- Wapner 2006 used a weekly course of betamethasone (two doses of 12 mg as betamethasone sodium phosphate 6 mg and betamethasone acetate 6 mg, intramuscularly in 24 hours) until birth or 33 weeks and six days, limited to four repeat courses after the first 67 women.

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

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

Three trials planned only a single repeat course of treatment; Garite 2009[a] used a single course consisting of two doses of betamethasone 12 mg, intramuscularly, 24 hours apart (preparation not specified); McEvoy 2010 used a single course of two doses of betamethasone 12 mg/dose (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, 24 hours apart; and Peltoniemi 2007 used a single intramuscular injection of intramuscular of betamethasone 12 mg (preparation not specified).

[a]Of note, Garite 2009, due to unavailability of betamethasone on occasion, used dexamethasone 6 mg, intramuscularly every 12 hours up to four doses or similar placebo regimen for 61 (14%) women.

Primary outcomes

Primary outcomes were predominantly focused on neonatal morbidity and mortality. Seven trials used a composite primary outcome incorporating both neonatal death, either RDS or severe RDS and other measures of neonatal morbidity (Aghajafari 2002; Garite 2009; Guinn 2001; Mazumder 2008; Murphy 2008; Peltoniemi 2007; Wapner 2006). Crowther 2006 reported primary outcomes of RDS, lung disease severity, measures of respiratory support and growth measurements. For TEAMS 1999, the primary outcomes were neonatal death and neurodevelopmental delay at age two years (corrected for gestational age at birth). Aghajafari 2002 reported primary outcomes focussed on the rate of recruitment over a 12-month period, risk of complications requiring discontinuation of study treatment, and measures of maternal and fetal HPA function following birth. The primary outcomes for McEvoy 2002 and McEvoy 2010 were measures of lung function: functional residual capacity and respiratory compliance.

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

At early childhood follow-up, primary outcomes varied by trial. For Crowther 2006, the prespecified primary outcomes were survival at two years' corrected age free of major neurodisability (defined as survival free of moderate or severe disability); and body size (weight, height and head circumference). For Murphy 2008, the primary outcome was death or the presence of neurological impairment at 18 to 24 months' corrected age. Neurological impairment was defined as the presence of cerebral palsy or cognitive delay. For Peltoniemi 2007, the power analysis at follow-up was based on survival without neurodevelopmental impairment. For Wapner 2006, the power analysis was based on the prespecified developmental outcome of the Bayley Mental Developmental Index score.

Two studies performed follow-up in mid-childhood (Crowther 2006; Murphy 2008). For Crowther 2006, the primary outcome for mid-childhood follow-up was survival free of any neurosensory disability at six to eight years' corrected age. For Murphy 2008, the primary outcome for mid-childhood follow-up was a composite of death or survival with a neurodevelopmental disability at five years of age.

Funding

All trials declared their sources of funding. One trial declared that it had no funding support (Mazumder 2008). The sources of funding support for the other 10 trials were as follows: the Canadian Institutes of Health Research Senior Scientist Award (Aghajafari

2002); the 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 (Crowther 2006); the Pediatrix Medical Group (Garite 2009); 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 (Guinn 2001); the American Lung Association (McEvoy 2002); Oregon Health and Science University, and the American Lung Association (McEvoy 2010); the Canadian Institutes of Health Research (Murphy 2008); the Foundation for Paediatric Research in Finland, the Alma and KA Snellmann Foundation, the Sigrid Juselius Foundation and hospital research funds (Peltoniemi 2007); Action Medical Research UK (TEAMS 1999); and the National Institute of Child Health and Human Development (Wapner 2006).

Declarations of interest

Seven trials declared there were no conflicts of interest (Aghajafari 2002; Crowther 2006; Garite 2009; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007).

For Wapner 2006, author Dr Mercer declared receiving consulting fees from Columbia Laboratories and reported no other conflicts of interest.

Three trials did not have an identified declaration of interest (Guinn 2001; McEvoy 2002; TEAMS 1999).

Trial registration

None of the trials were confirmed as being registered prospectively.

Five trials were registered during recruitment (Crowther 2006; Garite 2009; Murphy 2008; TEAMS 1999; Wapner 2006).

Two trials were registered retrospectively (McEvoy 2010; Peltoniemi 2007).

Four trials had no registration document identified (Aghajafari 2002; Guinn 2001; Mazumder 2008; McEvoy 2002).

Excluded studies

We excluded 16 studies; four were excluded in the last version of this review and 12 from the search for this update (Bontis 2011; CTRI/2017/04/008326; CTRI/2017/05/008721; Ernawati 2016; EUCTR2009-010759-29-BE; Gyamfi-Bannerman 2016; IRCT2014090912789N6; IRCT2015120415634N2; IRCT20191202045571N1; Kashanian 2018; Mercer 2001; NCT03446937; Romejko-Wolniewicz 2013; Schmitz 2019; Sohrabvand 2001; Thorp 2000).

The reasons for study exclusion were women not receiving a first course of corticosteroids prior to trial entry, trials that did not compare repeat dose(s) of corticosteroid to a single course of corticosteroid, trials that were using a different treatment and one trial that was not truly randomised. Descriptions of excluded studies and the reasons for exclusion are described in the Characteristics of excluded studies table.

Studies awaiting classification

One trial from Iran is awaiting classification to establish its eligibility for inclusion as it did not meet trustworthiness criteria and we received no response from the authors for clarification of concerns (Atarod 2014). See Characteristics of studies awaiting classification table.

Ongoing studies

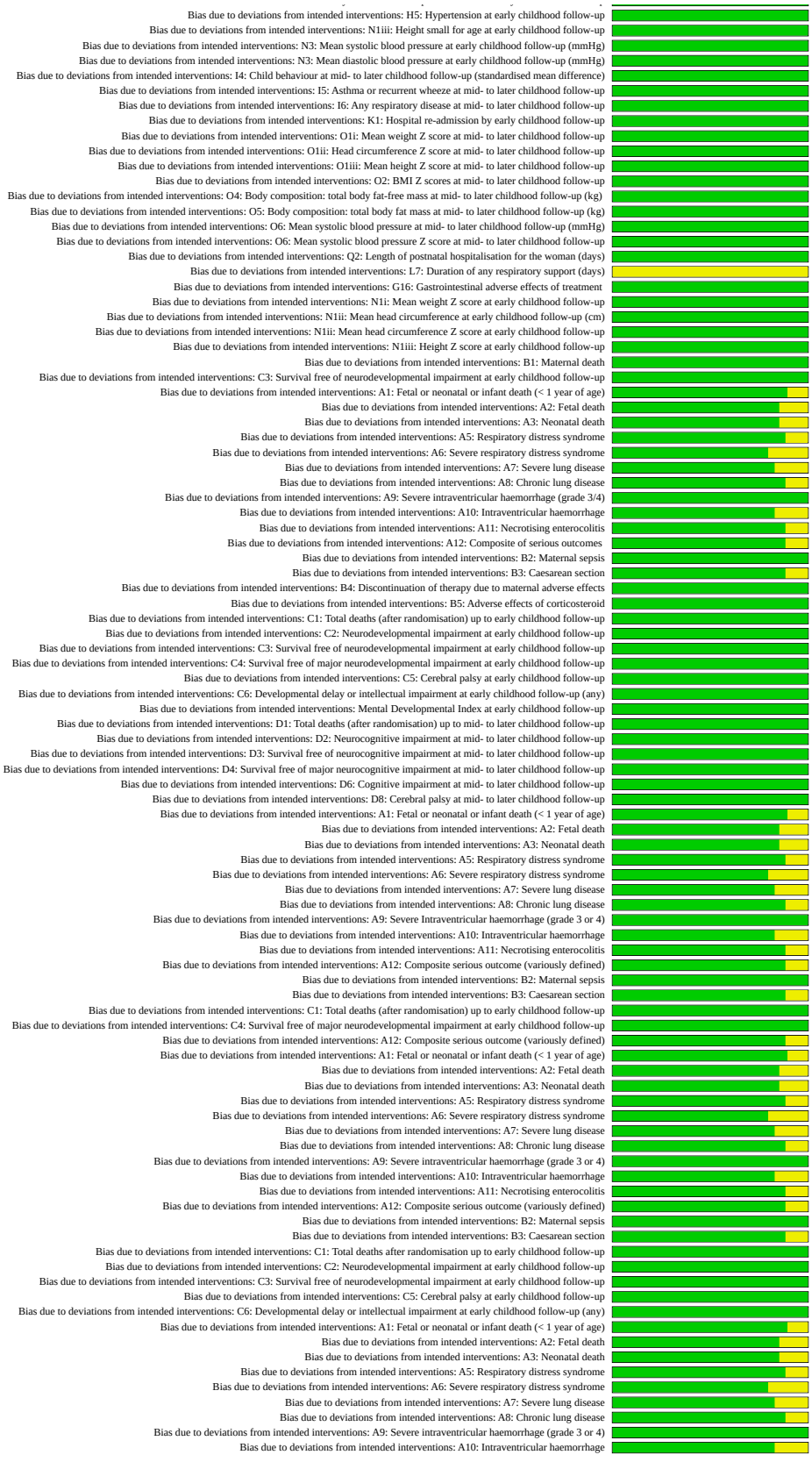
There are two ongoing trials of repeat prenatal corticosteroids in the context of preterm, prelabour rupture of membranes. The trials are set in the US and have yet to complete recruitment (NCT02469519; NCT02939742). See Characteristics of ongoing studies table.

Risk of bias in included studies

Overall and domain level risk of bias assessments for each outcome are included alongside forest plots for each outcome and in Figure 3. Domain level risk of bias judgements and supporting notes are included in the Risk of Bias tables (located after the Characteristics of included studies). To access further detailed risk of bias assessment data, including answers to signalling questions use the following link.

Figure 3.

Figure 3. (Continued)



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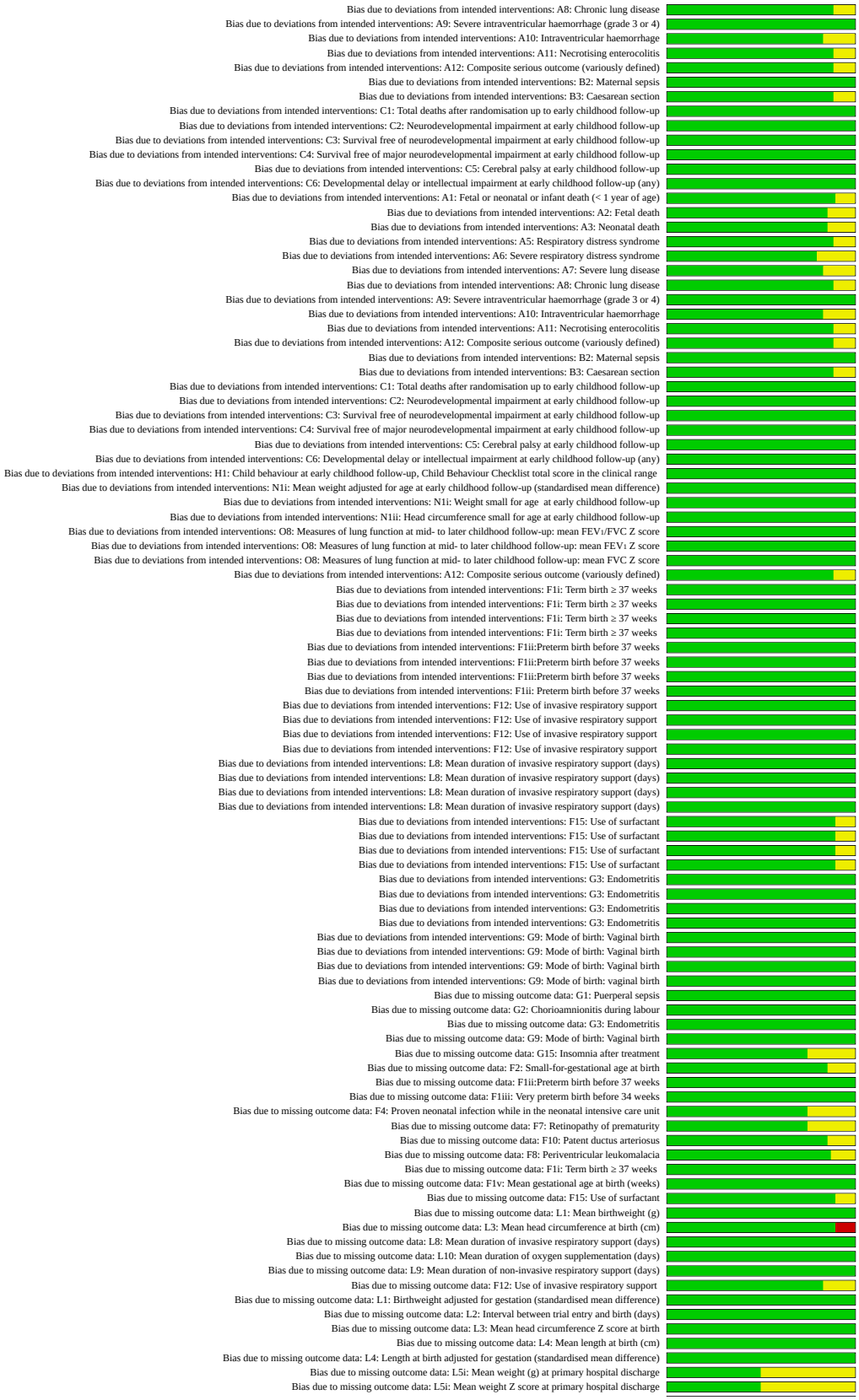

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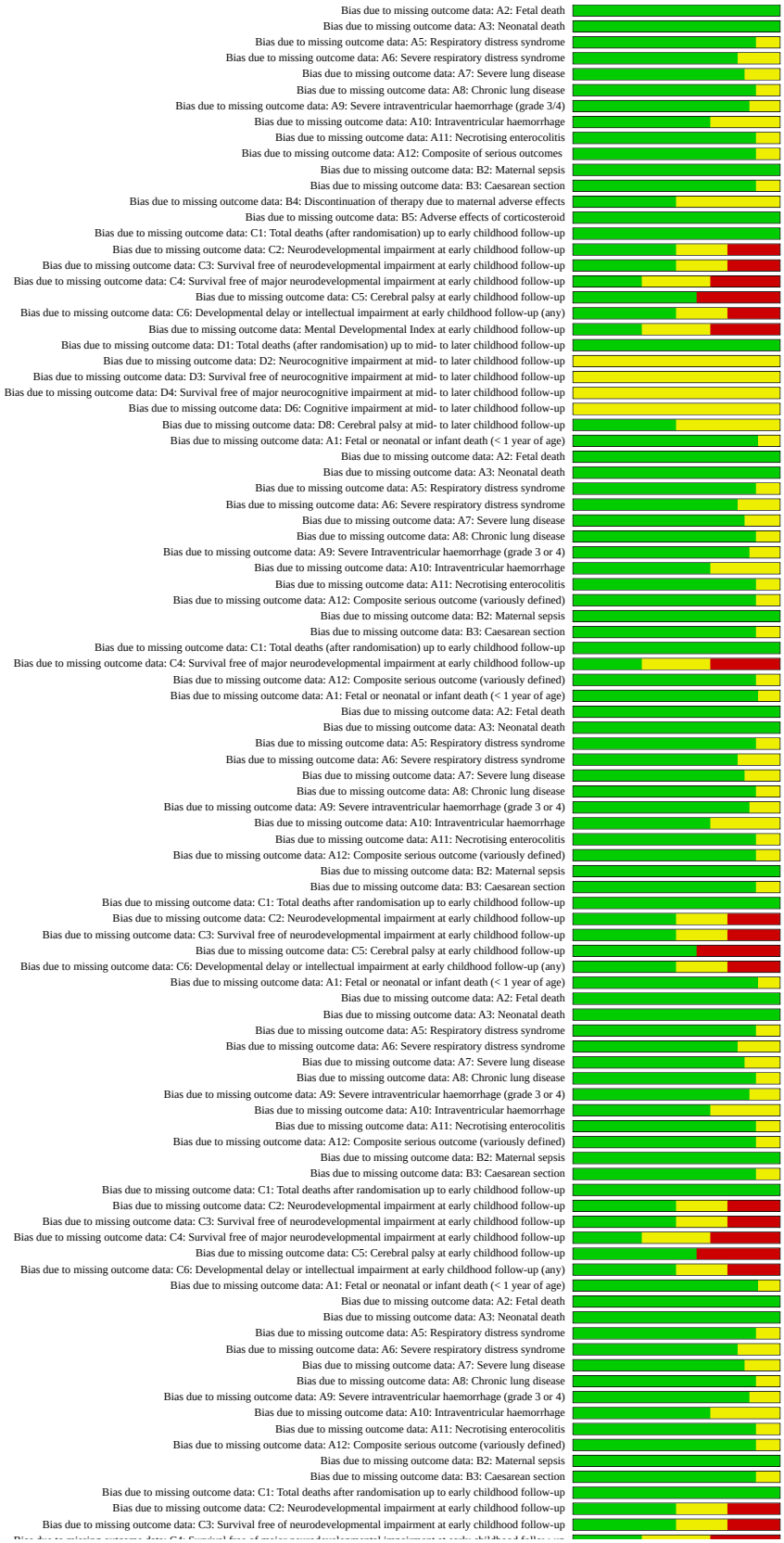

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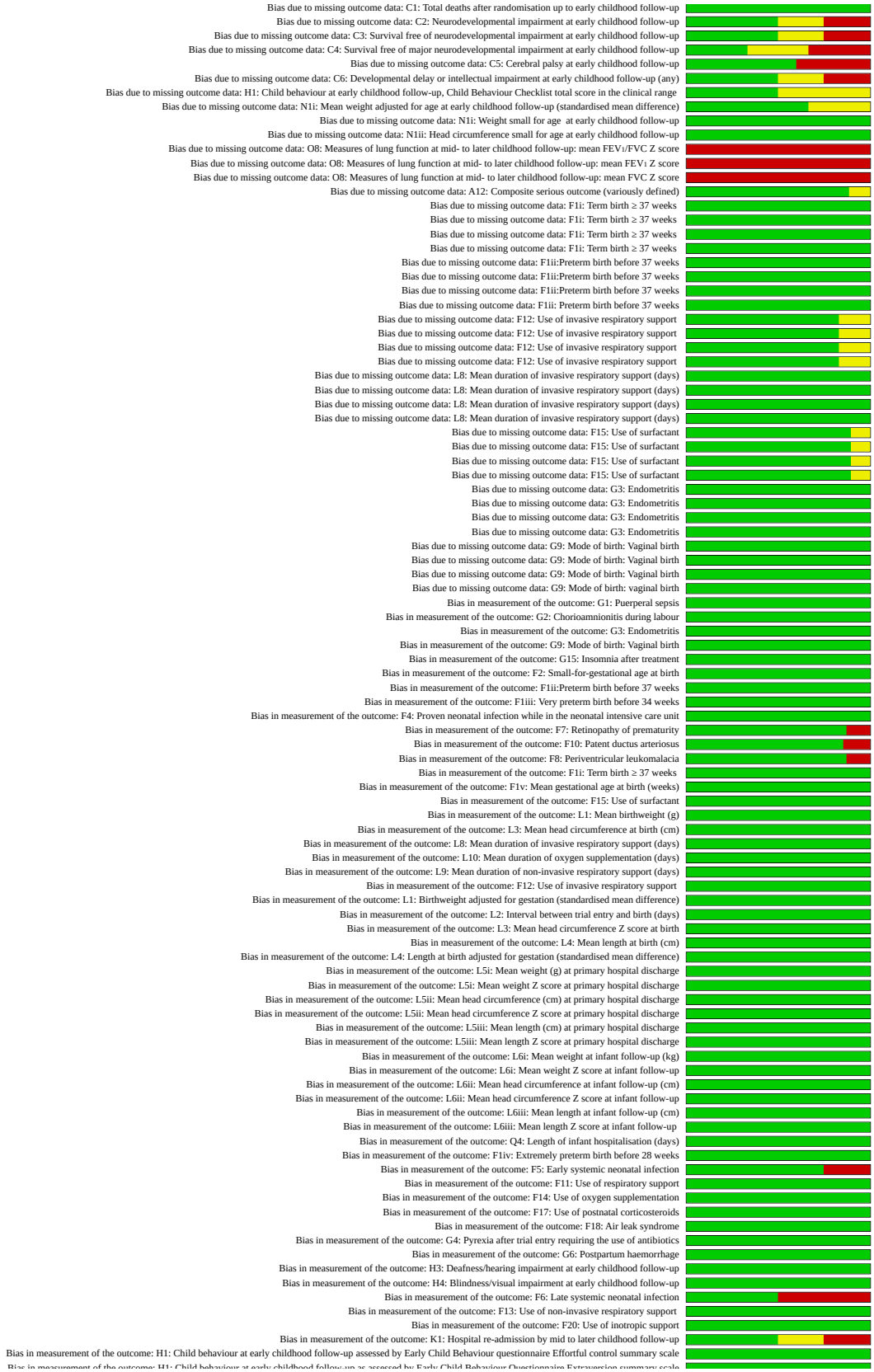

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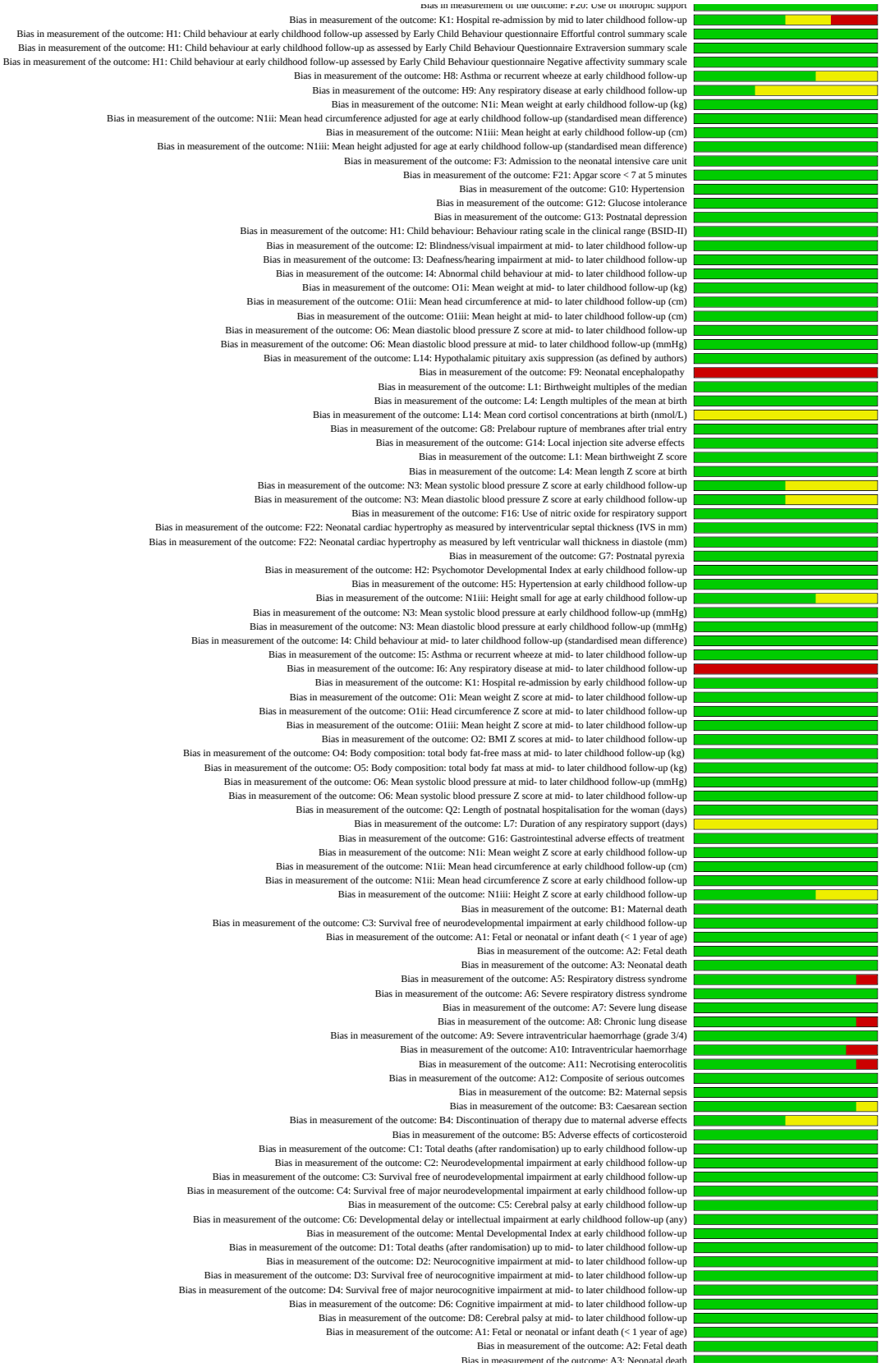

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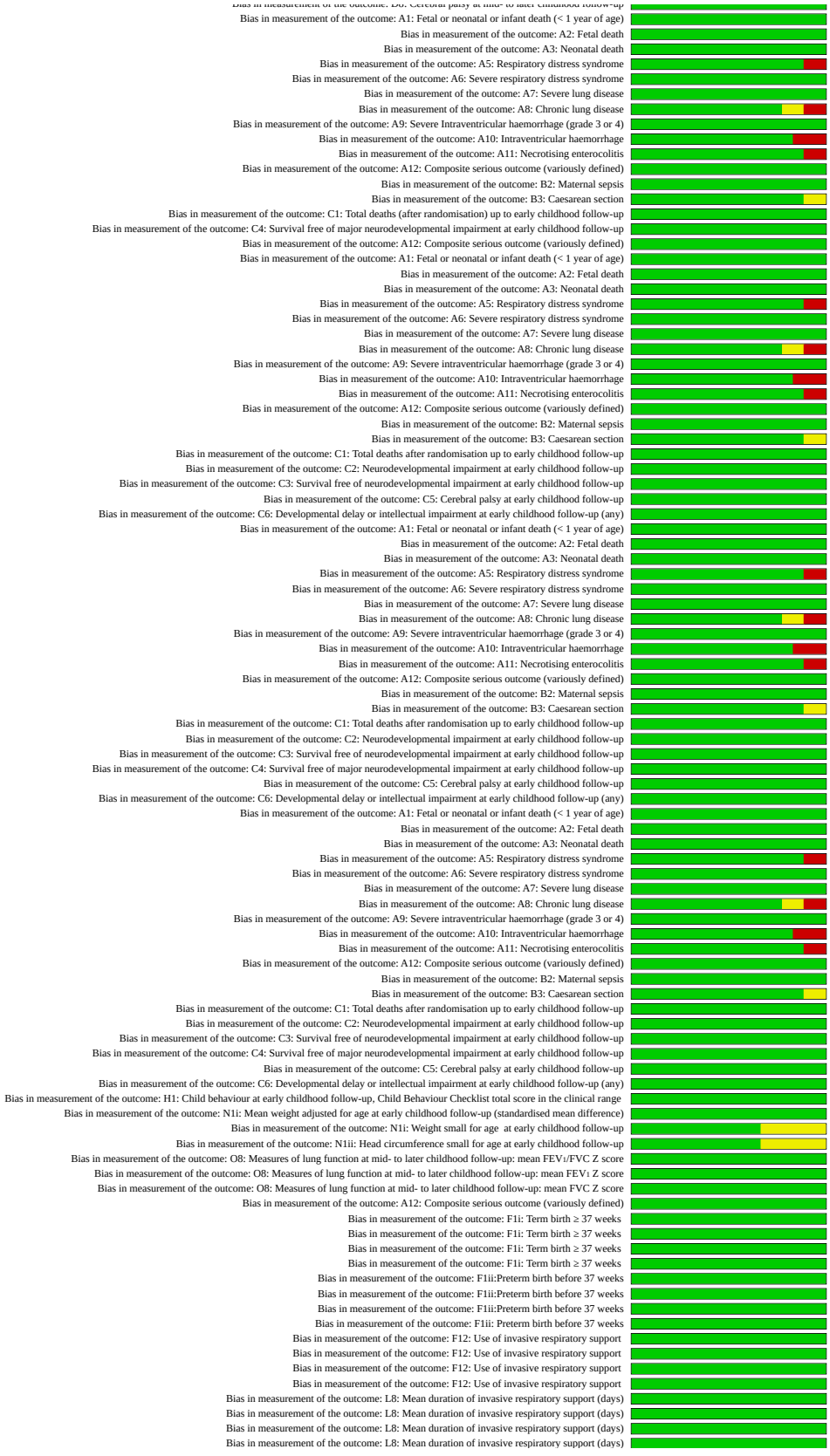

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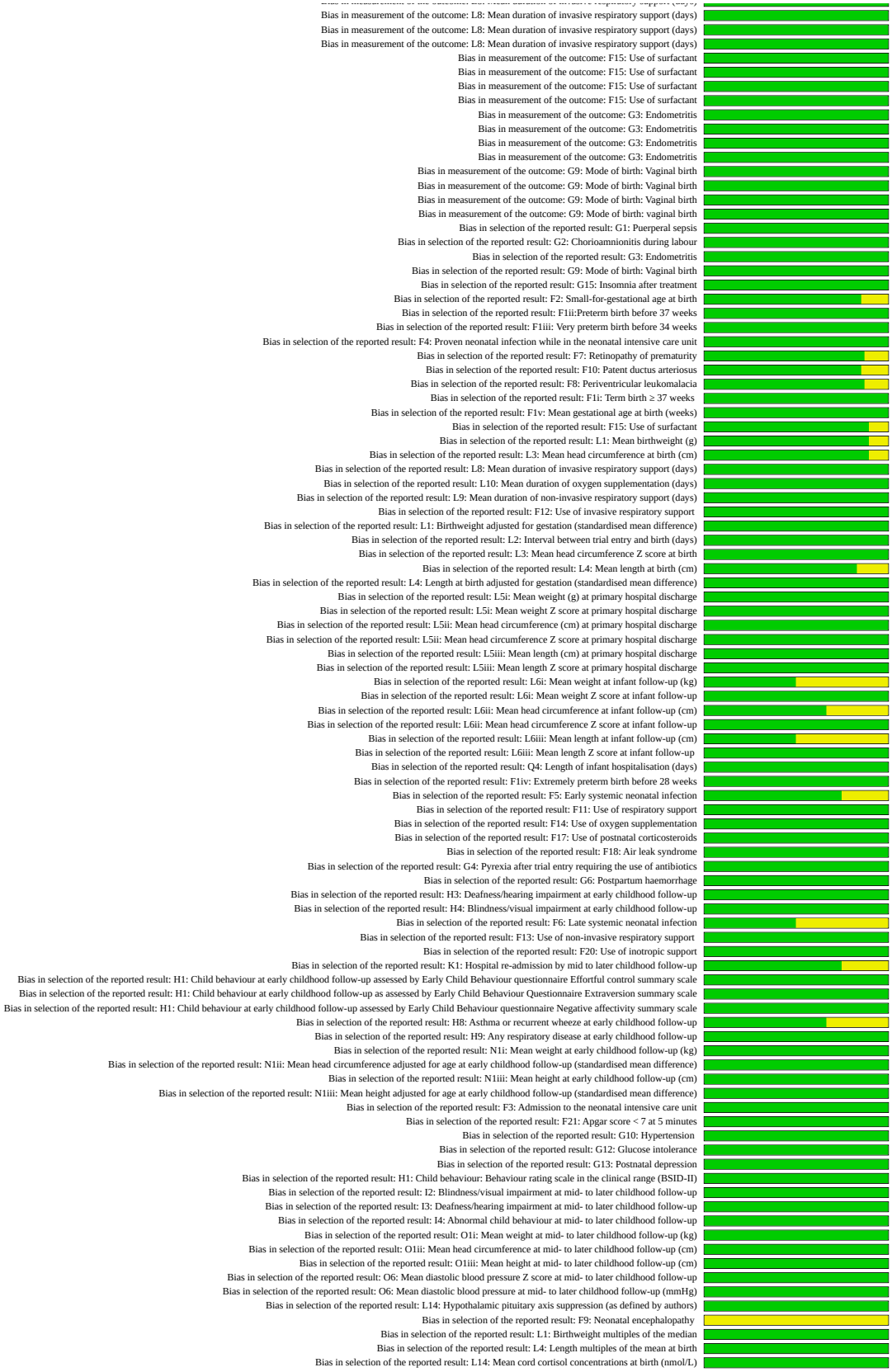

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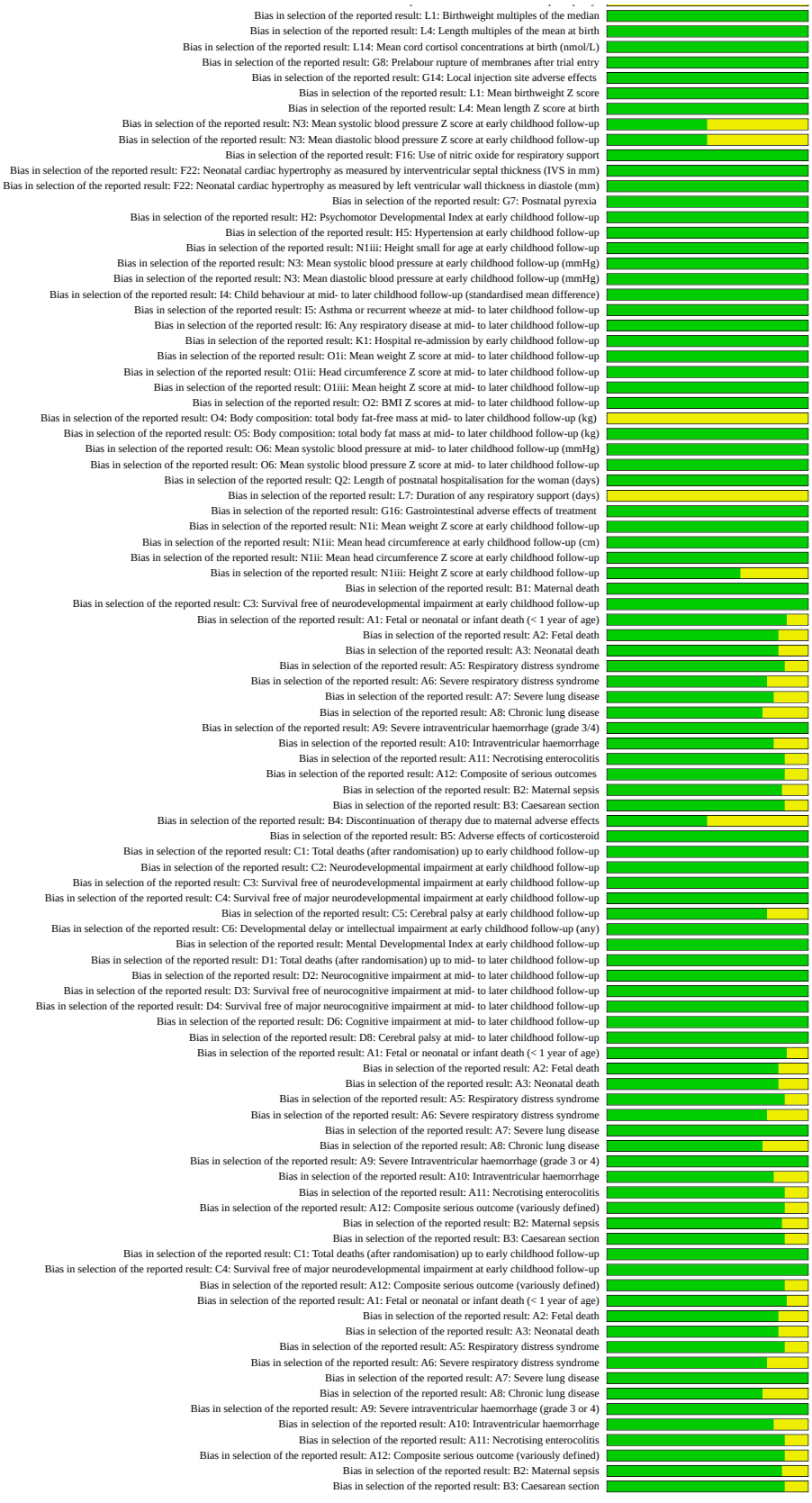

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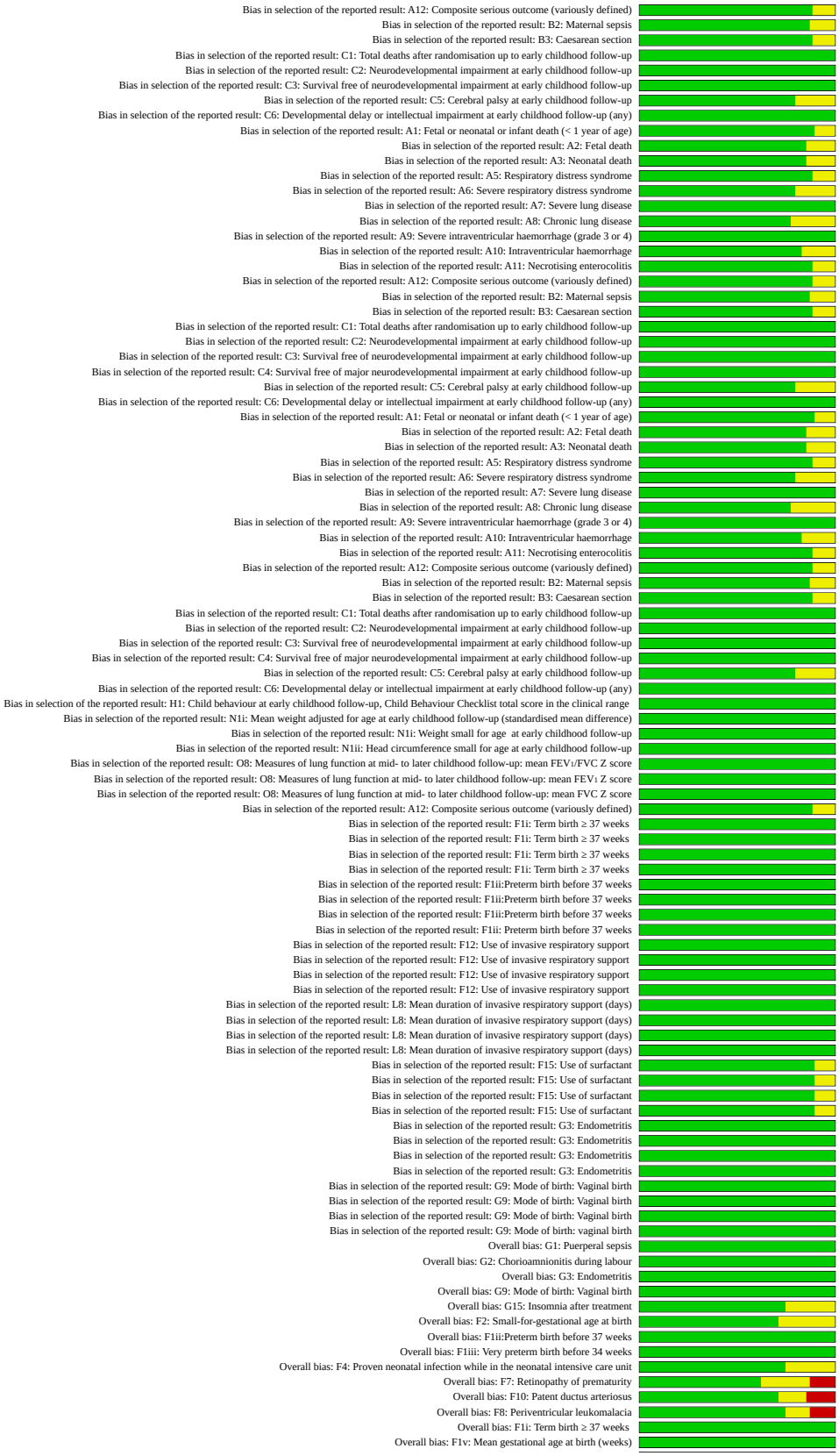

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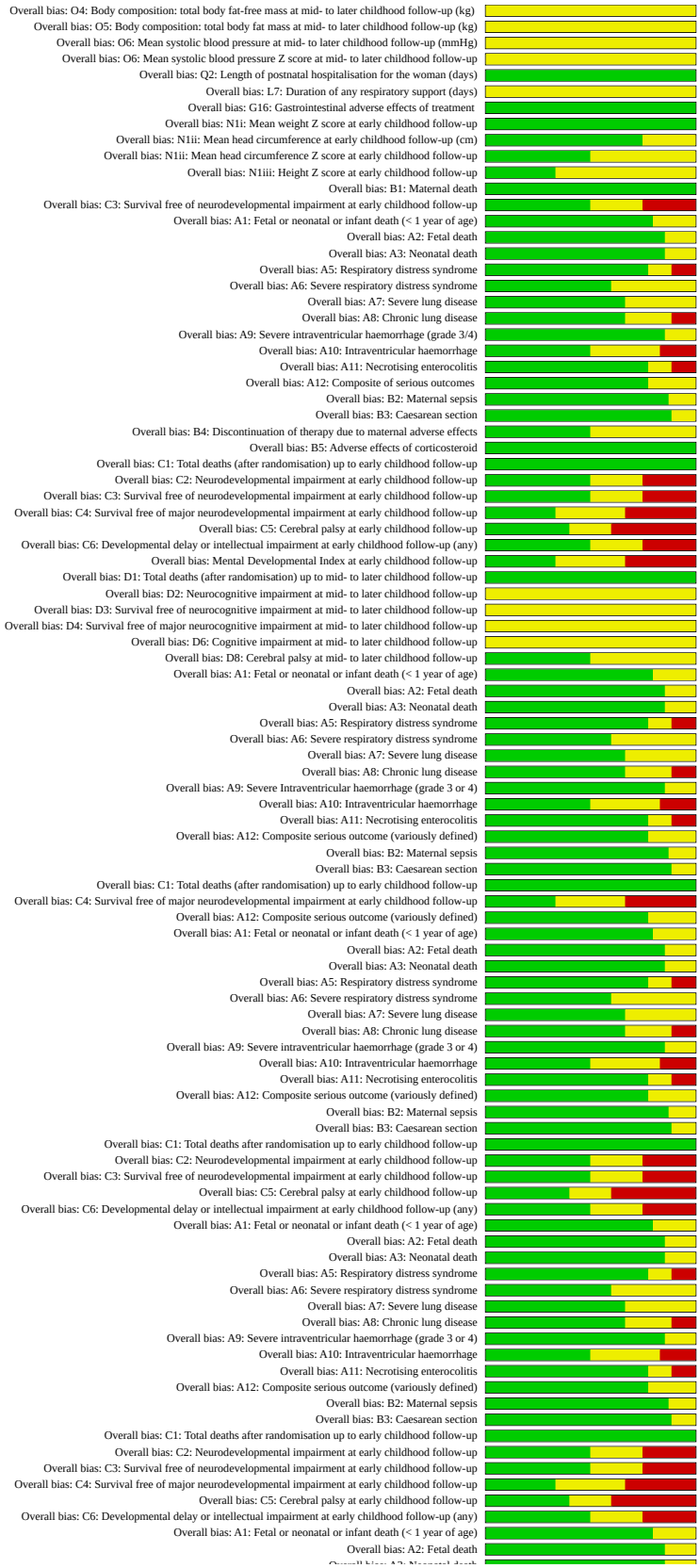

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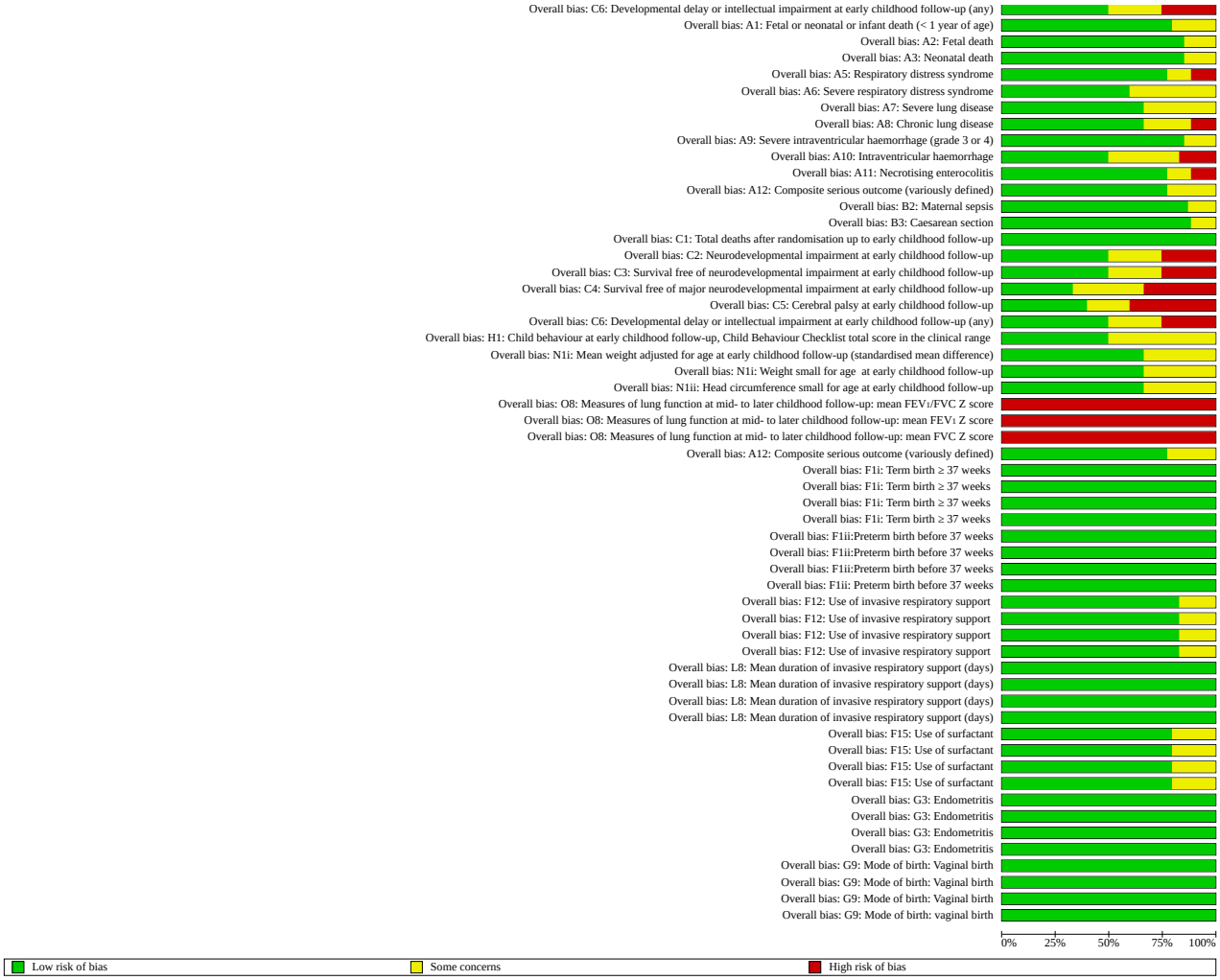


Risk of bias for the randomisation process is a study-level assessment and was low in all studies included.

The risk of bias for fetal/neonatal/infant outcomes was generally low for all outcomes. There were some concerns of risk of bias overall for Wapner 2006 for all outcomes due to missing data, as outcomes were only reported for one twin in the instance of multiple gestations. For Mazumder 2008, there were some concerns of risk of bias overall for all outcomes due to a lack of blinding of treatment allocation as this trial was open-label and details of analysis plans were not clearly described.

For the women, the risk of bias for all primary outcomes was low across all studies except for some concerns of risk of bias for selection of the reported result for Garite 2009 for the outcome of maternal sepsis.

At early childhood follow-up, there were some concerns of risk of bias for Wapner 2006 and high risk of bias for Peltoniemi 2007 for most of the primary outcomes. All trials had low risk of bias for the outcome of death since randomisation up to early childhood.

For outcomes at mid-childhood, missing data was an important source of risk of bias, resulting in judgements of some concerns of bias in all primary outcomes in this category except for the outcome risk of death after randomisation.

Published prospective statistical analysis plans were not available for review. Primary publications for trials were all published in 2010 or earlier. The lack of a published statistical analysis plan was not considered to indicate a risk of bias unless it was felt likely that analysis methods or reported results were likely to have been influenced by a lack of prespecified plans or chosen on the basis of results.

Effects of interventions

See: **Summary of findings 1** Summary of findings table - Repeat dose(s) of prenatal corticosteroid compared to single course for the fetus/neonate/infant; **Summary of findings 2** Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the woman; **Summary of findings 3** Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the child aged 2 to < 5 years; **Summary of findings 4** Summary of findings table - Repeat dose(s) of prenatal corticosteroids compared to single course for the child in mid- to late childhood (5 to < 18 years of age)

Repeat dose(s) of prenatal corticosteroids versus placebo/ standard care

Primary outcomes for the fetus/neonate/infant

Fetal or neonatal or infant death (less than one year of age)

For of *fetal or neonatal or infant death less than one year of age,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.95, 95% CI 0.73 to 1.24; I^2 = 0%, Chi^2 P= 0.64; 10 trials, 5849 fetuses randomised; Analysis 1.1).

All trials reported death at the fetal or neonatal stage of life either separately or as a combined outcome. No trials specifically reported infant death before one year of age.

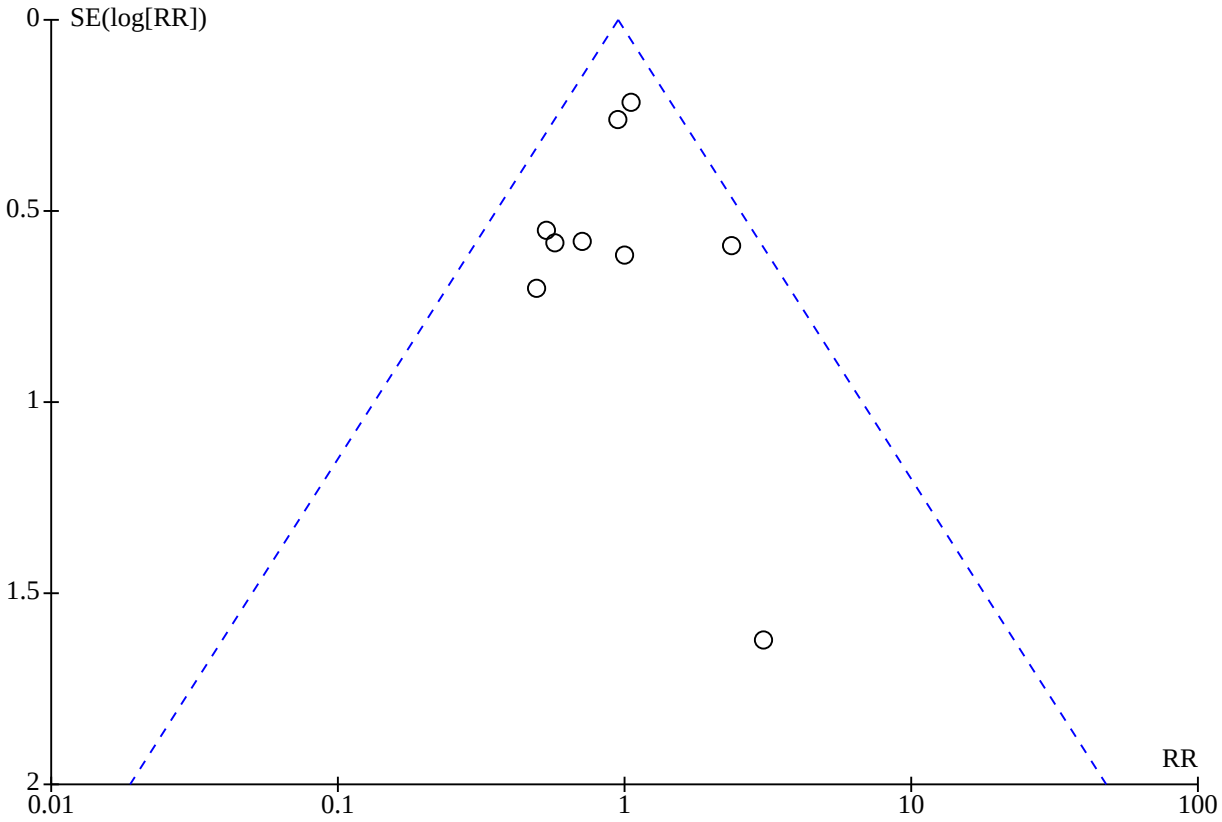
Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of bias (Mazumder 2008; Wapner 2006), but the result was similar to the overall analysis (RR 1.01, 95% CI 0.76 to 1.33; I^2 = 0%, Chi^2 P = 0.63; 8 trials, 5179 fetuses randomised).

Certainty of the evidence

The certainty of the evidence *moderate.* Certainty was downgraded one level due to imprecision as the 95% CI included both benefit and harm. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency or indirectness. Symmetry in the funnel plot was not suggestive of publication bias (Figure 4).

Figure 4.



Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.1; planned interval between corticosteroid treatments: Analysis 9.1; planned dose of corticosteroids to be given per treatment course: Analysis 10.1; planned dose of repeat dose of corticosteroid drug exposure per week: Analysis 11.1).

Fetal death

For *fetal death,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.82, 95% CI 0.24 to 2.84; I^2 = 0%, Chi^2 P = 0.98; 7 trials, 2758 fetuses randomised; Analysis 1.2).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of bias (Mazumder 2008), but the result was similar to the overall analysis (RR 1.01, 95% CI 0.25 to 4.01; I^2 = 0%, Chi^2 P = 1.00; 6 trials, 2682 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate.* Certainty was downgraded one level due to imprecision as evidenced by a few events and a 95% CI that included marked benefit and marked harm. Certainty was not downgraded for risk of bias as limiting analysis to only those trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.2; planned interval between corticosteroid treatments: Analysis 9.2; planned dose of corticosteroids to be given per treatment course: Analysis 10.2; planned dose of repeat dose of corticosteroid drug exposure per week: Analysis 11.2).

Neonatal death

For n*eonatal death,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.91, 95% CI 0.62 to 1.34; I^2 = 7%, Chi^2 P = 0.37; 7 trials, 2758 fetuses randomised; Analysis 1.3).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of bias (Mazumder 2008), but the result was similar to the overall analysis (RR 0.97, 95% CI 0.64 to 1.45; I^2 = 15%, Chi^2 P = 0.32; 6 trials, 2682 fetuses randomised)

Certainty of the evidence

The certainty of the evidence was *moderate.* Certainty was downgraded by one level due to imprecision as evidenced by a 95% CI that included possible benefit and possible harm. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.3; planned interval between corticosteroid treatments: Analysis 9.3; planned dose of corticosteroids to be given per treatment course: Analysis 10.3; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.3).

Infant death (less than one year of age)

No trials specifically reported *infant death* before one year of age.

Respiratory distress syndrome

Repeat dose(s) of corticosteroids reduced the risk of *RDS* compared with placebo or standard care (RR 0.82, 95% CI 0.74 to 0.90; I^2 = 25%, Chi^2 P = 0.22; 9 trials, 3540 fetuses randomised; NNTB 16, 95% CI 11 to 29; Analysis 1.4).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), and one trial with high risk of bias (Mazumder 2008), but the result was similar to the overall analysis (RR 0.82, 95% CI 0.75 to 0.91; I^2 = 41%, Chi^2 P = 0.12; 7 trials, 2870 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *high.* Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, imprecision, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.4; planned interval between corticosteroid treatments: Analysis 9.4; planned dose of corticosteroids to be given per treatment course: Analysis 10.4; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.4).

Severe respiratory distress syndrome

Repeat dose(s) of prenatal corticosteroid probably had little or no effect on the risk of *severe RDS* compared with placebo or standard care (RR 0.97, 95% CI 0.82 to 1.16; I^2 = 61%, Chi^2 P = 0.04; 5 trials, 3809 fetuses randomised; Analysis 1.5).

Sensitivity analysis

Heterogeneity was not directly explained by differing definitions of severe RDS. Based on prespecified subgroup analyses, heterogeneity may be partially explained by differing weekly drug exposure between trials. Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Mazumder 2008; Wapner 2006), but the result was similar to the overall analysis (RR 1.00, 95% CI 0.84 to 1.20; I^2 = 76%, Chi^2 P = 0.02; 3 trials, 3139 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate* due to inconsistency as evidenced by high levels of heterogeneity, likely due to differences in the definition of severe RDS across different trials. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding indirectness, imprecision or publication bias.

Subgroup analysis

Prespecified subgroup analysis identified an interaction between severe RDS and planned dose of repeat corticosteroid drug exposure per week (Chi^2 = 6.25, P = 0.01; I^2 = 84%; Analysis 11.5). Participants in those trials in which the planned dose of repeat corticosteroid was greater than 12 mg per week to 24 mg per week were more likely to experience benefit than participants in trials in which the planned dose was 12 mg per week or less.

Interaction tests were not significant for other clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.5; planned interval between

corticosteroid treatments: Analysis 9.5; planned dose of corticosteroids to be given per treatment course: Analysis 10.5).

Severe lung disease

Repeat dose(s) of prenatal corticosteroids probably resulted in a reduction in the risk of *severe lung disease* compared with placebo or standard care (RR 0.83, 95% CI 0.72 to 0.97; I^2 = 76%, Chi^2 P = 0.0009; NNTB 45, 95% CI 27 to 256; 6 trials, 4955 fetuses randomised; Analysis 1.6).

Sensitivity analysis

Heterogeneity was not explained by differing definitions of severe lung disease. Based on prespecified subgroup analyses, heterogeneity may be partially explained by differing planned number of treatment courses and treatment intervals between trials. Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Mazumder 2008; Wapner 2006), with a result that was similar to the overall analysis (RR 0.85, 95% CI 0.73 to 0.98; I^2 = 85%, Chi^2 P = 0.0002; 4 trials, 4285 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate.* Certainty was downgraded due to inconsistency as evidenced by high levels of heterogeneity, likely due to differences in the definition of severe lung disease across different trials. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding indirectness, imprecision or publication bias.

Subgroup analysis

Prespecified subgroup analysis identified an interaction between severe lung disease and the planned number of repeat courses of corticosteroids (Chi^2 = 9.16, P = 0.002, I^2 = 89%; Analysis 8.6). Participants in trials in which it was planned give one or more repeat treatment courses were more likely to experience benefit than participants in trials in which it was planned to give only one repeat treatment course.

There was also an interaction between severe lung disease and the planned interval between corticosteroid treatments (Chi^2 = 5.11, P = 0.02, I^2 = 80%; Analysis 9.6). Participants in trials that gave the treatment at a minimum interval of seven days were more likely to experience benefit than participants in trials in which the interval was 14 days or greater.

Interaction tests demonstrated no interactions between other clinical subgroups with available data (planned dose of corticosteroids to be given per treatment course: Analysis 10.6; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.6).

Chronic lung disease

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on the risk of *chronic lung disease* compared with placebo or standard care (RR 1.00, 95% CI 0.83 to 1.22; I^2 = 0%, Chi^2 P = 0.52; 9 trials, 5661 fetuses randomised; Analysis 1.7).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (McEvoy 2010; Wapner 2006), and one with high risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (RR 1.08, 95% CI 0.88 to 1.33; I^2 = 0%, Chi^2 P = 0.69; 6 trials, 4878 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness, imprecision or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.7; planned interval between corticosteroid treatments: Analysis 9.7; planned dose of corticosteroids to be given per treatment course: Analysis 10.7; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.7).

Severe intraventricular haemorrhage (grade 3 or 4)

For *severe intraventricular haemorrhage,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.13, 95% CI 0.69 to 1.86; I^2 = 22%, Chi^2 P = 0.27; 7 trials, 5066 fetuses randomised; Analysis 1.8).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (RR 1.06, 95% CI 0.61 to 1.83; I^2 = 33%, Chi^2 P = 0.20; 6 trials, 4738 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate* due to imprecision as the total number of events was low and the 95% CI included both moderate benefit and moderate harm. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.8; planned interval between corticosteroid treatments: Analysis 9.8; planned dose of corticosteroids to be given per treatment course: Analysis 10.8; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.8).

Intraventricular haemorrhage (any grade)

Repeat dose(s) of prenatal corticosteroids had little or no effect on the risk of *intraventricular haemorrhage (any grade)* compared with placebo or standard care (RR 0.95, 95% CI 0.75 to 1.19; I^2 = 0%, Chi^2 P = 0.54; 6 trials, 3223 fetuses randomised; Analysis 1.9).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Peltoniemi 2007; Wapner 2006), and one trial with high risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (RR 0.93, 95% CI 0.70 to 1.23; I^2 = 0%, Chi^2 P = 0.54; 3 trials, 2225 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded for risk of bias as limiting the analysis to studies at low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness, imprecision or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.9; planned interval between corticosteroid treatments: Analysis 9.9; planned dose of corticosteroids to be given per treatment course: Analysis 10.9; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.9).

Necrotising enterocolitis

For *necrotising enterocolitis,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.84, 95% CI 0.59 to 1.22; I^2 = 0%, Chi^2 P = 0.43; 9 trials, 5736 fetuses randomised; Analysis 1.10).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of bias (Wapner 2006), and one trial with high risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (RR 0.86, 95% CI 0.56 to 1.28; I^2 = 26%, Chi^2 P = 0.24; 7 trials, 5066 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate* due to imprecision as the 95% CI included both benefit and possible harm. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding inconsistency, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.10; planned interval between corticosteroid treatments: Analysis 9.10; planned dose of corticosteroids to be given per treatment course: Analysis 10.10; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.10).

Composite serious outcome

Repeat dose(s) of prenatal corticosteroids reduced the risk of the *composite of serious outcomes* compared with placebo or standard care (RR 0.88, 95% CI 0.80 to 0.97; NNTB 39, 95% CI 24 to 158; I^2 = 42%, Chi^2 P = 0.09; 9 trials, 5736 fetuses randomised; Analysis 1.11).

The composite outcome was variously defined by the trialists.

- Aghajafari 2002: one or more of: stillborn or neonatal death during the first 28 days of life or before hospital discharge, whichever was sooner; RDS; bronchopulmonary dysplasia (requiring oxygen at 36 corrected postnatal gestational age); grade 3 or 4 intraventricular haemorrhage and necrotising enterocolitis.
- Crowther 2006: one or more of: air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks' postmenstrual age, severe intraventricular haemorrhage (grade 3 or 4), periventricular leukomalacia, proven necrotising enterocolitis or retinopathy of prematurity.
- Garite 2009: one or more of: perinatal death in babies born before 34 weeks' gestation, perinatal death (defined as stillbirth or death before neonatal discharge); RDS (oxygen requirement, clinical diagnosis and consistent chest radiograph); bronchopulmonary dysplasia (defined as a requirement for oxygen at 30 days of age); severe intraventricular haemorrhage (grades 3 or 4); periventricular leukomalacia; blood culture-proven sepsis; or necrotising enterocolitis.
- Guinn 2001: any of: severe RDS, bronchopulmonary dysplasia, severe intraventricular haemorrhage, periventricular leukomalacia, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge.
- Mazumder 2008: severe RDS or death (or both) within 28 days.
- Murphy 2008: one of: stillbirth or neonatal death (defined as death during the first 28 days of life or before hospital discharge); severe RDS (defined as needing assisted ventilation via endotracheal tube and supplemental oxygen within the first 24 hours of life and for 24 hours or more, and either a radiographic scan compatible with RDS or surfactant given between the first two to 24 hours of life); bronchopulmonary dysplasia (defined as needing oxygen at a postmenstrual age of 36 completed weeks and radiographic scan compatible with bronchopulmonary dysplasia); intraventricular haemorrhage grade 3 or 4; cystic periventricular leukomalacia, necrotising enterocolitis.
- Peltoniemi 2007: death or RDS or severe intraventricular haemorrhage (expressed as survival without RDS or severe intraventricular haemorrhage during first hospitalisation).
- Wapner 2006: one of: severe RDS, intraventricular haemorrhage grade 3 or 4; 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.
- TEAMS 1999: a composite outcome was reported as part of the PRECISE-IPD analysis Crowther 2019, which included death (fetal, neonatal or infant), severe respiratory disease, severe intraventricular haemorrhage (grade 3 and 4), chronic lung disease (oxygen dependent at 36 weeks' postnatal age), definite necrotising enterocolitis, severe retinopathy of prematurity (stage 3 or worse in the better eye) or cystic periventricular leukomalacia.

Sensitivity analysis

Heterogeneity was not explained by differing definitions of severe lung disease or the prespecified subgroup analyses. Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Mazumder 2008; Wapner 2006), with a result that was similar to the overall analysis (RR 0.89, 95% CI 0.80 to 0.98; I^2 = 51%, Chi^2 P = 0.06; 7 trials, 5066 fetuses randomised).

Certainty of the evidence

The certainty of the evidence was *moderate* due to inconsistency as there was considerable statistical heterogeneity that may be due to differing definitions of the composite serious outcome between trials. Certainty was not downgraded for risk of bias as limiting the analysis to trials with low risk of bias did not markedly change the findings. There were no concerns regarding imprecision, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (number of babies in utero: Analysis 7.1; planned number of repeat courses of corticosteroids: Analysis 8.11; planned interval between corticosteroid treatments: Analysis 9.11; planned dose of corticosteroids to be given per treatment course: Analysis 10.11; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.11; gestational age at which the first repeat treatment was given: Analysis 12.1).

Primary outcomes for the women

Maternal death

It was unclear if repeat dose(s) of prenatal corticosteroids had an effect on *maternal death* as there was one death reported for a woman allocated to the placebo group and withdrawn from the trial before study treatment was given (Garite 2009). As there was only one trial, meta-analysis and sensitivity analysis was not possible (Analysis 2.1).

Certainty of the evidence

The certainty of the evidence was *low*. It was downgraded two levels due to imprecision with only one event occurring and wide 95% CIs included both marked benefit and marked harm. There were no concerns regarding indirectness or inconsistency. Publication bias was unable to be assessed as only one trial reported this outcome.

Maternal sepsis

For *maternal sepsis*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.13, 95% CI 0.93 to 1.39; I^2 = 23%, Chi^2 = 7.77,P = 0.26; 8 trials, 4666 mothers; Analysis 2.2).

Sensitivity analysis

All trials included in this analysis were at low risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate.* Certainty was downgraded for imprecision as the 95% CIs included possible benefit and harm. There were no concerns regarding inconsistency, indirectness or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.12; planned interval between corticosteroid treatments: Analysis 9.12; planned dose of corticosteroids to be given per treatment course: Analysis 10.12; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.12).

Caesarean section

Repeat dose(s) of prenatal corticosteroids had little or no effect on the risk of *caesarean section* compared with placebo or standard care (RR 1.03, 95% CI 0.98 to 1.09; I^2 = 46%, Chi^2 = 13.00,P = 0.07; 8 trials, 4266 mothers; Analysis 2.3)

Sensitivity analysis

Based on prespecified subgroup analyses, heterogeneity may be partially explained by differing planned number of treatment courses between trials. All trials included in this analysis were at low risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded by one level due to inconsistency of effect as evidenced by the degree of statistical heterogeneity. This inconsistency could have been due to differences in local practice or protocols regarding caesarean section. There were no concerns regarding indirectness, imprecision or publication bias.

Subgroup analysis

Prespecified subgroup analysis identified an interaction between caesarean section and the planned number of repeat courses of corticosteroids (Chi^2 = 4.59, P = 0.03, I^2 = 78%; Analysis 8.13). Participants in trials in which it was planned to give one or more repeat treatment courses had a higher likelihood of caesarean section than participants in trials in which it was planned to give only one repeat treatment course.

Interaction tests demonstrated no differences between the other clinical subgroups with available data (planned interval between corticosteroid treatments: Analysis 9.13; planned dose of corticosteroids to be given per treatment course: Analysis 10.13; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.13).

Discontinuation of therapy because of maternal side effects

It was unclear if repeat dose(s) of prenatal corticosteroids had an effect on *discontinuation of therapy due to maternal adverse effects* as only one trial reported this outcome and the outcome did not occur in any woman (Guinn 2001). As there was only one trial, 502 women and no events, meta-analysis was not possible.

Certainty of the evidence

The certainty of the evidence was *low*. Certainty was downgraded two levels due to imprecision as no events were recorded making it impossible to provide a relative effect estimate. There were no concerns regarding risk of bias, indirectness or inconsistency. Publication bias was unable to be assessed as only one trial reported this outcome.

Adverse effects of corticosteroids

It was unclear if repeat dose(s) of prenatal corticosteroids had an effect on the risk of *adverse effects.* Two trials reported this outcome with opposite treatment effects and substantial difference in event rates and the definition of the outcome (Crowther 2006; Wapner 2006). Meta-analysis was not performed as it was not considered appropriate to combine these results with such a marked difference in event rates and direction of effect.

Crowther 2006 defined adverse effects of treatment as any of pain/discomfort, haematoma, maternal distress, rash, sleeplessness, lethargy or other and identified a higher rate of adverse effects in the group who received repeat prenatal corticosteroid (10%) compared with the placebo group (5%) (RR 1.97, 95% CI 1.23 to 3.18; P = 0.005; 982 women).

Wapner 2006 defined any adverse effect of treatment as any of bruising, pain at the injection site, lump at the injection site, gastrointestinal upset, insomnia, contractions or cushingoid appearance and identified a lower rate of adverse effects in the group who received repeat prenatal corticosteroid (27%) compared with the placebo group (56%) (RR 0.49, 95% CI 0.39 to 0.61; P = 0.00001; 495 women).

The differences in adverse effects rates for intervention and placebo groups could be related to differences in placebo preparations. Crowther 2006 used a saline placebo. Wapner 2006 did not specify the placebo preparation

Certainty of the evidence

The certainty of the evidence was *low.* Certainty was downgraded two levels for marked inconsistency of effect as evidenced by marked heterogeneity in effect size and event rates. There were no concerns regarding risk of bias, imprecision or indirectness. Publication bias did not appear to be likely as there was one positive and one negative study for this outcome.

Admission to the intensive care unit

No trials reported data for *admission to the intensive care unit.*

Breastfeeding at hospital discharge

No trials reported data for *breastfeeding at hospital discharge*.

Primary outcomes for the child in early childhood (aged two to less than five years)

Five trials reported data in full for early childhood follow-up, and we included these in the meta-analysis (Crowther 2006; Murphy 2008; Peltoniemi 2007; TEAMS 1999; Wapner 2006). The outcome *total deaths after randomisation up to early childhood follow-up* used all fetuses randomised as the denominator. Denominators for all other analyses were defined as all babies randomised minus those children for whom there were no outcome data available.

Total deaths (after randomisation)

For *risk of death between randomisation and early childhood follow-up*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.06, 95% CI 0.81 to 1.40; I^2 = 0%, Chi^2 P = 0.63; 5 trials, 4565 fetuses randomised; Analysis 3.1).

Sensitivity analysis

All trials included in this analysis were at low risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level due to imprecision as the 95% CIs included possible benefit and harm. There were no concerns regarding imprecision, inconsistency or indirectness. Publication bias is unlikely as four of the five trials of varying size had effect estimates that were close to the no effect line.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.14; planned interval between corticosteroid treatments: Analysis 9.14; planned dose of corticosteroids to be given per treatment course: Analysis 10.14; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.14).

Neurodevelopmental impairment at age two to less than five years

Repeat dose(s) of prenatal corticosteroids had little or no effect on risk of *neurodevelopmental impairment at early childhood follow-up* compared with placebo (RR 0.97, 95% CI 0.85 to 1.10; I^2 = 0%, Chi^2 P = 0.87; 4 trials, 3616 children; Analysis 3.2).

The result from each trial that was used in the meta-analysis for neurodevelopmental impairment was as follows.

- Crowther 2006: "Neurosensory disability" defined as any of cerebral palsy, developmental delay (Mental Development Index greater than one SD below the mean), blindness or deafness.
- Murphy 2008: "Neurologic impairment" defined as either of cerebral palsy or cognitive delay (a score of two SD or more below the normative value for Bayley Scales of Infant Development-II or the local equivalent).
- TEAMS 1999: a composite outcome was reported as part of the PRECISE-IPD analysis Crowther 2019 that included "Neurosensory Disability" defined as any of developmental delay or intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), cerebral palsy, blindness (corrected visual acuity worse than 6/60 in the better eye), deafness (hearing loss requiring amplification or worse).
- Wapner 2006: children with Bayley Psychomotor Developmental Index less than 85 (one SD below normative data).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (TEAMS 1999), and one with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 0.99, 95% CI 0.86 to 1.14; I^2 = 0%, Chi^2 P = 0.85; 2 trials, 3007 children).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded due to risk of bias as limiting the analysis to trials with low risk of bias did not change the findings. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was

unlikely as the four trials were all clustered close to the no effect line except TEAMS 1999, which had wide 95% CIs.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned interval between corticosteroid treatments: Analysis 9.15; planned dose of corticosteroids to be given per treatment course: Analysis 10.15; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.15).

Survival free of neurodevelopmental impairment at age two to less than five years

Repeat dose(s) of prenatal corticosteroids had little or no effect on *survival free of neurodevelopmental impairment at early childhood follow-up* compared with placebo (RR 1.01, 95% CI 0.98 to 1.04; I^2 = 0%, Chi^2 P = 0.89; 4 trials, 3845 children; Analysis 3.3).

Denominators were defined as all babies randomised minus those children for whom there were no outcome data available. The result from each trial that was used in the meta-analysis for survival free of neurodevelopmental impairment was as follows.

- Crowther 2006: total with available data minus those with "death or any neurosensory disability" (defined as any of cerebral palsy, developmental delay (Mental Development Index greater than one SD below the mean), blindness or deafness).
- Murphy 2008: total children minus those with the outcome of "Death or neurologic impairment" (defined as either of cerebral palsy or cognitive delay (a score of two SD or more below the normative value for Bayley Scales of Infant Development-II or the local equivalent)).
- TEAMS 1999: total children with available data minus those with the outcome "death or neurosensory disability" reported as part of the PRECISE-IPD analysis (Crowther 2019), which defined "neurosensory disability" as any of developmental delay or intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), cerebral palsy, blindness (corrected visual acuity worse than 6/60 in the better eye), deafness (hearing loss requiring amplification or worse).
- Wapner 2006: total with available data minus those who had died prior to assessment and those children with Bayley Psychomotor Developmental Index less than 85 (one SD below normative data).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (TEAMS 1999), and one with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 1.00, 95% CI 0.97 to 1.04; I^2 = 0%, Chi^2 P = 0.71; 2 trials, 3164 children).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded due to risk of bias as limiting the analysis to trials with low risk of bias did not change the findings. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was unlikely as the four trials were all clustered close to the no effect line.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (number of babies in utero: Analysis 7.2; planned interval between corticosteroid treatments: Analysis 9.16; planned dose of corticosteroids to be given per treatment course: Analysis 10.16; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.16).

Survival free of major neurodevelopmental impairment at age two to less than five years

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *survival free of major neurodevelopmental impairment at early childhood follow-up* compared with placebo (RR 1.02, 95% CI 0.98 to 1.05; I^2 = 67%, Chi^2 P = 0.05; 3 trials, 1816 children; Analysis 3.4).

The result from each trial that was used in the meta-analysis for survival free of major neurodevelopmental impairment was as follows.

- Crowther 2006: total with available data minus those with "death or moderate to severe neurosensory disability" (defined as any of moderate-to-severe cerebral palsy, moderate-to-severe developmental delay (Mental Development Index greater than two SDs below the mean), blindness or deafness).
- Peltoniemi 2007: survival without "severe neurological, cognitive, or sensory impairment" (defined as survival without cerebral palsy, Mental Developmental Index less than 70, developmental quotient less than 70, deafness or blindness).
- Wapner 2006: total with available data minus those who had died prior to assessment and those children with Bayley Psychomotor Developmental Index less than 70 (two SDs below normative data).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (Peltoniemi 2007) and one with some concerns of risk of bias (Wapner 2006) which left only one trial at low risk of bias, with a result that was similar to the overall analysis (RR 1.04, 95% CI 0.99 to 1.10; 1060 children). Sensitivity analysis was not performed for heterogeneity as there were only three trials in this analysis.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded due to inconsistency as evidenced by the high level of statistical heterogeneity. Certainty was not downgraded due to risk of bias as limiting the analysis to the one trial with low risk of bias did not change the findings. There were no concerns of indirectness or imprecision. Publication bias was unlikely as the three trials were all clustered close to the no effect line.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned number of repeat courses of corticosteroids: Analysis 8.15; planned dose of corticosteroids to be given per treatment course: Analysis 10.17; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.17).

Cerebral palsy

For *cerebral palsy at early childhood follow-up,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.03, 95% CI 0.71 to 1.49; I^2 = 0%, Chi^2 P = 0.49; 5 trials, 3923 children; Analysis 3.5). There were too few children with cerebral palsy to analyse the subgroups of severity of cerebral palsy (mild, moderate and severe).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of two trials with high risk of bias (Peltoniemi 2007; TEAMS 1999), with a result that was similar to the overall analysis (RR 1.01, 95% CI 0.69 to 1.47; I^2 = 31%, Chi^2 P = 0.24; 3 trials, 3541 children).

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded due to imprecision as evidenced by wide 95% CIs that included both benefit and harm. Certainty was not downgraded due to risk of bias as limiting the analysis to trials with low risk of bias did not change the result. There were no concerns of indirectness or inconsistency. Publication bias was unlikely as the five trials were all clustered close to the no effect line except Wapner 2006, which had very wide 95% CIs that included both benefit and marked harm.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned interval between corticosteroid treatments: Analysis 9.17; planned dose of corticosteroids to be given per treatment course: Analysis 10.18; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.18).

Developmental delay or intellectual impairment at age two to less than five years

Repeat dose(s) of prenatal corticosteroids had little or no effect on *developmental delay at early childhood follow-up* compared with placebo (RR 0.95, 95% CI 0.84 to 1.09; I^2 = 0%, Chi^2 P = 0.86; 4 trials, 3581 children; Analysis 3.6).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (Peltoniemi 2007), and one with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 0.98, 95% CI 0.85 to 1.14; I^2 = 0%, Chi^2 P = 0.93; 2 trials, 2900 children).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded due to risk of bias as limiting the analysis to trials with low risk of bias did not change the findings. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was unlikely as the four trials were all clustered close to the no effect line.

Mental Developmental Index at age two to less than five years

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean Mental Developmental Index score* at early childhood follow-up compared with placebo (MD 0.89, 95% CI −0.61 to 2.39; I^2 = 0%, Chi^2 P = 0.46; 3 trials, 1627 children; Analysis 3.7).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (Peltoniemi 2007), and one with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (MD 0.60, 95% CI −1.59 to 2.79; 1 trial, 967 children).

Certainty of the evidence

The certainty of the evidence was *high*. Certainty was not downgraded due to risk of bias as limiting the analysis to trials with low risk of bias did not change the findings. There were no concerns of indirectness, imprecision, inconsistency or publication bias.

Subgroup analysis

Interaction tests demonstrated no differences between clinical subgroups with available data (planned interval between corticosteroid treatments: Analysis 9.18; planned dose of corticosteroids to be given per treatment course: Analysis 10.19; planned dose of repeat corticosteroid drug exposure per week: Analysis 11.19).

Primary outcomes for the child in mid- to late childhood (aged five to less than 18 years)

Two trials reported data for children in mid- to late childhood (Crowther 2006; Murphy 2008). The outcome *total deaths after randomisation up to mid- to late childhood follow-up* used all fetuses randomised as the denominator. Denominators for all other analyses were defined as all babies randomised minus those children for whom there was no outcome data available.

Total deaths (after randomisation)

For *risk of death between randomisation and mid- to late childhood follow-up*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.93, 95% CI 0.69 to 1.26; I^2 = 0%, Chi^2 P = 0.84; 2 trials, 2874 fetuses randomised; Analysis 4.1).

Sensitivity analysis

Both trials included in this analysis were at low risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level for imprecision due to wide 95% CIs that included benefit and possible harm. There were no concerns of indirectness or inconsistency. Publication bias was not formally assessed as there were only two trials and both had effect estimates close to the no effect line.

Neurocognitive impairment at age five to less than 18 years

For *neurocognitive impairment at mid- to late childhood follow-up*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.96, 95% CI 0.72 to 1.29; 1 trial, 897 children; Analysis 4.2).

Data came from the result "neurosensory disability", which was defined as any of cerebral palsy, intellectual quotient greater than one SD below the normative mean, blindness or deafness (Crowther 2006).

Sensitivity analysis

No sensitivity analysis was performed as only one trial reported this outcome.

Certainty of the evidence

The certainty of the evidence was *low*. Certainty was downgraded one level due to risk of bias as the single included trial had some concerns of risk of bias due to missing outcome data. Certainty was downgraded one further level for imprecision as the 95% CIs included both benefit and harm. There were no concerns of indirectness or inconsistency. Publication bias was not formally assessed as there was only one trial in this analysis.

Survival free of neurocognitive impairment at age five to less than 18 years

Repeat dose(s) of prenatal corticosteroids had little or no effect on *survival free of neurocognitive impairment at mid- to late childhood follow-up* compared with placebo (RR 1.01, 95% CI 0.95 to 1.08; 1 trial, 963 children; Analysis 4.3).

Data came from the result "survival free of neurosensory disability" in which neurosensory disability was defined as any of cerebral palsy, intellectual quotient greater than one SD below the normative mean, blindness or deafness (Crowther 2006).

Sensitivity analysis

No sensitivity analysis was performed as only one trial reported this outcome.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level due to risk of bias as the single included trial had some concerns of risk of bias due to missing outcome data. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was not formally assessed as there was only one trial in this analysis.

Survival free of major neurocognitive impairment at age five to less than 18 years

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *survival free of major neurocognitive impairment at mid- to late childhood follow-up* compared with placebo (RR 1.00, 95% CI 0.97 to 1.04; I^2 = 0%, Chi^2 P = 0.69; 2 trials, 2682 children; Analysis 4.4).

In the two trials that reported data, major neurocognitive impairment was defined as follows.

- Crowther 2006: any of blindness, severe cerebral palsy, or severe intellectual impairment (intellectual quotient less than −3 SD).
- Murphy 2008: "Severe disability", defined as any of neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness or deafness or need for visual or hearing aids), or neurocognitive disability (abnormal attention, memory or behaviour assessed by an abnormally elevated score (more than 1.5 SD greater than normative control sample) on either the Behaviour Rating Inventory of Executive Function – Preschool version and the Child Behaviour Checklist – 1.5–5).

Sensitivity analysis

Both trials included in this analysis were judged to have some concerns of risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level due to risk of bias as the included trials were judged to have some concerns of risk of bias due to missing outcome data. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was not formally assessed as there were only two trials and both had effect estimates close to the no effect line.

Motor impairment at age five to less than 18 years

Neither of the trials reporting data for follow-up at mid- to late childhood reported data for motor impairment. Murphy 2008 reported "neuromotor disability", which was classified as non-ambulatory cerebral palsy and is included under the outcome section '*Cerebral palsy*'.

Cognitive impairment at age five to less than 18 years

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *cognitive impairment at mid- to late childhood follow-up* compared with placebo (RR 1.00, 95% CI 0.81 to 1.22; I^2 = 0%, Chi^2 P = 0.59; 2 trials, 2504 children; Analysis 4.5).

Sensitivity analysis

Both trials included in this analysis were judged to have some concerns of risk of bias.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level due to risk of bias as the included trials were judged to have some concerns of risk of bias due to missing outcome data. There were no concerns of indirectness, imprecision or inconsistency. Publication bias was not formally assessed as there were only two trials and both had effect estimates close to the no effect line.

Educational achievement at age five to less than 18 years

Only one trial reported data for *educational achievement at mid- to late childhood* (Crowther 2006). Educational achievement was reported using the Wide Range Achievement Test 4 for spelling, mathematics and reading standardised to a mean of 100 and SD of 15. The authors reported little or no difference between groups (spelling: MD −0.9, 95% CI −3.4 to 1.6; mathematics: MD 0.1, 95% CI −2.3 to 2.4; reading: MD −0.2, 95% CI −2.7 to 2.4).

Sensitivity analysis

No sensitivity analysis was performed as only one trial reported this outcome.

Certainty of the evidence

The certainty of the evidence was *moderate*. Certainty was downgraded one level due to risk of bias as the included trial was judged to have some concerns of risk of bias due to missing outcome data. There were no concerns of indirectness, imprecision

or inconsistency. Publication bias was not formally assessed as there was only one trial that assessed this outcome.

Cerebral palsy

For *cerebral palsy*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo (RR 0.74, 95% CI 0.43 to 1.26; I^2 = 55%, Chi^2 P = 0.13; 2 trials, 2622 children; Analysis 4.6).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias due to missing data (Murphy 2008). The result from the remaining trial was similar to the overall analysis but with greater imprecision (RR 0.95, 95% CI 0.51 to 1.76; 987 children). Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Certainty of the evidence

The certainty of the evidence was *low*. Certainty was downgraded one level due to imprecision as the 95% CI included marked benefit and harm and the total number of events was low. It was downgraded one further level due to inconsistency as evidenced by the marked statistical heterogeneity. Heterogeneity may have been related to differing classifications of cerebral palsy as Crowther 2006 reported data for any cerebral palsy whereas Murphy 2008 reported non-ambulatory cerebral palsy. Evidence was not downgraded due to risk of bias as limiting the analysis to only the trial with low risk of bias did not change the findings. There were no concerns of indirectness. Publication bias was not formally assessed as there were only two trials and both had effect estimates crossing the no effect line.

Hypertension

No trials reported *hypertension*. Crowther 2006 reported that the proportion of children in the pre-hypertensive range (greater than 90th centile for systolic or diastolic blood pressure) was not different between the repeat doses of corticosteroids group and the placebo group (RR 1.07, 95% CI 0.64 to 1.80; 848 children).

Primary outcomes for the child as an adult (aged 18 years or greater)

No trials reported data for follow-up into adulthood.

Secondary outcomes for the fetus/neonate/infant

Birthweight

Mean birthweight

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in *mean birthweight* compared with placebo or standard care (MD −74 g, 95% CI −116 to −33; I^2 = 0%, Chi^2 P = 0.82; 10 trials, 5808 infants; Analysis 1.38; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to only those trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (MD −73 g, 95% CI −116 to −32; I^2 = 0%, Chi^2 P = 0.74; 9 trials, 5734 infants).

Birthweight adjusted for gestational age

Repeat dose(s) of prenatal corticosteroids also resulted in a small reduction in *birthweight adjusted for gestational age* compared with placebo or standard care (SMD −0.15, 95% CI −0.23 to −0.06; I^2 = 0%, Chi^2 P = 0.64; 4 trials, 2028 infants; Analysis 1.41; high-certainty evidence; Table 1). Data for this analysis were reported as birthweight Z scores for three trials (Crowther 2006; McEvoy 2010; TEAMS 1999), and multiples of the median for one trial (Wapner 2006).

Small-for-gestational age

Repeat dose(s) of prenatal corticosteroids resulted in an increase in infants born *small-for-gestational age* compared with placebo or standard care (RR 1.25, 95% CI 1.08 to 1.44; NNTH 29, 95% CI 16 to 90; I^2 = 0%, Chi^2 P = 0.69; 7 trials, 4013 fetuses randomised; Analysis 1.17; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials at some concerns of risk of bias (Mazumder 2008; Wapner 2006), with a result similar to the overall analysis (RR 1.20, 95% CI 1.03 to 1.41; I^2 = 0%, Chi^2 P = 0.71; 5 trials, 3343 fetuses randomised).

Length at birth

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in *mean length at birth* compared with placebo or standard care (MD −0.6 cm, 95% CI −0.9 to −0.2; I^2 = 0%, Chi^2 P = 0.47; 6 trials, 4550 infants; Analysis 1.45; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial judged at some concerns of risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (MD −0.6 cm, 95% CI −0.9 to −0.2; I^2 = 11%, Chi^2 P = 0.34; 5 trials, 4476 infants).

Repeat dose(s) of prenatal corticosteroids resulted in little or no change in *length at birth adjusted for gestational age* compared with placebo or standard care (SMD −0.09, 95% CI −0.18 to 0.01; I^2 = 0%, Chi^2 P = 0.37; 3 trials, 1846 infants; Analysis 1.48; high-certainty evidence; Table 1). Data for this analysis were reported as birthweight Z scores for two trials (Crowther 2006; McEvoy 2010) and multiples of the median for one trial (Wapner 2006).

Head circumference at birth

Mean head circumference at birth

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in *mean head circumference at birth* compared with placebo or standard care (MD −0.3 cm, 95% CI −0.5 to −0.2; I^2 = 16%, Chi^2 P = 0.30; 10 trials, 5731 infants; Analysis 1.43; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial judged at some concerns of risk of bias (Mazumder 2008) and one trial at high risk of bias (TEAMS 1999),

with a result that was similar to the overall analysis (MD −0.3 cm, 95% CI −0.5 to −0.2; I^2 = 30%, Chi^2 P = 0.18; 8 trials, 5568 infants).

Mean head circumference at birth adjusted for gestational age

Repeat dose(s) of prenatal corticosteroids resulted in little or no change in *mean head circumference at birth adjusted for gestational age* compared with placebo or standard care (MD −0.14, 95% CI −0.27 to 0.00; I^2 = 0%, Chi^2 P = 0.43; 2 trials, 1251 infants; Analysis 1.44; high-certainty evidence; Table 1).

Growth assessments at primary hospital discharge

Mean weight at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean weight at primary hospital discharge* compared with placebo or standard care (MD 18 g, 95% CI −52 to 88; I^2 = 37%, Chi^2 P = 0.21; 2 trials, 1195 infants; Analysis 1.49; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD −1 g, 95% CI −77 to 75; 1 trial, 1090 infants). Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Mean weight Z score at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean weight Z score at primary hospital discharge* compared with placebo or standard care (MD −0.05, 95% CI −0.16 to 0.06; I^2 = 0%, Chi^2 P = 0.92; 2 trials, 1195 infants; Analysis 1.50; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD −0.05, 95% CI −0.16 to 0.06; 1 trial, 1090 infants).

Mean length at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean length at primary hospital discharge* compared with placebo or standard care (MD 0.0 cm, 95% CI −0.4 to 0.5; I^2 = 0%, Chi^2 P = 0.87; 2 trials, 1189 infants; Analysis 1.53; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD 0.0, 95% CI −0.5 to 0.5; 1 trial, 1090 infants).

Mean length Z score at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean length Z score at primary hospital discharge* compared with placebo or standard care (MD −0.06, 95% CI −0.23 to 0.10; I^2 = 0%, Chi^2 P = 0.34; 2 trials, 1189 infants; Analysis 1.54; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD −0.03, 95% CI −0.21 to 0.15; 1 trial, 1090 infants).

Mean head circumference at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean head circumference at primary hospital discharge* compared with placebo or standard care (MD 0.1 cm, 95% CI −0.1 to 0.4; I^2 = 0%, Chi^2 P = 0.56; 2 trials; 1195 infants; Analysis 1.51; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD 0.0, 95% CI −0.2 to 0.2; 1 trial, 1090 infants).

Mean head circumference Z score at primary hospital discharge

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean head circumference Z score at primary hospital discharge* compared with placebo or standard care (MD −0.03 cm, 95% CI −0.15 to 0.10; I^2 = 0%, Chi^2 P = 0.53; 2 trials, 1195 infants; Analysis 1.52; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (McEvoy 2010), with a result that was similar to the overall analysis (MD −0.04, 95% CI −0.17 to 0.09; 1 trial, 1090 infants).

Growth assessments at infant follow-up

Mean weight at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly caused a small reduction in *mean weight at infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −0.60 kg, 95% CI −0.87 to −0.34; I^2 = 23%, Chi^2 P = 0.25; 2 trials, 149 infants; Analysis 1.55; very low-certainty evidence; Table 1).

Mean weight Z score at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly had little or no effect on *mean weight Z score at infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −0.12, 95% CI −0.84 to 0.6; 1 trial, 75 infants; Analysis 1.56; very low-certainty evidence; Table 1).

Mean length at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly decreased *mean length at infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −1.6 cm, 95% CI −2.3 to −0.8; I^2 = 0%, Chi^2 P = 0.59; 2 trials, 149 infants; Analysis 1.59; very low-certainty evidence; Table 1).

Mean length Z score at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly had little or no effect on *mean length Z score at infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −0.24, 95% CI −1.21 to 0.73; 1 trial, 75 infants; Analysis 1.60; very low-certainty evidence; Table 1).

Mean head circumference at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly decreased *mean head circumference at infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −0.5 cm, 95% CI −0.9 to −0.1; I^2 = 0%, Chi^2 P = 0.59; 2 trials, 136 infants; Analysis 1.57; very low-certainty evidence; Table 1).

Mean head circumference Z score at infant follow-up

Repeat dose(s) of prenatal corticosteroids possibly had little or no effect on *mean head circumference Z scoreat infant follow-up* compared with placebo or standard care, but the evidence was very uncertain (MD −0.04, 95% CI −0.78 to 0.70; 1 trial, 62 infants; Analysis 1.58; very low-certainty evidence; Table 1).

Gestational age at birth

Term birth

Repeat dose(s) of prenatal corticosteroids possibly had little or no effect of the likelihood of *term birth* compared with placebo or standard care (RR 0.96, 95% CI 0.86 to 1.06; I^2 = 43%, Chi^2 P = 0.12; 7 trials, 4068 fetuses randomised; Analysis 1.12; low-certainty evidence; Table 1).

Sensitivity analysis

Subgroup analysis based on prespecified subgroups suggests that some of the heterogeneity may be related to different planned numbers of treatment courses. Different gestational ages at trial entry could have contributed to heterogeneity but this was not directly assessed in sensitivity analysis.

Preterm birth

Repeat dose(s) of prenatal corticosteroids possibly had little or no effect of the likelihood of *preterm birth* compared with placebo or standard care (RR 1.02, 95% CI 0.98 to 1.05; I^2 = 60%, Chi^2 P = 0.02; 7 trials, 4068 fetuses randomised; Analysis 1.13; low-certainty evidence; Table 1).

Sensitivity analysis

Subgroup analysis based on prespecified subgroups suggests that some of the heterogeneity may be related to different planned numbers of treatment courses and the dose given per treatment course. Different gestational ages at trial entry could have contributed to heterogeneity but this was not directly assessed in sensitivity analysis.

Very preterm birth

Repeat dose(s) of prenatal corticosteroids probably had little or no effect of the likelihood of *very preterm birth less than 34 weeks* compared with placebo or standard care (RR 1.02, 95% CI 0.97 to 1.08; I^2 = 0%, Chi^2 P = 0.75; 6 trials, 2682 fetuses randomised; Analysis 1.14; moderate-certainty evidence; Table 1).

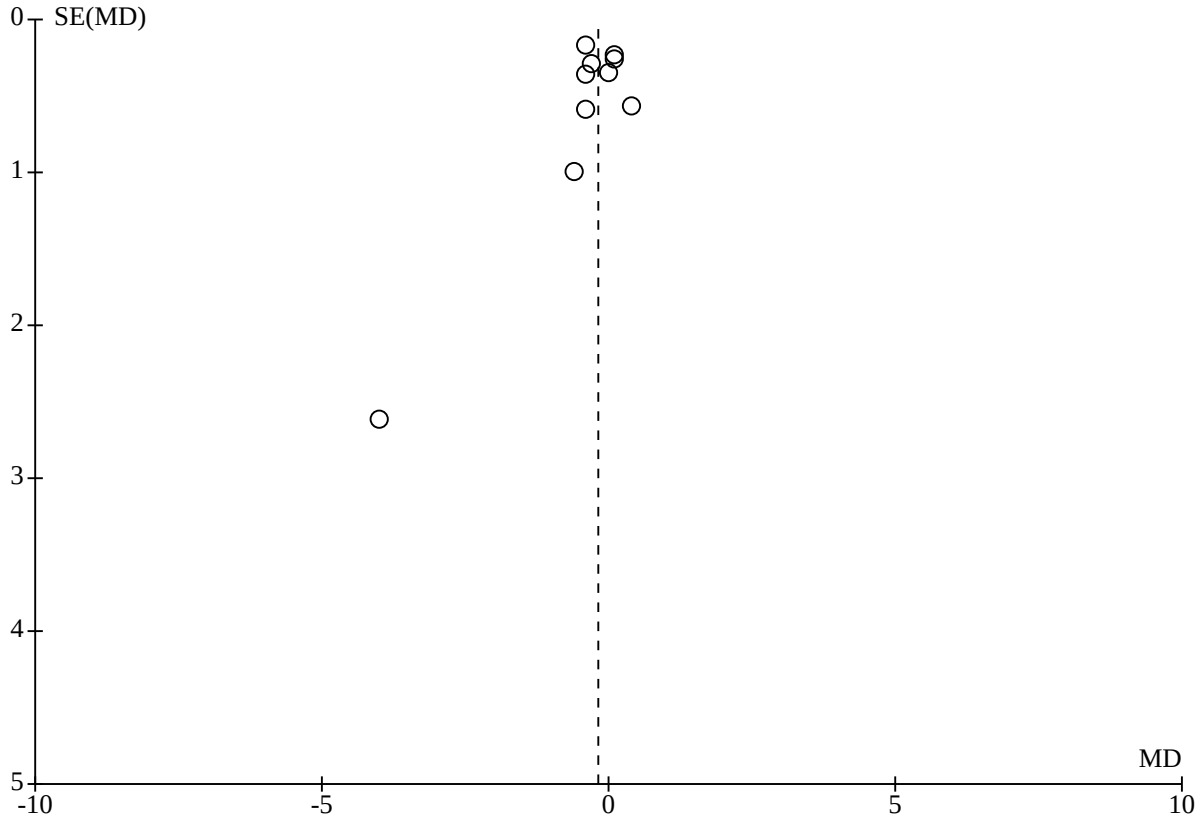
Extremely preterm birth

For *extremely preterm birth less than 28 weeks*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.13, 95% CI 0.92 to 1.38; I^2 = 0%, Chi^2 P = 0.87; 5 trials, 4022 fetuses randomised; Analysis 1.15; low-certainty evidence; Table 1).

Mean gestational age at birth

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean gestational age at birth* compared with placebo or standard care (MD −0.18 weeks, 95% CI −0.37 to 0.01; I^2 = 0%, Chi^2 P = 0.46; 10 trials, fetuses randomised; Analysis 1.16; moderate-certainty evidence; Table 1). The funnel plot to investigate publication bias was symmetrical, with the exception of one small study showing a negative effect (Figure 5).

Figure 5.



Interval between trial entry and birth

Repeat dose(s) of prenatal corticosteroids probably resulted in a small reduction in the *interval between trial entry and birth* compared with placebo or standard care (MD −0.71 days, 95% CI −1.36 to −0.06; I^2 = 0%, Chi^2 P = 0.75; 4 trials, 1309 fetuses randomised; Analysis 1.42; moderate-certainty evidence; Table 1).

Admission to neonatal intensive care unit

Repeat dose(s) of prenatal corticosteroids had little or no effect on risk of *admission to the NICU* compared with placebo or standard care (RR 1.01, 95% CI 0.95 to 1.07; I^2 = 0%, Chi^2 P = 0.36; 2 trials, 3455 fetuses randomised; Analysis 1.18; high-certainty evidence; Table 1).

Proven neonatal infection while in the neonatal intensive care unit

Repeat dose(s) of prenatal corticosteroids had little or no effect on risk of *proven neonatal infection while in the NICU* compared with placebo or standard care (RR 1.03, 95% CI 0.86 to 1.22; I^2 = 0%, Chi^2 P = 0.56; 8 trials, 5660 fetuses randomised; Analysis 1.19; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (TEAMS 1999; Wapner 2006), with a result that was similar to the overall analysis (RR 1.07, 95% CI 0.89 to 1.28; I^2 = 0%, Chi^2 P = 0.60; 6 trials, 4878 fetuses randomised).

Early systemic neonatal infection

Repeat dose(s) of prenatal corticosteroids had little or no effect on risk of *early systemic neonatal infection* compared with placebo or standard care (RR 0.93, 95% CI 0.79 to 1.11; I^2 = 0%, Chi^2 P = 0.80; 4 trials, 1738 fetuses randomised; Analysis 1.20; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial at high risk of bias (Mazumder 2008), with a result that was similar to the overall analysis (RR 0.93, 95% CI 0.78 to 1.10; I^2 = 0%, Chi^2 P = 0.69; 3 trials, 1662 fetuses randomised).

Late systemic neonatal infection

For *late systemic neonatal infection*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.37, 95% CI 0.78 to 2.41; I^2 = 0%, Chi^2 P = 0.38; 2 trials, 404 fetuses randomised; Analysis 1.21; low-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with high risk of bias (Mazumder 2008), but did not markedly change the findings (RR 1.51, 95% CI 0.83 to 2.75; 1 trial, 328 fetuses randomised).

Retinopathy of prematurity

For *retinopathy of prematurity*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.01, 95% CI 0.81 to 1.27; I^2 = 0%, Chi^2 P = 0.85; 8 trials, 5234 fetuses randomised; Analysis 1.22; moderate-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Murphy 2008; Wapner 2006) and one trial with high risk of bias (Mazumder 2008), but did not markedly change the results of the analysis (RR 0.95, 95% CI 0.71 to 1.27; I^2 = 0%, Chi^2 P = 0.94; 5 trials, 2255 fetuses randomised).

Periventricular leukomalacia

For *periventricular leukomalacia,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.75, 95% CI 0.43 to 1.31; I^2 = 0%, Chi^2 P = 0.77; 8 trials, 5142 fetuses randomised; Analysis 1.23; moderate-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007) and one at high risk of bias (Mazumder 2008), but did not markedly change the findings (RR 0.67, 95% CI 0.38 to 1.20; I^2 = 0%, Chi^2 P = 0.93; 6 trials, 4738 fetuses randomised).

Neonatal encephalopathy

For *neonatal encephalopathy,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.50, 95% CI 0.10 to 2.57; 1 trial, 76 fetuses randomised; Analysis 1.24; very low-certainty evidence; Table 1).

Patent ductus arteriosus

Repeat dose(s) of prenatal corticosteroids possibly reduced the risk of patent ductus arteriosus compared with placebo or standard care (RR 0.78, 95% CI 0.63 to 0.96; I^2 = 30%, Chi^2 P = 0.20; 7 trials, 4657 fetuses randomised; Analysis 1.25; low-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006) and one trial with high risk of bias (Mazumder 2008), and moved the CIs of the effect estimate past the no effect line (RR 0.81, 95% CI 0.65 to 1.01; I^2 = 40%, Chi^2 P = 0.15; 5 trials, 3987 fetuses randomised).

Use of respiratory support

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in the *use of respiratory support* compared with placebo or standard care (RR 0.88, 95% CI 0.80 to 0.97; I^2 = 5%, Chi^2 P = 0.30; 2 trials, 2497 fetuses randomised; Analysis 1.26; high-certainty evidence; Table 1).

Duration of respiratory support

No trials reported data for *duration of respiratory support*.

Use of invasive respiratory support

Repeat dose(s) of prenatal corticosteroids probably resulted in a small reduction in the *use of invasive respiratory support* compared with placebo or standard care (RR 0.86, 95% CI 0.80 to 0.93; I^2 = 60%, Chi^2 P = 0.03; 6 trials, 5067 fetuses randomised; Analysis 1.27; moderate-certainty evidence; Table 1).

Sensitivity analysis

Based on prespecified subgroup analyses, some of the heterogeneity may be associated with differences in the planned dose of corticosteroid drug exposure per week. Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 0.88, 95% CI 0.82 to 0.95; I^2 = 51%, Chi^2 P = 0.09; 5 trials, 4473 fetuses randomised).

Duration of invasive respiratory support

Repeat dose(s) of prenatal corticosteroids probably slightly reduced the *duration of invasive respiratory support* compared with placebo or standard care (MD −0.27 days, 95% CI −0.38 to −0.16; I^2 = 47%, Chi^2 P = 0.13; 4 trials, 1620 neonates; Analysis 1.61; moderate-certainty evidence; Table 1).

Sensitivity analysis

Prespecified subgroup analyses did not appear to explain the observed heterogeneity.

Use of non-invasive respiratory support

Repeat dose(s) of prenatal corticosteroids had little or no effect on the *use of non-invasive respiratory support* compared with placebo or standard care (RR 0.91, 95% CI 0.82 to 1.01; I^2 = 13%, Chi^2 P = 0.32; 3 trials, 3231 fetuses randomised; Analysis 1.28; high-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 0.94, 95% CI 0.84 to 1.05; I^2 = 0%, Chi^2 P = 0.64; 2 trials, 2637 fetuses randomised).

Duration of non-invasive respiratory support

For *duration of non-invasive respiratory support*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD −0.59 days, 95% CI −1.29 to 0.11; 1 trial, 326 neonates; Analysis 1.62; low-certainty evidence; Table 1).

Use of oxygen supplementation

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in the use of oxygen supplementation compared with placebo or standard care (RR 0.91, 95% CI 0.85 to 0.98; I^2 = 9%, Chi^2 P = 0.33; 3 trials, 3643 fetuses randomised; Analysis 1.29; high-certainty evidence; Table 1).

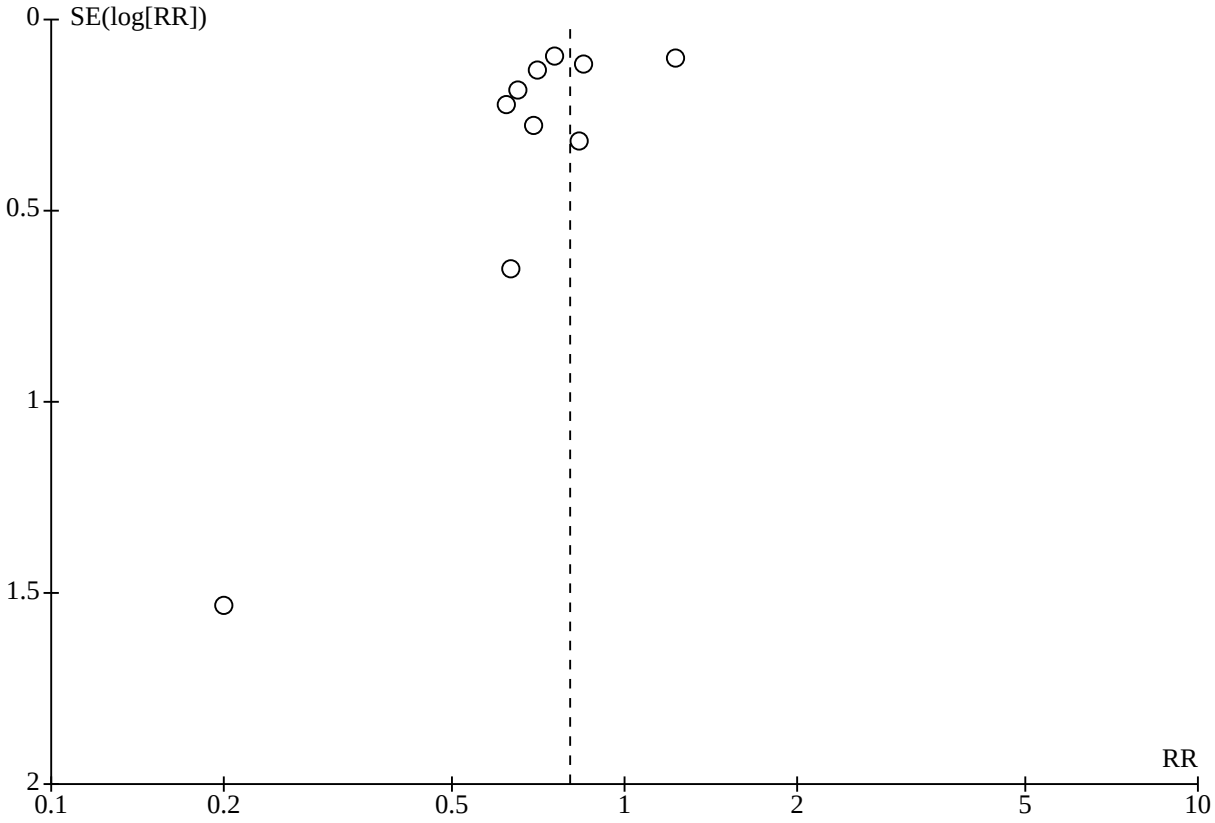
Duration of oxygen supplementation

For *duration of oxygen supplementation*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD −0.32 days, 95% CI −0.94 to 0.30; I^2 = 14%, Chi^2 P = 0.32; 4 trials, 1619 fetuses randomised; Analysis 1.63; moderate-certainty evidence; Table 1).

Use of surfactant

Repeat dose(s) of prenatal corticosteroids probably reduced the *use of surfactant* compared with placebo or standard care (RR 0.80, 95% CI 0.73 to 0.89; I^2 = 61%, Chi^2 P = 0.006; 10 trials, 5870 fetuses randomised; Analysis 1.30; moderate-certainty evidence; Table 1). Symmetry in the funnel plot was not suggestive of publication bias (Figure 6).

Figure 6.



Sensitivity analysis

Based on prespecified subgroup analyses, some of the heterogeneity observed may be associated with the planned dose of corticosteroid per treatment course. Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Mazumder 2008; Wapner 2006), with a result that was similar to the overall analysis (RR 0.82, 95% CI 0.74 to 0.91; I^2 = 65%, Chi^2 P = 0.005; 8 trials, 5200 fetuses randomised).

Use of postnatal corticosteroids

For *use of postnatal corticosteroids*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.37, 95% CI 0.99 to 1.91; I^2 = 0%, Chi^2 P = 0.82; 4 trials, 4145 fetuses randomised; Analysis 1.31; moderate-certainty evidence; Table 1).

Use of nitric oxide for respiratory support

For *use of nitric oxide for respiratory support*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.58, 95% CI 0.29 to 1.17; 1 trial, 1146 fetuses randomised; Analysis 1.32; moderate-certainty evidence; Table 1).

Pulmonary hypertension

No trials reported data for *pulmonary hypertension*.

Use of inotropic support

Repeat dose(s) of prenatal corticosteroids resulted in a reduction in the *use of inotropic support* compared with placebo or standard care (RR 0.80, 95% CI 0.66 to 0.97; I^2 = 0%, Chi^2 P = 0.50; 2 trials, 1474 fetuses randomised; Analysis 1.33; high-certainty evidence; Table 1).

Duration of inotropic support

No trials reported data for *duration of inotropic support*.

Air leak syndrome

For *air leak syndrome*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.83, 95% CI 0.50 to 1.36; I^2 = 14%, Chi^2 P = 0.32; 4 trials, 2505 fetuses randomised; Analysis 1.34; moderate-certainty evidence; Table 1).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 1.01, 95% CI 0.59 to 1.73; I^2 = 0%, Chi^2 P = 0.91; 3 trials, 1911 fetuses randomised).

Measures of renal function

No trials reported data for *measures of renal function*.

Feed tolerance

No trials reported data for *feed tolerance*.

Apgar score less than 7 at five minutes

For *Apgar score less than seven at five minutes*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.83, 95% CI 0.64 to 1.09; I^2 = 0%, Chi^2 P = 0.89; 3 trials, 4032 fetuses randomised; Analysis 1.35; moderate-certainty evidence; Table 1).

Cardiac hypertrophy

Only one trial reported neonatal cardiac hypertrophy, using measures of interventricular septal thickness and left ventricular wall thickness in diastole (Crowther 2006). Repeat dose(s) of prenatal corticosteroids probably had little or no effect on thickness of the interventricular septum (MD 0 mm, 95% CI −0.2 to 0.3; 1 trial, 175 neonates; Analysis 1.36) or of the left ventricular posterior wall (MD 0 mm, 95% CI −0.3 to 0.2; 1 trial, 175 neonates; Analysis 1.37) compared with placebo or standard care (moderate-certainty evidence; Table 1).

Measures of hypothalamic-pituitary-adrenal axis function

For measures of HPA *axis function,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (very low-certainty evidence; Table 1).

Five trials reported data relevant to this outcome.

- Crowther 2006 and Wapner 2006 both reported cord blood cortisol concentrations (MD −50 nmol/L, 95% CI −73 to −28; I^2 = 0%, Chi^2 P = 0.66; 2 trials, 442 neonates; Analysis 1.64).
- Crowther 2006 reported data for days three, seven, 14 and 21 unstressed and day three poststress (heel prick or nasopharyngeal suction) salivary cortisol. There were lower salivary cortisol concentrations with the repeat doses of corticosteroids compared with placebo on day three poststress samples (median: 11.9 nmol/L with repeat doses versus 21.3 nmol/L with placebo; P = 0.02; 27 neonates) and day seven unstressed samples (median: 11.7 nmol/L with repeat doses versus 18.2 nmol/L with placebo; P = 0.04; 39 neonates). Day 3 prestress (34 neonates, day 14 (39 neonates) and day 21 (35 neonates) salivary cortisol concentrations) and cortisol on did not differ between treatment groups.
- Crowther 2006 also reported basal and post-metyrapone cortisol concentrations at days two to three postbirth with no differences between baseline cortisol concentrations (63 neonates), baseline adrenocorticotrophic hormone (ACTH) concentrations or post-metyrapone cortisol, ACTH or 11-deoxycortisol concentrations (26 neonates).
- Aghajafari 2002 reported median (5th/95th centiles) for cord cortisol concentration and cord ACTH concentration at birth. The authors reported no difference but the overall sample size was low (11 neonates) and data were unable to be included in the meta-analysis as there were insufficient data to derive estimates of mean and SD.
- McEvoy 2002 reported cortisol concentrations on day five at baseline and 30-minute post-ACTH stimulation test for 11 neonates, although the numbers in each treatment group were unclear. The authors described a lower post-ACTH stimulation cortisol concentration and no difference in baseline cortisol concentrations.
- TEAMS 1999 had data available for "HPA axis suppression" although the outcome occurred in only one neonate in the repeat dose(s) of prenatal corticosteroids group.

Secondary outcomes for the woman

Puerperal sepsis

For *puerperal sepsis,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.05, 95% CI 0.78 to 1.43; I^2 = 29%, Chi^2 = 5.65, P = 0.23; 6 trials, 3246 women; Analysis 2.5; moderate-certainty evidence; Table 2).

Chorioamnionitis during labour

For *chorioamnionitis during labour,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.13, 95% CI 0.90 to 1.42; I^2 = 0%, Chi^2 = 3.31,P = 0.65; 7 trials, 4417 women; Analysis 2.6; moderate-certainty evidence; Table 2).

Endometritis

For *endometritis,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.17, 95% CI 0.74 to 1.84; I^2 = 63%, Chi^2 = 5.36,P = 0.07; 4 trials, 2842 women; Analysis 2.7; low-certainty evidence; Table 2).

Sensitivity analysis

Based on prespecified subgroup analyses, some of the heterogeneity may be associated with differences in the planned interval between treatment courses and the planned dose per treatment course.

Pyrexia after trial entry requiring the use of antibiotics

For *pyrexia after trial entry requiring the use of antibiotics,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.56, 95% CI 0.25 to 1.25; 1 trial, 156 women; Analysis 2.8; low-certainty evidence; Table 2).

Intrapartum fever requiring the use of antibiotics

No trials reported data for *intrapartum fever requiring the use of antibiotics*.

Postpartum haemorrhage

Repeat dose(s) of prenatal corticosteroids probably reduced the risk *of postpartum haemorrhage* compared with placebo or standard care (RR 0.54, 95% CI 0.31 to 0.96; I^2 = 0%, Chi^2 = 0.92,P = 0.34; 2 trials, 641 women; Analysis 2.9; moderate-certainty evidence; Table 2).

Postnatal pyrexia

For *postnatal pyrexia,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.87, 95% CI 0.55 to 1.38; 1 trial, 982 women; Analysis 2.10; moderate-certainty evidence; Table 2).

Preterm prelabour rupture of the membranes after trial entry

For *preterm prelabour rupture of the membranes after trial entry,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.91, 95% CI 0.65 to 1.29; I^2 = 0%, Chi^2 = 0.75,P = 0.39; 2 trials, 977 women; Analysis 2.11; moderate-certainty evidence; Table 2).

Mode of birth

Vaginal birth was the only mode of birth reported by more than one study and able to be combined with meta-analysis.

Repeat dose(s) of prenatal corticosteroids had little or no effect on the outcome of *vaginal birth* compared with placebo or standard care (RR 0.94, 95% CI 0.87 to 1.00; I^2 = 32%, Chi^2 = 7.34,P = 0.2; 6 trials, 4025 women; Analysis 2.12; high-certainty evidence; Table 2).

Sensitivity analysis

Prespecified subgroup analyses did not appear to explain the observed heterogeneity.

Hypertension

For *hypertension,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.08, 95% CI 0.87 to 1.32; I^2 = 14%, Chi^2 = 2.31,P = 0.31; 3 trials, 3327 women; Analysis 2.13; moderate-certainty evidence; Table 2).

Pulmonary oedema

No trials reported data for *pulmonary oedema*.

Glucose intolerance

For *glucose intolerance,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.23, 95% CI 0.90 to 1.67; I^2 = 0%, Chi^2 = 0.23,P = 0.63; 2 trials, 2345 women; Analysis 2.13; moderate-certainty evidence; Table 2).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 1.12, 95% CI 0.68 to 1.85; 1 trial, 1853 women).

Postnatal depression

For *postnatal depression,* benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.88, 95% CI 0.70 to 1.10; 1 trial, 1671 women; Analysis 2.15; moderate-certainty evidence; Table 2).

Local injection site adverse effects

Repeat dose(s) of prenatal corticosteroids possibly resulted in a lower risk of *local injection site adverse effects* compared with placebo (RR 0.44, 95% CI 0.32 to 0.60; I^2 = 95%, Chi^2 P = 0.00001; 2 trials, 1477 women; Analysis 2.16; low-certainty evidence; Table 2).

Sensitivity analysis

Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Insomnia after treatment

Repeat dose(s) of prenatal corticosteroids increased the risk of *insomnia after treatment* compared with placebo (RR 1.21, 95% CI 1.04 to 1.40; I^2 = 15%, Chi^2 = 3.54, P = 0.32; 4 trials, 3198 women; Analysis 2.17; high-certainty evidence; Table 2).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Aghajafari 2002), with a result that was similar to the overall analysis (RR 1.21, 95% CI 1.05 to 1.41; I^2 = 23%, Chi^2 P = 0.27; 3 trials, 3335 women).

Gastrointestinal adverse effects of treatment

Repeat dose(s) of prenatal corticosteroids probably reduced the risk of *gastrointestinal adverse effects of treatment* compared with placebo or standard care (RR 0.34, 95% CI 0.14 to 0.85; 1 trial, 495 women; Analysis 2.18; moderate-certainty evidence; Table 2).

Satisfaction with the therapy

No trials reported data for *satisfaction with the therapy*.

Quality of life

No trials reported data for *quality of life*.

Secondary outcomes for the child in early childhood (aged two to less than five years)

Child behaviour

For *child behaviour*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (moderate-certainty evidence; Table 3).

Three trials reported on *child behaviour* (Crowther 2006; Murphy 2008; Peltoniemi 2007). Crowther 2006 used the Child Behavior Checklist, a rating scale that screens for behavioural and emotional problems with higher scores indicating higher levels of behavioural and emotional problems. The trial showed no differences between groups in the total (MD 0.8, 95% CI −1.9 to 3.4; P = 0.56; 1045 children) or individual domain scores for internalising, externalising, emotional reactivity, anxiety or depression, somatic complaints, withdrawal, sleep problems, attention problems or aggressive behaviour between groups. The proportion of children in the clinical range (defined as the top 2.5th centile) did not differ between treatment groups in total (RR 1.11, 95% CI 0.79 to 1.57; P = 0.544; 1045 children) or across the individual domains, except for attention problems (RR 1.87, 95% CI 1.03 to 3.42; P = 0.04; 1045 children).

Murphy 2008 used the Behavior Rating Scale of the Bayley Scales of Infant Development II (BSID-II) and found scores were non-optimal or questionable for 285/902 (31.6%) children in the prenatal corticosteroid therapy group and 239/874 (27.3%) children in the placebo group (RR 1.16, 95% CI 1.00 to 1.34; Analysis 3.9).

Peltoniemi 2007 used the Early Childhood Behaviour Questionnaire, which uses a 201-point scale to describe child behaviour in different daily situations. The trial found no differences between the treatment groups for 148 children for any of the variables in the questionnaire (activity, attentional focusing, attentional shifting, cuddliness, discomfort, fear, frustration, high-intensity pleasure, impulsivity, inhibition, low-intensity pleasure, motor activity, perceptual sensitivity, positive anticipation, sadness, shyness, soothability, sociability), including the summary subscales of extraversion, negative affectivity and effortful control (Analysis 3.10; Analysis 3.11; Analysis 3.12).

Differences in the measurement of these outcomes precluded meaningful combination with meta-analysis.

Motor impairment

Motor impairment at early childhood follow-up was not reported separate to cerebral palsy, but three trials assessed motor development using the BSID II Psychomotor Developmental Index (Crowther 2006; Murphy 2008; Wapner 2006). Wapner 2006 used the median and range to estimate mean and SD as described by Wan 2014. Murphy 2008 reported a mean Psychomotor Developmental Index of 97.86 for the repeat doses of corticosteroid group and 98.98 for the placebo group, but the data were unable to be included in the meta-analysis as SDs were not reported (1901 children).

Repeat dose(s) of prenatal corticosteroids probably has little or no effect on *mean Psychomotor Developmental Index* compared with placebo (MD 1.26, 95% CI −0.45 to 2.96; I^2 = 39%, Chi^2 P = 0.20; 2 trials, 1423 children; Analysis 3.13; moderate-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Wapner 2006), with a result that was similar to the overall analysis (RR 0.40, 95% CI −1.75 to 2.55; 1 trial, 958 children). Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Deafness/hearing impairment

For *deafness/hearing impairment*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.97, 95% CI 0.56 to 1.71; I^2 = 0%, Chi^2 P = 0.74; 4 trials, 3528 children; Analysis 3.14; moderate-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Peltoniemi 2007; TEAMS 1999), with a result that was similar to the overall analysis (RR 0.97, 95% CI 0.56 to 1.71; I^2 = 0%, Chi^2 P = 0.74; 2 trials, 3146 children).

Blindness/visual impairment

For *blindness/visual impairment*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.17, 95% CI 0.65 to 2.10; I^2 = 0%, Chi^2 P = 0.38; 3 trials, 3274 children; Analysis 3.15; moderate-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (TEAMS 1999), with a result that was similar to the overall analysis (RR 1.17, 95% CI 0.65 to 2.10; I^2 = 0%, Chi^2 P = 0.38; 2 trials, 3151 children).

Growth assessments

Mean weight at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids resulted in a small reduction in *mean weight at early childhood follow-up* compared with placebo (MD −0.16 kg, 95% CI −0.25 to −0.07; I^2 = 6%, Chi^2 P = 0.36; 4 trials, 3784 children; Analysis 3.19; high-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (MD −0.17 kg, 95% CI −0.26 to −0.08; I^2 = 19%, Chi^2 P = 0.29; 3 trials, 3541 children).

Weight for age at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids resulted in little or no effect on *weight for age at early childhood follow-up* compared with placebo (SMD −0.06, 95% CI −0.15 to 0.04; I^2 = 0%, Chi^2 P = 0.54; 3 trials, 1776 children; Analysis 3.21; high-certainty evidence; Table 3). Three trials measured weight for age at early childhood follow-up (Crowther 2006; Peltoniemi 2007; Wapner 2006). Crowther 2006 reported weight Z scores. Peltoniemi 2007 reported relative weight as a percentage. Wapner 2006 reported weight as a percentile for age based on a published standard population.

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (SMD −0.06, 95% CI −0.16 to 0.04; I^2 = 14%, Chi^2 P = 0.28; 2 trials, 1514 children).

Low weight for age

For *low weight for age*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.92, 95% CI 0.72 to 1.19; I^2 = 0%, Chi^2 P = 0.32; 2 trials, 1533 children; Analysis 3.22; moderate-certainty evidence; Table 3). Two trials reported low weight for age, defined as weight less than 10th centile (Crowther 2006; Wapner 2006).

High weight for age

Crowther 2006 also reported high weight for age (greater than 90th centile) with no difference reported between the repeat doses of

corticosteroids group and placebo but with CIs that included both benefit and harm (RR 1.01, 95% CI 0.73 to 1.39; 1047 children).

Mean height at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean height at early childhood follow-up* compared with placebo (MD −0.1 cm, 95% CI −0.3 to 0.2; I^2 = 0%, Chi^2 P = 0.77; 4 trials, 3784 children; Analysis 3.27; high-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (MD −0.1 cm, 95% CI −0.3 to 0.2; I^2 = 0%, Chi^2 P = 0.63; 3 trials, 3541 children).

Height for age at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect on *height for age at early childhood follow-up* compared with placebo (SMD −0.06, 95% CI −0.15 to 0.04; I^2 = 0%, Chi^2 P = 0.41; 3 trials, 1776 children; Analysis 3.29; high-certainty evidence; Table 3). Three trials measured height for age at early childhood follow-up (Crowther 2006; Peltoniemi 2007; Wapner 2006). Crowther 2006 and Peltoniemi 2007 reported height Z scores. Wapner 2006 reported height as a percentile for age based on a published standard population.

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (SMD −0.08, 95% CI −0.18 to 0.02; I^2 = 0%, Chi^2 P = 0.55; 2 trials, 1533 children).

Short for age

For *short for age*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.03, 95% CI 0.77 to 1.36; I^2 = 71%, Chi^2 P = 0.07; 2 trials, 1526 children; Analysis 3.30; low-certainty evidence; Table 3). Two trials reported short for age, defined as height less than 10th centile (Crowther 2006; Wapner 2006).

Sensitivity analysis

Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Mean head circumference at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean head circumference at early childhood follow-up* compared with placebo (MD −0.1 cm, 95% CI −0.2 to 0.1; I^2 = 0%, Chi^2 P = 0.86; 4 trials, 3784 children; Analysis 3.23; high-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (MD −0.1 cm, 95% CI −0.2 to 0.1; I^2 = 0%, Chi^2 P = 0.84; 3 trials, 3541 children).

Head circumference for age at early childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect *head circumference for age at early childhood follow-up* compared with placebo (SMD 0.02, 95% CI −0.07 to 0.11; I^2 = 0%, Chi^2 P = 0.74; 3 trials, 1776 children; Analysis 3.25; high-certainty evidence; Table 3). Three trials measured head circumference for age at early childhood follow-up (Crowther 2006; Peltoniemi 2007; Wapner 2006). Crowther 2006 and Peltoniemi 2007 reported head circumference Z scores. Wapner 2006 reported head circumference as a percentile for age based on a published standard population.

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (SMD 0.01, 95% CI −0.09 to 0.18; I^2 = 0%, Chi^2 P = 0.78; 2 trials, 1533 children).

Small head circumference for age

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *small head circumference for age* compared with placebo (RR 1.02, 95% CI 0.87 to 1.21; I^2 = 63%, Chi^2 P = 0.10; 2 trials, 1527 children; Analysis 3.26; moderate-certainty evidence; Table 3). Both trials reported small head circumference for age, defined as head circumference less than 10th centile (Crowther 2006; Wapner 2006).

Sensitivity analysis

Sensitivity analysis was not performed for heterogeneity as there were only two trials in this analysis.

Body mass index

No trials reported data for *BMI*.

Obesity/overweight

No trials reported data for *obesity/overweight*.

Blood pressure

Mean systolic blood pressure

Repeat dose(s) of prenatal corticosteroids probably resulted in a reduction in *mean systolic blood pressure at early childhood follow-up* compared with placebo (MD −2.9 mmHg, 95% CI −5.4 to −0.4; 1 trial, 486 children; Analysis 3.31; high-certainty evidence; Table 3).

Mean systolic blood pressure Z score

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean systolic blood pressure Z score at early childhood follow-up* compared with placebo (MD −0.10, 95% CI −0.28 to 0.08; 1 trial, 672 children; Analysis 3.32; moderate-certainty evidence; Table 3).

Mean diastolic blood pressure

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean diastolic blood pressure at early childhood follow-up* compared with placebo (MD −1.0 mmHg, 95% CI −2.9 to 0.9; 1 trial, 486 children; Analysis 3.33; high-certainty evidence; Table 3).

Mean diastolic blood pressure Z score

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean diastolic blood pressure Z score at early childhood follow-up* compared with placebo (MD 0.10, 95% CI −0.05 to 0.25; 1 trial, 628 children; Analysis 3.34; moderate-certainty evidence; Table 3).

Hypertension

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on risk of *hypertension at early childhood follow-up* compared with placebo (RR 0.97, 95% CI 0.77 to 1.23; 1 trial, 628 children; Analysis 3.16; moderate-certainty evidence; Table 3).

Measures of lung function

No trials reported data for *measures of lung function*.

Chronic lung disease of infancy

No trials reported data for *chronic lung disease of infancy at early childhood follow-up*.

Asthma or recurrent wheeze

For asthma or recurrent wheeze, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.89, 95% CI 0.74 to 1.06; I^2 = 62%, Chi^2 P = 0.07; 3 trials, 1720 children; Analysis 3.17; moderate-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Peltoniemi 2007; Wapner 2006), with a result that was similar to the overall analysis (RR 0.87, 95% CI 0.70 to 1.07; 1 trial, 1060 children). Sensitivity analysis was not performed for heterogeneity as there were only three trials in this analysis.

Any respiratory disease

Three trials reported data on respiratory disease (Crowther 2006; Murphy 2008; Peltoniemi 2007). Crowther 2006 reported admissions for respiratory illness. Murphy 2008 reported admission for respiratory infections. Peltoniemi 2007 reported severe lung disease including pneumonia and recurrent wheeze or asthma. Repeat dose(s) of prenatal corticosteroids probably had little or no effect on risk of *any respiratory disease* compared with placebo (RR 1.04, 95% CI 0.92 to 1.18; I^2 = 0%, Chi^2 P = 0.52; 3 trials, 3423 children; Analysis 3.18; high-certainty evidence; Table 3).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of two trials with some concerns of risk of bias (Crowther 2006; Peltoniemi 2007), with a result that was similar to the overall analysis (RR 1.04, 95% CI 0.85 to 1.28; 1 trial, 2104 children).

Measures of insulin and glucose homeostasis

No trials reported data for *measures of insulin and glucose homeostasis*.

Measures of lipid profile

No trials reported data for *lipid profile*.

Measures of hypothalamic-pituitary-adrenal axis function

No trials reported data for *measures of HPA axis function*.

Body composition

No trials reported data for *body composition*.

Bone density

No trials reported data for *bone density*.

Secondary outcomes for the child in mid- to late childhood (aged five to less than 18 years)

Child behaviour

Two trials reported data for *child behaviour* from a parent-administered questionnaire (Crowther 2006; Murphy 2008). Crowther 2006 reported mean scores on a parent administered Strengths and Difficulties Questionnaire (SDQ). Murphy 2008 reported mean scores for the Child Behaviour Checklist 1.5–5 years. For both questionnaires, higher scores represent more behavioural problems. Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *child behaviour* compared with placebo (SMD 0.00, 95% CI −0.08 to 0.08; I^2 = 0%, Chi^2 P = 0.39; 2 trials, 2480 children; Analysis 4.10; moderate-certainty evidence; Table 4).

Murphy 2008 also reported the proportion with neurocognitive/neurobehavioural disability, which included those with elevated score on the Behaviour Rating Inventory of Executive Function (BRIEF) – preschool version (RR 0.96, 95% CI 0.75 to 1.22; 1615 children; Analysis 4.9).

Deafness/hearing impairment

For *deafness/hearing impairment*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.62, 95% CI 0.77 to 3.41; I^2 = 0%, Chi^2 P = 0.75; 2 trials, 2532 children; Analysis 4.8; low-certainty evidence; Table 4).

Blindness/visual impairment

For *blindness/visual impairment*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 1.12, 95% CI 0.79 to 1.59; I^2 = 0%, Chi^2 P = 0.56; 2 trials, 2532 children; Analysis 4.7; low-certainty evidence; Table 4).

Growth assessments

Mean weight at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean weight at mid- to late childhood follow-up* compared with placebo (MD −0.2 kg, 95% CI −0.6 to 0.2; 1 trial, 1635 children; Analysis 4.13; moderate-certainty evidence; Table 4).

Mean weight Z score at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean weight Z score at mid- to late childhood follow-up* compared with placebo (MD −0.06, 95% CI −0.23 to 0.11; 1 trial, 940 children; Analysis 4.14; high-certainty evidence; Table 4).

Low weight for age

Crowther 2006 also reported *low weight for age* (less than 10th centile) (RR 0.96, 95% CI 0.67 to 1.39; P = 0.83; 940 children).

Mean height at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean height at mid- to late childhood follow-up* compared with placebo (MD −0.4 cm, 95% CI −1.1 to 0.3; 1 trial, 1635 children; Analysis 4.17; moderate-certainty evidence; Table 4).

Mean height Z score at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids had little or no effect on *mean height Z score at mid- to late childhood follow-up* compared with placebo (MD 0.02, 95% CI −0.13 to 0.17; 1 trial, 912 children; Analysis 4.18; high-certainty evidence; Table 4).

Short for age

Crowther 2006 also reported *short for age* (less than 10th centile) (RR 0.94, 95% CI 0.64 to 1.40; P = 0.78; 912 children).

Mean head circumference at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean head circumference at mid- to late childhood follow-up* compared with placebo (MD −0.1 cm, 95% CI −0.4 to 0.2; 1 trial, 1635 children; Analysis 4.15; moderate-certainty evidence; Table 4).

Mean head circumference Z score at mid- to late childhood follow-up

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean head circumference Z score at mid- to late childhood follow-up* compared with placebo (MD −0.04, 95% CI −0.22 to 0.14; 1 trial, 885 children; Analysis 4.16; moderate-certainty evidence; Table 4).

Body mass index

Repeat dose(s) of prenatal corticosteroids had little or no effect on *BMI Z score* compared with placebo (MD −0.13, 95% CI −0.30 to 0.04; 1 trial, 910 children; Analysis 4.19; high-certainty evidence; Table 4).

Obesity/overweight

No trials reported data for obesity/overweight.

Blood pressure

Mean systolic blood pressure

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean systolic blood pressure* compared with placebo (MD 0.3 mmHg, 95% CI −1.1 to 1.7; 1 trial, 1635 children; Analysis 4.22; moderate-certainty evidence; Table 4).

Mean systolic blood pressure Z score

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean systolic blood pressure Z score* compared with placebo (MD 0.07, 95% CI −0.06 to 0.20; 1 trial, 848 children; Analysis 4.24; moderate-certainty evidence; Table 4).

Mean diastolic blood pressure

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean diastolic blood pressure* compared with placebo (MD 0.7 mmHg, 95% CI −0.5 to 1.9; 1 trial, 1635 children; Analysis 4.23; moderate-certainty evidence; Table 4).

Mean diastolic blood pressure Z score

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *mean diastolic blood pressure* Z score compared with placebo (MD −0.09, 95% CI −0.25 to 0.07; 1 trial, 848 children; Analysis 4.25; moderate-certainty evidence; Table 4).

Measures of lung function

Forced expiratory volume in 1 second Z score

For *forced expiratory volume in 1 second (FEV_1) Z score*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD −0.06, 95% CI −0.34 to 0.22; 1 trial, 185 children; Analysis 4.26; very low-certainty evidence; Table 4).

Forced vital capacity Z score

For *forced vital capacity (FVC) Z score*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD −0.18, 95% CI −0.49 to 0.13; 1 trial, 185 children; Analysis 4.27; very low-certainty evidence; Table 4).

FEV_1/FVC ratio Z score

For *FEV_1/FVC ratio Z score*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD −0.19, 95% CI −0.44 to 0.06; 1 trial, 185 children; Analysis 4.28; very low-certainty evidence; Table 4).

Asthma or recurrent wheeze

Repeat dose(s) of prenatal corticosteroids had little or no effect on risk of *asthma* compared with placebo (RR 1.01, 95% CI 0.85 to 1.19; 1 trial, 979 children; Analysis 4.11; high-certainty evidence; Table 4).

Respiratory disease

For *any respiratory disease*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (RR 0.79, 95% CI 0.36 to 1.72; 1 trial, 979 children; Analysis 4.12; very low-certainty evidence; Table 4).

Measure of insulin and glucose homeostasis

Repeat dose(s) of prenatal corticosteroids had little or no effect on *measures of insulin and glucose homeostasis* compared with placebo (moderate-certainty evidence; Table 4).

Only one trial reported measures of insulin and glucose homeostasis (Crowther 2006). Testing included a fasting plasma glucose (MD −0.1 mmol/L, 95% CI −0.2 to 0.0), fasting plasma insulin concentration (ratio of geometric means (RGM) 1.02, 95% CI 0.86 to 1.22) and a 90-minute, frequently sampled intravenous glucose tolerance test (IVGTT) for 182 children. The IVGTT was used to derive measures of insulin sensitivity index (RGM 0.89, 95% CI 0.74 to 1.08), glucose effectiveness (RGM 0.93, 95% CI 0.81 to 1.06), acute insulin release (RGM 1.05, 95% CI 0.84 to 1.31) and glucose disappearance constant (RGM 0.92, 95% CI 0.80 to 1.07).

Lipid profile

No trials reported data for lipid profile.

Measures of hypothalamic-pituitary-adrenal axis function

Repeat dose(s) of prenatal corticosteroids possibly has little or no effect on *mean salivary cortisol* compared with placebo (moderate-certainty evidence; Table 4). One trial reported data for measures of HPA axis function in 212 children (Crowther 2006). Morning and evening salivary cortisol concentrations were similar between those children who had received repeat doses of prenatal corticosteroids and those who received placebo after adjusting for time of sampling (morning RGM 1.05, 95% CI 0.91 to 1.20; P = 0.52; evening RGM 0.78, 95% CI 0.60 to 1.01; P = 0.11).

Bone density

Repeat dose(s) of prenatal corticosteroids probably had little or no effect on *total body bone mineral content* compared with placebo (moderate-certainty evidence; Table 4). One trial reported data for measures of total body bone mineral content in 185 children (Crowther 2006). There were no differences between treatment groups for whole-body bone mineral content adjusted for height (RGM 0.99, 95% CI 0.97 to 1.01), whole-body bone area adjusted for height (RGM 0.99, 95% CI 0.95 to 1.02) and spinal bone mineral content (RGM 0.97, 95% CI 0.92 to 1.03).

Body composition

Repeat dose(s) of prenatal corticosteroids possibly has little or no effect on *body composition* compared with placebo (moderate-certainty evidence; Table 4). One trial reported data for body composition assessed using dual energy x-ray absorptiometry (DEXA) (Crowther 2006). There were no differences between treatment groups for whole-body fat free mass adjusted for height (RGM 0.98, 95% CI 0.95 to 1.00) and whole-body fat mass adjusted for height (RGM 0.96, 95% CI 0.76 to 1.20). There were also no differences for fat mass in gynoid (thigh) and android (abdominal) distributions.

Secondary outcomes for the child as an adult

No trials reported data for follow-up into adulthood.

Secondary outcomes on use of health services

Length of prenatal hospitalisation for the woman

No trials reported data for *length of prenatal hospitalisation for the woman*.

Length of postnatal hospitalisation for the woman

Repeat dose(s) of prenatal corticosteroids had little or no effect on length of postnatal hospitalisation for the women compared with placebo (MD 0.00 days, 95% CI −0.22 to 0.22; 1 trial, 483 women; Analysis 6.3; high-certainty evidence; Table 5).

Maternal admission to the intensive care unit

No trials reported data for *maternal admission to the ICU*.

Admission to and length of stay in neonatal intensive care unit

Admission to the NICU was reported under 'Secondary outcomes for the fetus/neonate/infant: admission to neonatal intensive care unit' and no trials reported data for the *length of stay in the NICU* to date.

Length of infant hospitalisation

For *length of infant hospitalisation*, benefit or harm could not be excluded for repeat dose(s) of corticosteroids compared with placebo or standard care (MD 0.18 days, 95% CI −2.60 to 2.96; I^2 = 14%, Chi^2 P = 0.31; 3 trials, 1733 infants; Analysis 6.4; moderate-certainty evidence; Table 5).

Costs of maternal care

No trials reported data for *costs of maternal care*.

Costs of neonatal care

No trials reported data for *costs of neonatal care*.

Hospital re-admission at childhood follow-up

Early childhood follow-up

Repeat dose of prenatal corticosteroid probably had little or no effect on hospital readmission by early childhood follow-up compared with placebo (RR 1.02, 95% CI 0.93 to 1.11; I^2 = 0%, Chi^2 P = 0.39; 4 trials, 3824 children; Analysis 6.1; high-certainty evidence; Table 5).

Sensitivity analysis

Restricting the analysis to trials at low risk of bias resulted in the exclusion of one trial with some concerns of risk of bias (Peltoniemi 2007), with a result that was similar to the overall analysis (RR 1.00, 95% CI 0.91 to 1.09; I^2 = 0%, Chi^2 P = 0.52; 3 trials, 35654 children).

Mid- to late childhood follow-up

For *hospital readmission by mid- to late childhood follow-up*, benefit or harm was unable to be excluded for repeat dose(s) of prenatal corticosteroids compared with placebo (RR 1.10, 95% CI 0.80 to 1.52; 1 trial, 980 children; Analysis 6.2; very low-certainty evidence; Table 5).

DISCUSSION

Summary of main results

Outcomes for the fetus/neonate/infant

A total of 4895 women (5975 babies) who had received a course of prenatal corticosteroids seven or more days previously were randomised to repeat dose(s) of prenatal corticosteroids or placebo/standard care ("no repeat dose(s)"). The use of repeat dose(s) of corticosteroid for women at risk of preterm birth reduced the relative risk of neonatal RDS by 18% (NNTB 16, 95% CI 11 to 29 women; 62 fewer babies with RDS per 1000 women treated) and the relative risk of serious infant outcome by 12% (NNTB 39, 95% CI 24 to 158 women; 26 fewer babies with a serious health outcome per 1000 women treated). These are clinically important neonatal benefits, observed with high-certainty (neonatal RDS) and moderate-certainty (serious infant outcome) evidence. There is also high-certainty evidence that repeat dose(s) results in no difference in the risk of chronic lung disease (RR 1.00, 95% CI 0.83 to 1.22; 5661 babies) and moderate-certainty evidence that it reduces the risk of severe lung disease (RR 0.83, 95% CI 0.72 to 0.97, NNTB 45, 95% CI 27 to 256; 4955 babies). The information available could not exclude benefit or harm for the outcomes fetal or neonatal or infant death less than one year of age (RR 0.95, 95% CI 0.73 to 1.24; 5849 babies), severe intraventricular haemorrhage (RR 1.13, 95%

CI 0.69 to 1.86; 5066 babies) and necrotising enterocolitis (RR 0.84, 95% CI 0.59 to 1.22; 5736 babies).

Outcomes for the woman

For the women, there was moderate-certainty evidence of no increase in the likelihood of a caesarean birth, providing some reassurance about the safety of repeat prenatal corticosteroid treatment for the mothers. Benefit or harm was unable to be excluded for maternal sepsis. There was significant heterogeneity for the trials reporting on adverse effects and only one trial reported on each of maternal death and discontinuation of therapy due to adverse effects so it was not possible to determine if repeat dose(s) of corticosteroid resulted in benefit, harm or no effect on these outcomes. No trials reported data for breastfeeding status at hospital discharge or risk of admission to the intensive care unit.

Outcomes for the child in early childhood (age two to less than five years)

Moderate- to high-certainty evidence identified little or no effect of repeat dose(s) of prenatal corticosteroids compared with no repeat doses for neurodevelopmental outcomes (neurodevelopmental impairment: RR 0.97, 95% CI 0.85 to 1.10; 3616 children; survival without neurodevelopmental impairment: RR 1.01, 95% CI 0.98 to 1.04; 3845 children; survival without major neurodevelopmental impairment; RR 1.02, 95% CI 0.98 to 1.05; 1816 children). An increase or decrease in the risk of death since randomisation could not be excluded (RR 1.06, 95% CI 0.81 to 1.40; 5 trials, 4565 babies randomised).

Outcomes for the child in mid- to late childhood (age five to less than 18 years)

Long-term neurodevelopmental outcomes at mid- childhood follow-up did not differ between treatment groups for survival free of neurocognitive impairment (RR 1.01, 95% CI 0.95 to 1.08; 963 children) and survival free of major neurocognitive impairment (RR 1.00, 95% CI 0.97 to 1.04; 2682 children) (moderate-certainty evidence). Benefit or harm could not be excluded for death since randomisation (RR 0.93, 95% CI 0.69 to 1.26; 2874 babies randomised) and neurocognitive impairment (RR 0.96, 95% CI 0.72 to 1.29; 897 children).

Outcomes for the child in adulthood

No trials reported data for follow-up into adolescence or adulthood.

Subgroup analyses

Prespecified subgroup analyses indicated significant interactions for three outcomes: severe RDS, severe lung disease and caesarean section. For severe RDS, participants in trials with corticosteroid exposure of greater than 12 mg to 24 mg per week were more likely to benefit from repeat doses than those with exposure of 12 mg or less per week. For severe lung disease, participants were more likely to experience benefit from repeat doses of corticosteroids in trials that planned to give one or more repeat treatment courses compared with trials that planned to give only one repeat treatment course, and in trials that planned to give the treatment at a minimum interval of seven days compared with trials in which the interval was 14 days or greater. Caesarean section was more likely to occur in trials that planned to give one or more repeat treatment courses than in trials that planned to give only one repeat treatment course, but it was not more likely to occur with repeat corticosteroids compared with placebo in the overall analysis. There were no significant interactions for the limited number of outcomes with data available between the effect of repeat doses of corticosteroids and the number of fetuses (singleton versus multiple) or gestation at the time of the first repeat dose (less than 28 weeks' gestation versus 28 weeks' gestation or greater).

Overall completeness and applicability of evidence

Women in the included trials were recruited in a range of countries and settings. The trials were conducted at either tertiary or provincial hospitals, with participants from high-, middle- and low-income countries. The trials included a wide variety of reasons for being at risk of preterm birth and all trials included women with both singleton and multiple pregnancies. The results are considered applicable to hospital settings worldwide. Betamethasone has been the only corticosteroid evaluated in randomised trials of repeat prenatal corticosteroids prior to preterm birth. Dexamethasone is often used because it is less expensive and often more easily available, particularly in low- to middle-income countries. It is uncertain whether the effects seen for betamethasone would be the same for dexamethasone. Appropriate trials are needed.

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

The evidence available provides reassurance about the health of infants into early to mid-childhood when repeat prenatal corticosteroids are used for women at risk of preterm birth. However, there is as yet no information on health, neurodevelopmental, growth, cardiovascular or metabolic outcomes at older ages to assess the long-term benefits or risks of this treatment.

Quality of the evidence

The risk of bias of the trials included in this review ranged from low to high risk across different outcomes, with most being assessed as low risk or having some concerns of risk of bias. All trials had adequate randomisation and all except one used a placebo. Losses to follow-up to the time of primary hospital discharge after birth were nil or minimal. At early childhood follow-up losses to follow-up in the five trials that reported data ranged between 7.5% and 21.0%. At mid- to late childhood follow-up, losses to follow-up were 14% and 19% in the two trials that reported data. Four trials stopped recruitment early (Guinn 2001; Peltoniemi 2007; TEAMS 1999; Wapner 2006).

The evidence was mostly of moderate and high certainty for the primary outcomes with reasons for downgrading the certainty being predominantly inconsistency of effect or imprecision due to wide CIs including both appreciable benefit and harm. Secondary outcomes were also mostly of moderate to high certainty although for some outcomes the certainty was downgraded to low or very low because of risk of bias or marked imprecision. Outcomes assessed at mid- to late childhood follow-up were mainly at risk of bias due to missing data, resulting in moderate certainty of evidence for most of these outcomes.

Potential biases in the review process

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

Unit of analysis issues were considered as a potential source of bias. In accordance with the Pregnancy and Childbirth Cochrane Group guidelines, for neonatal outcomes we used the number of fetuses alive at the point of randomisation as the denominator for analysis. This avoids bias by ensuring analysis is based on the total group of women and their fetuses initially randomised but may bias the analysis by underestimating the occurrence of neonatal morbidity, as the most unwell fetuses may die in utero or soon after birth and contribute to the denominator but not to measures of neonatal morbidity. However, stillbirth was an infrequent occurrence, making this unlikely to be a major contributor to bias.

Not all trials reported data using the same unit of analysis. For multiple pregnancies, Guinn 2001 randomly selected one of the fetuses for inclusion in the analysis, an approach that may underestimate the occurrence of neonatal morbidity and therefore the effects of interventions because infants from multiple pregnancies have higher rates of many neonatal morbidities. Mazumder 2008 reported data using the pregnancy as the unit of analysis but did not detail which fetus or infant would be assessed for dichotomous outcomes. Wapner 2006 used the pregnancy as the unit of analysis and considered an outcome to have occurred if any of the fetuses randomised experienced the outcome. For these two trials the effect of interventions may be overestimated as the rate of occurrence of neonatal morbidity will be artificially elevated through the use of a smaller denominator and this may increase the apparent efficacy of interventions that may reduce neonatal morbidity.

Two trials have studied long-term outcomes; Murphy 2008 at five years and Crowther 2006 at six to eight years of age; but the proportion of participants lost to follow-up was high enough for there to be some concerns of bias due to missing outcome data for most outcomes reported. The relative paucity of studies that have performed long-term follow-up means that long-term outcomes are unknown for most trials included in this review.

The large number of outcomes included in the review does introduce a risk of Type 1 error (i.e. finding a difference between treatment groups purely by chance rather than observing a true difference). The concordance between findings for risk of RDS and need for respiratory treatments such as surfactant makes this less likely for many of the respiratory outcomes but this is still an important potential bias for other outcomes.

The assessment of risk of bias and GRADE assessments have subjective elements that may be a source of bias in the review process. To reduce this risk, two review authors performed risk of bias assessments, and two review authors performed all GRADE assessments of certainty of evidence for completeness and accuracy.

Three review authors (CAC, JEH, CM) were investigators for the ACTORDS trial or its follow-up studies (Crowther 2006). Other review authors (PM and AW) performed assessment of trustworthiness, risk of bias and data extraction for this trial without direct involvement of the investigators or authors of the trial or its follow-up studies.

Agreements and disagreements with other studies or reviews

The results and conclusions of this systematic review are consistent with the results of an IPD meta-analysis of trials of repeat doses of corticosteroids compared with placebo or standard care for woman with an ongoing risk of preterm labour (Crowther 2019). The results of the IPD subgroup analyses also suggested interactions between use of respiratory support and the repeat course interval, the number of courses and the total dose received; findings broadly consistent with the findings of the subgroup analyses in this review for severe RDS and severe lung disease.

The current international guideline from the World Health Organization regarding the use of interventions for preterm birth have used an earlier version of this review on which to base their recommendations (WHO 2015).

One systematic review performed for the production of clinical guidelines for practice in Australia and New Zealand had similar conclusions regarding repeat doses of prenatal corticosteroids and a number of the recommendations for further research have been addressed in the mid-childhood follow-up outcomes included in this review (Antenatal Corticosteroids CPG Panel 2015).

The American College of Obstetrics and Gynecology committee on obstetric practice produced a committee opinion statement in 2017, reaffirmed in 2020, that the use of repeat doses of prenatal corticosteroids in the context of threatened preterm birth should be considered for women with a pregnancy of less than 34 weeks' gestation for whom their last course of prenatal corticosteroids was 14 or more days prior (ACOG 2017).

AUTHORS' CONCLUSIONS

Implications for practice

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

Repeat dose(s) of prenatal corticosteroids given to women at risk of preterm birth, compared to no repeat treatment, reduce the occurrence of respiratory distress syndrome (RDS) by 18% and the risk of serious health problems in the first few weeks of life for the infant by 12%. For one baby to benefit by not developing RDS, 16 women (95% confidence interval (CI) 11 to 29) would need to be treated with repeat prenatal corticosteroids, resulting in 62 fewer babies with RDS per 1000 women treated. The number needed to treat for an additional beneficial outcome (NNTB) for serious neonatal outcome is 39 women (95% CI 24 to 158), resulting in 26 fewer babies with a serious health outcome per 1000 women treated. At birth, the neonatal benefits are

associated with a reduction in measures of mean body size (mean weight, head circumference and length) including weight adjusted for gestational age and an increase in the proportion of infants born small for gestational age (number needed to treat for an additional harmful outcome of 29, 95% CI 16 to 89). These effects were not observed for other anthropometric assessments that adjusted for gestational age (length and head circumference). Differences in body size measurements were no longer seen by hospital discharge in the two trials that report data. The limited evidence available from early and mid- childhood reassuringly shows no significant harm, although no benefit. There was a small reduction in mean weight at early childhood in those exposed to repeat dose(s) of prenatal corticosteroids, but this was not observed at mid-childhood follow-up. There were no differences in neurodevelopmental outcomes or childhood head circumference or height at early or mid-childhood.

The reduction in RDS and serious neonatal outcome are of clinical importance, despite the absence of an effect on severe RDS or severe lung disease. The benefits of a reduction in neonatal morbidity with repeat dose(s) of prenatal corticosteroids must be weighed against the potential risks of the reduction in birthweight. Although the association of low birthweight with poorer health outcomes in later life is well established, long-term follow-up in adults exposed to prenatal corticosteroids has thus far shown minimal effects on health up to 30 years of age when compared with those exposed to placebo (Dalziel 2005a). The implications of a small reduction in birthweight on long-term health for the infant exposed to repeat doses(s) of prenatal corticosteroids are unclear but there is little or no effect on health outcomes in follow-up to eight years of age and, as yet, there is insufficient evidence in adolescence and adulthood.

The use of corticosteroids for women at risk of preterm birth is supported by evidence of overall benefit for its use in low-, middle- and high-income settings (McGoldrick 2020). Repeat prenatal corticosteroids should be considered for women who have received a course of prenatal corticosteroids seven or more days previously, and who remain at risk of preterm birth before 34 weeks' gestation. Women eligible for repeat prenatal corticosteroid treatment should be informed of the known benefits and risks and counselled about the available information about early and mid-childhood health outcomes.

Implications for research

We are aware of two ongoing trials in the US of repeat prenatal corticosteroids for women at risk of preterm birth in the setting of preterm prelabour rupture of membranes prior to trial entry (NCT02469519; NCT02939742).

There are still no data published for health and neurocognitive outcomes in adulthood. Such information would be valuable for assessing the overall benefits and risks of using repeat prenatal corticosteroids for women at risk of preterm birth.

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

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

ACKNOWLEDGEMENTS

We acknowledge the support from the Cochrane Pregnancy and Childbirth Review editorial team in Liverpool, the Australia and New Zealand Satellite of Cochrane Pregnancy and Childbirth and the Liggins Institute, The University of Auckland, New Zealand.

As part of the prepublication editorial process, this review has been commented on by four peers (an editor and three referees who are external to the editorial team), a member of Cochrane Pregnancy and Childbirth's international panel of consumers and the Group's Statistical Adviser. The authors are grateful to the following peer reviewers for their time and comments: Liz Bickerdike, Associate Editor, Cochrane Editorial & Methods Department, UK; Doris Chou, Department of Sexual and Reproductive Health, Maternal Perinatal Health Team, World Health Organization (WHO), Geneva, Switzerland; Jim Thornton, Emeritus Professor, University of Nottingham, Nottingham, UK.

Unpublished trial data was provided for TEAMS 1999 by Professor Peter Brocklehurst.

This project was supported by the National Institute for Health Research (NIHR), via Cochrane Infrastructure funding to Cochrane Pregnancy and Childbirth. The views and opinions expressed herein are those of the review authors and do not necessarily reflect those of the Evidence Synthesis Programme, the NIHR, National Health Service (NHS) or the Department of Health and Social Care.

This review is supported by funding from the WHO and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP) to Cochrane Pregnancy and Childbirth (University of Liverpool). HRP supports and co-ordinates research on a global scale, synthesises research through systematic reviews of literature, builds research capacity in low-income countries and develops dissemination tools to make efficient use of ever-increasing research information. In addition to its co-sponsors, the International Planned Parenthood Federation (IPPF) and UNAIDS are both members of HRP's governing body.

We thank Anne Lawson for copyediting this review.

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* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Aghajafari 2002

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial Small pilot study to determine the feasibility of a larger trial
Participants	Location: 2 hospitals in Toronto, Canada Dates of study: September 1999 to August 2000 Eligibility criteria: women at 24–30 weeks' gestation at continued increased risk of preterm birth who remained undelivered ≥ 7 days following a single course of prenatal corticosteroids (defined as 2 doses of intramuscular betamethasone 12 mg/dose, given at 12- or 24-hour intervals; or 4 doses of intramuscular dexamethasone 5–6 mg/dose, given at 12-hour intervals). At increased risk of preterm birth, women had to have ≥ 1 of the following: regular uterine contractions; shortened cervical length or cervical dilation; preterm prelabour rupture of the membranes; prepartum bleeding secondary to placental separation or placenta praevia; history of preterm birth; maternal hypertension; other medical con-

Aghajafari 2002 *(Continued)*

	dition 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: required chronic doses of corticosteroids secondary to medical conditions; contraindication to corticosteroids; clinical evidence of chorioamnionitis or if their fetus(es) had a known lethal congenital anomaly Total recruited: 12 women (16 fetuses): 6 women (9 fetuses) in multiple course of prenatal corticosteroid group and 6 women (7 fetuses) in placebo group
Interventions	Multiple course of prenatal corticosteroid group: weekly course of betamethasone (2 doses of betamethasone 12 mg/dose (Celestone Soluspan; Schering Canada Inc) intramuscularly, 24 hours apart) until 33 weeks or delivery if the woman remained at increased risk of preterm birth Placebo group: weekly course of placebo consisting of 2 doses of normal saline, intramuscularly 24 hours apart, until 33 weeks or delivery if the woman remained at increased risk of preterm birth
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 ≥ 1 of the following: stillborn or neonatal death during the first 28 days of life or prior to hospital discharge, whichever was sooner; RDS; BPD (requiring oxygen at 36 corrected postnatal gestational age); IVH (grade 3 or 4); and necrotising enterocolitis
Funding Support	Support from Canadian Institutes of Health Research Senior Scientist Award
Notes	Sample-size calculation: no. Declarations of interest: declared no conflict of interest. Ethical approval: approved by the research ethics committees of participating hospitals. Trial registration: not located.

Crowther 2006

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: 23 hospitals in Australia and New Zealand Dates of study: April 1998 to July 2004 Inclusion criteria: single, twin or triplet pregnancy at < 32 weeks' gestation if women had received an initial treatment of corticosteroid ≥ 7 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 essential Gestational age: recruited up to < 32 weeks Total recruited: 982 women (1146 fetuses); 489 women (568 fetuses) in repeat corticosteroid group and 493 women (578 fetuses) in placebo group

Crowther 2006 *(Continued)*

Interventions	Repeat corticosteroids group: betamethasone 11.4 mg (Celestone Chronodose) (as betamethasone sodium phosphate 7.8 mg and betamethasone acetate 6 mg by intramuscular injection Placebo group: saline intramuscular injection Every week, if the woman remained undelivered and < 32 weeks' gestation, and the responsible clinician regarded her as at continued risk of preterm birth, a further treatment pack from the same treatment group was allocated by the telephone randomisation service
Outcomes	To time of primary hospital discharge: primary outcomes: frequency and severity of RDS (defined as clinical signs of respiratory distress and a ground-glass appearance on chest radiograph); weight, length and head circumference at birth and primary discharge from hospital. Secondary outcomes included clinical chorioamnionitis (defined as requiring intrapartum antibiotics); maternal postpartum pyrexia (≥ 38.0 °C); any adverse effects of the injection for the mother and other measures of neonatal morbidity. Composite outcome was post hoc (defined as 1 of air leak syndrome, patent ductus arteriosus, need for oxygen at 36 weeks' postmenstrual age, severe IVH (grade 3 or 4), periventricular haemorrhage, proven necrotising enterocolitis or retinopathy of prematurity) For the early childhood follow-up at 2 years' corrected age: primary outcomes: survival at 2 years' corrected age free of major neurosensory disability, defined as survival free of moderate-to-severe disability. Body size (weight, height and head circumference). Secondary outcomes were general health, including the use of health services since primary hospital discharge; respiratory morbidity; blood pressure; child behaviour; incidence of neurosensory impairments and disabilities; total number of deaths by 2 years of corrected age; and the combined adverse outcome of death or any neurosensory disability at 2 years' corrected age For the mid-childhood follow-up at 6–8 years' corrected age: primary outcomes: survival free of any neurosensory disability and categorisation of neurosensory disability as none, mild, moderate or severe. Secondary outcomes were mortality; cerebral palsy; blindness or deafness; Z scores for height, weight, BMI and head circumference; expiratory flows on lung function; blood pressure Z scores and proportions in the abnormal ranges; IQ; attention and executive function; memory and learning; visual perception; academic achievement; behaviour; health service utilisation and reason for use; general health and health-related quality of life
Funding Support	Funding: Australian National Health and Medical Research Council, The Channel 7 Research Foundation of South Australia, The Women's and Children's Hospital Research Foundation, Adelaide, and The Department of Obstetrics and Gynaecology, The University of Adelaide, South Australia
Notes	Sample-size calculation: yes. 980 women needed to detect a 25% reduction in the risk of RDS from 30% to 22.5% with 80% power and a 2-sided significance level of 5%. Declarations of interest: declared no conflict of interest. Ethical approval: yes, obtained at each of the 23 collaborating hospitals. Trial registration: during recruitment.

Garite 2009

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: 15 private and 3 university centres, USA. Participants were largely private/non-government funded Dates of study: May 2003 to February 2008

Garite 2009 *(Continued)*

	Included: women with singleton or twin pregnancies from 25 weeks' to < 33 weeks' gestation who had received a course of betamethasone ≥ 14 days previously and who were judged to have recurrent or continued risk of preterm birth Exclusion criteria: major fetal anomaly, cervical dilatation ≥ 5 cm, higher order multiples, ruptured membranes, documented lung maturity, receiving corticosteroids for other indications, HIV infection or active tuberculosis Total recruited: 437 women; 223 in repeat corticosteroids group and 214 in placebo group. 577 infants enrolled; 289 in repeat corticosteroids group and 288 in placebo group, although 1 fetal twin in the corticosteroid group died before randomisation
Interventions	Repeat corticosteroid group: single course of intramuscular betamethasone given as 2 doses of 12 mg, 24 hours apart (preparation not specified) Placebo group: similarly administered saline intramuscular injection In some centres betamethasone became unavailable and was replaced with dexamethasone 6 mg intramuscularly, 4 doses, every 12 hours. 31 women received dexamethasone and 30 women received an equivalent placebo
Outcomes	Primary outcome: composite neonatal mortality/morbidity in babies born before 34 weeks' gestation. Composite outcome defined as ≥ 1 of: perinatal death (defined as stillbirth or death before neonatal discharge); RDS (oxygen requirement, clinical diagnosis and consistent chest radiograph); BPD (defined as a requirement for oxygen at 30 days of age); severe IVH (grades 3 or 4); PVL; blood culture-proven sepsis; or necrotising enterocolitis (not defined) Secondary outcomes: preterm birth before 34 weeks' gestation; RDS; gestational age at birth; small-for-gestational age (< 10th percentile); head circumference; birthweight; surfactant therapy; pneumothorax; maternal infectious morbidity
Funding Support	Funding: Pediatrix Medical Group
Notes	Sample-size calculation: yes, based on a 40% reduction in the primary outcome, which was estimated to be 28% in the control group. The planned sample size was 217 women in each arm (2-tailed alpha 0.05, beta 0.2). Declarations of interest: declared no conflict of interest. Ethical approval: yes, at each institution. Trial registration: during recruitment.

Guinn 2001

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: 13 academic centres in the US Dates of study: February 1996 to April 2000 Inclusion 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 prenatal corticosteroids (defined as 2 doses of intramuscular betamethasone 12 mg/dose, repeated at 24 hours; or 4 doses of intramuscular dexamethasone 6 mg/dose, given at 12 hour-intervals). High risk of preterm birth qualifying criteria were: preterm labour with intact membranes (either a history of regular uterine contractions associated with cervical dilation of ≥ 2 cm and effacement ≥ 80% in a nulliparous participant or cervical dilation of ≥ 3 cm and ≥ 80% effacement in a multiparous participant at the time of presentation; or regular uterine

Guinn 2001 *(Continued)*

	contractions with documented cervical change); preterm prelabour 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 prepartum testing, progression of a fetal anomaly compatible with like, twin–twin transfusion syndrome) Gestational age range: 24 weeks to < 33 weeks' gestation Exclusion criteria: required immediate delivery, fetal anomalies incompatible with life, documented fetal lung maturity, maternal active tuberculosis or HIV infection Total recruited: 502 women (589 fetuses); 256 women in weekly course group and 246 women in single-course group. Outcomes reported using the pregnancy as the unit of analysis. For infant outcomes from multiple gestations, a single infant was randomly selected for analysis
Interventions	Weekly course group: weekly course of betamethasone (2 doses of betamethasone 12 mg/dose repeated after 24 hours, intramuscularly), until 34 weeks or birth whichever came first Single-course group: similarly administered placebo
Outcomes	Primary outcomes: composite neonatal morbidity defined as presence of any of the following: severe RDS, BPD, severe IVH, PVL, necrotising enterocolitis, proven sepsis or death between randomisation and nursery discharge Secondary outcomes: frequency and severity of RDS; need for and duration of oxygen therapy; need for and duration of ventilatory support; BPD (defined as need for oxygen > 21% and usually ventilatory therapy for ≥ 28 days of life; in cases were no additional ventilatory support was needed but oxygen was required, chest radiographs consistent with BPD were used; in the case of neonatal death, BPD was diagnosed on postmortem findings); severe IVH was defined as intraventricular bleeding with dilation of the cerebral ventricles (grade 3) or parenchymal haemorrhage (grade 4), as diagnosed with an imaging technique or postmortem, PVL was defined as the presence of > 1 obvious hypoechoic cyst in the periventricular white matter; necrotising enterocolitis (defined as proven); proven sepsis; perinatal death defined as death of a fetus or neonate at any time between randomisation and nursery discharge
Funding Support	Funding: March of Dimes grant, the Berlex Foundation, the Wisconsin Perinatal Association, the Perinatal Clinical Research Center at the University of Colorado Health Sciences Center (grant from the General Clinical Research Centers Program, National Centers for Research Resources, National Institutes of Health), and the participating departments
Notes	Sample-size calculation: yes. A sample of 1000 women was required to have a 90% power to detect a 1/3 reduction in composite morbidity from 25.0% to 16.5% (2-tailed alpha = 0.05). 2 interim analyses were planned for efficacy and safety. Recruitment was stopped early based on safety concerns. Declarations of interest: no declaration. Ethical approval: the investigational review board at each centre approved the study protocol. Trial registration: not located.

Mazumder 2008

Study characteristics	
Methods	Type of study: parallel, open-label, randomised trial
Participants	Location: tertiary hospital in northern India Dates of study: August 2004 onwards

Mazumder 2008 *(Continued)*

	Included: mothers 26–33 weeks' gestation who were at risk of preterm birth and who had received a course of betamethasone ≥ 7 days previously. Mothers had to be available for follow-up every week until birth Exclusion criteria: unreliable gestational age, frank chorioamnionitis and major fetal malformation Total recruited: 76 women (38 in repeat corticosteroids group and 38 in control group). 83 babies were born to 75 mothers but only the firstborn of multiple pregnancies were assessed (37 repeat corticosteroids, 38 control). The pregnancy was used as the unit of analysis but for multiple pregnancies it was not detailed how it was decided which infant would contribute to the outcome
Interventions	Repeat corticosteroid: betamethasone 12 mg intramuscularly, 2 doses, 24 hours apart. The course was repeated every 7 days until delivery or the end of the 33rd week of gestation Control: no intervention
Outcomes	Primary outcome: severe RDS. RDS defined as respiratory distress within 6 hours of birth in a preterm infant with either a negative gastric shake test or a typical chest radiograph. Severe RDS defined as requiring mechanical ventilation for ≥ 12 hours. Mechanical ventilation started in infants with hypoxaemia (PaO_2 < 50 mmHg) or hypercapnic acidosis ($PaCO_2$ > 50 mmHg with pH < 7.25) or worsening acidosis or clinically worsening respiratory fatigue/apnoea/work of breathing despite continuous positive airway pressure (maximum 8 cmH_2O pressure) Secondary outcomes: RDS; IVH; necrotising enterocolitis (not defined); patent ductus arteriosus (not defined); BPD (not defined), sepsis (not defined), retinopathy of prematurity, stillbirth and neonatal death, weight, length and occipital-frontal circumference at birth and at 6 months' corrected age, and body size and development (evaluated by the Denver Development Screening Test II) at 6 months' corrected age
Funding Support	None
Notes	Sample-size calculation: yes, based on a reduction in severe RDS from an estimated 33% in the control group to 6% in the repeat corticosteroid group (2-tailed alpha 0.05, beta 0.2). The planned sample size was 70 (35 women in each arm). Declarations of interest: declared no conflict of interest. Ethical approval: approved by the institute ethics committee. Trial registration: not located.

McEvoy 2002

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: single centre in the USA (Sacred Heart Hospital, University of Florida, Pensacola, Florida) Dates of study: 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 prenatal corticosteroids (defined as 2 doses of betamethasone 12 mg/dose intramuscular), given because of increased risk of preterm delivery Gestational age range: 25–33 weeks Exclusion criteria: insulin-dependent diabetes, drug-addiction, fetus had a known lethal congenital anomaly

McEvoy 2002 *(Continued)*

	Total recruited: 37 women (37 babies). 18 women in repetitive courses of prenatal corticosteroid group and 19 women in single course remote group
Interventions	Repeat course prenatal corticosteroid group: weekly course of betamethasone (2 doses of betamethasone 12 mg/dose (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey)), intramuscularly, until birth or 34 weeks' gestation Single-course remote group: weekly courses of placebo intramuscularly, until 34 weeks or birth
Outcomes	Primary outcomes: functional residual capacity, respiratory compliance Secondary outcomes: admission head circumference, surfactant administration, days on oxygen and mechanical ventilation
Funding Support	American Lung Association
Notes	Sample-size calculation: yes. Based on 37 women the mean functional residual capacity in the single course remote group was not > 12% smaller than the functional residual capacity in the repetitive group (P = 0.05, power 80%). Declarations of interest: no declaration of interest. Ethical approval: approved by the hospital's institutional review board. Trial registration: not located.

McEvoy 2010

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: 2 centres in the US (Sacred Heart Hospital, University of Florida, Pensacola, Florida recruited first 8 participants; Oregon Health and Science University) Dates of study: June 2001 to May 2007 Eligibility criteria: women at 26 to < 34 weeks' gestation; ≥ 14 days after first course of prenatal corticosteroids (93% received betamethasone); at continued risk of preterm delivery as determined by their care provider; who provided informed consent Gestational age range: 26 to < 34 weeks' gestation Exclusion criteria: insulin-dependent diabetes, major documented fetal or chromosomal abnormality; multiple pregnancy greater than twins; clinical chorioamnionitis; first course of prenatal corticosteroids given < 24 weeks' gestation; chronic steroid use during pregnancy for clinical care Total recruited: 85 women randomised (113 babies alive at randomisation); 44 women (56 babies) in rescue corticosteroids group and 41 women (57 babies) in placebo group
Interventions	Rescue group: betamethasone 2 doses of 12 mg/dose (Celestone Soluspan; Schering Corporation, Kenilworth, New Jersey), intramuscularly, 24 hours apart Placebo group: placebo 2 doses (cortisone acetate 25 mg, an inactive steroid identical in appearance to betamethasone)
Outcomes	Primary outcomes: respiratory compliance and functional residual capacity (measured within 72 hours of birth (before any surfactant)

McEvoy 2010 *(Continued)*

	Secondary outcomes: growth measurements including weight, head circumference and length at birth and hospital discharge; surfactant administration; diagnosis of RDS (defined as clinical signs of respiratory distress with radiographic appearance and needing supplemental oxygen with $FiO_2 > 0.21$); respiratory distress requiring ≥ 0.30 and ≥ 0.40 at 24 hours of age; days on mechanical ventilation and days on supplemental oxygen
Funding Support	Oregon Health and Science University, GCRC/PHS Grant 5 MO1 RR000334; OCTRI UL1 RR02414001; and The American Lung Association
Notes	Recruitment was terminated early, after 85 women had been randomised, primarily because of safety concerns of possible adverse effects of weekly prenatal corticosteroid therapy. Declarations of interest: no conflict of interest. Ethics approval: approved by the institutional review board at each institution. Trial registration: retrospective.

Murphy 2008

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: 80 centres, 20 countries Dates of study: April 2001 to August 2006 Inclusion criteria: single, twin or triplet pregnancy 25–32 weeks' gestation if women remained undelivered 14–21 days after an initial course of prenatal corticosteroids (either betamethasone or dexamethasone) and continued to be at high risk of preterm birth Gestational age recruited: up to < 32 weeks Exclusion criteria: contraindication to corticosteroid use, needed chronic doses of these drugs, evidence of chorioamnionitis, carried a fetus with a known lethal congenital abnormality, had an initial course of corticosteroids before 23 weeks' gestation, previously participated in MACS, women with a multiple pregnancy with fetal death after 13 weeks' gestation Total recruited: 1858 women (2309 babies); 935 women (1166 infants) in prenatal corticosteroid group and 918 women (1143 infants) in placebo group
Interventions	Repeat corticosteroid group: each course consisted of 2 intramuscular injections of betamethasone 12 mg (as betamethasone sodium phosphate 6 mg and betamethasone acetate 6 mg; Celestone Schering-Plough Corporation, Madison, New Jersey) 24 hours apart Placebo group: similarly appearing intramuscular injection of dilute concentration of aluminium monostearate (an inert substance used as a filler in pharmaceutical preparations) Women who remained at risk of preterm birth after their first course of study medication continued to receive 2 doses of betamethasone 12 mg or placebo, 24 hours apart, every 14 days until 33 weeks' gestation or birth, whichever happened first. For women with preterm rupture of the membranes the recommendation was to stop the study medication at 32 weeks' gestation
Outcomes	Primary outcomes: composite of perinatal or neonatal mortality and neonatal morbidity; 1 of the following: stillbirth or neonatal death (defined as death during the first 28 days of life or before hospital discharge); severe RDS (defined as needing assisted ventilation via endotracheal tube and supplemental oxygen within the first 24 hours of life and for ≥ 24 hours, and either a radiographic scan compatible with RDS or surfactant given between the first 2 and 24 hours of life); BPD (defined as needing oxygen

Murphy 2008 *(Continued)*

	at a postmenstrual age of 36 completed weeks and radiographic scan compatible with BPD); IVH grade III or IV; cystic PVL, necrotising enterocolitis For the early childhood follow-up at 2 years' corrected age: primary outcome was death or the presence of a neurological impairment at 18–24 months of age, corrected for gestational age at birth. Neurological impairment defined as presence of cerebral palsy or cognitive delay. Cerebral palsy diagnosed if child had a non-progressive motor impairment characterised by abnormal muscle tone and decreased range of movements. Cognitive delay defined as Mental Developmental Index scores of 70 (2 SDs below the mean of 100) on the BSID-II or equivalent scores on another standardised assessment Secondary outcomes: anthropometric measurements (weight, height and head circumference), general health, illnesses, and operations occurring after the primary hospitalisation was recorded, Psychomotor Developmental Index and the Behavior Rating Scale of the BSID-II For the 5 years of age childhood follow-up: primary outcome: composite of death or survival with a neurodevelopmental disability in ≥ 1 of the following domains: neuromotor (non-ambulatory cerebral palsy), neurosensory (blindness, deafness, or need for visual or hearing aids), or neurocognitive/neurobehavioural function (abnormal attention, memory, or behaviour) Secondary outcomes: growth (height, weight and head circumference) and blood pressure. For those in Canadian centres, intelligence (The Wechsler Preschool and Primary Scale of Intelligence – Third Edition) and specific cognitive skills were assessed (Test of Visual-Motor Integration – Fifth Edition for visual and motor abilities and integration; and the Peabody Picture Vocabulary Test – Third Edition for vocabulary knowledge development and receptive language abilities)
Funding Support	Funding: Canadian Institutes of Health Research (CIHR)
Notes	Sample-size calculation: yes. A sample size of 1900 women (950 per group) was needed to have 80% probability of achieving a significant difference between groups (2-tailed type 1 error 0.05), if multiple courses of prenatal corticosteroids reduced the risk of RDS from 12% to 8%. Declarations of interest: declared no conflict of interest. Ethics approval: from University of Toronto, Mount Sinai Hospital and all participating centres. Trial registration: during recruitment (ISRCTN 72654148).

Peltoniemi 2007

Study characteristics	
Methods	Type of study: parallel, placebo-controlled, randomised trial
Participants	Location: 5 Finnish university and 3 central hospitals Dates of study: May 2001 to March 2005 Included: women at < 34 weeks' gestation who had received a single course of betamethasone > 7 days previously and were to have elective delivery within 48 hours or were at very high risk of spontaneous delivery within 48 hours (cervical opening ≥ 3 cm, and regular contractions at 5- to 10-minute intervals) Gestational ages: < 34 weeks' gestation Exclusion criteria: long-term maternal corticosteroid use, clinical chorioamnionitis or lethal disease of the fetus Total recruited: 249 women (125 in betamethasone group and 124 in placebo group), 328 fetuses (160 in betamethasone group and 168 in placebo group)
Interventions	Repeat corticosteroid: a single dose betamethasone 12 mg intramuscularly

Peltoniemi 2007 *(Continued)*

	Placebo: isotonic saline intramuscularly
Outcomes	To time of primary hospital discharge: primary outcome: survival without severe RDS or severe IVH (grade 3 or 4) during the first hospital admission. RDS defined on the basis of typical chest radiograph findings, requirement for continuous distending airway pressure, supplemental oxygen for ≥ 48 hours, or requirement for surfactant in cases of established respiratory failure. Severe IVH defined as IVH with ventricular dilation (grade 3) or parenchymal haemorrhage (grade 4). Cranial ultrasound performed for all infants at 4–8 days of age and at 36 weeks postmenstrual age or before discharge. The most severe grade of IVH was recorded Secondary outcomes: cystic PVL; necrotising enterocolitis grade ≥ 2; BPD (defined as a requirement for supplemental oxygen or any form of ventilation with continuous distending pressures at postnatal age of 36 weeks or at postnatal age of 4 weeks for those born after postmenstrual age of 31 weeks); patent ductus arteriosus requiring treatment (defined as a requirement for prostaglandin inhibitor therapy or surgery for closure) For the early childhood follow-up at 2 years' corrected age: survival without serious neurological, cognitive or sensory impairment (NDI); respiratory problems; infections, medical history; child's weight, length and head circumference; cerebral palsy; speech; deafness; blindness; child behaviour
Funding Support	Funding: Foundation for Paediatric Research in Finland, Alma and KA Snellmann Foundation, Sigrid Juselius Foundation, hospital research funds
Notes	Tocolytics were not used and 79% of mothers gave birth < 24 hours after the intervention. All infants were born < 36 weeks' gestation. Sample-size calculation: yes. Sample size based on a 25% increase in the primary outcome rate, from an estimated 50% in the control group to 62.5% in the repeat group. The planned sample size was 220 women in each arm (2-tailed alpha 0.05, beta 0.2). Recruitment was terminated early, after 249 women had been enrolled, primarily because of safety concerns due a decrease in intact survival in the repeat corticosteroid group. In addition, recruitment was slower than expected. Declarations of interest: declared no conflict of interest. Ethical approval: approved by the ethics committee of Oulu University Hospital and the National Agency for Medicines. Trial registration: retrospective.

TEAMS 1999

Study characteristics	
Methods	Type of study: parallel, randomised, placebo-controlled trial
Participants	Location: hospitals in the UK Dates of study: January 2000 to April 2003 Inclusion criteria: women who had received 1 course of prenatal corticosteroids to improve foetal maturity and with clinical uncertainty that a second course of steroids is indicated, and gestational age < 32 weeks Gestational age: < 32 weeks' gestation Exclusion criteria: maternal long-term systemic corticosteroid therapy (not including inhaled or topical therapy)

TEAMS 1999 *(Continued)*

	Total recruited: 162 women (82 in repeat prenatal corticosteroid group and 80 in placebo group). 188 infants (94 in each group)
Interventions	Repeat prenatal corticosteroid group: 2 doses betamethasone 12 mg, 12 or 24 hours apart, usually repeated every 7 days but could be 10–14 days depending on unit's protocol Placebo group: placebo administered to match corticosteroid group
Outcomes	Primary outcomes: neonatal death; neurodevelopmental delay at age 2 years (corrected for gestational age at birth) Secondary outcomes: short-term outcomes: stillbirth, death at any time before discharge from neonatal unit, diagnosis of RDS, pneumothorax or other pulmonary air leak, IVH confirmed by ultrasound, diagnosis of necrotising enterocolitis, chronic lung disease (oxygen dependency at 28 days of life), neonatal sepsis, birthweight, maternal sepsis. Long-term outcomes: growth delay at age 2 years (corrected), respiratory symptoms at age 2 years (corrected), subscale scores for the Vineland Adaptive Behaviour Scales and Bayley II Scales at age 2 years (corrected), readmission to hospital Measures of health service utilisation: admission to, and duration of stay in, a neonatal intensive care unit, use of, and length of time on, mechanical ventilation; use of surfactant, postnatal corticosteroids, high-frequency oscillation, nitric oxide and extracorporeal membrane oxygenation
Funding Support	Action Medical Research (UK)
Notes	Declarations of interest: no declaration statement. Ethical approval: protocol was approved by the Multicentre Research Ethics Committee (ref: 98/5/70). Trial registration: during recruitment (ISRCTN46614711).

Wapner 2006

Study characteristics	
Methods	Type of study: parallel, randomised placebo-controlled trial
Participants	Location: 18 US hospitals (NICHD MFMU network centres) Dates of study: 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 prelabour rupture of the membranes prior to randomisation, confirmed fetal lung maturity, chorioamnionitis, major fetal anomaly, non-reassuring fetal status, systemic corticosteroid use during the current pregnancy, or insulin-dependent diabetes. Gestational age 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), 594 fetuses/infants; 252 women (299 fetuses) in repeat corticosteroid group and 243 women (295 fetuses) in placebo The pregnancy was used as the unit of analysis and for infant outcomes from multiple pregnancies the outcome was considered to have occurred if either infant had the outcome of interest. For outcomes with a severity grading, the most severe of the infant outcomes contributed to the result

Wapner 2006 *(Continued)*

Interventions	Repeat corticosteroid group: each course consisted of 2 injections of betamethasone 12 mg (as betamethasone sodium phosphate 6 mg and betamethasone acetate 6 mg) 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 study courses
Outcomes	To time of primary hospital discharge: primary outcome: composite endpoint of 1 of the following: severe RDS (defined as clinical features of RDS with the need for oxygen and respiratory support for 6–24 hours or more of age, an abnormal chest radiograph, and either administration of a full course of surfactant or a fraction of inspired oxygen (FiO_2 of ≥ 60%); grade 3 or 3 IVH; PVL; chronic lung disease (defined as the need for supplemental oxygen at 36 weeks' corrected age in infants born before 34 weeks' gestation); or stillbirth or neonatal death. Secondary outcomes not stated in the paper For the early childhood follow-up at 2 years' corrected age: the prespecified developmental outcome was the Bayley Mental Developmental Index Score. Other outcomes included Bayley Psychomotor Developmental Index Score; measurements of weight, height and head circumference; and the occurrence of cerebral palsy
Funding Support	Funding: National Institute of Child Health and Human Development
Notes	Sample-size calculation: yes. Planned sample size was 2400 women. Quote: "A primary outcome rate of 11.5% was anticipated for patients assigned to placebo. Detection of a 30% reduction for patients assigned to repeat corticosteroids required a sample of 1200 patients in each group" (80% power and type 1 error rate of 5% (2-sided)). Recruitment was stopped early based on safety concerns (because of a tendency towards decreased birthweight in the repeat corticosteroid group without any reduction in the primary morbidity outcome and also because of difficulties in recruitment). Declarations of interest: author Dr Mercer declared receiving consulting fees from Columbia Laboratories. No other reported conflict of interest. Ethical approval: institutional board review approved at all participating centres. Trial registration: during recruitment.

ACTH: adrenocorticotropic hormone; BMI: body mass index; BPD: bronchopulmonary dysplasia; BSID-II: Bayley Scales of Infant Development II; FiO_2: fraction of inspired oxygen; IQ: intelligence quotient; IVH: intraventricular haemorrhage; MFMU: Maternal Fetal Medicine Units; NICHD: National Institute of Child Health and Human Development; $PaCO_2$: partial pressure of carbon dioxide; PaO_2: partial pressure of oxygen; PVL: periventricular leukomalacia; RDS: respiratory distress syndrome; SD: standard deviation.

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

Study	Reason for exclusion
Bontis 2011	'Non-randomised' trial.
CTRI/2017/04/008326	Compared a single course of prenatal corticosteroid to placebo without prior corticosteroid.
CTRI/2017/05/008721	Compared a single course of prenatal corticosteroid to placebo without prior corticosteroid.
Ernawati 2016	Study of use of methylprednisolone in the management of pre-eclampsia.

Study	Reason for exclusion
EUCTR2009-010759-29-BE	Trial of prenatal corticosteroid compared with placebo in women with twin pregnancies without prior prenatal corticosteroid exposure.
Gyamfi-Bannerman 2016	Secondary analysis of prenatal corticosteroids compared with placebo for preterm birth in women who had not already received corticosteroid.
IRCT2014090912789N6	Study comparing different doses of a single course of prenatal corticosteroid for women at risk of preterm birth.
IRCT2015120415634N2	Compared different doses for a single course of prenatal corticosteroid for women at risk of preterm birth.
IRCT20191202045571N1	Compared a single course of prenatal corticosteroid with placebo for women at risk of late preterm birth.
Kashanian 2018	Compared different doses for a single course of prenatal corticosteroid for women at risk preterm birth.
Mercer 2001	Women recruited to the trial did not have corticosteroids before entry. Objective of trial was to evaluate the need for and benefits of weekly prenatal corticosteroids in women at risk of preterm birth. 189 women between 23 and 32 weeks' gestation at risk of preterm birth were randomised to weekly prenatal corticosteroids or a control group where corticosteroids were given if indicated before 35 weeks, if the pregnancy was expected to last > 1 week. Primary outcome: prenatal corticosteroids given within 7 days of preterm birth (< 35 weeks) (optimal exposure). In control group, only 1/3 of infants < 35 weeks' gestation received optimal prenatal corticosteroid exposure. Weekly corticosteroids doubled optimal exposure although the most gave birth at > 34 weeks.
NCT03446937	Trial of prenatal corticosteroid compared with placebo for late preterm birth, without prior corticosteroid exposure.
Romejko-Wolniewicz 2013	Head-to-head trial of 2 different prenatal corticosteroid regimens without prior prenatal corticosteroid exposure.
Schmitz 2019	Trial of different prenatal corticosteroid regimens in women with twin pregnancies without prior prenatal corticosteroid exposure.
Sohrabvand 2001	Women had not already received a single course of corticosteroid (randomisation was to 1 or > 1 course of prenatal corticosteroid).
Thorp 2000	Women recruited to the trial were not randomised to receive repeat corticosteroids but prenatal phenobarbital. Abstract is a secondary multivariate analysis of this trial assessing if duration of prenatal betamethasone is associated with perinatal outcome.

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

Atarod 2014

Methods	Parallel, randomised placebo-controlled trial
Participants	Women at risk of preterm birth between 28 and 35 weeks' gestation

Atarod 2014 *(Continued)*

	Exclusion criteria: PROM prior to entering the study, major fetal anomalies, chorioamnionitis, systemic corticosteroid use during pregnancy, insulin-dependent diabetes mellitus and IUGR. Total randomised 1348 women (674 to repeat prenatal corticosteroid group and 674 to placebo group).
Interventions	Repeat prenatal corticosteroid group: a treatment course including an intramuscular injection of betamethasone 12 mg repeated after 24 hours, followed by 2 other treatment doses every 10 days Placebo group: a treatment course including an intramuscular injection of betamethasone 12 mg repeated after 24 hours, followed by 2 doses of placebo every 10 days
Outcomes	RDS, need for oxygen, surfactant, need for ventilation, duration of hospital stay, mortality to hospital discharge, birthweight, height, head circumference
Notes	It is unclear as to the time point at which randomisation to repeat betamethasone or no repeat occurred. The authors had been contacted for this information in February 2015 and no response was received. This study was moved to awaiting classification after trustworthiness screening due to concerns about randomisation processes as identical numbers were randomised to each group while using simple randomisation for 1348 participants. There was also no explanation provided for exclusion of 104 women after randomisation. The corresponding author was contacted in July and August 2021 and a response was not received.

IUGR: intrauterine growth restriction; PROM: Premature rupture of membranes; RDS: respiratory distress syndrome.

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

NCT02469519

Study name	Impact of a booster course of antenatal steroids on neonatal outcome in patients with premature rupture of the membranes (ACSinPROM)
Methods	Study type: parallel randomised, placebo-controlled trial
Participants	Setting: 10 study sites in the US hospitals Inclusion criteria: all of: aged ≥ 18 years, 24 weeks and 0 days to 32 weeks and 6 days' gestation, singleton pregnancy, received first course of prenatal corticosteroids at or prior to 31 weeks 6 days' gestation, began first course of prenatal corticosteroids ≥ 7 days prior to randomisation, expectant management planned, PROM before onset of labour Exclusion criteria: any of: known major fetal anomalies, multiple gestation, not a candidate for expectant management, clinical chorioamnionitis (≥ 2 of: temperature > 38.0 °C; uterine tenderness; foul-smelling vaginal discharge or amniotic fluid; maternal tachycardia > 100 beats per minute; fetal tachycardia > 160 beats per minute; maternal white blood cell count > 20×10^9/L; C-reactive protein > 5.9 mg/L), already receiving corticosteroids for another condition, any contraindications to the maternal use of corticosteroids
Interventions	Experimental group: booster course of prenatal corticosteroids consisting of betamethasone 12 mg intramuscular injection, 24 hours apart for 2 doses, or if unavailable may give dexamethasone 6 mg intramuscularly 12 hours apart for 4 doses Placebo: normal saline of equivalent volume given intramuscularly at the equivalent dosing regimens listed in experimental group
Outcomes	Primary outcomes: composite neonatal morbidity from birth through the first 28 days of life; composite neonatal morbidity includes ≥ 1 of: RDS, bronchopulmonary dysplasia, severe IVH, periventricular leukomalacia, proven sepsis, necrotising enterocolitis or neonatal death

NCT02469519 *(Continued)*

	Secondary outcomes: gestational age of baby, baby's birth weight, IUGR, baby's head circumference within the first 24 hours following birth, mechanical ventilatory days, newborn oxygen support days, newborn surfactant therapy, newborn hospital days, pneumothorax, maternal infectious morbidity, time from first dose of study drug to birth
Starting date	3 March 2016
Contact information	As stated on trial registration document: kimberly_maurel@mednax.com
Notes	Status: currently recruiting. Confirmed after contact with study contact Kimberly Maurel.

NCT02939742

Study name	Does a rescue course of betamethasone in pregnant women with PPROM decrease neonatal morbidity?
Methods	Parallel, randomised, placebo-controlled trial
Participants	Setting: John Sealy Hospital in the US Inclusion criteria (all): maternal age ≥ 18 years, preterm prelabour rupture of membranes (demonstrated clinically by speculum examination), cervical dilation visually ≤ 5 cm on sterile speculum examination, planned delivery at John Sealy Hospital, gestational age of membrane rupture and initiation of first course of prenatal corticosteroids between 23 weeks 5 days to 32 weeks 5 days, planned pregnancy continuation with no indication for delivery for ≥ 7 days Exclusion criteria (any): maternal age > 50 years, gestational age < 23 weeks 5 days or > 32 weeks 5 days, known major congenital abnormalities, aneuploidy, or genetic syndrome, intrauterine fetal demise, any indication for expedited delivery, maternal chorioamnionitis, known allergy or adverse reaction to corticosteroids
Interventions	Experimental group: a second course of 2 betamethasone 12 mg intramuscular injections given 24 hours apart Placebo group: intramuscular saline placebo, given as 2 injections 24 hours apart
Outcomes	Primary outcome: length of stay in the neonatal intensive care unit Secondary outcomes: composite neonatal morbidity; defined as ≥ 1 of the following: RDS (oxygen requirement, clinical diagnosis, and consistent chest radiograph), bronchopulmonary dysplasia (requirement for oxygen support at 30 days of life), severe IVH (grades III or IV), periventricular leukomalacia, blood culture-proven sepsis, necrotising enterocolitis or perinatal death (stillbirth or death before neonatal hospital discharge), duration of oxygen and ventilatory support, development of RDS, grade III or IV IVH, neonatal sepsis, necrotising enterocolitis stage 2 or 3, perinatal death Other outcomes: labour latency, infectious morbidities including chorioamnionitis
Starting date	November 2016
Contact information	As per trial registration: Antonio Saad, MD; 409-772-1571; afsaad@utmb.edu Sara O Jacobs, MD; 409-772-1571; sojacobs@utmb.edu
Notes	Status: ongoing recruitment

IUGR: intrauterine growth restriction; IVH: intraventricular haemorrhage; PPROM: preterm prelabour rupture of the membranes; RDS: respiratory distress syndrome.

RISK OF BIAS

Legend: ✓ Low risk of bias ✗ High risk of bias ~ Some concerns

Risk of bias for analysis 1.1 A1: Fetal or neonatal or infant death (< 1 year of age)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.1.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.2 A2: Fetal death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.2.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.3 A3: Neonatal death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.3.1 In all neonates						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2010	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.4 A5: Respiratory distress syndrome

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.4.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.5 A6: Severe respiratory distress syndrome

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.5.1 All fetuses randomised						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.6 A7: Severe lung disease

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.6.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.7 A8: Chronic lung disease

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.7.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
McEvoy 2010	✓	✓	✓	✓	~	~
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.8 A9: Severe intraventricular haemorrhage (grade 3/4)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.8.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.9 A10: Intraventricular haemorrhage

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.9.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.10 A11: Necrotising enterocolitis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.10.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.11 A12: Composite of serious outcomes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.11.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
Murphy 2008	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.12 F1i: Term birth ≥ 37 weeks

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.12.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2002	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.13 F1ii: Preterm birth before 37 weeks

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.13.1 All fetuses randomised						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2002	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.14 F1iii: Very preterm birth before 34 weeks

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.14.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.15 F1iv: Extremely preterm birth before 28 weeks

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.15.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.16 F1v: Mean gestational age at birth (weeks)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.16.1 In all neonates						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.17 F2: Small-for-gestational age at birth

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.17.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.18 F3: Admission to the neonatal intensive care unit

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.18.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.19 F4: Proven neonatal infection while in the neonatal intensive care unit

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.19.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.20 F5: Early systemic neonatal infection

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.20.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Mazumder 2008	✓	~	✓	✗	~	✗
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.21 F6: Late systemic neonatal infection

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.21.1 All fetuses randomised						
Mazumder 2008	✓	~	✓	✗	~	✗
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.22 F7: Retinopathy of prematurity

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.22.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
Murphy 2008	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.23 F8: Periventricular leukomalacia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.23.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.24 F9: Neonatal encephalopathy

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.24.1 All fetuses randomised						
Mazumder 2008	✓	~	✓	✗	~	✗

Risk of bias for analysis 1.25 F10: Patent ductus arteriosus

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.25.1 All fetuses randomised						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✗	~	✗
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.26 F11: Use of respiratory support

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.26.1 All fetuses randomised						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.27 F12: Use of invasive respiratory support

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.27.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.28 F13: Use of non-invasive respiratory support

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.28.1 All fetuses randomised						
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.29 F14: Use of oxygen supplementation

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.29.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.30 F15: Use of surfactant

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.30.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.31 F17: Use of postnatal corticosteroids

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.31.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.32 F16: Use of nitric oxide for respiratory support

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.32.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.33 F20: Use of inotropic support

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.33.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.34 F18: Air leak syndrome

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.34.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.35 F21: Apgar score < 7 at 5 minutes

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.35.1 All fetuses randomised						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.36 F22: Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVS in mm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.36.1 In all neonates						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.37 F22: Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole (mm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.37.1 In all neonates						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.38 L1: Mean birthweight (g)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.38.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.39 L1: Mean birthweight Z score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.39.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.40 L1: Birthweight multiples of the median

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.40.1 In all babies						
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.41 L1: Birthweight adjusted for gestation (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.41.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.42 L2: Interval between trial entry and birth (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Guinn 2001	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.43 L3: Mean head circumference at birth (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.43.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✗	✓	✓	✗
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.44 L3: Mean head circumference Z score at birth

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.44.1 In all babies						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.45 L4: Mean length at birth (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.45.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
Mazumder 2008	✓	~	✓	✓	~	~
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.46 L4: Mean length Z score at birth

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.46.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.47 L4: Length multiples of the mean at birth

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.47.1 In all neonates						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.48 L4: Length at birth adjusted for gestation (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.48.1 In all neonates						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.49 L5i: Mean weight (g) at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.49.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.50 L5i: Mean weight Z score at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.50.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.51 L5ii: Mean head circumference (cm) at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.51.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.52 L5ii: Mean head circumference Z score at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.52.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.53 L5iii: Mean length (cm) at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.53.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.54 L5iii: Mean length Z score at primary hospital discharge

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.54.1 In all infants						
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	~	✓	✓	~

Risk of bias for analysis 1.55 L6i: Mean weight at infant follow-up (kg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Mazumder 2008	✓	~	~	✓	~	✗
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.56 L6i: Mean weight Z score at infant follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.57 L6ii: Mean head circumference at infant follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Mazumder 2008	✓	~	~	✓	~	✗
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.58 L6ii: Mean head circumference Z score at infant follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.59 L6iii: Mean length at infant follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Mazumder 2008	✓	~	~	✓	~	✗
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.60 L6iii: Mean length Z score at infant follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
McEvoy 2010	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 1.61 L8: Mean duration of invasive respiratory support (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.62 L9: Mean duration of non-invasive respiratory support (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.63 L10: Mean duration of oxygen supplementation (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
McEvoy 2002	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 1.64 L14: Mean cord cortisol concentrations at birth (nmol/L)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 1.64.1 In all neonates						
Crowther 2006	✓	✓	~	~	✓	~
Wapner 2006	✓	✓	~	~	✓	~

Risk of bias for analysis 2.1 B1: Maternal death

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.1.1 All women						
Garite 2009	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.2 B2: Maternal sepsis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.2.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	~	~
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.3 B3: Caesarean section

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.3.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.4 B4: Discontinuation of therapy due to maternal adverse effects

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.4.1 In all women						
Guinn 2001	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.5 G1: Puerperal sepsis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.5.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.6 G2: Chorioamnionitis during labour

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.6.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.7 G3: Endometritis

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.7.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.8 G4: Pyrexia after trial entry requiring the use of antibiotics

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.8.1 In all women						
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.9 G6: Postpartum haemorrhage

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.9.1 In all women						
Guinn 2001	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.10 G7: Postnatal pyrexia

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.10.1 In all women						
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.11 G8: Prelabour rupture of membranes after trial entry

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.11.1 In all women						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Guinn 2001	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.12 G9: Mode of birth: vaginal birth

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.12.1 In all women						
Aghajafari 2002	✓	✓	✓	✓	✓	✓
Crowther 2006	✓	✓	✓	✓	✓	✓
Garite 2009	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.13 G10: Hypertension

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.13.1 In all women						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.14 G12: Glucose intolerance

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.14.1 In all women						
Murphy 2008	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 2.15 G13: Postnatal depression

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.16 G14: Local injection site adverse effects

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.17 G15: Insomnia after treatment

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 2.17.1 In all women						
Aghajafari 2002	✓	✓	~	✓	✓	~
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 2.18 G16: Gastrointestinal adverse effects of treatment

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.1 C1: Total deaths (after randomisation) up to early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.1.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.2 C2: Neurodevelopmental impairment at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.2.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✗	✓	✓	✗
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.3 C3: Survival free of neurodevelopmental impairment at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.3.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
TEAMS 1999	✓	✓	✗	✓	✓	✗
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.4 C4: Survival free of major neurodevelopmental impairment at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.4.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✗	✓	✓	✗
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.5 C5: Cerebral palsy at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.5.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	✗	✓	✓	✗
TEAMS 1999	✓	✓	✗	✓	✓	✗
Wapner 2006	✓	✓	✓	✓	~	~

Risk of bias for analysis 3.6 C6: Developmental delay or intellectual impairment at early childhood follow-up (any)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.6.1 In all children						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006						
Murphy 2008						
Peltoniemi 2007						
Wapner 2006						

Risk of bias for analysis 3.7 Mental Developmental Index at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.7.1 In all children						
Crowther 2006						
Peltoniemi 2007						
Wapner 2006						

Risk of bias for analysis 3.8 H1: Child behaviour at early childhood follow-up, Child Behaviour Checklist total score in the clinical range

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006						

Risk of bias for analysis 3.9 H1: Child behaviour: Behaviour rating scale in the clinical range (BSID-II)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.10 H1: Child behaviour at early childhood follow-up as assessed by Early Child Behaviour Questionnaire Extraversion summary scale

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.11 H1: Child behaviour at early childhood follow-up assessed by Early Child Behaviour questionnaire Negative affectivity summary scale

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.12 H1: Child behaviour at early childhood follow-up assessed by Early Child Behaviour questionnaire Effortful control summary scale

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Peltoniemi 2007	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.13 H2: Psychomotor Developmental Index at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.13.1 In all babies						
Crowther 2006	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.14 H3: Deafness/hearing impairment at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.14.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
TEAMS 1999	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.15 H4: Blindness/visual impairment at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.15.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
TEAMS 1999	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.16 H5: Hypertension at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.16.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.17 H8: Asthma or recurrent wheeze at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.17.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	~	✓	~
Wapner 2006	✓	✓	✓	✓	~	~

Risk of bias for analysis 3.18 H9: Any respiratory disease at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	~	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	~	✓	~

Risk of bias for analysis 3.19 N1i: Mean weight at early childhood follow-up (kg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.19.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.20 N1i: Mean weight Z score at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.20.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.21 N1i: Mean weight adjusted for age at early childhood follow-up (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.21.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.22 N1i: Weight small for age at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.22.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.23 N1ii: Mean head circumference at early childhood follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.23.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.24 N1ii: Mean head circumference Z score at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.24.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.25 N1ii: Mean head circumference adjusted for age at early childhood follow-up (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.25.1 In all babies						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.26 N1ii: Head circumference small for age at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.26.1 In all babies						
Crowther 2006	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.27 N1iii: Mean height at early childhood follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.27.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.28 N1iii: Height Z score at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.28.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.29 N1iii: Mean height adjusted for age at early childhood follow-up (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.29.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.30 N1iii: Height small for age at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.30.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.31 N3: Mean systolic blood pressure at early childhood follow-up (mmHg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.31.1 In all children						
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.32 N3: Mean systolic blood pressure Z score at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.32.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 3.33 N3: Mean diastolic blood pressure at early childhood follow-up (mmHg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.33.1 In all children						
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 3.34 N3: Mean diastolic blood pressure Z score at early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 3.34.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.1 D1: Total deaths (after randomisation) up to mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.1.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.2 D2: Neurocognitive impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.2.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.3 D3: Survival free of neurocognitive impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.3.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.4 D4: Survival free of major neurocognitive impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.4.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.5 D6: Cognitive impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.5.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.6 D8: Cerebral palsy at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.6.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.7 I2: Blindness/visual impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.7.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.8 I3: Deafness/hearing impairment at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.8.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.9 I4: Abnormal child behaviour at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.10 I4: Child behaviour at mid- to later childhood follow-up (standardised mean difference)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	~	✓	✓	~
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.11 I5: Asthma or recurrent wheeze at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.11.1 In all babies						

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.12 I6: Any respiratory disease at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 4.13 O1i: Mean weight at mid- to later childhood follow-up (kg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.13.1 In all children						
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.14 O1i: Mean weight Z score at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.14.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.15 O1ii: Mean head circumference at mid- to later childhood follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.15.1 In all children						
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.16 O1ii: Head circumference Z score at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.16.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.17 O1iii: Mean height at mid- to later childhood follow-up (cm)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.17.1 In all children						
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.18 O1iii: Mean height Z score at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.18.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.19 O2: BMI Z scores at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 4.20 O4: Body composition: total body fat-free mass at mid- to later childhood follow-up (kg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	~	✓	~	~

Risk of bias for analysis 4.21 O5: Body composition: total body fat mass at mid- to later childhood follow-up (kg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.22 O6: Mean systolic blood pressure at mid- to later childhood follow-up (mmHg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.22.1 In all children						
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.23 O6: Mean diastolic blood pressure at mid- to later childhood follow-up (mmHg)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.23.1 In all children						
Murphy 2008	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.24 O6: Mean systolic blood pressure Z score at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.24.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.25 O6: Mean diastolic blood pressure Z score at mid- to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 4.25.1 In all children						
Crowther 2006	✓	✓	~	✓	✓	~

Risk of bias for analysis 4.26 O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1 Z score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 4.27 O8: Measures of lung function at mid- to later childhood follow-up: mean FVC Z score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 4.28 O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1/FVC Z score

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✗	✓	✓	✗

Risk of bias for analysis 6.1 K1: Hospital re-admission by early childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.1.1 In all children						
Crowther 2006	✓	✓	✓	✓	✓	✓
Murphy 2008	✓	✓	✓	✓	✓	✓
Peltoniemi 2007	✓	✓	~	✓	✓	~
Wapner 2006	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.2 K1: Hospital re-admission by mid to later childhood follow-up

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.2.1 In all children						
Crowther 2006	✓	✓	✓	✗	✓	✗

Risk of bias for analysis 6.3 Q2: Length of postnatal hospitalisation for the woman (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Subgroup 6.3.1 For all women						
Guinn 2001	✓	✓	✓	✓	✓	✓

Risk of bias for analysis 6.4 Q4: Length of infant hospitalisation (days)

	Bias					
Study	**Randomisation process**	**Deviations from intended interventions**	**Missing outcome data**	**Measurement of the outcome**	**Selection of the reported results**	**Overall**
Crowther 2006	✓	✓	✓	✓	✓	✓
Guinn 2001	✓	✓	✓	✓	✓	✓
McEvoy 2010	✓	✓	✓	✓	✓	✓

DATA AND ANALYSES

Comparison 1. Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.1 A1: Fetal or neonatal or infant death (< 1 year of age)	10	5849	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.24]
1.1.1 All fetuses randomised	10	5849	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.24]
1.2 A2: Fetal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
1.2.1 All fetuses randomised	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
1.3 A3: Neonatal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
1.3.1 In all neonates	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
1.4 A5: Respiratory distress syndrome	9	3540	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
1.4.1 All fetuses randomised	9	3540	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
1.5 A6: Severe respiratory distress syndrome	5	3809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
1.5.1 All fetuses randomised	5	3809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
1.6 A7: Severe lung disease	6	4955	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
1.6.1 All fetuses randomised	6	4955	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
1.7 A8: Chronic lung disease	9	5661	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.22]
1.7.1 All fetuses randomised	9	5661	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.22]
1.8 A9: Severe intraventricular haemorrhage (grade 3/4)	7	5066	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
1.8.1 All fetuses randomised	7	5066	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
1.9 A10: Intraventricular haemorrhage	6	3223	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.9.1 All fetuses randomised	6	3223	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
1.10 A11: Necrotising enterocolitis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.22]
1.10.1 All fetuses randomised	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.22]
1.11 A12: Composite of serious outcomes	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
1.11.1 All fetuses randomised	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
1.12 F1i: Term birth ≥ 37 weeks	7	4068	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.06]
1.12.1 All fetuses randomised	7	4068	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.86, 1.06]
1.13 F1ii: Preterm birth before 37 weeks	7	4068	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
1.13.1 All fetuses randomised	7	4068	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
1.14 F1iii: Very preterm birth before 34 weeks	6	2682	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.08]
1.14.1 All fetuses randomised	6	2682	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.97, 1.08]
1.15 F1iv: Extremely preterm birth before 28 weeks	5	4022	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.92, 1.38]
1.15.1 All fetuses randomised	5	4022	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.92, 1.38]
1.16 F1v: Mean gestational age at birth (weeks)	10	5235	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.37, 0.01]
1.16.1 In all neonates	10	5235	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.37, 0.01]
1.17 F2: Small-for-gestational age at birth	7	4013	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.08, 1.44]
1.17.1 All fetuses randomised	7	4013	Risk Ratio (M-H, Fixed, 95% CI)	1.25 [1.08, 1.44]
1.18 F3: Admission to the neonatal intensive care unit	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.18.1 All fetuses randomised	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.07]
1.19 F4: Proven neonatal infection while in the neonatal intensive care unit	8	5660	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.22]
1.19.1 All fetuses randomised	8	5660	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.86, 1.22]
1.20 F5: Early systemic neonatal infection	4	1738	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.11]
1.20.1 All fetuses randomised	4	1738	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.79, 1.11]
1.21 F6: Late systemic neonatal infection	2	404	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.78, 2.41]
1.21.1 All fetuses randomised	2	404	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.78, 2.41]
1.22 F7: Retinopathy of prematurity	8	5234	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.27]
1.22.1 All fetuses randomised	8	5234	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.81, 1.27]
1.23 F8: Periventricular leukomalacia	8	5142	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.31]
1.23.1 All fetuses randomised	8	5142	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.43, 1.31]
1.24 F9: Neonatal encephalopathy	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.57]
1.24.1 All fetuses randomised	1	76	Risk Ratio (M-H, Fixed, 95% CI)	0.50 [0.10, 2.57]
1.25 F10: Patent ductus arteriosus	7	4657	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.63, 0.96]
1.25.1 All fetuses randomised	7	4657	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.63, 0.96]
1.26 F11: Use of respiratory support	2	2497	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
1.26.1 All fetuses randomised	2	2497	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
1.27 F12: Use of invasive respiratory support	6	5067	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.80, 0.93]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.27.1 All fetuses randomised	6	5067	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.80, 0.93]
1.28 F13: Use of non-invasive respiratory support	3	3231	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.82, 1.01]
1.28.1 All fetuses randomised	3	3231	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.82, 1.01]
1.29 F14: Use of oxygen supplementation	3	3643	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.85, 0.98]
1.29.1 All fetuses randomised	3	3643	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.85, 0.98]
1.30 F15: Use of surfactant	10	5870	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.73, 0.89]
1.30.1 All fetuses randomised	10	5870	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.73, 0.89]
1.31 F17: Use of postnatal corticosteroids	4	4145	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.99, 1.91]
1.31.1 All fetuses randomised	4	4145	Risk Ratio (M-H, Fixed, 95% CI)	1.37 [0.99, 1.91]
1.32 F16: Use of nitric oxide for respiratory support	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.29, 1.17]
1.32.1 All fetuses randomised	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.29, 1.17]
1.33 F20: Use of inotropic support	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]
1.33.1 All fetuses randomised	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]
1.34 F18: Air leak syndrome	4	2505	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.36]
1.34.1 All fetuses randomised	4	2505	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.50, 1.36]
1.35 F21: Apgar score < 7 at 5 minutes	3	4032	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.09]
1.35.1 All fetuses randomised	3	4032	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.64, 1.09]
1.36 F22: Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVS in mm)	1	175	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.24, 0.26]

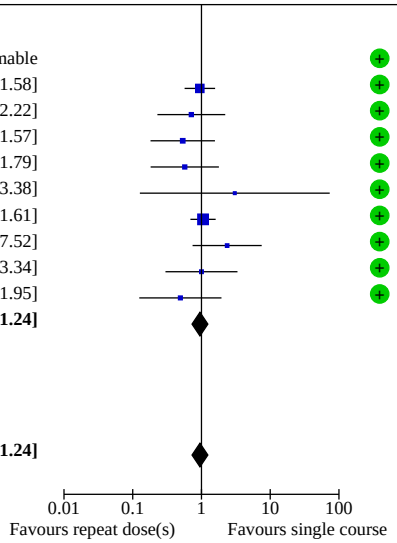
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.36.1 In all neonates	1	175	Mean Difference (IV, Fixed, 95% CI)	0.01 [-0.24, 0.26]
1.37 F22: Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole (mm)	1	175	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.27, 0.19]
1.37.1 In all neonates	1	175	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.27, 0.19]
1.38 L1: Mean birthweight (g)	10	5808	Mean Difference (IV, Fixed, 95% CI)	-74.49 [-115.80, -33.18]
1.38.1 In all neonates	10	5808	Mean Difference (IV, Fixed, 95% CI)	-74.49 [-115.80, -33.18]
1.39 L1: Mean birthweight Z score	3	1438	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.25, -0.02]
1.39.1 In all neonates	3	1438	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.25, -0.02]
1.40 L1: Birthweight multiples of the median	1	590	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.03, 0.03]
1.40.1 In all babies	1	590	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.03, 0.03]
1.41 L1: Birthweight adjusted for gestation (standardised mean difference)	4		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.41.1 In all neonates	4	2028	Std. Mean Difference (IV, Fixed, 95% CI)	-0.15 [-0.23, -0.06]
1.42 L2: Interval between trial entry and birth (days)	4	1309	Mean Difference (IV, Fixed, 95% CI)	-0.71 [-1.36, -0.06]
1.43 L3: Mean head circumference at birth (cm)	10	5731	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.49, -0.15]
1.43.1 In all neonates	10	5731	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.49, -0.15]
1.44 L3: Mean head circumference Z score at birth	2	1251	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.27, -0.00]
1.44.1 In all babies	2	1251	Mean Difference (IV, Fixed, 95% CI)	-0.14 [-0.27, -0.00]
1.45 L4: Mean length at birth (cm)	6	4550	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.89, -0.23]
1.45.1 In all neonates	6	4550	Mean Difference (IV, Fixed, 95% CI)	-0.56 [-0.89, -0.23]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.46 L4: Mean length Z score at birth	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.19, 0.09]
1.46.1 In all neonates	2	1256	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.19, 0.09]
1.47 L4: Length multiples of the mean at birth	1	590	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, -0.00]
1.47.1 In all neonates	1	590	Mean Difference (IV, Fixed, 95% CI)	-0.01 [-0.02, -0.00]
1.48 L4: Length at birth adjusted for gestation (standardised mean difference)	3	1846	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.18, 0.01]
1.48.1 In all neonates	3	1846	Std. Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.18, 0.01]
1.49 L5i: Mean weight (g) at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.49.1 In all infants	2	1195	Mean Difference (IV, Fixed, 95% CI)	17.91 [-52.35, 88.18]
1.50 L5i: Mean weight Z score at primary hospital discharge	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.16, 0.06]
1.50.1 In all infants	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.05 [-0.16, 0.06]
1.51 L5ii: Mean head circumference (cm) at primary hospital discharge	2	1195	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.10, 0.35]
1.51.1 In all infants	2	1195	Mean Difference (IV, Fixed, 95% CI)	0.12 [-0.10, 0.35]
1.52 L5ii: Mean head circumference Z score at primary hospital discharge	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.15, 0.10]
1.52.1 In all infants	2	1195	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.15, 0.10]
1.53 L5iii: Mean length (cm) at primary hospital discharge	2	1189	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.44, 0.47]
1.53.1 In all infants	2	1189	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.44, 0.47]
1.54 L5iii: Mean length Z score at primary hospital discharge	2		Mean Difference (IV, Fixed, 95% CI)	Subtotals only
1.54.1 In all infants	2	1189	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.23, 0.10]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1.55 L6i: Mean weight at infant follow-up (kg)	2	149	Mean Difference (IV, Fixed, 95% CI)	-0.60 [-0.87, -0.34]
1.56 L6i: Mean weight Z score at infant follow-up	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.12 [-0.84, 0.60]
1.57 L6ii: Mean head circumference at infant follow-up (cm)	2	136	Mean Difference (IV, Fixed, 95% CI)	-0.45 [-0.85, -0.05]
1.58 L6ii: Mean head circumference Z score at infant follow-up	1	62	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.78, 0.70]
1.59 L6iii: Mean length at infant follow-up (cm)	2	149	Mean Difference (IV, Fixed, 95% CI)	-1.57 [-2.32, -0.82]
1.60 L6iii: Mean length Z score at infant follow-up	1	75	Mean Difference (IV, Fixed, 95% CI)	-0.24 [-1.21, 0.73]
1.61 L8: Mean duration of invasive respiratory support (days)	4	1620	Mean Difference (IV, Fixed, 95% CI)	-0.27 [-0.38, -0.16]
1.62 L9: Mean duration of non-invasive respiratory support (days)	1	326	Mean Difference (IV, Fixed, 95% CI)	-0.59 [-1.29, 0.11]
1.63 L10: Mean duration of oxygen supplementation (days)	4	1619	Mean Difference (IV, Fixed, 95% CI)	-0.32 [-0.94, 0.30]
1.64 L14: Mean cord cortisol concentrations at birth (nmol/L)	2	442	Mean Difference (IV, Fixed, 95% CI)	-50.49 [-73.14, -27.85]
1.64.1 In all neonates	2	442	Mean Difference (IV, Fixed, 95% CI)	-50.49 [-73.14, -27.85]

Analysis 1.1. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 1: A1: Fetal or neonatal or infant death (< 1 year of age)

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.1.1 All fetuses randomised												
Aghajafari 2002	0	9	0	7		Not estimable	+	+	+	+	+	+
Crowther 2006	27	568	29	578	26.7%	0.95 [0.57 , 1.58]	+	+	+	+	+	+
Garite 2009	5	289	7	288	6.5%	0.71 [0.23 , 2.22]	+	+	+	+	+	+
Guinn 2001	5	256	9	246	8.5%	0.53 [0.18 , 1.57]	+	+	+	+	+	+
Mazumder 2008	4	38	7	38	6.5%	0.57 [0.18 , 1.79]	+	?	+	+	?	?
McEvoy 2010	1	56	0	57	0.5%	3.05 [0.13 , 73.38]	+	+	+	+	+	+
Murphy 2008	43	1166	40	1143	37.5%	1.05 [0.69 , 1.61]	+	+	+	+	+	+
Peltoniemi 2007	9	160	4	168	3.6%	2.36 [0.74 , 7.52]	+	+	+	+	+	+
TEAMS 1999	5	94	5	94	4.6%	1.00 [0.30 , 3.34]	+	+	+	+	+	+
Wapner 2006	3	299	6	295	5.6%	0.49 [0.12 , 1.95]	+	+	?	+	+	?
Subtotal (95% CI)		**2935**		**2914**	**100.0%**	**0.95 [0.73 , 1.24]**						
Total events:	102		107									
Heterogeneity: Chi² = 6.11, df = 8 (P = 0.64); I² = 0%												
Test for overall effect: Z = 0.38 (P = 0.71)												
Total (95% CI)		**2935**		**2914**	**100.0%**	**0.95 [0.73 , 1.24]**						
Total events:	102		107									
Heterogeneity: Chi² = 6.11, df = 8 (P = 0.64); I² = 0%												
Test for overall effect: Z = 0.38 (P = 0.71)												
Test for subgroup differences: Not applicable												

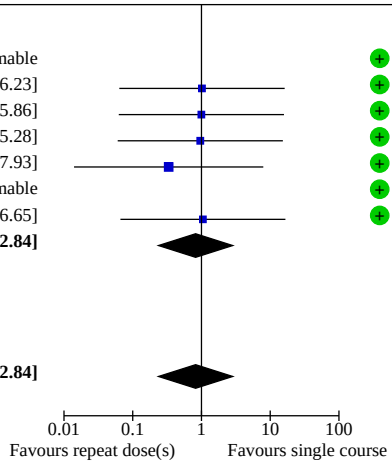


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.2. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 2: A2: Fetal death

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.2.1 All fetuses randomised												
Aghajafari 2002	0	9	0	7		Not estimable	+	+	+	+	+	+
Crowther 2006	1	568	1	578	18.1%	1.02 [0.06 , 16.23]	+	+	+	+	+	+
Garite 2009	1	289	1	288	18.3%	1.00 [0.06 , 15.86]	+	+	+	+	+	+
Guinn 2001	1	256	1	246	18.6%	0.96 [0.06 , 15.28]	+	+	+	+	+	+
Mazumder 2008	0	38	1	38	27.3%	0.33 [0.01 , 7.93]	+	?	+	+	?	?
McEvoy 2010	0	56	0	57		Not estimable	+	+	+	+	+	+
Peltoniemi 2007	1	160	1	168	17.8%	1.05 [0.07 , 16.65]	+	+	+	+	+	+
Subtotal (95% CI)		**1376**		**1382**	**100.0%**	**0.82 [0.24 , 2.84]**						
Total events:	4		5									
Heterogeneity: Chi² = 0.40, df = 4 (P = 0.98); I² = 0%												
Test for overall effect: Z = 0.31 (P = 0.76)												
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.82 [0.24 , 2.84]**						
Total events:	4		5									
Heterogeneity: Chi² = 0.40, df = 4 (P = 0.98); I² = 0%												
Test for overall effect: Z = 0.31 (P = 0.76)												
Test for subgroup differences: Not applicable												

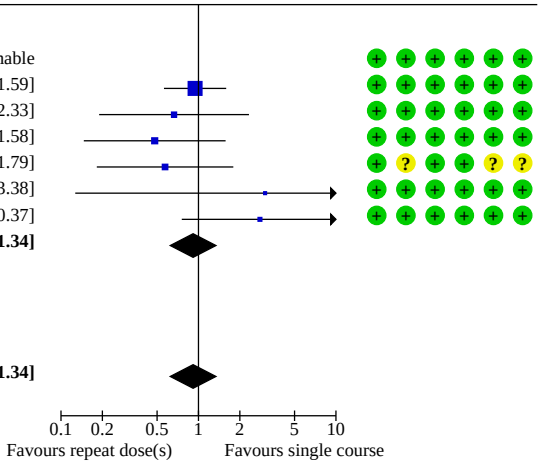


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.3. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 3: A3: Neonatal death

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.3.1 In all neonates						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	26	568	28	578	53.0%	0.94 [0.56 , 1.59]
Garite 2009	4	289	6	288	11.5%	0.66 [0.19 , 2.33]
Guinn 2001	4	256	8	246	15.6%	0.48 [0.15 , 1.58]
Mazumder 2008	4	38	7	38	13.4%	0.57 [0.18 , 1.79]
McEvoy 2010	1	56	0	57	0.9%	3.05 [0.13 , 73.38]
Peltoniemi 2007	8	160	3	168	5.6%	2.80 [0.76 , 10.37]
Subtotal (95% CI)		**1376**		**1382**	**100.0%**	**0.91 [0.62 , 1.34]**
Total events:	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.91 [0.62 , 1.34]**
Total events:	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Not applicable						

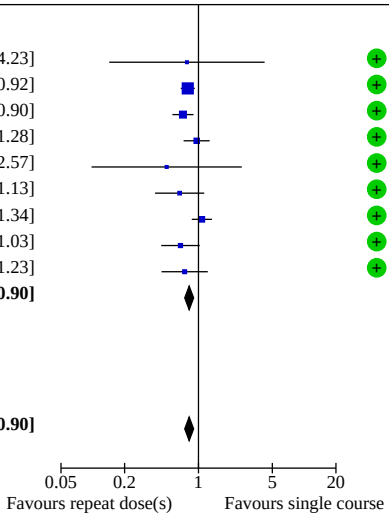


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.4. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 4: A5: Respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.4.1 All fetuses randomised												
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14 , 4.23]	+	+	+	+	+	+
Crowther 2006	186	568	239	578	39.5%	0.79 [0.68 , 0.92]	+	+	+	+	+	+
Garite 2009	83	289	116	288	19.4%	0.71 [0.57 , 0.90]	+	+	+	+	+	+
Guinn 2001	69	256	69	246	11.7%	0.96 [0.72 , 1.28]	+	+	+	+	+	+
Mazumder 2008	2	38	4	38	0.7%	0.50 [0.10 , 2.57]	+	?	+	-	?	-
McEvoy 2010	15	56	23	57	3.8%	0.66 [0.39 , 1.13]	+	+	+	+	+	+
Peltoniemi 2007	82	160	80	168	13.0%	1.08 [0.86 , 1.34]	+	+	+	+	+	+
TEAMS 1999	25	94	37	94	6.2%	0.68 [0.44 , 1.03]	+	+	+	+	+	+
Wapner 2006	24	299	32	295	5.4%	0.74 [0.45 , 1.23]	+	+	?	+	+	?
Subtotal (95% CI)		**1769**		**1771**	**100.0%**	**0.82 [0.74 , 0.90]**						
Total events:	488		602									
Heterogeneity: Chi² = 10.71, df = 8 (P = 0.22); I² = 25%												
Test for overall effect: Z = 4.12 (P < 0.0001)												
Total (95% CI)		**1769**		**1771**	**100.0%**	**0.82 [0.74 , 0.90]**						
Total events:	488		602									
Heterogeneity: Chi² = 10.71, df = 8 (P = 0.22); I² = 25%												
Test for overall effect: Z = 4.12 (P < 0.0001)												
Test for subgroup differences: Not applicable												

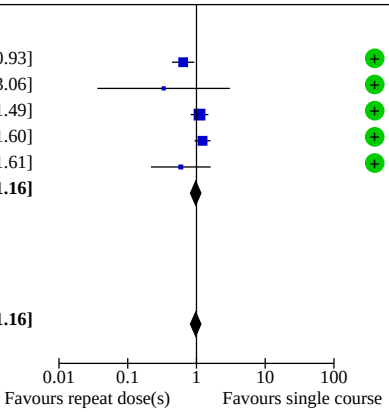


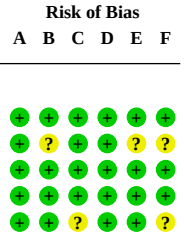
Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.5. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 5: A6: Severe respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.5.1 All fetuses randomised						
Guinn 2001	38	256	57	246	28.0%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	1.4%	0.33 [0.04 , 3.06]
Murphy 2008	87	1166	77	1143	37.5%	1.11 [0.82 , 1.49]
Peltoniemi 2007	70	160	60	168	28.2%	1.23 [0.94 , 1.60]
Wapner 2006	6	299	10	295	4.9%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**1919**		**1890**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	202		207			
Heterogeneity: Chi² = 10.28, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**1919**		**1890**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	202		207			
Heterogeneity: Chi² = 10.28, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Test for subgroup differences: Not applicable						

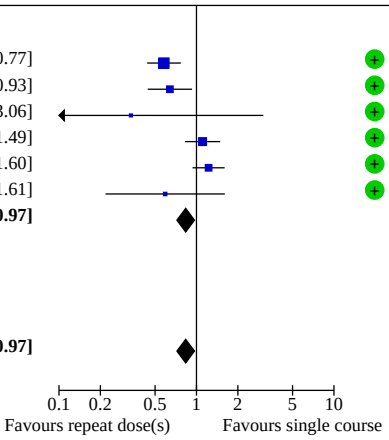


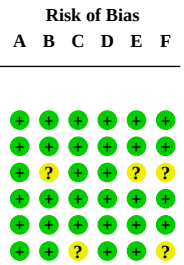


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.6. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 6: A7: Severe lung disease

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.6.1 All fetuses randomised						
Crowther 2006	65	568	114	578	35.3%	0.58 [0.44 , 0.77]
Guinn 2001	38	256	57	246	18.1%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	0.9%	0.33 [0.04 , 3.06]
Murphy 2008	87	1166	77	1143	24.3%	1.11 [0.82 , 1.49]
Peltoniemi 2007	70	160	60	168	18.3%	1.23 [0.94 , 1.60]
Wapner 2006	6	299	10	295	3.1%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**2487**		**2468**	**100.0%**	**0.83 [0.72 , 0.97]**
Total events:	267		321			
Heterogeneity: Chi² = 20.83, df = 5 (P = 0.0009); I² = 76%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Total (95% CI)		**2487**		**2468**	**100.0%**	**0.83 [0.72 , 0.97]**
Total events:	267		321			
Heterogeneity: Chi² = 20.83, df = 5 (P = 0.0009); I² = 76%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Not applicable						

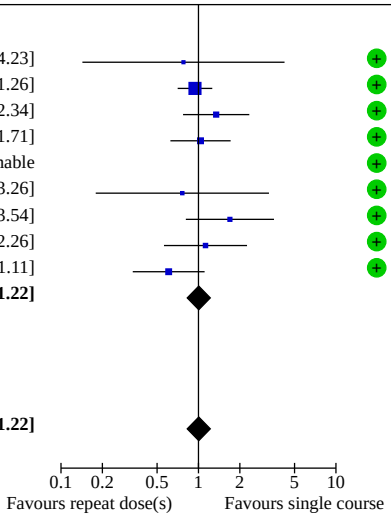




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.7. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 7: A8: Chronic lung disease

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.7.1 All fetuses randomised												
Aghajafari 2002	2	9	2	7	1.2%	0.78 [0.14 , 4.23]	+	+	+	+	+	+
Crowther 2006	76	568	82	578	43.9%	0.94 [0.71 , 1.26]	+	+	+	+	+	+
Garite 2009	27	289	20	288	10.8%	1.35 [0.77 , 2.34]	+	+	+	+	+	+
Guinn 2001	28	256	26	246	14.3%	1.03 [0.62 , 1.71]	+	+	+	+	+	+
Mazumder 2008	0	38	0	38		Not estimable	+	?	+	-	?	-
McEvoy 2010	3	56	4	57	2.1%	0.76 [0.18 , 3.26]	+	+	+	+	?	?
Murphy 2008	19	1166	11	1143	6.0%	1.69 [0.81 , 3.54]	+	+	+	+	+	+
Peltoniemi 2007	15	160	14	168	7.4%	1.13 [0.56 , 2.26]	+	+	+	+	+	+
Wapner 2006	16	299	26	295	14.1%	0.61 [0.33 , 1.11]	+	+	?	+	+	?
Subtotal (95% CI)		**2841**		**2820**	**100.0%**	**1.00 [0.83 , 1.22]**						
Total events:	186		185									
Heterogeneity: Chi² = 6.20, df = 7 (P = 0.52); I² = 0%												
Test for overall effect: Z = 0.05 (P = 0.96)												
Total (95% CI)		**2841**		**2820**	**100.0%**	**1.00 [0.83 , 1.22]**						
Total events:	186		185									
Heterogeneity: Chi² = 6.20, df = 7 (P = 0.52); I² = 0%												
Test for overall effect: Z = 0.05 (P = 0.96)												
Test for subgroup differences: Not applicable												

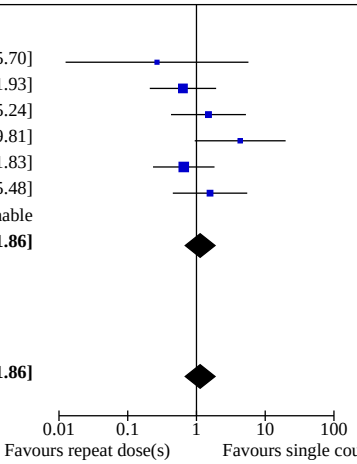


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.8. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 8: A9: Severe intraventricular haemorrhage (grade 3/4)

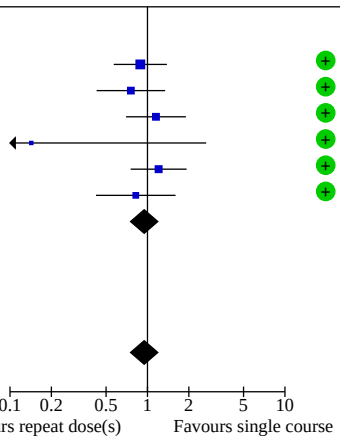
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.8.1 All fetuses randomised												
Aghajafari 2002	0	9	1	7	5.8%	0.27 [0.01 , 5.70]	+	+	+	+	+	+
Crowther 2006	5	568	8	578	27.7%	0.64 [0.21 , 1.93]	+	+	+	+	+	+
Garite 2009	6	289	4	288	14.0%	1.49 [0.43 , 5.24]	+	+	+	+	+	+
Guinn 2001	9	256	2	246	7.1%	4.32 [0.94 , 19.81]	+	+	+	+	+	+
Murphy 2008	6	1166	9	1143	31.7%	0.65 [0.23 , 1.83]	+	+	+	+	+	+
Peltoniemi 2007	6	160	4	168	13.6%	1.57 [0.45 , 5.48]	+	+	?	+	+	?
TEAMS 1999	0	94	0	94		Not estimable	+	+	+	+	+	+
Subtotal (95% CI)		**2542**		**2524**	**100.0%**	**1.13 [0.69 , 1.86]**						
Total events:	32		28									
Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%												
Test for overall effect: Z = 0.48 (P = 0.63)												
Total (95% CI)		**2542**		**2524**	**100.0%**	**1.13 [0.69 , 1.86]**						
Total events:	32		28									
Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%												
Test for overall effect: Z = 0.48 (P = 0.63)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.9. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 9: A10: Intraventricular haemorrhage

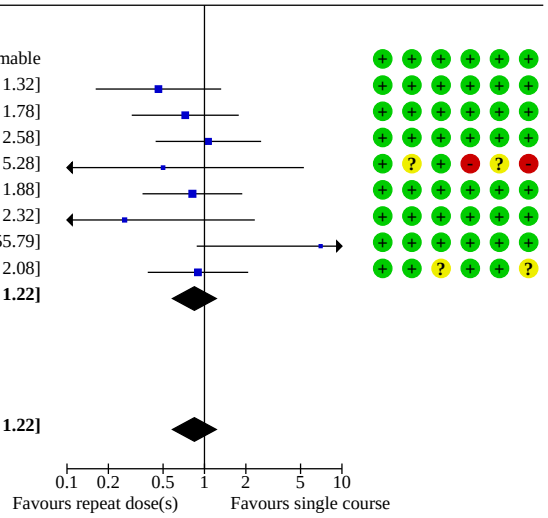
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.9.1 All fetuses randomised												
Crowther 2006	34	568	39	578	28.2%	0.89 [0.57 , 1.38]	+	+	+	+	+	+
Garite 2009	19	289	25	288	18.3%	0.76 [0.43 , 1.34]	+	+	+	+	+	+
Guinn 2001	30	256	25	246	18.6%	1.15 [0.70 , 1.90]	+	+	+	+	+	+
Mazumder 2008	0	38	3	38	2.6%	0.14 [0.01 , 2.67]	+	?	+	-	?	-
Peltoniemi 2007	31	160	27	168	19.2%	1.21 [0.75 , 1.93]	+	+	?	+	+	?
Wapner 2006	15	299	18	295	13.2%	0.82 [0.42 , 1.60]	+	+	?	+	+	?
Subtotal (95% CI)		**1610**		**1613**	**100.0%**	**0.95 [0.75 , 1.19]**						
Total events:	129		137									
Heterogeneity: Chi² = 4.05, df = 5 (P = 0.54); I² = 0%												
Test for overall effect: Z = 0.47 (P = 0.64)												
Total (95% CI)		**1610**		**1613**	**100.0%**	**0.95 [0.75 , 1.19]**						
Total events:	129		137									
Heterogeneity: Chi² = 4.05, df = 5 (P = 0.54); I² = 0%												
Test for overall effect: Z = 0.47 (P = 0.64)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.10. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 10: A11: Necrotising enterocolitis

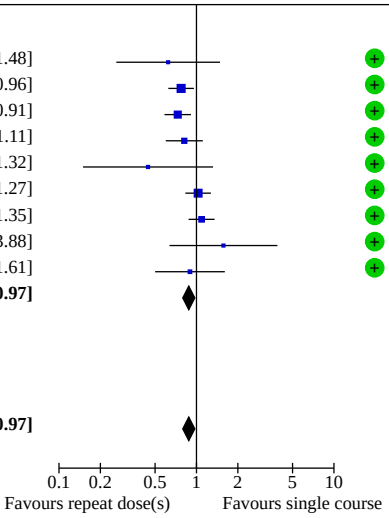
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.10.1 All fetuses randomised						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	5	568	11	578	17.8%	0.46 [0.16 , 1.32]
Garite 2009	8	289	11	288	18.0%	0.72 [0.30 , 1.78]
Guinn 2001	10	256	9	246	15.0%	1.07 [0.44 , 2.58]
Mazumder 2008	1	38	2	38	3.3%	0.50 [0.05 , 5.28]
Murphy 2008	10	1166	12	1143	19.8%	0.82 [0.35 , 1.88]
Peltoniemi 2007	1	160	4	168	6.4%	0.26 [0.03 , 2.32]
TEAMS 1999	7	94	1	94	1.6%	7.00 [0.88 , 55.79]
Wapner 2006	10	299	11	295	18.1%	0.90 [0.39 , 2.08]
Subtotal (95% CI)		**2879**		**2857**	**100.0%**	**0.84 [0.59 , 1.22]**
Total events:	52		61			
Heterogeneity: Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.84 [0.59 , 1.22]**
Total events:	52		61			
Heterogeneity: Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.11. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 11: A12: Composite of serious outcomes

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.11.1 All fetuses randomised							
Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]	+ + + + + +
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]	+ + + + + +
Garite 2009	88	289	120	288	20.0%	0.73 [0.59 , 0.91]	+ + + + + +
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]	+ + + + + +
Mazumder 2008	4	38	9	38	1.5%	0.44 [0.15 , 1.32]	+ ? + + ? ?
Murphy 2008	150	1166	143	1143	24.0%	1.03 [0.83 , 1.27]	+ + + + + +
Peltoniemi 2007	83	160	80	168	13.0%	1.09 [0.88 , 1.35]	+ + + + + +
TEAMS 1999	11	94	7	94	1.2%	1.57 [0.64 , 3.88]	+ + + + + +
Wapner 2006	20	299	22	295	3.7%	0.90 [0.50 , 1.61]	+ + ? + + ?
Subtotal (95% CI)		**2879**		**2857**	**100.0%**	**0.88 [0.80 , 0.97]**	
Total events:	530		602				
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%							
Test for overall effect: Z = 2.51 (P = 0.01)							
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.88 [0.80 , 0.97]**	
Total events:	530		602				
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%							
Test for overall effect: Z = 2.51 (P = 0.01)							
Test for subgroup differences: Not applicable							

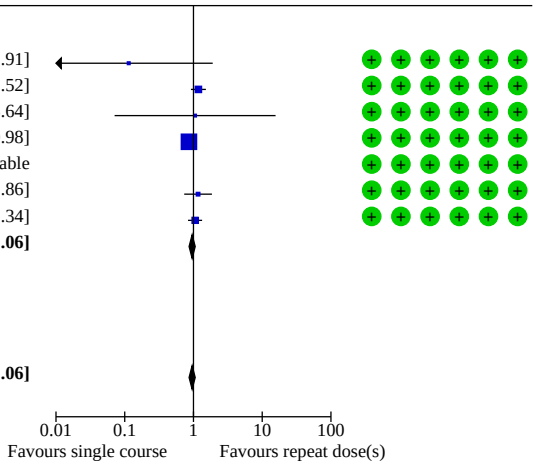


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.12. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 12: F1i: Term birth ≥ 37 weeks

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.12.1 All fetuses randomised						
Aghajafari 2002	0	9	3	7	0.7%	0.11 [0.01 , 1.91]
Crowther 2006	109	568	94	578	17.6%	1.18 [0.92 , 1.52]
McEvoy 2002	1	18	1	19	0.2%	1.06 [0.07 , 15.64]
Murphy 2008 (1)	278	937	318	921	60.6%	0.86 [0.75 , 0.98]
Peltoniemi 2007	0	160	0	168		Not estimable
TEAMS 1999	28	94	24	94	4.5%	1.17 [0.73 , 1.86]
Wapner 2006	93	252	85	243	16.4%	1.06 [0.83 , 1.34]
Subtotal (95% CI)		**2038**		**2030**	**100.0%**	**0.96 [0.86 , 1.06]**
Total events:	509		525			
Heterogeneity: Chi² = 8.77, df = 5 (P = 0.12); I² = 43%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Total (95% CI)		**2038**		**2030**	**100.0%**	**0.96 [0.86 , 1.06]**
Total events:	509		525			
Heterogeneity: Chi² = 8.77, df = 5 (P = 0.12); I² = 43%						
Test for overall effect: Z = 0.85 (P = 0.39)						
Test for subgroup differences: Not applicable						



Footnotes

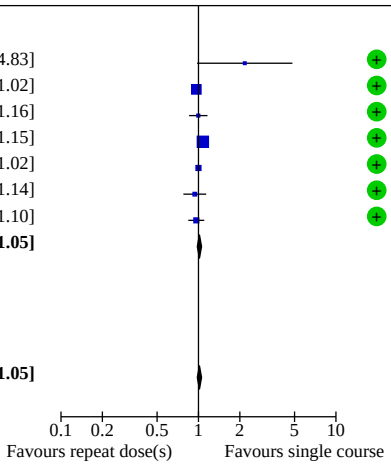
(1) For Murphy 2008, the gestation at birth for multiple pregnancies was reported for the festus delivered earliest.

Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.13. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 13: F1ii: Preterm birth before 37 weeks

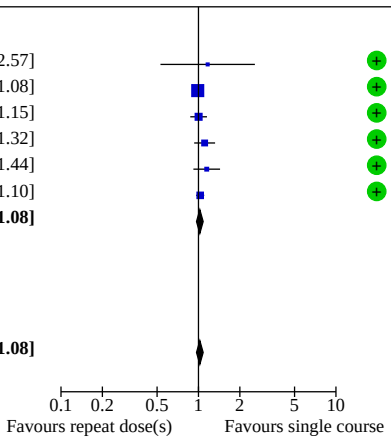
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.13.1 All fetuses randomised							
Aghajafari 2002	9	9	3	7	0.3%	2.17 [0.98 , 4.83]	+ + + + + +
Crowther 2006	458	568	483	578	32.0%	0.96 [0.91 , 1.02]	+ + + + + +
McEvoy 2002	17	18	18	19	1.2%	1.00 [0.85 , 1.16]	+ + + + + +
Murphy 2008	657	937	600	921	40.5%	1.08 [1.01 , 1.15]	+ + + + + +
Peltoniemi 2007	159	160	167	168	10.9%	1.00 [0.98 , 1.02]	+ + + + + +
TEAMS 1999	63	94	67	94	4.5%	0.94 [0.78 , 1.14]	+ + + + + +
Wapner 2006	157	252	157	243	10.7%	0.96 [0.84 , 1.10]	+ + + + + +
Subtotal (95% CI)		**2038**		**2030**	**100.0%**	**1.02 [0.98 , 1.05]**	
Total events:	1520		1495				
Heterogeneity: Chi² = 15.00, df = 6 (P = 0.02); I² = 60%							
Test for overall effect: Z = 0.89 (P = 0.38)							
Total (95% CI)		**2038**		**2030**	**100.0%**	**1.02 [0.98 , 1.05]**	
Total events:	1520		1495				
Heterogeneity: Chi² = 15.00, df = 6 (P = 0.02); I² = 60%							
Test for overall effect: Z = 0.89 (P = 0.38)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.14. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 14: F1iii: Very preterm birth before 34 weeks

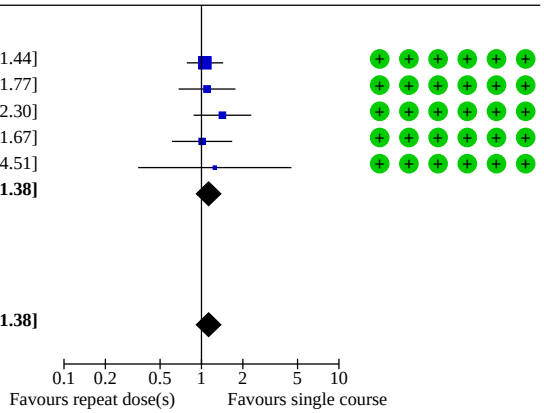
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.14.1 All fetuses randomised							
Aghajafari 2002	6	9	4	7	0.5%	1.17 [0.53 , 2.57]	+ + + + + +
Crowther 2006	362	568	373	578	43.7%	0.99 [0.91 , 1.08]	+ + + + + +
Garite 2009	167	289	166	288	19.7%	1.00 [0.87 , 1.15]	+ + + + + +
Guinn 2001	135	256	117	246	14.1%	1.11 [0.93 , 1.32]	+ + + + + +
McEvoy 2010	44	56	39	57	4.6%	1.15 [0.92 , 1.44]	+ + + + + +
Peltoniemi 2007	148	160	151	168	17.4%	1.03 [0.96 , 1.10]	+ + + + + +
Subtotal (95% CI)		**1338**		**1344**	**100.0%**	**1.02 [0.97 , 1.08]**	
Total events:	862		850				
Heterogeneity: Chi² = 2.69, df = 5 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.81 (P = 0.42)							
Total (95% CI)		**1338**		**1344**	**100.0%**	**1.02 [0.97 , 1.08]**	
Total events:	862		850				
Heterogeneity: Chi² = 2.69, df = 5 (P = 0.75); I² = 0%							
Test for overall effect: Z = 0.81 (P = 0.42)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.15. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 15: F1iv: Extremely preterm birth before 28 weeks

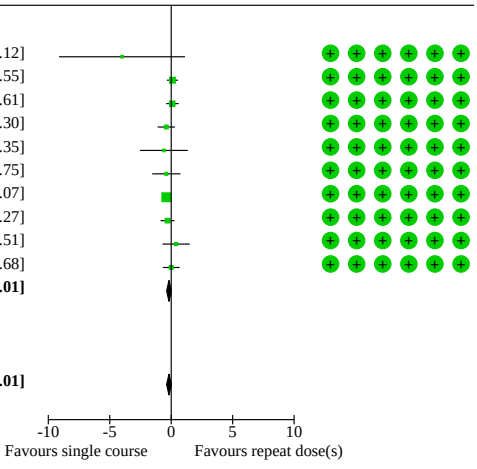
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.15.1 All fetuses randomised						
Crowther 2006	74	568	71	578	45.3%	1.06 [0.78 , 1.44]
Guinn 2001	32	256	28	246	18.4%	1.10 [0.68 , 1.77]
Murphy 2008	39	937	27	921	17.5%	1.42 [0.88 , 2.30]
Peltoniemi 2007	25	160	26	168	16.3%	1.01 [0.61 , 1.67]
TEAMS 1999	5	94	4	94	2.6%	1.25 [0.35 , 4.51]
Subtotal (95% CI)		**2015**		**2007**	**100.0%**	**1.13 [0.92 , 1.38]**
Total events:	175		156			
Heterogeneity: Chi² = 1.25, df = 4 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Total (95% CI)		**2015**		**2007**	**100.0%**	**1.13 [0.92 , 1.38]**
Total events:	175		156			
Heterogeneity: Chi² = 1.25, df = 4 (P = 0.87); I² = 0%						
Test for overall effect: Z = 1.15 (P = 0.25)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.16. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 16: F1v: Mean gestational age at birth (weeks)

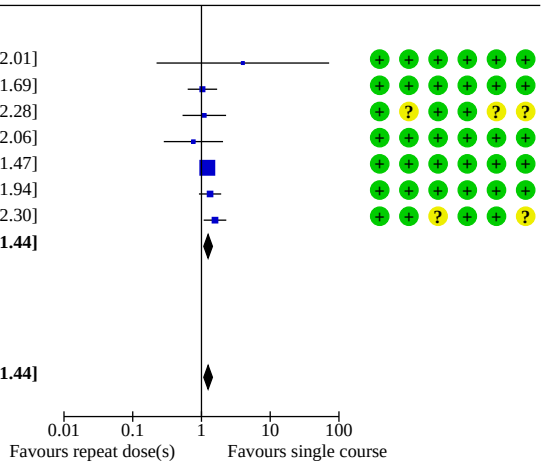
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.16.1 In all neonates								
Aghajafari 2002	31	4	6	35	5	6	0.1%	-4.00 [-9.12 , 1.12]
Crowther 2006	32.5	3.9	567	32.4	3.9	577	17.9%	0.10 [-0.35 , 0.55]
Garite 2009	33.1	3.1	289	33	3.1	288	14.3%	0.10 [-0.41 , 0.61]
Guinn 2001	33.1	4	255	33.5	4	245	7.4%	-0.40 [-1.10 , 0.30]
McEvoy 2002	32.2	3.3	18	32.8	2.7	19	1.0%	-0.60 [-2.55 , 1.35]
McEvoy 2010	31.9	3.3	56	32.3	2.9	56	2.8%	-0.40 [-1.55 , 0.75]
Murphy 2008	34.5	3.6	935	34.9	3.6	918	34.1%	-0.40 [-0.73 , -0.07]
Peltoniemi 2007	30.7	2.7	159	31	2.5	167	11.5%	-0.30 [-0.87 , 0.27]
TEAMS 1999	34.2	4.1	91	33.8	3.5	91	3.0%	0.40 [-0.71 , 1.51]
Wapner 2006	34.8	3.8	250	34.8	3.9	242	7.9%	0.00 [-0.68 , 0.68]
Subtotal (95% CI)			**2626**			**2609**	**100.0%**	**-0.18 [-0.37 , 0.01]**
Heterogeneity: Chi² = 8.71, df = 9 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.83 (P = 0.07)								
Total (95% CI)			**2626**			**2609**	**100.0%**	**-0.18 [-0.37 , 0.01]**
Heterogeneity: Chi² = 8.71, df = 9 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.83 (P = 0.07)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.17. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 17: F2: Small-for-gestational age at birth

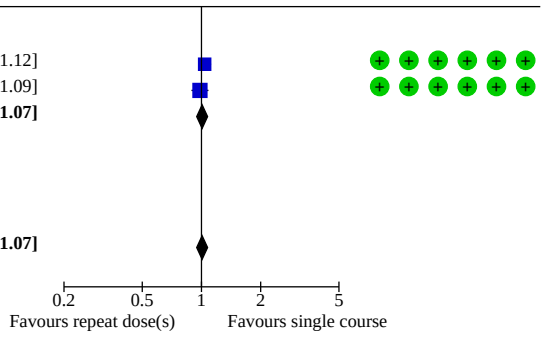
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.17.1 All fetuses randomised						
Aghajafari 2002	2	9	0	7	0.2%	4.00 [0.22 , 72.01]
Garite 2009	29	289	28	288	10.0%	1.03 [0.63 , 1.69]
Mazumder 2008	11	38	10	38	3.6%	1.10 [0.53 , 2.28]
McEvoy 2010	6	56	8	57	2.8%	0.76 [0.28 , 2.06]
Murphy 2008	196	1166	158	1143	57.1%	1.22 [1.00 , 1.47]
Peltoniemi 2007	47	160	37	168	12.9%	1.33 [0.92 , 1.94]
Wapner 2006	59	299	37	295	13.3%	1.57 [1.08 , 2.30]
Subtotal (95% CI)		**2017**		**1996**	**100.0%**	**1.25 [1.08 , 1.44]**
Total events:	350		278			
Heterogeneity: Chi² = 3.88, df = 6 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Total (95% CI)		**2017**		**1996**	**100.0%**	**1.25 [1.08 , 1.44]**
Total events:	350		278			
Heterogeneity: Chi² = 3.88, df = 6 (P = 0.69); I² = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.18. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 18: F3: Admission to the neonatal intensive care unit

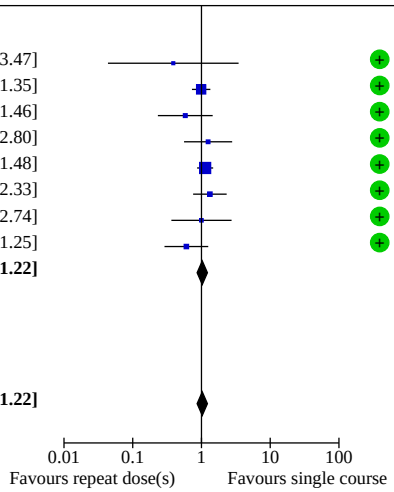
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.18.1 All fetuses randomised						
Crowther 2006	407	568	399	578	45.8%	1.04 [0.96 , 1.12]
Murphy 2008	465	1166	464	1143	54.2%	0.98 [0.89 , 1.09]
Subtotal (95% CI)		**1734**		**1721**	**100.0%**	**1.01 [0.95 , 1.07]**
Total events:	872		863			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Total (95% CI)		**1734**		**1721**	**100.0%**	**1.01 [0.95 , 1.07]**
Total events:	872		863			
Heterogeneity: Chi² = 0.84, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
Test for subgroup differences: Not applicable						

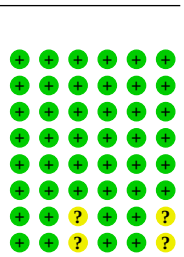


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.19. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 19: F4: Proven neonatal infection while in the neonatal intensive care unit

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.19.1 All fetuses randomised						
Aghajafari 2002	1	9	2	7	1.0%	0.39 [0.04 , 3.47]
Crowther 2006	70	568	72	578	30.8%	0.99 [0.73 , 1.35]
Garite 2009	7	289	12	288	5.2%	0.58 [0.23 , 1.46]
Guinn 2001	13	256	10	246	4.4%	1.25 [0.56 , 2.80]
Murphy 2008	105	1166	91	1143	39.7%	1.13 [0.86 , 1.48]
Peltoniemi 2007	24	160	19	168	8.0%	1.33 [0.76 , 2.33]
TEAMS 1999	7	94	7	94	3.0%	1.00 [0.36 , 2.74]
Wapner 2006	11	299	18	295	7.8%	0.60 [0.29 , 1.25]
Subtotal (95% CI)		**2841**		**2819**	**100.0%**	**1.03 [0.86 , 1.22]**
Total events:	238		231			
Heterogeneity: Chi² = 5.84, df = 7 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Total (95% CI)		**2841**		**2819**	**100.0%**	**1.03 [0.86 , 1.22]**
Total events:	238		231			
Heterogeneity: Chi² = 5.84, df = 7 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Test for subgroup differences: Not applicable						

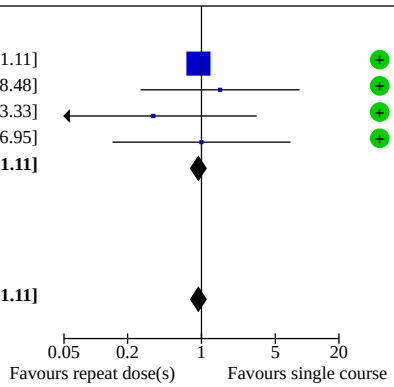


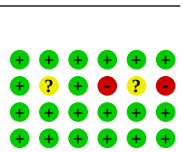


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.20. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 20: F5: Early systemic neonatal infection

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.20.1 All fetuses randomised						
Crowther 2006	173	568	188	578	96.4%	0.94 [0.79 , 1.11]
Mazumder 2008	3	38	2	38	1.0%	1.50 [0.27 , 8.48]
Peltoniemi 2007	1	160	3	168	1.5%	0.35 [0.04 , 3.33]
TEAMS 1999	2	94	2	94	1.0%	1.00 [0.14 , 6.95]
Subtotal (95% CI)		**860**		**878**	**100.0%**	**0.93 [0.79 , 1.11]**
Total events:	179		195			
Heterogeneity: Chi² = 1.02, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Total (95% CI)		**860**		**878**	**100.0%**	**0.93 [0.79 , 1.11]**
Total events:	179		195			
Heterogeneity: Chi² = 1.02, df = 3 (P = 0.80); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
Test for subgroup differences: Not applicable						

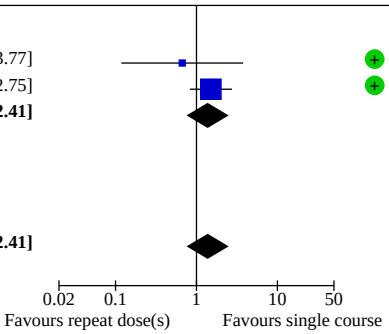




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.21. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 21: F6: Late systemic neonatal infection

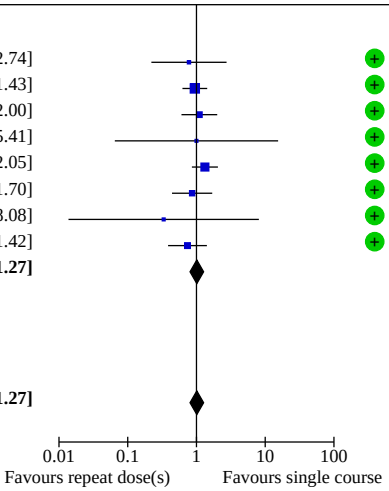
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.21.1 All fetuses randomised							
Mazumder 2008	2	38	3	38	16.1%	0.67 [0.12 , 3.77]	+ ? + - ? -
Peltoniemi 2007	23	160	16	168	83.9%	1.51 [0.83 , 2.75]	+ + + + + +
Subtotal (95% CI)		**198**		**206**	**100.0%**	**1.37 [0.78 , 2.41]**	
Total events:	25		19				
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 1.11 (P = 0.27)							
Total (95% CI)		**198**		**206**	**100.0%**	**1.37 [0.78 , 2.41]**	
Total events:	25		19				
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 1.11 (P = 0.27)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.22. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 22: F7: Retinopathy of prematurity

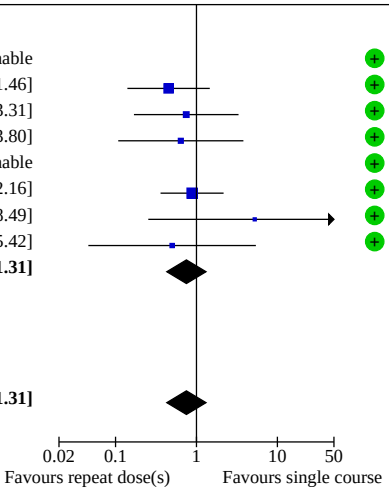
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.22.1 All fetuses randomised							
Aghajafari 2002	3	9	3	7	2.4%	0.78 [0.22 , 2.74]	+ + + + + +
Crowther 2006	40	568	43	578	30.8%	0.95 [0.63 , 1.43]	+ + + + + +
Garite 2009	21	289	19	288	13.7%	1.10 [0.61 , 2.00]	+ + + + + +
Mazumder 2008	1	38	1	38	0.7%	1.00 [0.06 , 15.41]	+ ? + - ? -
Murphy 2008	46	1166	34	1143	24.8%	1.33 [0.86 , 2.05]	+ + ? + + ?
Peltoniemi 2007	14	160	17	168	12.0%	0.86 [0.44 , 1.70]	+ + + + + +
TEAMS 1999	0	94	1	94	1.1%	0.33 [0.01 , 8.08]	+ + + + + +
Wapner 2006	15	299	20	295	14.5%	0.74 [0.39 , 1.42]	+ + ? + + ?
Subtotal (95% CI)		**2623**		**2611**	**100.0%**	**1.01 [0.81 , 1.27]**	
Total events:	140		138				
Heterogeneity: Chi² = 3.39, df = 7 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.10 (P = 0.92)							
Total (95% CI)		**2623**		**2611**	**100.0%**	**1.01 [0.81 , 1.27]**	
Total events:	140		138				
Heterogeneity: Chi² = 3.39, df = 7 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.10 (P = 0.92)							
Test for subgroup differences: Not applicable							

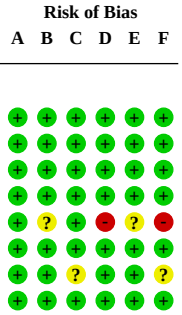


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.23. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 23: F8: Periventricular leukomalacia

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.23.1 All fetuses randomised						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	4	568	9	578	31.2%	0.45 [0.14 , 1.46]
Garite 2009	3	289	4	288	14.0%	0.75 [0.17 , 3.31]
Guinn 2001	2	256	3	246	10.7%	0.64 [0.11 , 3.80]
Mazumder 2008	0	38	0	38		Not estimable
Murphy 2008	9	1166	10	1143	35.3%	0.88 [0.36 , 2.16]
Peltoniemi 2007	2	160	0	168	1.7%	5.25 [0.25 , 108.49]
TEAMS 1999	1	94	2	94	7.0%	0.50 [0.05 , 5.42]
Subtotal (95% CI)		**2580**		**2562**	**100.0%**	**0.75 [0.43 , 1.31]**
Total events:	21		28			
Heterogeneity: Chi² = 2.57, df = 5 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Total (95% CI)		**2580**		**2562**	**100.0%**	**0.75 [0.43 , 1.31]**
Total events:	21		28			
Heterogeneity: Chi² = 2.57, df = 5 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.01 (P = 0.31)						
Test for subgroup differences: Not applicable						

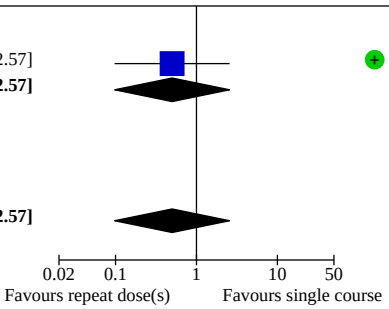




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.24. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 24: F9: Neonatal encephalopathy

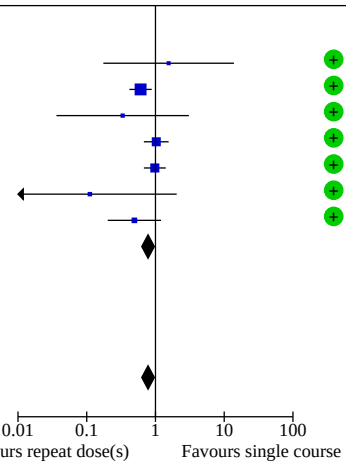
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.24.1 All fetuses randomised						
Mazumder 2008	2	38	4	38	100.0%	0.50 [0.10 , 2.57]
Subtotal (95% CI)		**38**		**38**	**100.0%**	**0.50 [0.10 , 2.57]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
Total (95% CI)		**38**		**38**	**100.0%**	**0.50 [0.10 , 2.57]**
Total events:	2		4			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.83 (P = 0.41)						
Test for subgroup differences: Not applicable						

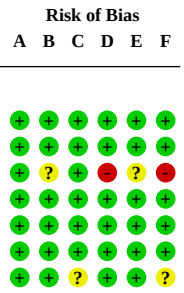


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.25. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 25: F10: Patent ductus arteriosus

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.25.1 All fetuses randomised						
Aghajafari 2002	2	9	1	7	0.6%	1.56 [0.17 , 13.87]
Crowther 2006	40	568	67	578	38.1%	0.61 [0.42 , 0.88]
Mazumder 2008	1	38	3	38	1.7%	0.33 [0.04 , 3.06]
Murphy 2008	44	1166	42	1143	24.3%	1.03 [0.68 , 1.55]
Peltoniemi 2007	41	160	44	168	24.6%	0.98 [0.68 , 1.41]
TEAMS 1999	0	94	4	94	2.6%	0.11 [0.01 , 2.04]
Wapner 2006	7	299	14	295	8.1%	0.49 [0.20 , 1.20]
Subtotal (95% CI)		**2334**		**2323**	**100.0%**	**0.78 [0.63 , 0.96]**
Total events:	135		175			
Heterogeneity: Chi² = 8.56, df = 6 (P = 0.20); I² = 30%						
Test for overall effect: Z = 2.31 (P = 0.02)						
Total (95% CI)		**2334**		**2323**	**100.0%**	**0.78 [0.63 , 0.96]**
Total events:	135		175			
Heterogeneity: Chi² = 8.56, df = 6 (P = 0.20); I² = 30%						
Test for overall effect: Z = 2.31 (P = 0.02)						
Test for subgroup differences: Not applicable						

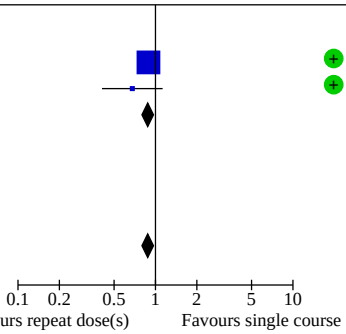


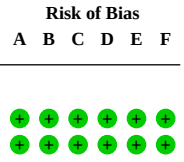


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.26. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 26: F11: Use of respiratory support

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.26.1 All fetuses randomised						
Murphy 2008	449	1166	495	1143	94.7%	0.89 [0.81 , 0.98]
TEAMS 1999	19	94	28	94	5.3%	0.68 [0.41 , 1.13]
Subtotal (95% CI)		**1260**		**1237**	**100.0%**	**0.88 [0.80 , 0.97]**
Total events:	468		523			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 2.64 (P = 0.008)						
Total (95% CI)		**1260**		**1237**	**100.0%**	**0.88 [0.80 , 0.97]**
Total events:	468		523			
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.30); I² = 5%						
Test for overall effect: Z = 2.64 (P = 0.008)						
Test for subgroup differences: Not applicable						

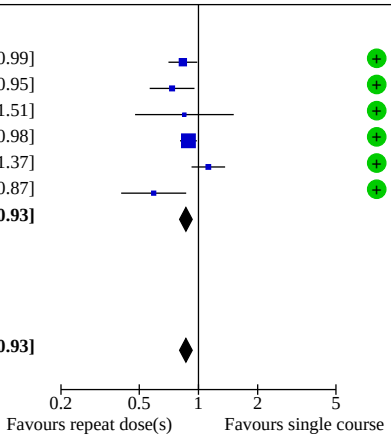




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.27. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 27: F12: Use of invasive respiratory support

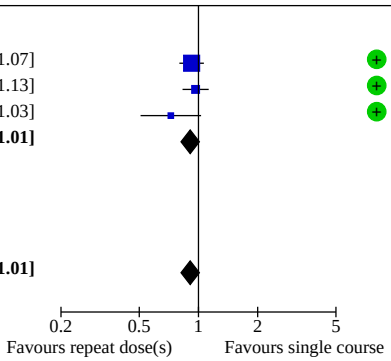
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.27.1 All fetuses randomised												
Crowther 2006	167	568	204	578	21.1%	0.83 [0.70 , 0.99]	+	+	+	+	+	+
Garite 2009	70	289	95	288	9.9%	0.73 [0.57 , 0.95]	+	+	+	+	+	+
McEvoy 2010	15	56	18	57	1.9%	0.85 [0.48 , 1.51]	+	+	+	+	+	+
Murphy 2008	449	1166	495	1143	52.1%	0.89 [0.81 , 0.98]	+	+	+	+	+	+
Peltoniemi 2007	93	160	87	168	8.8%	1.12 [0.92 , 1.37]	+	+	+	+	+	+
Wapner 2006	36	299	60	295	6.3%	0.59 [0.40 , 0.87]	+	+	?	+	+	?
Subtotal (95% CI)		**2538**		**2529**	**100.0%**	**0.86 [0.80 , 0.93]**						
Total events:	830		959									
Heterogeneity: Chi² = 12.63, df = 5 (P = 0.03); I² = 60%												
Test for overall effect: Z = 3.93 (P < 0.0001)												
Total (95% CI)		**2538**		**2529**	**100.0%**	**0.86 [0.80 , 0.93]**						
Total events:	830		959									
Heterogeneity: Chi² = 12.63, df = 5 (P = 0.03); I² = 60%												
Test for overall effect: Z = 3.93 (P < 0.0001)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.28. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 28: F13: Use of non-invasive respiratory support

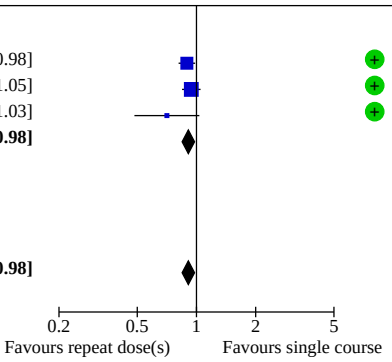
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A	B	C	D	E	F
1.28.1 All fetuses randomised												
Murphy 2008	274	1166	291	1143	63.1%	0.92 [0.80 , 1.07]	+	+	+	+	+	+
Peltoniemi 2007	105	160	114	168	23.9%	0.97 [0.83 , 1.13]	+	+	+	+	+	+
Wapner 2006	44	299	60	295	13.0%	0.72 [0.51 , 1.03]	+	+	?	+	+	?
Subtotal (95% CI)		**1625**		**1606**	**100.0%**	**0.91 [0.82 , 1.01]**						
Total events:	423		465									
Heterogeneity: Chi² = 2.29, df = 2 (P = 0.32); I² = 13%												
Test for overall effect: Z = 1.78 (P = 0.08)												
Total (95% CI)		**1625**		**1606**	**100.0%**	**0.91 [0.82 , 1.01]**						
Total events:	423		465									
Heterogeneity: Chi² = 2.29, df = 2 (P = 0.32); I² = 13%												
Test for overall effect: Z = 1.78 (P = 0.08)												
Test for subgroup differences: Not applicable												



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.29. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 29: F14: Use of oxygen supplementation

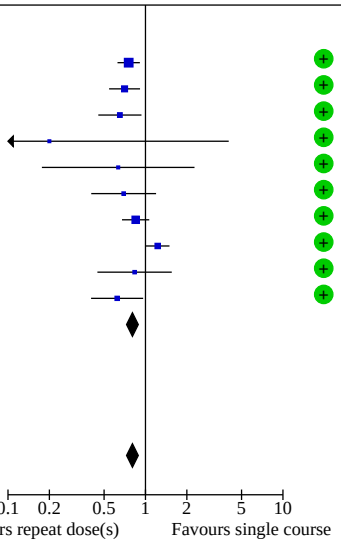
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.29.1 All fetuses randomised							
Crowther 2006	317	568	361	578	43.1%	0.89 [0.81 , 0.98]	+ + + + + +
Murphy 2008	410	1166	427	1143	52.0%	0.94 [0.84 , 1.05]	+ + + + + +
TEAMS 1999	29	94	41	94	4.9%	0.71 [0.48 , 1.03]	+ + + + + +
Subtotal (95% CI)		**1828**		**1815**	**100.0%**	**0.91 [0.85 , 0.98]**	
Total events:	756		829				
Heterogeneity: Chi² = 2.19, df = 2 (P = 0.33); I² = 9%							
Test for overall effect: Z = 2.58 (P = 0.01)							
Total (95% CI)		**1828**		**1815**	**100.0%**	**0.91 [0.85 , 0.98]**	
Total events:	756		829				
Heterogeneity: Chi² = 2.19, df = 2 (P = 0.33); I² = 9%							
Test for overall effect: Z = 2.58 (P = 0.01)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.30. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 30: F15: Use of surfactant

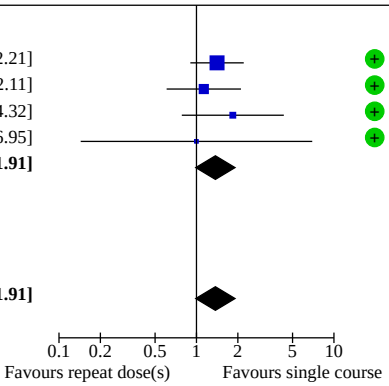
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.30.1 All fetuses randomised							
Crowther 2006	138	568	186	578	27.9%	0.75 [0.63 , 0.91]	+ + + + + +
Garite 2009	70	289	99	288	15.0%	0.70 [0.54 , 0.91]	+ + + + + +
Guinn 2001	40	256	59	246	9.1%	0.65 [0.45 , 0.93]	+ + + + + +
Mazumder 2008	0	38	2	38	0.4%	0.20 [0.01 , 4.03]	+ ? + + ? ?
McEvoy 2002	3	18	5	19	0.7%	0.63 [0.18 , 2.27]	+ + + + + +
McEvoy 2010	15	56	22	57	3.3%	0.69 [0.40 , 1.19]	+ + + + + +
Murphy 2008	122	1166	141	1143	21.6%	0.85 [0.68 , 1.07]	+ + + + + +
Peltoniemi 2007	97	160	83	168	12.3%	1.23 [1.01 , 1.50]	+ + + + + +
TEAMS 1999	15	94	18	94	2.7%	0.83 [0.45 , 1.55]	+ + + + + +
Wapner 2006	29	299	46	295	7.0%	0.62 [0.40 , 0.96]	+ + ? + + ?
Subtotal (95% CI)		**2944**		**2926**	**100.0%**	**0.80 [0.73 , 0.89]**	
Total events:	529		661				
Heterogeneity: Chi² = 23.14, df = 9 (P = 0.006); I² = 61%							
Test for overall effect: Z = 4.37 (P < 0.0001)							
Total (95% CI)		**2944**		**2926**	**100.0%**	**0.80 [0.73 , 0.89]**	
Total events:	529		661				
Heterogeneity: Chi² = 23.14, df = 9 (P = 0.006); I² = 61%							
Test for overall effect: Z = 4.37 (P < 0.0001)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.31. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 31: F17: Use of postnatal corticosteroids

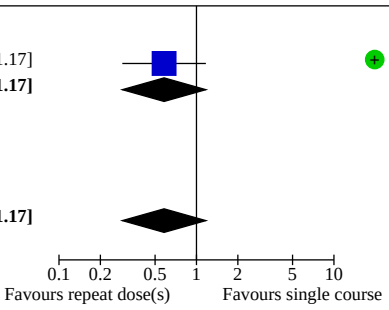
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.31.1 All fetuses randomised							
Crowther 2006	43	568	31	578	52.8%	1.41 [0.90 , 2.21]	+ + + + + +
Guinn 2001	20	256	17	246	29.8%	1.13 [0.61 , 2.11]	+ + + + + +
Murphy 2008	15	1166	8	1143	13.9%	1.84 [0.78 , 4.32]	+ + + + + +
TEAMS 1999	2	94	2	94	3.4%	1.00 [0.14 , 6.95]	+ + + + + +
Subtotal (95% CI)		**2084**		**2061**	**100.0%**	**1.37 [0.99 , 1.91]**	
Total events:	80		58				
Heterogeneity: Chi² = 0.94, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.89 (P = 0.06)							
Total (95% CI)		**2084**		**2061**	**100.0%**	**1.37 [0.99 , 1.91]**	
Total events:	80		58				
Heterogeneity: Chi² = 0.94, df = 3 (P = 0.82); I² = 0%							
Test for overall effect: Z = 1.89 (P = 0.06)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.32. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 32: F16: Use of nitric oxide for respiratory support

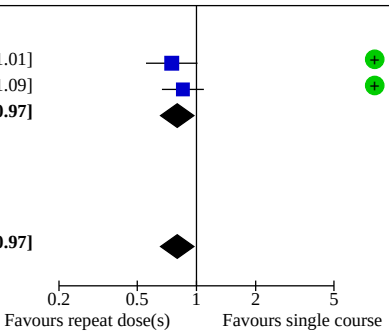
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
1.32.1 All fetuses randomised							
Crowther 2006	12	568	21	578	100.0%	0.58 [0.29 , 1.17]	+ + + + + +
Subtotal (95% CI)		**568**		**578**	**100.0%**	**0.58 [0.29 , 1.17]**	
Total events:	12		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
Total (95% CI)		**568**		**578**	**100.0%**	**0.58 [0.29 , 1.17]**	
Total events:	12		21				
Heterogeneity: Not applicable							
Test for overall effect: Z = 1.52 (P = 0.13)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.33. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 33: F20: Use of inotropic support

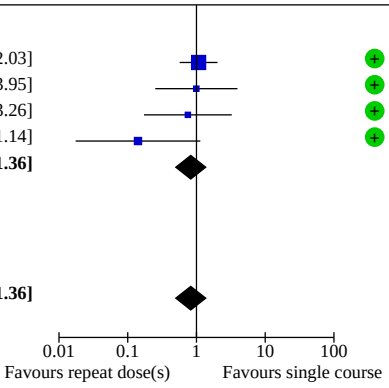
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.33.1 All fetuses randomised						
Crowther 2006	64	568	87	578	52.5%	0.75 [0.55 , 1.01]
Peltoniemi 2007	65	160	80	168	47.5%	0.85 [0.67 , 1.09]
Subtotal (95% CI)		**728**		**746**	**100.0%**	**0.80 [0.66 , 0.97]**
Total events:	129		167			
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.27 (P = 0.02)						
Total (95% CI)		**728**		**746**	**100.0%**	**0.80 [0.66 , 0.97]**
Total events:	129		167			
Heterogeneity: Chi² = 0.46, df = 1 (P = 0.50); I² = 0%						
Test for overall effect: Z = 2.27 (P = 0.02)						
Test for subgroup differences: Not applicable						

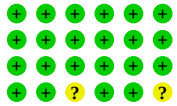


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.34. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 34: F18: Air leak syndrome

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.34.1 All fetuses randomised						
Crowther 2006	19	568	18	578	54.2%	1.07 [0.57 , 2.03]
Garite 2009	4	289	4	288	12.2%	1.00 [0.25 , 3.95]
TEAMS 1999	3	94	4	94	12.2%	0.75 [0.17 , 3.26]
Wapner 2006	1	299	7	295	21.4%	0.14 [0.02 , 1.14]
Subtotal (95% CI)		**1250**		**1255**	**100.0%**	**0.83 [0.50 , 1.36]**
Total events:	27		33			
Heterogeneity: Chi² = 3.50, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.75 (P = 0.45)						
Total (95% CI)		**1250**		**1255**	**100.0%**	**0.83 [0.50 , 1.36]**
Total events:	27		33			
Heterogeneity: Chi² = 3.50, df = 3 (P = 0.32); I² = 14%						
Test for overall effect: Z = 0.75 (P = 0.45)						
Test for subgroup differences: Not applicable						

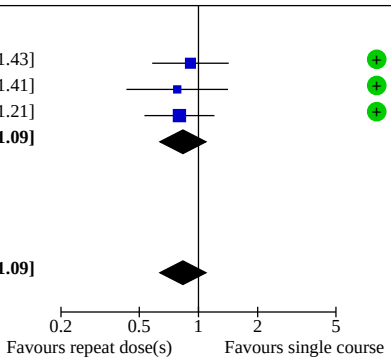


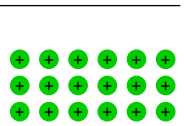


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.35. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 35: F21: Apgar score < 7 at 5 minutes

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
1.35.1 All fetuses randomised						
Crowther 2006	34	568	38	578	34.2%	0.91 [0.58 , 1.43]
Garite 2009	18	289	23	288	20.9%	0.78 [0.43 , 1.41]
Murphy 2008	40	1166	49	1143	44.9%	0.80 [0.53 , 1.21]
Subtotal (95% CI)		**2023**		**2009**	**100.0%**	**0.83 [0.64 , 1.09]**
Total events:	92		110			
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**2023**		**2009**	**100.0%**	**0.83 [0.64 , 1.09]**
Total events:	92		110			
Heterogeneity: Chi² = 0.24, df = 2 (P = 0.89); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Not applicable						

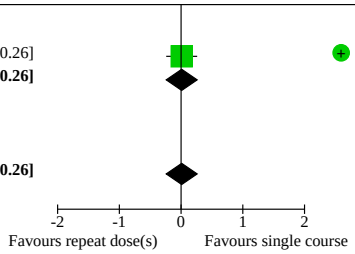




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.36. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 36: F22: Neonatal cardiac hypertrophy as measured by interventricular septal thickness (IVS in mm)

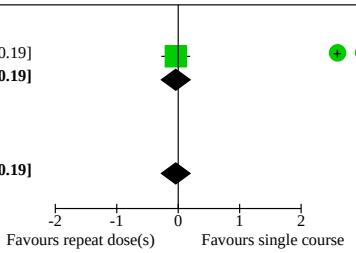
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.36.1 In all neonates								
Crowther 2006	2.95	0.86	85	2.94	0.83	90	100.0%	0.01 [-0.24 , 0.26]
Subtotal (95% CI)			**85**			**90**	**100.0%**	**0.01 [-0.24 , 0.26]**
Heterogeneity: Not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

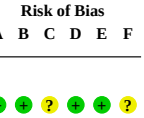


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.37. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 37: F22: Neonatal cardiac hypertrophy as measured by left ventricular wall thickness in diastole (mm)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.37.1 In all neonates								
Crowther 2006	3.02	0.86	85	3.06	0.71	90	100.0%	-0.04 [-0.27 , 0.19]
Subtotal (95% CI)			**85**			**90**	**100.0%**	**-0.04 [-0.27 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Total (95% CI)			**85**			**90**	**100.0%**	**-0.04 [-0.27 , 0.19]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.33 (P = 0.74)								
Test for subgroup differences: Not applicable								

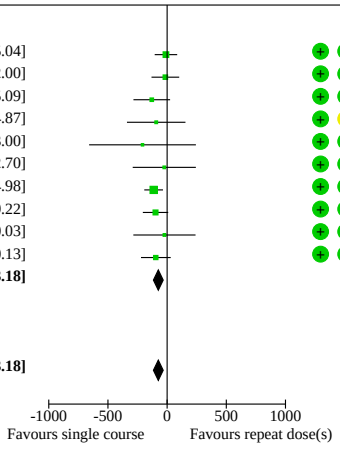


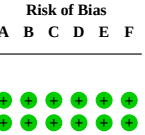


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.38. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 38: L1: Mean birthweight (g)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.38.1 In all neonates								
Crowther 2006	1867	824	567	1877	816	577	18.9%	-10.00 [-105.04 , 85.04]
Garite 2009	1905	738	275	1920	667	281	12.5%	-15.00 [-132.00 , 102.00]
Guinn 2001	2009.1	858.7	248	2138.8	875.8	235	7.1%	-129.70 [-284.49 , 25.09]
Mazumder 2008	1553.4	441.4	37	1645.6	627	37	2.8%	-92.20 [-339.27 , 154.87]
McEvoy 2002	1767	659	18	1975	740	19	0.8%	-208.00 [-659.00 , 243.00]
McEvoy 2010	1806	778	56	1830	657	56	2.4%	-24.00 [-290.70 , 242.70]
Murphy 2008	2216	966	1164	2330	969	1140	27.3%	-114.00 [-193.02 , -34.98]
Peltoniemi 2007	1460	500	159	1558	487	167	14.8%	-98.00 [-205.22 , 9.22]
TEAMS 1999	2078.2	882.7	91	2100.9	925.2	91	2.5%	-22.70 [-285.43 , 240.03]
Wapner 2006	2194.3	762.3	296	2289.6	791.8	294	10.8%	-95.30 [-220.73 , 30.13]
Subtotal (95% CI)			**2911**			**2897**	**100.0%**	**-74.49 [-115.80 , -33.18]**
Heterogeneity: Chi² = 5.14, df = 9 (P = 0.82); I² = 0%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
Total (95% CI)			**2911**			**2897**	**100.0%**	**-74.49 [-115.80 , -33.18]**
Heterogeneity: Chi² = 5.14, df = 9 (P = 0.82); I² = 0%								
Test for overall effect: Z = 3.53 (P = 0.0004)								
Test for subgroup differences: Not applicable								

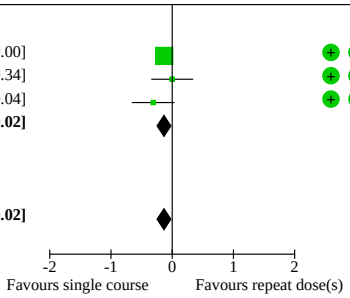




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.39. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 39: L1: Mean birthweight Z score

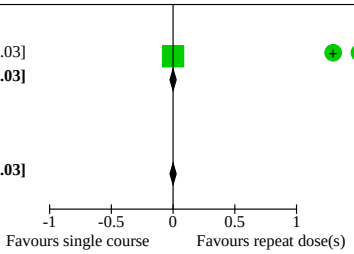
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.39.1 In all neonates									
Crowther 2006	-0.4	1.05	567	-0.27	1.14	577	78.7%	-0.13 [-0.26 , -0.00]	+ + + + + +
McEvoy 2010	-0.14	0.86	56	-0.14	0.98	56	10.9%	0.00 [-0.34 , 0.34]	+ + + + + +
TEAMS 1999	-0.38	1.05	91	-0.07	1.34	91	10.4%	-0.31 [-0.66 , 0.04]	+ + + + + +
Subtotal (95% CI)			**714**			**724**	**100.0%**	**-0.13 [-0.25 , -0.02]**	
Heterogeneity: Chi² = 1.57, df = 2 (P = 0.46); I² = 0%									
Test for overall effect: Z = 2.34 (P = 0.02)									
Total (95% CI)			**714**			**724**	**100.0%**	**-0.13 [-0.25 , -0.02]**	
Heterogeneity: Chi² = 1.57, df = 2 (P = 0.46); I² = 0%									
Test for overall effect: Z = 2.34 (P = 0.02)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.40. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 40: L1: Birthweight multiples of the median

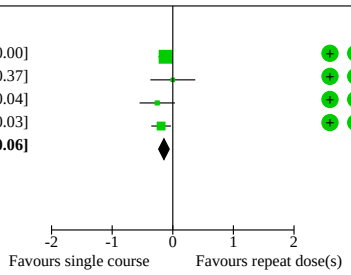
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.40.1 In all babies									
Wapner 2006	0.88	0.16	296	0.88	0.15	294	100.0%	0.00 [-0.03 , 0.03]	+ + + + + +
Subtotal (95% CI)			**296**			**294**	**100.0%**	**0.00 [-0.03 , 0.03]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
Total (95% CI)			**296**			**294**	**100.0%**	**0.00 [-0.03 , 0.03]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.41. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 41: L1: Birthweight adjusted for gestation (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.41.1 In all neonates										
Crowther 2006 (1)	-0.4	1.05	567	-0.27	1.14	577	56.5%	-0.12 [-0.23 , -0.00]		+ + + + + +
McEvoy 2010 (1)	-0.14	0.86	56	-0.14	0.98	56	5.5%	0.00 [-0.37 , 0.37]		+ + + + + +
TEAMS 1999 (1)	-0.38	1.05	91	-0.07	1.34	91	8.9%	-0.26 [-0.55 , 0.04]		+ + + + + +
Wapner 2006 (2)	0.88	0.16	296	0.91	0.15	294	29.0%	-0.19 [-0.35 , -0.03]		+ + + + + +
Subtotal (95% CI)			**1010**			**1018**	**100.0%**	**-0.15 [-0.23 , -0.06]**		
Heterogeneity: Chi² = 1.69, df = 3 (P = 0.64); I² = 0%										
Test for overall effect: Z = 3.28 (P = 0.001)										
Test for subgroup differences: Not applicable										

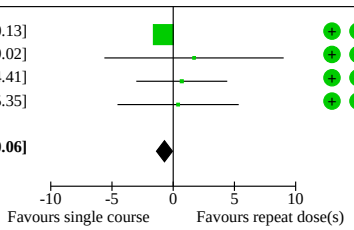


Footnotes
(1) Z score
(2) Multiples of the median

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.42. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 42: L2: Interval between trial entry and birth (days)

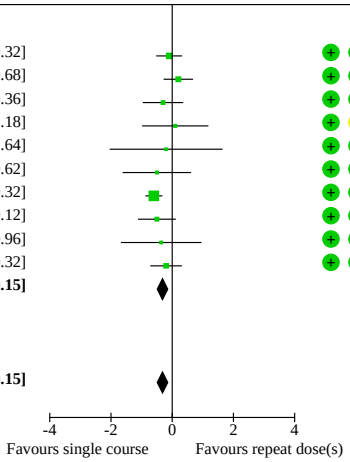
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Guinn 2001	5	3.7	248	5.8	3.8	235	94.4%	-0.80 [-1.47 , -0.13]		+ + + + + +
McEvoy 2010	16.3	18.6	44	14.6	15.8	41	0.8%	1.70 [-5.62 , 9.02]		+ + + + + +
Peltoniemi 2007	11.7	14.9	125	11	15	124	3.1%	0.70 [-3.01 , 4.41]		+ + + + + +
Wapner 2006	47.4	28.9	250	47	27.1	242	1.7%	0.40 [-4.55 , 5.35]		+ + + + + +
Total (95% CI)			**667**			**642**	**100.0%**	**-0.71 [-1.36 , -0.06]**		
Heterogeneity: Chi² = 1.23, df = 3 (P = 0.75); I² = 0%										
Test for overall effect: Z = 2.15 (P = 0.03)										
Test for subgroup differences: Not applicable										



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.43. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 43: L3: Mean head circumference at birth (cm)

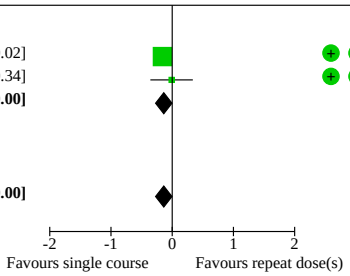
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.43.1 In all neonates									
Crowther 2006	29.6	3.7	567	29.7	3.6	577	16.4%	-0.10 [-0.52 , 0.32]	+ + + + + +
Garite 2009	30.2	3	289	30	2.9	288	12.7%	0.20 [-0.28 , 0.68]	+ + + + + +
Guinn 2001	29.1	4	248	29.4	3.4	235	6.7%	-0.30 [-0.96 , 0.36]	+ + + + + +
Mazumder 2008	29.7	2	37	29.6	2.7	37	2.5%	0.10 [-0.98 , 1.18]	+ ? + + ? ?
McEvoy 2002	29.4	3	18	29.6	2.7	19	0.9%	-0.20 [-2.04 , 1.64]	+ + + + + +
McEvoy 2010	28.7	3	53	29.2	2.9	54	2.3%	-0.50 [-1.62 , 0.62]	+ + + + + +
Murphy 2008	31.1	3.4	1164	31.7	3.4	1140	38.1%	-0.60 [-0.88 , -0.32]	+ + + + + +
Peltoniemi 2007	28.1	2.9	159	28.6	2.8	167	7.7%	-0.50 [-1.12 , 0.12]	+ + + + + +
TEAMS 1999	29	3.19	46	29.36	3.15	43	1.7%	-0.36 [-1.68 , 0.96]	+ + - + + -
Wapner 2006	30.6	3.1	296	30.8	3.3	294	11.0%	-0.20 [-0.72 , 0.32]	+ + + + + +
Subtotal (95% CI)			**2877**			**2854**	**100.0%**	**-0.32 [-0.49 , -0.15]**	
Heterogeneity: Chi² = 10.66, df = 9 (P = 0.30); I² = 16%									
Test for overall effect: Z = 3.63 (P = 0.0003)									
Total (95% CI)			**2877**			**2854**	**100.0%**	**-0.32 [-0.49 , -0.15]**	
Heterogeneity: Chi² = 10.66, df = 9 (P = 0.30); I² = 16%									
Test for overall effect: Z = 3.63 (P = 0.0003)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.44. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 44: L3: Mean head circumference Z score at birth

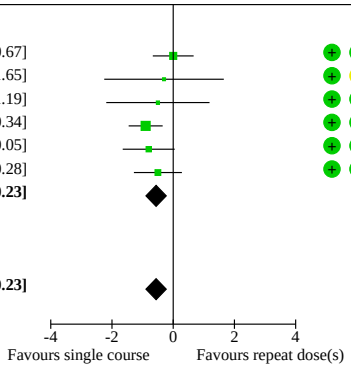
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.44.1 In all babies									
Crowther 2006	-0.3	1.22	567	-0.14	1.28	577	85.1%	-0.16 [-0.30 , -0.02]	+ + + + + +
McEvoy 2010	-0.19	0.9	53	-0.18	0.93	54	14.9%	-0.01 [-0.36 , 0.34]	+ + + + + +
Subtotal (95% CI)			**620**			**631**	**100.0%**	**-0.14 [-0.27 , -0.00]**	
Heterogeneity: Chi² = 0.61, df = 1 (P = 0.43); I² = 0%									
Test for overall effect: Z = 2.02 (P = 0.04)									
Total (95% CI)			**620**			**631**	**100.0%**	**-0.14 [-0.27 , -0.00]**	
Heterogeneity: Chi² = 0.61, df = 1 (P = 0.43); I² = 0%									
Test for overall effect: Z = 2.02 (P = 0.04)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.45. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 45: L4: Mean length at birth (cm)

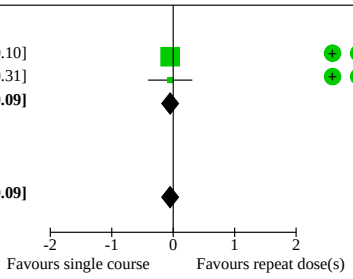
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.45.1 In all neonates									
Crowther 2006	42.1	5.9	567	42.1	5.6	577	24.7%	0.00 [-0.67 , 0.67]	+ + + + + +
Mazumder 2008	41.2	3.7	37	41.5	4.8	37	2.9%	-0.30 [-2.25 , 1.65]	+ ? + + ? ?
McEvoy 2010	41.9	4.7	56	42.4	4.4	56	3.9%	-0.50 [-2.19 , 1.19]	+ + + + + +
Murphy 2008	44.5	6.8	1164	45.4	6.8	1140	35.6%	-0.90 [-1.46 , -0.34]	+ + + + + +
Peltoniemi 2007	39.4	4.1	159	40.2	3.7	167	15.2%	-0.80 [-1.65 , 0.05]	+ + + + + +
Wapner 2006	44.2	4.6	296	44.7	5.1	294	17.8%	-0.50 [-1.28 , 0.28]	+ + + + + +
Subtotal (95% CI)			**2279**			**2271**	**100.0%**	**-0.56 [-0.89 , -0.23]**	
Heterogeneity: Chi² = 4.55, df = 5 (P = 0.47); I² = 0%									
Test for overall effect: Z = 3.31 (P = 0.0009)									
Total (95% CI)			**2279**			**2271**	**100.0%**	**-0.56 [-0.89 , -0.23]**	
Heterogeneity: Chi² = 4.55, df = 5 (P = 0.47); I² = 0%									
Test for overall effect: Z = 3.31 (P = 0.0009)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.46. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 46: L4: Mean length Z score at birth

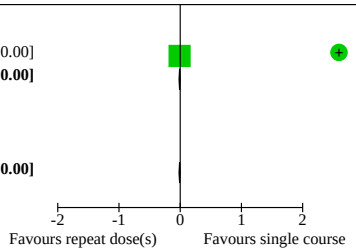
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.46.1 In all neonates									
Crowther 2006	-0.53	1.31	567	-0.48	1.22	577	85.8%	-0.05 [-0.20 , 0.10]	+ + + + + +
McEvoy 2010	-0.11	0.99	56	-0.06	0.96	56	14.2%	-0.05 [-0.41 , 0.31]	+ + + + + +
Subtotal (95% CI)			**623**			**633**	**100.0%**	**-0.05 [-0.19 , 0.09]**	
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%									
Test for overall effect: Z = 0.72 (P = 0.47)									
Total (95% CI)			**623**			**633**	**100.0%**	**-0.05 [-0.19 , 0.09]**	
Heterogeneity: Chi² = 0.00, df = 1 (P = 1.00); I² = 0%									
Test for overall effect: Z = 0.72 (P = 0.47)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.47. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 47: L4: Length multiples of the mean at birth

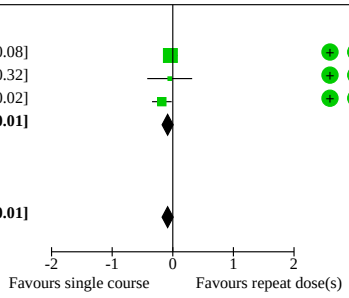
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.47.1 In all neonates									
Wapner 2006	0.98	0.06	296	0.99	0.05	294	100.0%	-0.01 [-0.02 , -0.00]	+ + + + + +
Subtotal (95% CI)			**296**			**294**	**100.0%**	**-0.01 [-0.02 , -0.00]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.20 (P = 0.03)									
Total (95% CI)			**296**			**294**	**100.0%**	**-0.01 [-0.02 , -0.00]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 2.20 (P = 0.03)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.48. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 48: L4: Length at birth adjusted for gestation (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.48.1 In all neonates									
Crowther 2006 (1)	-0.53	1.31	567	-0.48	1.22	577	62.0%	-0.04 [-0.16 , 0.08]	+ + + + + +
McEvoy 2010 (1)	-0.11	0.99	56	-0.06	0.96	56	6.1%	-0.05 [-0.42 , 0.32]	+ + + + + +
Wapner 2006 (2)	0.98	0.06	296	0.99	0.05	294	31.9%	-0.18 [-0.34 , -0.02]	+ + + + + +
Subtotal (95% CI)			**919**			**927**	**100.0%**	**-0.09 [-0.18 , 0.01]**	
Heterogeneity: Chi² = 1.97, df = 2 (P = 0.37); I² = 0%									
Test for overall effect: Z = 1.83 (P = 0.07)									
Total (95% CI)			**919**			**927**	**100.0%**	**-0.09 [-0.18 , 0.01]**	
Heterogeneity: Chi² = 1.97, df = 2 (P = 0.37); I² = 0%									
Test for overall effect: Z = 1.83 (P = 0.07)									
Test for subgroup differences: Not applicable									

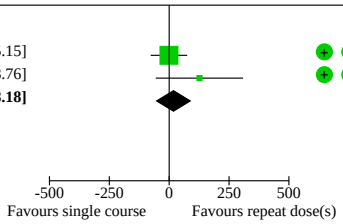


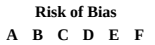
Footnotes
(1) Z score
(2) Multiples of the mean

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.49. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 49: L5i: Mean weight (g) at primary hospital discharge

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.49.1 In all infants								
Crowther 2006	2692	726	541	2693	542	549	85.2%	-1.00 [-77.15 , 75.15]
McEvoy 2010	2508.7	503.8	50	2382.3	443.8	55	14.8%	126.40 [-55.96 , 308.76]
Subtotal (95% CI)			**591**			**604**	**100.0%**	**17.91 [-52.35 , 88.18]**
Heterogeneity: Chi² = 1.60, df = 1 (P = 0.21); I² = 37%								
Test for overall effect: Z = 0.50 (P = 0.62)								
Test for subgroup differences: Not applicable								

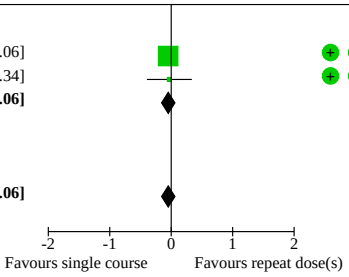


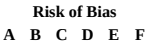


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.50. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 50: L5i: Mean weight Z score at primary hospital discharge

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.50.1 In all infants								
Crowther 2006	-1.07	0.98	541	-1.02	0.93	549	91.2%	-0.05 [-0.16 , 0.06]
McEvoy 2010	-0.8	0.88	50	-0.77	1.03	55	8.8%	-0.03 [-0.40 , 0.34]
Subtotal (95% CI)			**591**			**604**	**100.0%**	**-0.05 [-0.16 , 0.06]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Total (95% CI)			**591**			**604**	**100.0%**	**-0.05 [-0.16 , 0.06]**
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.92); I² = 0%								
Test for overall effect: Z = 0.87 (P = 0.38)								
Test for subgroup differences: Not applicable								

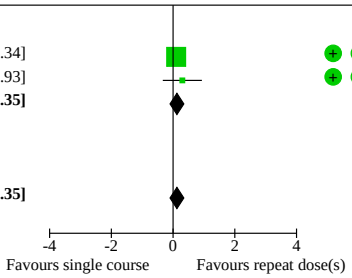


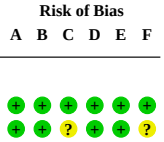


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.51. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 51: L5ii: Mean head circumference (cm) at primary hospital discharge

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.51.1 In all infants								
Crowther 2006	33.7	2.1	541	33.6	1.9	549	87.6%	0.10 [-0.14 , 0.34]
McEvoy 2010	32.6	1.7	50	32.3	1.6	55	12.4%	0.30 [-0.33 , 0.93]
Subtotal (95% CI)			**591**			**604**	**100.0%**	**0.12 [-0.10 , 0.35]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Total (95% CI)			**591**			**604**	**100.0%**	**0.12 [-0.10 , 0.35]**
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%								
Test for overall effect: Z = 1.10 (P = 0.27)								
Test for subgroup differences: Not applicable								

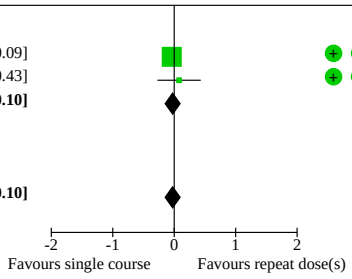




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.52. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 52: L5ii: Mean head circumference Z score at primary hospital discharge

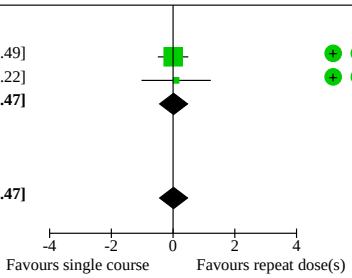
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
1.52.1 In all infants								
Crowther 2006	-0.19	1.12	541	-0.15	1.06	549	88.1%	-0.04 [-0.17 , 0.09]
McEvoy 2010	-0.26	0.9	50	-0.34	0.94	55	11.9%	0.08 [-0.27 , 0.43]
Subtotal (95% CI)			**591**			**604**	**100.0%**	**-0.03 [-0.15 , 0.10]**
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%								
Test for overall effect: Z = 0.41 (P = 0.68)								
Total (95% CI)			**591**			**604**	**100.0%**	**-0.03 [-0.15 , 0.10]**
Heterogeneity: Chi² = 0.39, df = 1 (P = 0.53); I² = 0%								
Test for overall effect: Z = 0.41 (P = 0.68)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.53. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 53: L5iii: Mean length (cm) at primary hospital discharge

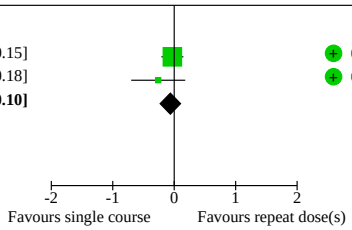
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.53.1 In all infants									
Crowther 2006	47.4	4.3	541	47.4	4	549	83.8%	0.00 [-0.49 , 0.49]	+ + + + + +
McEvoy 2010	46.5	2.9	49	46.4	2.8	50	16.2%	0.10 [-1.02 , 1.22]	+ + ? + + ?
Subtotal (95% CI)			**590**			**599**	**100.0%**	**0.02 [-0.44 , 0.47]**	
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%									
Test for overall effect: Z = 0.07 (P = 0.94)									
Total (95% CI)			**590**			**599**	**100.0%**	**0.02 [-0.44 , 0.47]**	
Heterogeneity: Chi² = 0.03, df = 1 (P = 0.87); I² = 0%									
Test for overall effect: Z = 0.07 (P = 0.94)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.54. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 54: L5iii: Mean length Z score at primary hospital discharge

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
1.54.1 In all infants									
Crowther 2006	-1.11	1.47	541	-1.08	1.55	549	85.7%	-0.03 [-0.21 , 0.15]	+ + + + + +
McEvoy 2010	-0.63	1.14	49	-0.37	1.09	50	14.3%	-0.26 [-0.70 , 0.18]	+ + ? + + ?
Subtotal (95% CI)			**590**			**599**	**100.0%**	**-0.06 [-0.23 , 0.10]**	
Heterogeneity: Chi² = 0.90, df = 1 (P = 0.34); I² = 0%									
Test for overall effect: Z = 0.74 (P = 0.46)									
Test for subgroup differences: Not applicable									

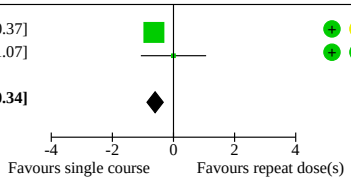


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.55. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 55: L6i: Mean weight at infant follow-up (kg)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mazumder 2008	6.66928	0.6413	37	7.3104	0.562	37	93.8%	-0.64 [-0.92 , -0.37]	+ ? ? + ? -
McEvoy 2010	10.6	2.3	40	10.6	2.4	35	6.2%	0.00 [-1.07 , 1.07]	+ + - + + -
Total (95% CI)			**77**			**72**	**100.0%**	**-0.60 [-0.87 , -0.34]**	

Heterogeneity: Chi² = 1.30, df = 1 (P = 0.25); I² = 23%
Test for overall effect: Z = 4.43 (P < 0.00001)
Test for subgroup differences: Not applicable

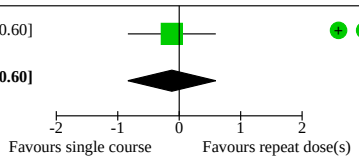


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.56. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 56: L6i: Mean weight Z score at infant follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
McEvoy 2010	-0.02	1.72	40	0.1	1.44	35	100.0%	-0.12 [-0.84 , 0.60]	+ + - + + -
Total (95% CI)			**40**			**35**	**100.0%**	**-0.12 [-0.84 , 0.60]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.33 (P = 0.74)
Test for subgroup differences: Not applicable

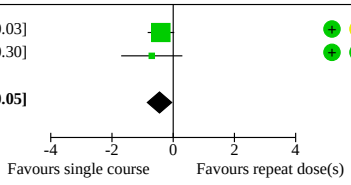


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.57. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 57: L6ii: Mean head circumference at infant follow-up (cm)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mazumder 2008	42.8	0.9	37	43.2	1	37	84.2%	-0.40 [-0.83 , 0.03]	+ ? ? + ? -
McEvoy 2010	46.1	2.1	30	46.8	1.9	32	15.8%	-0.70 [-1.70 , 0.30]	+ + - + + -
Total (95% CI)			**67**			**69**	**100.0%**	**-0.45 [-0.85 , -0.05]**	

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 2.21 (P = 0.03)
Test for subgroup differences: Not applicable

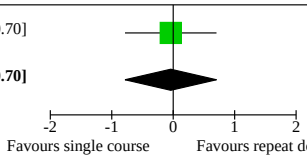


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.58. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 58: L6ii: Mean head circumference Z score at infant follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
McEvoy 2010	0.18	1.47	30	0.22	1.52	32	100.0%	-0.04 [-0.78 , 0.70]	+ + - + + -
Total (95% CI)			**30**			**32**	**100.0%**	**-0.04 [-0.78 , 0.70]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.11 (P = 0.92)
Test for subgroup differences: Not applicable

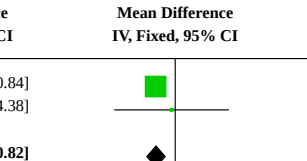


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.59. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 59: L6iii: Mean length at infant follow-up (cm)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Mazumder 2008	64.8	1.9	37	66.4	1.4	37	97.4%	-1.60 [-2.36 , -0.84]	+ ? ? + ? -
McEvoy 2010	77.6	11.1	40	77.9	9.6	35	2.6%	-0.30 [-4.98 , 4.38]	+ + - + + -
Total (95% CI)			**77**			**72**	**100.0%**	**-1.57 [-2.32 , -0.82]**	

Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%
Test for overall effect: Z = 4.09 (P < 0.0001)
Test for subgroup differences: Not applicable

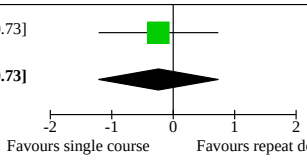


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.60. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 60: L6iii: Mean length Z score at infant follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
McEvoy 2010	-0.64	2.49	40	-0.4	1.79	35	100.0%	-0.24 [-1.21 , 0.73]	+ + - + + -
Total (95% CI)			**40**			**35**	**100.0%**	**-0.24 [-1.21 , 0.73]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.48 (P = 0.63)
Test for subgroup differences: Not applicable

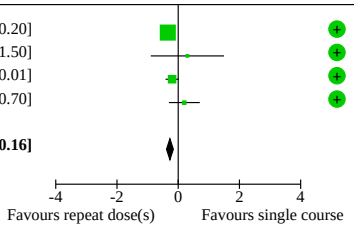


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.61. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 61: L8: Mean duration of invasive respiratory support (days)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Crowther 2006	0.33	0.74	567	0.67	1.48	577	67.4%	-0.34 [-0.48 , -0.20]
McEvoy 2002	0.8	2.4	18	0.5	1	19	0.9%	0.30 [-0.90 , 1.50]
McEvoy 2010	0.13	0.3	56	0.33	0.76	56	26.9%	-0.20 [-0.41 , 0.01]
Peltoniemi 2007	1.28	2.4	159	1.08	2.24	168	4.9%	0.20 [-0.30 , 0.70]
Total (95% CI)			**800**			**820**	**100.0%**	**-0.27 [-0.38 , -0.16]**

Heterogeneity: Chi² = 5.65, df = 3 (P = 0.13); I² = 47%
Test for overall effect: Z = 4.78 (P < 0.00001)
Test for subgroup differences: Not applicable



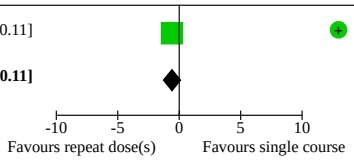
Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.62. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 62: L9: Mean duration of non-invasive respiratory support (days)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Peltoniemi 2007	1.58	2	159	2.17	4.11	167	100.0%	-0.59 [-1.29 , 0.11]
Total (95% CI)			**159**			**167**	**100.0%**	**-0.59 [-1.29 , 0.11]**

Heterogeneity: Not applicable
Test for overall effect: Z = 1.66 (P = 0.10)
Test for subgroup differences: Not applicable



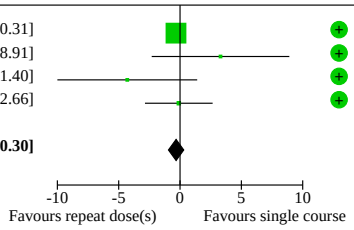
Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.63. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 63: L10: Mean duration of oxygen supplementation (days)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
Crowther 2006	2.67	5.19	567	3	5.92	577	92.5%	-0.33 [-0.97 , 0.31]
McEvoy 2002	4	12	18	0.7	1.9	19	1.2%	3.30 [-2.31 , 8.91]
McEvoy 2010	4.6	10.6	56	8.9	19	56	1.2%	-4.30 [-10.00 , 1.40]
Peltoniemi 2007	6.2	12.3	159	6.3	13.1	167	5.1%	-0.10 [-2.86 , 2.66]
Total (95% CI)			**800**			**819**	**100.0%**	**-0.32 [-0.94 , 0.30]**

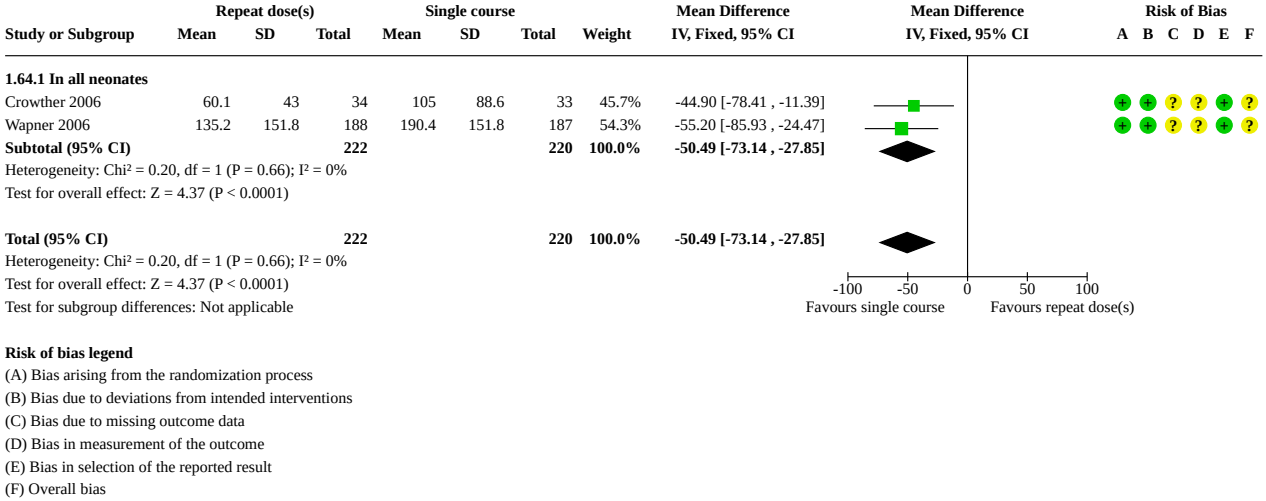
Heterogeneity: Chi² = 3.50, df = 3 (P = 0.32); I² = 14%
Test for overall effect: Z = 1.01 (P = 0.31)
Test for subgroup differences: Not applicable



Risk of Bias: A B C D E F

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 1.64. Comparison 1: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the fetus/neonate/infant, Outcome 64: L14: Mean cord cortisol concentrations at birth (nmol/L)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

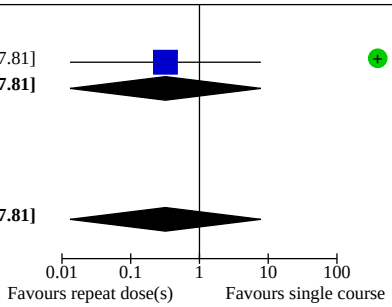
Comparison 2. Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.1 B1: Maternal death	1	437	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.81]
2.1.1 All women	1	437	Risk Ratio (M-H, Fixed, 95% CI)	0.32 [0.01, 7.81]
2.2 B2: Maternal sepsis	8	4666	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.39]
2.2.1 In all women	8	4666	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.39]
2.3 B3: Caesarean section	8	4266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
2.3.1 In all women	8	4266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
2.4 B4: Discontinuation of therapy due to maternal adverse effects	1	502	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.4.1 In all women	1	502	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
2.5 G1: Puerperal sepsis	6	3246	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.78, 1.43]
2.5.1 In all women	6	3246	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.78, 1.43]
2.6 G2: Chorioamnionitis during labour	7	4417	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.42]
2.6.1 In all women	7	4417	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.42]
2.7 G3: Endometritis	4	2842	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.74, 1.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
2.7.1 In all women	4	2842	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.74, 1.84]
2.8 G4: Pyrexia after trial entry requiring the use of antibiotics	1	156	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.25]
2.8.1 In all women	1	156	Risk Ratio (M-H, Fixed, 95% CI)	0.56 [0.25, 1.25]
2.9 G6: Postpartum haemorrhage	2	641	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.31, 0.96]
2.9.1 In all women	2	641	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.31, 0.96]
2.10 G7: Postnatal pyrexia	1	982	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.55, 1.38]
2.10.1 In all women	1	982	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.55, 1.38]
2.11 G8: Prelabour rupture of membranes after trial entry	2	977	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.29]
2.11.1 In all women	2	977	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.65, 1.29]
2.12 G9: Mode of birth: vaginal birth	6	4025	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.87, 1.00]
2.12.1 In all women	6	4025	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.87, 1.00]
2.13 G10: Hypertension	3	3327	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.32]
2.13.1 In all women	3	3327	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [0.87, 1.32]
2.14 G12: Glucose intolerance	2	2345	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.67]
2.14.1 In all women	2	2345	Risk Ratio (M-H, Fixed, 95% CI)	1.23 [0.90, 1.67]
2.15 G13: Postnatal depression	1	1671	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.70, 1.10]
2.16 G14: Local injection site adverse effects	2	1477	Risk Ratio (M-H, Fixed, 95% CI)	0.44 [0.32, 0.60]
2.17 G15: Insomnia after treatment	4	3198	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.04, 1.40]
2.17.1 In all women	4	3198	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [1.04, 1.40]
2.18 G16: Gastrointestinal adverse effects of treatment	1	495	Risk Ratio (M-H, Fixed, 95% CI)	0.34 [0.14, 0.85]

Analysis 2.1. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 1: B1: Maternal death

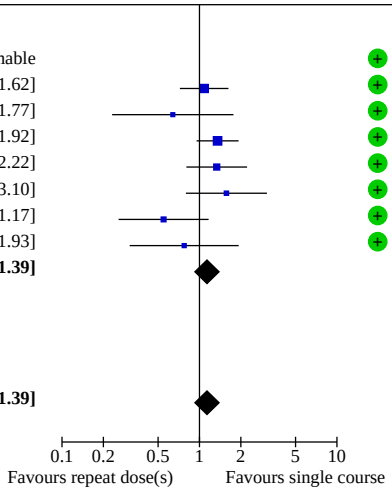
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.1.1 All women						
Garite 2009	0	223	1	214	100.0%	0.32 [0.01 , 7.81]
Subtotal (95% CI)		**223**		**214**	**100.0%**	**0.32 [0.01 , 7.81]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Total (95% CI)		**223**		**214**	**100.0%**	**0.32 [0.01 , 7.81]**
Total events:	0		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.48)						
Test for subgroup differences: Not applicable						

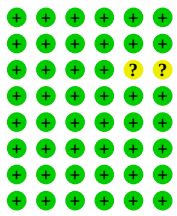


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.2. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 2: B2: Maternal sepsis

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.2.1 In all women						
Aghajafari 2002	0	6	0	6		Not estimable
Crowther 2006	44	489	41	493	26.0%	1.08 [0.72 , 1.62]
Garite 2009	6	223	9	214	5.9%	0.64 [0.23 , 1.77]
Guinn 2001	60	249	42	236	27.5%	1.35 [0.95 , 1.92]
Murphy 2008	34	935	25	918	16.1%	1.34 [0.80 , 2.22]
Peltoniemi 2007	19	125	12	124	7.7%	1.57 [0.80 , 3.10]
TEAMS 1999	9	79	16	77	10.3%	0.55 [0.26 , 1.17]
Wapner 2006	8	250	10	242	6.5%	0.77 [0.31 , 1.93]
Subtotal (95% CI)		**2356**		**2310**	**100.0%**	**1.13 [0.93 , 1.39]**
Total events:	180		155			
Heterogeneity: Chi² = 7.77, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Total (95% CI)		**2356**		**2310**	**100.0%**	**1.13 [0.93 , 1.39]**
Total events:	180		155			
Heterogeneity: Chi² = 7.77, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Not applicable						

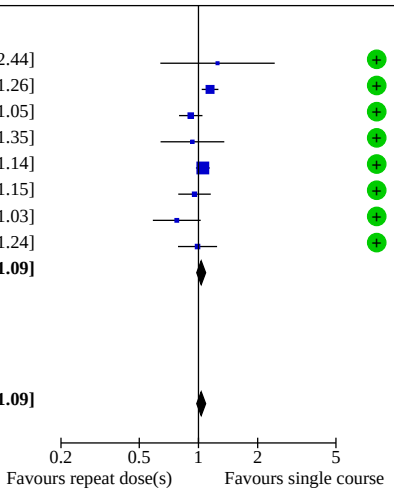




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.3. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 3: B3: Caesarean section

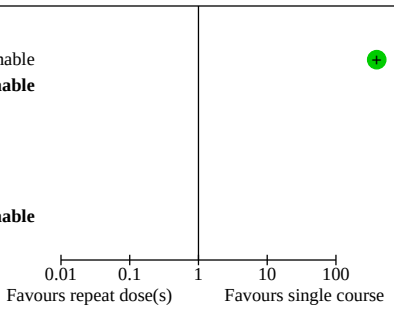
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.3.1 In all women							
Aghajafari 2002	5	6	4	6	0.3%	1.25 [0.64 , 2.44]	+ + + + + +
Crowther 2006	326	489	287	493	24.0%	1.15 [1.04 , 1.26]	+ + + + + +
Garite 2009	139	223	146	214	12.5%	0.91 [0.80 , 1.05]	+ + + + + +
McEvoy 2010	24	44	24	41	2.1%	0.93 [0.64 , 1.35]	+ + + + + +
Murphy 2008	537	935	501	918	42.4%	1.05 [0.97 , 1.14]	+ + + + + +
Peltoniemi 2007	77	125	80	124	6.7%	0.95 [0.79 , 1.15]	+ + + + + +
TEAMS 1999	39	79	49	77	4.2%	0.78 [0.59 , 1.03]	+ + + + + +
Wapner 2006	93	250	91	242	7.8%	0.99 [0.79 , 1.24]	+ + + + + +
Subtotal (95% CI)		**2151**		**2115**	**100.0%**	**1.03 [0.98 , 1.09]**	
Total events:	1240		1182				
Heterogeneity: Chi² = 13.00, df = 7 (P = 0.07); I² = 46%							
Test for overall effect: Z = 1.21 (P = 0.23)							
Total (95% CI)		**2151**		**2115**	**100.0%**	**1.03 [0.98 , 1.09]**	
Total events:	1240		1182				
Heterogeneity: Chi² = 13.00, df = 7 (P = 0.07); I² = 46%							
Test for overall effect: Z = 1.21 (P = 0.23)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.4. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 4: B4: Discontinuation of therapy due to maternal adverse effects

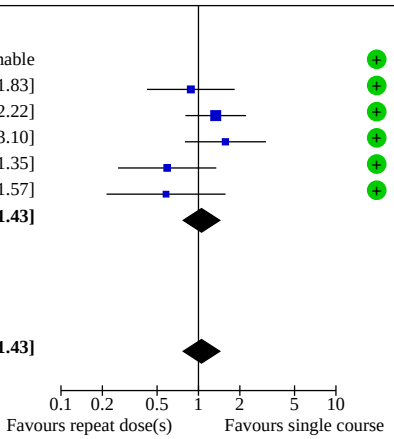
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.4.1 In all women							
Guinn 2001	0	256	0	246		Not estimable	+ + + + + +
Subtotal (95% CI)		**256**		**246**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**256**		**246**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.5. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 5: G1: Puerperal sepsis

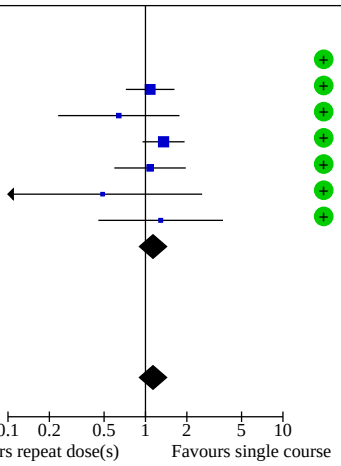
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.5.1 In all women							
Aghajafari 2002	0	6	0	6		Not estimable	+ + + + + +
Guinn 2001	13	249	14	236	19.1%	0.88 [0.42 , 1.83]	+ + + + + +
Murphy 2008	34	935	25	918	33.6%	1.34 [0.80 , 2.22]	+ + + + + +
Peltoniemi 2007	19	125	12	124	16.0%	1.57 [0.80 , 3.10]	+ + + + + +
TEAMS 1999	8	79	13	76	17.7%	0.59 [0.26 , 1.35]	+ + + + + +
Wapner 2006	6	250	10	242	13.5%	0.58 [0.21 , 1.57]	+ + + + + +
Subtotal (95% CI)		**1644**		**1602**	**100.0%**	**1.05 [0.78 , 1.43]**	
Total events:	80		74				
Heterogeneity: Chi² = 5.65, df = 4 (P = 0.23); I² = 29%							
Test for overall effect: Z = 0.33 (P = 0.74)							
Total (95% CI)		**1644**		**1602**	**100.0%**	**1.05 [0.78 , 1.43]**	
Total events:	80		74				
Heterogeneity: Chi² = 5.65, df = 4 (P = 0.23); I² = 29%							
Test for overall effect: Z = 0.33 (P = 0.74)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.6. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 6: G2: Chorioamnionitis during labour

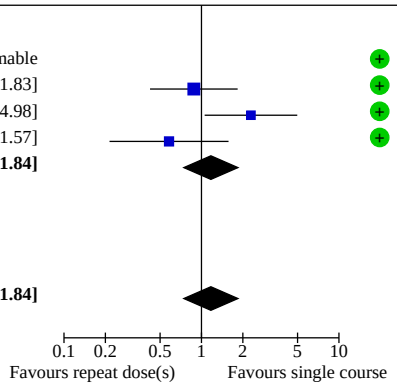
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.6.1 In all women							
Aghajafari 2002	0	6	0	6		Not estimable	+ + + + + +
Crowther 2006	44	489	41	493	33.1%	1.08 [0.72 , 1.62]	+ + + + + +
Garite 2009	6	223	9	214	7.4%	0.64 [0.23 , 1.77]	+ + + + + +
Guinn 2001	60	249	42	236	34.9%	1.35 [0.95 , 1.92]	+ + + + + +
Murphy 2008	22	935	20	918	16.3%	1.08 [0.59 , 1.97]	+ + + + + +
TEAMS 1999	2	79	4	77	3.3%	0.49 [0.09 , 2.58]	+ + + + + +
Wapner 2006	8	250	6	242	4.9%	1.29 [0.45 , 3.66]	+ + + + + +
Subtotal (95% CI)		**2231**		**2186**	**100.0%**	**1.13 [0.90 , 1.42]**	
Total events:	142		122				
Heterogeneity: Chi² = 3.31, df = 5 (P = 0.65); I² = 0%							
Test for overall effect: Z = 1.09 (P = 0.28)							
Total (95% CI)		**2231**		**2186**	**100.0%**	**1.13 [0.90 , 1.42]**	
Total events:	142		122				
Heterogeneity: Chi² = 3.31, df = 5 (P = 0.65); I² = 0%							
Test for overall effect: Z = 1.09 (P = 0.28)							
Test for subgroup differences: Not applicable							

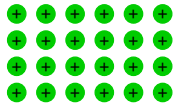


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.7. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 7: G3: Endometritis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.7.1 In all women						
Aghajafari 2002	0	6	0	6		Not estimable
Guinn 2001	13	249	14	236	42.8%	0.88 [0.42 , 1.83]
Murphy 2008	21	935	9	918	27.0%	2.29 [1.05 , 4.98]
Wapner 2006	6	250	10	242	30.2%	0.58 [0.21 , 1.57]
Subtotal (95% CI)		**1440**		**1402**	**100.0%**	**1.17 [0.74 , 1.84]**
Total events:	40		33			
Heterogeneity: Chi² = 5.36, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Total (95% CI)		**1440**		**1402**	**100.0%**	**1.17 [0.74 , 1.84]**
Total events:	40		33			
Heterogeneity: Chi² = 5.36, df = 2 (P = 0.07); I² = 63%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Not applicable						

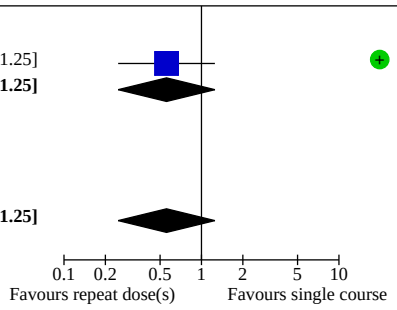




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.8. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 8: G4: Pyrexia after trial entry requiring the use of antibiotics

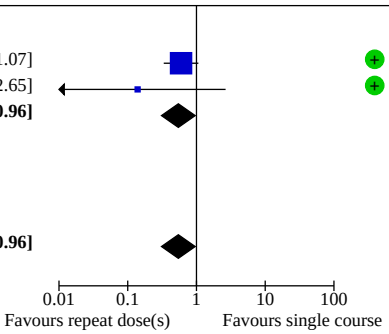
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.8.1 In all women						
TEAMS 1999	8	79	14	77	100.0%	0.56 [0.25 , 1.25]
Subtotal (95% CI)		**79**		**77**	**100.0%**	**0.56 [0.25 , 1.25]**
Total events:	8		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
Total (95% CI)		**79**		**77**	**100.0%**	**0.56 [0.25 , 1.25]**
Total events:	8		14			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.42 (P = 0.16)						
Test for subgroup differences: Not applicable						

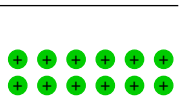


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.9. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 9: G6: Postpartum haemorrhage

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.9.1 In all women						
Guinn 2001	17	249	27	236	88.7%	0.60 [0.33 , 1.07]
TEAMS 1999	0	79	3	77	11.3%	0.14 [0.01 , 2.65]
Subtotal (95% CI)		**328**		**313**	**100.0%**	**0.54 [0.31 , 0.96]**
Total events:	17		30			
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 2.11 (P = 0.03)						
Total (95% CI)		**328**		**313**	**100.0%**	**0.54 [0.31 , 0.96]**
Total events:	17		30			
Heterogeneity: Chi² = 0.92, df = 1 (P = 0.34); I² = 0%						
Test for overall effect: Z = 2.11 (P = 0.03)						
Test for subgroup differences: Not applicable						

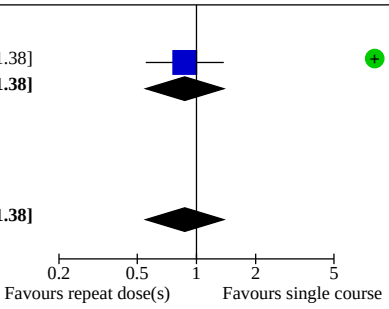




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.10. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 10: G7: Postnatal pyrexia

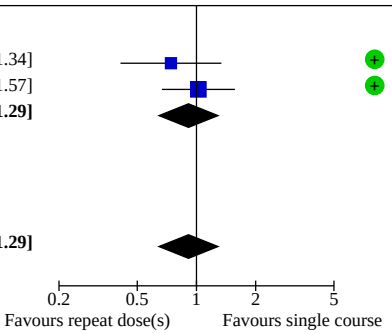
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.10.1 In all women						
Crowther 2006	32	489	37	493	100.0%	0.87 [0.55 , 1.38]
Subtotal (95% CI)		**489**		**493**	**100.0%**	**0.87 [0.55 , 1.38]**
Total events:	32		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Total (95% CI)		**489**		**493**	**100.0%**	**0.87 [0.55 , 1.38]**
Total events:	32		37			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.59 (P = 0.56)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.11. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 11: G8: Prelabour rupture of membranes after trial entry

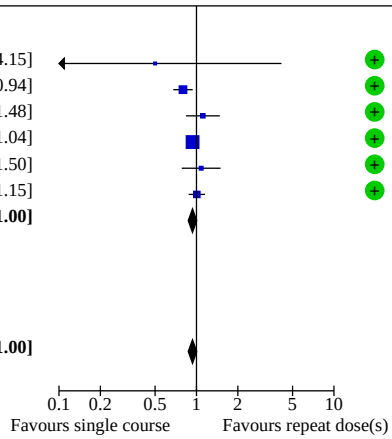
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.11.1 In all women							
Guinn 2001	18	249	23	236	39.9%	0.74 [0.41 , 1.34]	+ + + + + +
Wapner 2006	37	250	35	242	60.1%	1.02 [0.67 , 1.57]	+ + + + + +
Subtotal (95% CI)		**499**		**478**	**100.0%**	**0.91 [0.65 , 1.29]**	
Total events:	55		58				
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Total (95% CI)		**499**		**478**	**100.0%**	**0.91 [0.65 , 1.29]**	
Total events:	55		58				
Heterogeneity: Chi² = 0.75, df = 1 (P = 0.39); I² = 0%							
Test for overall effect: Z = 0.53 (P = 0.60)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.12. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 12: G9: Mode of birth: vaginal birth

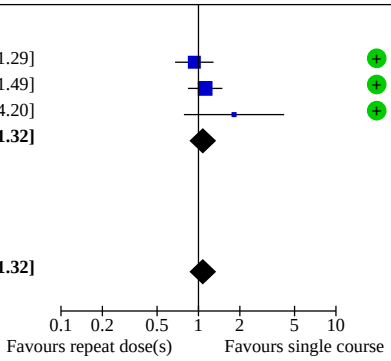
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.12.1 In all women							
Aghajafari 2002	1	6	2	6	0.2%	0.50 [0.06 , 4.15]	+ + + + + +
Crowther 2006	163	489	206	493	23.1%	0.80 [0.68 , 0.94]	+ + + + + +
Garite 2009	72	223	62	214	7.1%	1.11 [0.84 , 1.48]	+ + + + + +
Murphy 2008	396	935	415	918	47.2%	0.94 [0.84 , 1.04]	+ + + + + +
Peltoniemi 2007	48	125	44	124	5.0%	1.08 [0.78 , 1.50]	+ + + + + +
Wapner 2006	157	250	151	242	17.3%	1.01 [0.88 , 1.15]	+ + + + + +
Subtotal (95% CI)		**2028**		**1997**	**100.0%**	**0.94 [0.87 , 1.00]**	
Total events:	837		880				
Heterogeneity: Chi² = 7.34, df = 5 (P = 0.20); I² = 32%							
Test for overall effect: Z = 1.84 (P = 0.07)							
Total (95% CI)		**2028**		**1997**	**100.0%**	**0.94 [0.87 , 1.00]**	
Total events:	837		880				
Heterogeneity: Chi² = 7.34, df = 5 (P = 0.20); I² = 32%							
Test for overall effect: Z = 1.84 (P = 0.07)							
Test for subgroup differences: Not applicable							

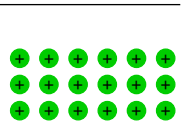


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.13. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 13: G10: Hypertension

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.13.1 In all women						
Crowther 2006	62	489	67	493	43.2%	0.93 [0.68 , 1.29]
Murphy 2008	90	935	79	918	51.6%	1.12 [0.84 , 1.49]
Wapner 2006	15	250	8	242	5.3%	1.81 [0.78 , 4.20]
Subtotal (95% CI)		**1674**		**1653**	**100.0%**	**1.08 [0.87 , 1.32]**
Total events:	167		154			
Heterogeneity: Chi² = 2.31, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Total (95% CI)		**1674**		**1653**	**100.0%**	**1.08 [0.87 , 1.32]**
Total events:	167		154			
Heterogeneity: Chi² = 2.31, df = 2 (P = 0.31); I² = 14%						
Test for overall effect: Z = 0.68 (P = 0.49)						
Test for subgroup differences: Not applicable						

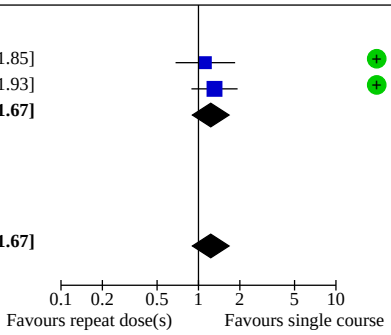




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.14. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 14: G12: Glucose intolerance

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
2.14.1 In all women						
Murphy 2008	32	935	28	918	42.9%	1.12 [0.68 , 1.85]
Wapner 2006	50	250	37	242	57.1%	1.31 [0.89 , 1.93]
Subtotal (95% CI)		**1185**		**1160**	**100.0%**	**1.23 [0.90 , 1.67]**
Total events:	82		65			
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Total (95% CI)		**1185**		**1160**	**100.0%**	**1.23 [0.90 , 1.67]**
Total events:	82		65			
Heterogeneity: Chi² = 0.23, df = 1 (P = 0.63); I² = 0%						
Test for overall effect: Z = 1.32 (P = 0.19)						
Test for subgroup differences: Not applicable						

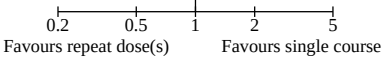


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.15. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 15: G13: Postnatal depression

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Murphy 2008	119	847	132	824	100.0%	0.88 [0.70 , 1.10]		+ + + + + +
Total (95% CI)		**847**		**824**	**100.0%**	**0.88 [0.70 , 1.10]**		
Total events:	119		132					

Heterogeneity: Not applicable
Test for overall effect: Z = 1.13 (P = 0.26)
Test for subgroup differences: Not applicable

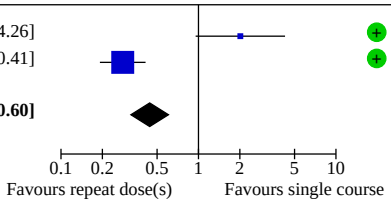


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.16. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 16: G14: Local injection site adverse effects

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	20	489	10	493	9.2%	2.02 [0.95 , 4.26]		+ + + + + +
Wapner 2006	28	252	96	243	90.8%	0.28 [0.19 , 0.41]		+ + + + + +
Total (95% CI)		**741**		**736**	**100.0%**	**0.44 [0.32 , 0.60]**		
Total events:	48		106					

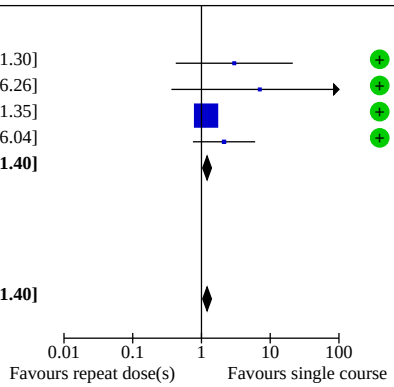
Heterogeneity: $Chi^2 = 21.15$, df = 1 (P < 0.00001); $I^2 = 95\%$
Test for overall effect: Z = 5.10 (P < 0.00001)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.17. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 17: G15: Insomnia after treatment

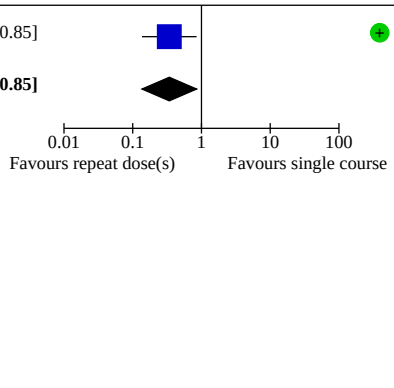
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
2.17.1 In all women							
Aghajafari 2002	3	6	1	6	0.4%	3.00 [0.42 , 21.30]	+ + ? + + ?
Crowther 2006	3	489	0	493	0.2%	7.06 [0.37 , 136.26]	+ + + + + +
Murphy 2008	276	868	230	844	97.3%	1.17 [1.01 , 1.35]	+ + + + + +
Wapner 2006	11	250	5	242	2.1%	2.13 [0.75 , 6.04]	+ + + + + +
Subtotal (95% CI)		**1613**		**1585**	**100.0%**	**1.21 [1.04 , 1.40]**	
Total events:	293		236				
Heterogeneity: Chi² = 3.54, df = 3 (P = 0.32); I² = 15%							
Test for overall effect: Z = 2.54 (P = 0.01)							
Total (95% CI)		**1613**		**1585**	**100.0%**	**1.21 [1.04 , 1.40]**	
Total events:	293		236				
Heterogeneity: Chi² = 3.54, df = 3 (P = 0.32); I² = 15%							
Test for overall effect: Z = 2.54 (P = 0.01)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 2.18. Comparison 2: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the woman, Outcome 18: G16: Gastrointestinal adverse effects of treatment

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Wapner 2006	6	252	17	243	100.0%	0.34 [0.14 , 0.85]	+ + + + + +
Total (95% CI)		**252**		**243**	**100.0%**	**0.34 [0.14 , 0.85]**	
Total events:	6		17				
Heterogeneity: Not applicable							
Test for overall effect: Z = 2.31 (P = 0.02)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 3. Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1 C1: Total deaths (after randomisation) up to early childhood follow-up	5	4565	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]

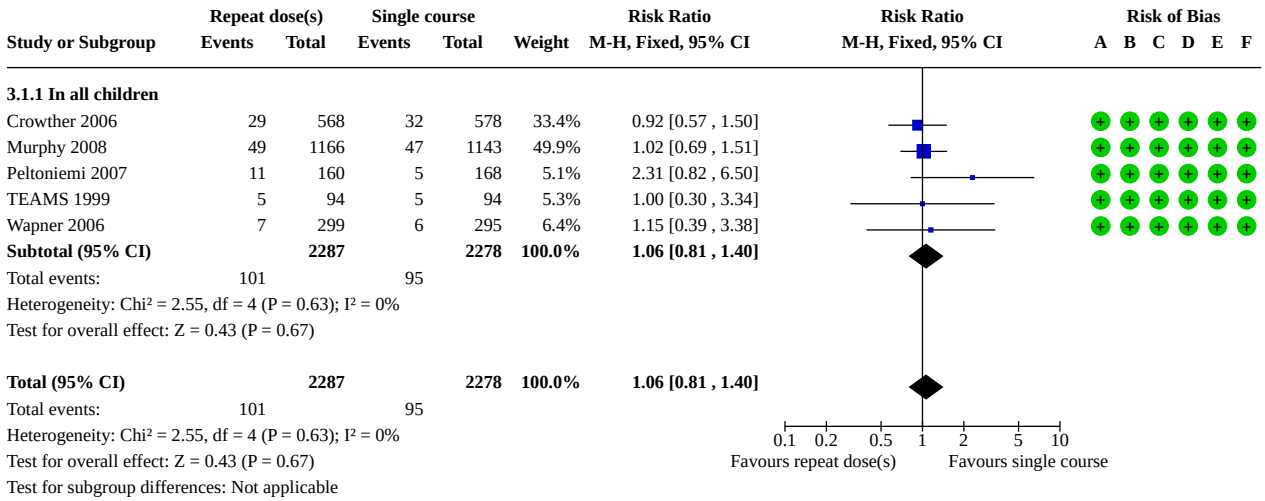
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.1.1 In all children	5	4565	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]
3.2 C2: Neurodevelopmental impairment at early childhood follow-up	4	3616	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
3.2.1 In all children	4	3616	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
3.3 C3: Survival free of neurodevelopmental impairment at early childhood follow-up	4	3845	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]
3.3.1 In all children	4	3845	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]
3.4 C4: Survival free of major neurodevelopmental impairment at early childhood follow-up	3	1816	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
3.4.1 In all children	3	1816	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
3.5 C5: Cerebral palsy at early childhood follow-up	5	3923	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
3.5.1 In all children	5	3923	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
3.6 C6: Developmental delay or intellectual impairment at early childhood follow-up (any)	4	3581	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.09]
3.6.1 In all children	4	3581	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.09]
3.7 Mental Developmental Index at early childhood follow-up	3	1627	Mean Difference (IV, Fixed, 95% CI)	0.89 [-0.61, 2.39]
3.7.1 In all children	3	1627	Mean Difference (IV, Fixed, 95% CI)	0.89 [-0.61, 2.39]
3.8 H1: Child behaviour at early childhood follow-up, Child Behaviour Checklist total score in the clinical range	1	1045	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [0.79, 1.51]
3.9 H1: Child behaviour: Behaviour rating scale in the clinical range (BSID-II)	1	1776	Risk Ratio (M-H, Fixed, 95% CI)	1.16 [1.00, 1.34]
3.10 H1: Child behaviour at early childhood follow-up as assessed by Early Child Behaviour Questionnaire Extraversion summary scale	1	142	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.18, 0.18]
3.11 H1: Child behaviour at early childhood follow-up assessed by Early Child	1	142	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.27, 0.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
Behaviour questionnaire Negative affectivity summary scale				
3.12 H1: Child behaviour at early childhood follow-up assessed by Early Child Behaviour questionnaire Effortful control summary scale	1	142	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.17, 0.17]
3.13 H2: Psychomotor Developmental Index at early childhood follow-up	2	1423	Mean Difference (IV, Fixed, 95% CI)	1.26 [-0.45, 2.96]
3.13.1 In all babies	2	1423	Mean Difference (IV, Fixed, 95% CI)	1.26 [-0.45, 2.96]
3.14 H3: Deafness/hearing impairment at early childhood follow-up	4	3528	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.56, 1.71]
3.14.1 In all children	4	3528	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.56, 1.71]
3.15 H4: Blindness/visual impairment at early childhood follow-up	3	3274	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.65, 2.10]
3.15.1 In all children	3	3274	Risk Ratio (M-H, Fixed, 95% CI)	1.17 [0.65, 2.10]
3.16 H5: Hypertension at early childhood follow-up	1	628	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
3.16.1 In all children	1	628	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.77, 1.23]
3.17 H8: Asthma or recurrent wheeze at early childhood follow-up	3	1720	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.06]
3.17.1 In all children	3	1720	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.74, 1.06]
3.18 H9: Any respiratory disease at early childhood follow-up	3	3423	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.92, 1.18]
3.19 N1i: Mean weight at early childhood follow-up (kg)	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.25, -0.07]
3.19.1 In all children	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.16 [-0.25, -0.07]
3.20 N1i: Mean weight Z score at early childhood follow-up	1	1047	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
3.20.1 In all children	1	1047	Mean Difference (IV, Fixed, 95% CI)	-0.03 [-0.19, 0.13]
3.21 N1i: Mean weight adjusted for age at early childhood follow-up (standardised mean difference)	3	1776	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.15, 0.04]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.21.1 In all children	3	1776	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.15, 0.04]
3.22 N1i: Weight small for age at early childhood follow-up	2	1533	Risk Ratio (IV, Fixed, 95% CI)	0.92 [0.72, 1.19]
3.22.1 In all children	2	1533	Risk Ratio (IV, Fixed, 95% CI)	0.92 [0.72, 1.19]
3.23 N1ii: Mean head circumference at early childhood follow-up (cm)	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.18, 0.06]
3.23.1 In all children	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.18, 0.06]
3.24 N1ii: Mean head circumference Z score at early childhood follow-up	2	1290	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.18]
3.24.1 In all children	2	1290	Mean Difference (IV, Fixed, 95% CI)	0.04 [-0.09, 0.18]
3.25 N1ii: Mean head circumference adjusted for age at early childhood follow-up (standardised mean difference)	3		Std. Mean Difference (IV, Fixed, 95% CI)	Subtotals only
3.25.1 In all babies	3	1776	Std. Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.07, 0.11]
3.26 N1ii: Head circumference small for age at early childhood follow-up	2	1527	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.87, 1.21]
3.26.1 In all babies	2	1527	Risk Ratio (IV, Fixed, 95% CI)	1.02 [0.87, 1.21]
3.27 N1iii: Mean height at early childhood follow-up (cm)	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.31, 0.17]
3.27.1 In all children	4	3784	Mean Difference (IV, Fixed, 95% CI)	-0.07 [-0.31, 0.17]
3.28 N1iii: Height Z score at early childhood follow-up	2	1290	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.17, 0.09]
3.28.1 In all children	2	1290	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.17, 0.09]
3.29 N1iii: Mean height adjusted for age at early childhood follow-up (standardised mean difference)	3	1776	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.15, 0.04]
3.29.1 In all children	3	1776	Std. Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.15, 0.04]
3.30 N1iii: Height small for age at early childhood follow-up	2	1526	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.77, 1.36]
3.30.1 In all children	2	1526	Risk Ratio (IV, Fixed, 95% CI)	1.03 [0.77, 1.36]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
3.31 N3: Mean systolic blood pressure at early childhood follow-up (mmHg)	1	486	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-5.40, -0.40]
3.31.1 In all children	1	486	Mean Difference (IV, Fixed, 95% CI)	-2.90 [-5.40, -0.40]
3.32 N3: Mean systolic blood pressure Z score at early childhood follow-up	1	672	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.08]
3.32.1 In all children	1	672	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.28, 0.08]
3.33 N3: Mean diastolic blood pressure at early childhood follow-up (mmHg)	1	486	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-2.86, 0.86]
3.33.1 In all children	1	486	Mean Difference (IV, Fixed, 95% CI)	-1.00 [-2.86, 0.86]
3.34 N3: Mean diastolic blood pressure Z score at early childhood follow-up	1	628	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.05, 0.25]
3.34.1 In all children	1	628	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.05, 0.25]

Analysis 3.1. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 1: C1: Total deaths (after randomisation) up to early childhood follow-up

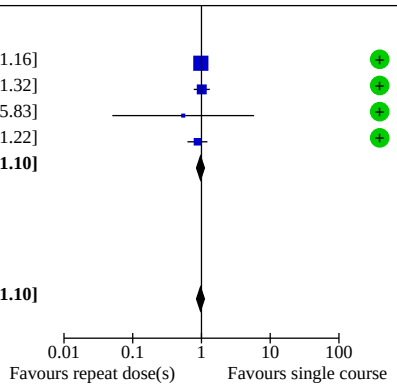


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.2. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 2: C2: Neurodevelopmental impairment at early childhood follow-up

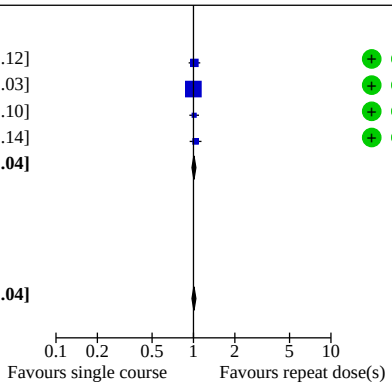
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.2.1 In all children							
Crowther 2006	175	495	182	504	53.7%	0.98 [0.83 , 1.16]	+ + + + + +
Murphy 2008	99	1020	95	988	28.7%	1.01 [0.77 , 1.32]	+ + + + + +
TEAMS 1999	1	59	2	64	0.6%	0.54 [0.05 , 5.83]	+ + - + + -
Wapner 2006	51	248	56	238	17.0%	0.87 [0.63 , 1.22]	+ + ? + + ?
Subtotal (95% CI)		**1822**		**1794**	**100.0%**	**0.97 [0.85 , 1.10]**	
Total events:	326		335				
Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Total (95% CI)		**1822**		**1794**	**100.0%**	**0.97 [0.85 , 1.10]**	
Total events:	326		335				
Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² = 0%							
Test for overall effect: Z = 0.49 (P = 0.62)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.3. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 3: C3: Survival free of neurodevelopmental impairment at early childhood follow-up

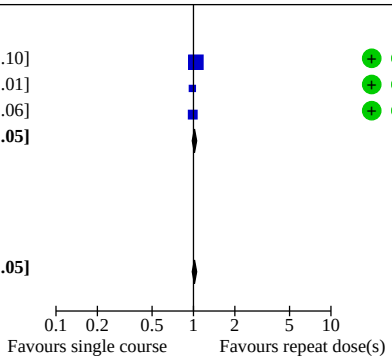
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.3.1 In all children							
Crowther 2006	320	524	322	536	21.3%	1.02 [0.92 , 1.12]	+ + + + + +
Murphy 2008	921	1069	893	1035	60.7%	1.00 [0.97 , 1.03]	+ + + + + +
TEAMS 1999	85	91	84	91	5.6%	1.01 [0.93 , 1.10]	+ + - + + -
Wapner 2006	197	255	182	244	12.4%	1.04 [0.94 , 1.14]	+ + ? + + ?
Subtotal (95% CI)		**1939**		**1906**	**100.0%**	**1.01 [0.98 , 1.04]**	
Total events:	1523		1481				
Heterogeneity: Chi² = 0.61, df = 3 (P = 0.89); I² = 0%							
Test for overall effect: Z = 0.47 (P = 0.64)							
Total (95% CI)		**1939**		**1906**	**100.0%**	**1.01 [0.98 , 1.04]**	
Total events:	1523		1481				
Heterogeneity: Chi² = 0.61, df = 3 (P = 0.89); I² = 0%							
Test for overall effect: Z = 0.47 (P = 0.64)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.4. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 4: C4: Survival free of major neurodevelopmental impairment at early childhood follow-up

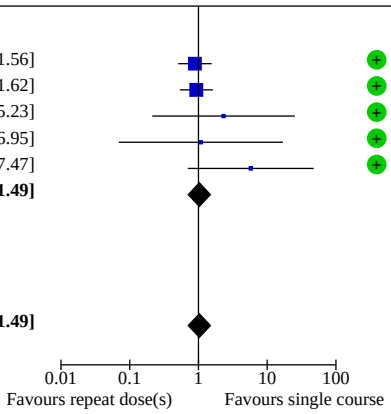
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.4.1 In all children							
Crowther 2006	442	524	434	536	55.3%	1.04 [0.99 , 1.10]	+ + + + + +
Peltoniemi 2007	115	118	138	139	16.3%	0.98 [0.95 , 1.01]	+ + - + + -
Wapner 2006	222	255	215	244	28.3%	0.99 [0.92 , 1.06]	+ + ? + + ?
Subtotal (95% CI)		**897**		**919**	**100.0%**	**1.02 [0.98 , 1.05]**	
Total events:	779		787				
Heterogeneity: Chi² = 5.98, df = 2 (P = 0.05); I² = 67%							
Test for overall effect: Z = 0.89 (P = 0.37)							
Total (95% CI)		**897**		**919**	**100.0%**	**1.02 [0.98 , 1.05]**	
Total events:	779		787				
Heterogeneity: Chi² = 5.98, df = 2 (P = 0.05); I² = 67%							
Test for overall effect: Z = 0.89 (P = 0.37)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.5. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 5: C5: Cerebral palsy at early childhood follow-up

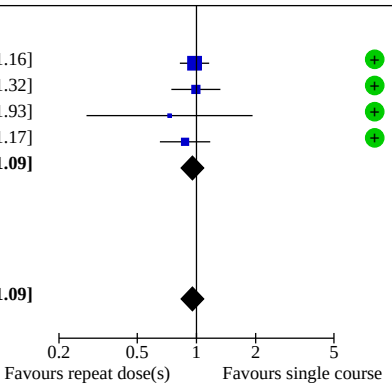
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.5.1 In all children							
Crowther 2006	22	521	25	526	46.8%	0.89 [0.51 , 1.56]	+ + + + + +
Murphy 2008	24	1020	25	988	47.8%	0.93 [0.53 , 1.62]	+ + + + + +
Peltoniemi 2007	2	120	1	139	1.7%	2.32 [0.21 , 25.23]	+ + - + + -
TEAMS 1999	1	59	1	64	1.8%	1.08 [0.07 , 16.95]	+ + - + + -
Wapner 2006	6	248	1	238	1.9%	5.76 [0.70 , 47.47]	+ + + + ? ?
Subtotal (95% CI)		**1968**		**1955**	**100.0%**	**1.03 [0.71 , 1.49]**	
Total events:	55		53				
Heterogeneity: Chi² = 3.40, df = 4 (P = 0.49); I² = 0%							
Test for overall effect: Z = 0.16 (P = 0.88)							
Total (95% CI)		**1968**		**1955**	**100.0%**	**1.03 [0.71 , 1.49]**	
Total events:	55		53				
Heterogeneity: Chi² = 3.40, df = 4 (P = 0.49); I² = 0%							
Test for overall effect: Z = 0.16 (P = 0.88)							
Test for subgroup differences: Not applicable							

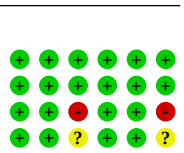


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.6. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 6: C6: Developmental delay or intellectual impairment at early childhood follow-up (any)

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.6.1 In all children						
Crowther 2006	168	495	175	504	51.4%	0.98 [0.82 , 1.16]
Murphy 2008	86	965	84	936	25.3%	0.99 [0.75 , 1.32]
Peltoniemi 2007	6	88	10	107	2.7%	0.73 [0.28 , 1.93]
Wapner 2006	62	248	68	238	20.6%	0.88 [0.65 , 1.17]
Subtotal (95% CI)		**1796**		**1785**	**100.0%**	**0.95 [0.84 , 1.09]**
Total events:	322		337			
Heterogeneity: Chi² = 0.78, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Total (95% CI)		**1796**		**1785**	**100.0%**	**0.95 [0.84 , 1.09]**
Total events:	322		337			
Heterogeneity: Chi² = 0.78, df = 3 (P = 0.86); I² = 0%						
Test for overall effect: Z = 0.71 (P = 0.48)						
Test for subgroup differences: Not applicable						

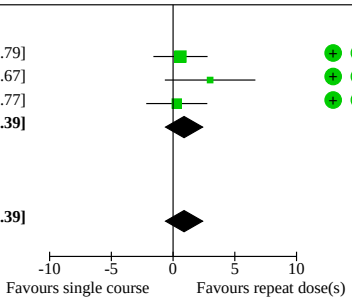


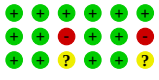


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.7. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 7: Mental Developmental Index at early childhood follow-up

Study or Subgroup	Repeat dose(s) Mean	Repeat dose(s) SD	Repeat dose(s) Total	Single course Mean	Single course SD	Single course Total	Weight	Mean Difference IV, Fixed, 95% CI
3.7.1 In all children								
Crowther 2006	91.1	17.1	474	90.5	17.7	493	46.6%	0.60 [-1.59 , 2.79]
Peltoniemi 2007	104	13	88	101	13	107	16.7%	3.00 [-0.67 , 6.67]
Wapner 2006	87.8	13.5	235	87.5	13.7	230	36.7%	0.30 [-2.17 , 2.77]
Subtotal (95% CI)			**797**			**830**	**100.0%**	**0.89 [-0.61 , 2.39]**
Heterogeneity: Chi² = 1.56, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.17 (P = 0.24)								
Total (95% CI)			**797**			**830**	**100.0%**	**0.89 [-0.61 , 2.39]**
Heterogeneity: Chi² = 1.56, df = 2 (P = 0.46); I² = 0%								
Test for overall effect: Z = 1.17 (P = 0.24)								
Test for subgroup differences: Not applicable								



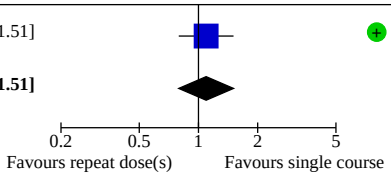


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.8. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 8: H1: Child behaviour at early childhood follow-up, Child Behaviour Checklist total score in the clinical range

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	68	519	63	526	100.0%	1.09 [0.79 , 1.51]	+ + + + + +
Total (95% CI)		**519**		**526**	**100.0%**	**1.09 [0.79 , 1.51]**	
Total events:	68		63				

Heterogeneity: Not applicable
Test for overall effect: Z = 0.55 (P = 0.58)
Test for subgroup differences: Not applicable

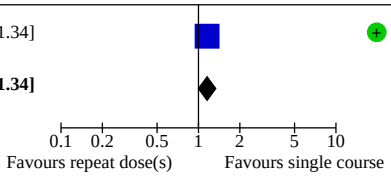


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.9. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 9: H1: Child behaviour: Behaviour rating scale in the clinical range (BSID-II)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Murphy 2008	285	902	239	874	100.0%	1.16 [1.00 , 1.34]	+ + ? + + ?
Total (95% CI)		**902**		**874**	**100.0%**	**1.16 [1.00 , 1.34]**	
Total events:	285		239				

Heterogeneity: Not applicable
Test for overall effect: Z = 1.96 (P = 0.05)
Test for subgroup differences: Not applicable

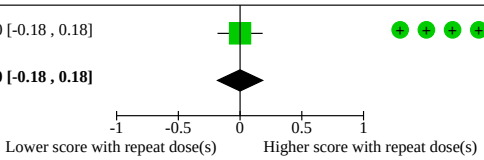


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.10. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 10: H1: Child behaviour at early childhood follow-up as assessed by Early Child Behaviour Questionnaire Extraversion summary scale

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Peltoniemi 2007	5	0.4	62	5	0.7	80	100.0%	0.00 [-0.18 , 0.18]	+ + + + + +
Total (95% CI)			**62**			**80**	**100.0%**	**0.00 [-0.18 , 0.18]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

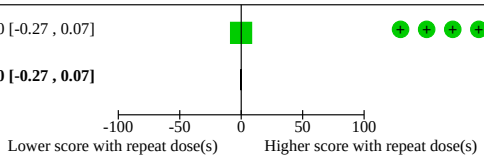


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.11. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 11: H1: Child behaviour at early childhood follow-up assessed by Early Child Behaviour questionnaire Negative affectivity summary scale

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Peltoniemi 2007	2.7	0.5	62	2.8	0.5	80	100.0%	-0.10 [-0.27 , 0.07]	+ + + + + +
Total (95% CI)			**62**			**80**	**100.0%**	**-0.10 [-0.27 , 0.07]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.18 (P = 0.24)
Test for subgroup differences: Not applicable

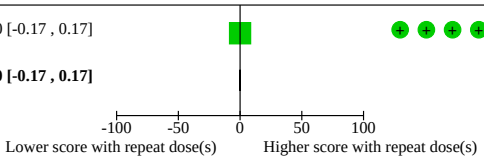


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.12. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 12: H1: Child behaviour at early childhood follow-up assessed by Early Child Behaviour questionnaire Effortful control summary scale

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Peltoniemi 2007	4.8	0.5	62	4.8	0.5	80	100.0%	0.00 [-0.17 , 0.17]	+ + + + + +
Total (95% CI)			**62**			**80**	**100.0%**	**0.00 [-0.17 , 0.17]**	

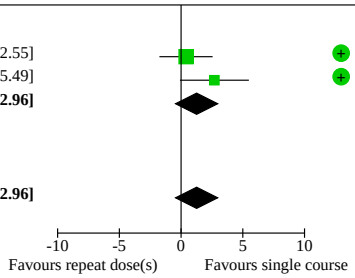
Heterogeneity: Not applicable
Test for overall effect: Z = 0.00 (P = 1.00)
Test for subgroup differences: Not applicable

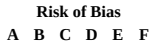


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.13. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 13: H2: Psychomotor Developmental Index at early childhood follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.13.1 In all babies								
Crowther 2006	92.5	17.3	472	92.1	16.7	486	62.7%	0.40 [-1.75 , 2.55]
Wapner 2006	96.5	15.8	235	93.8	14.9	230	37.3%	2.70 [-0.09 , 5.49]
Subtotal (95% CI)			**707**			**716**	**100.0%**	**1.26 [-0.45 , 2.96]**
Heterogeneity: Chi² = 1.63, df = 1 (P = 0.20); I² = 39%								
Test for overall effect: Z = 1.45 (P = 0.15)								
Total (95% CI)			**707**			**716**	**100.0%**	**1.26 [-0.45 , 2.96]**
Heterogeneity: Chi² = 1.63, df = 1 (P = 0.20); I² = 39%								
Test for overall effect: Z = 1.45 (P = 0.15)								
Test for subgroup differences: Not applicable								

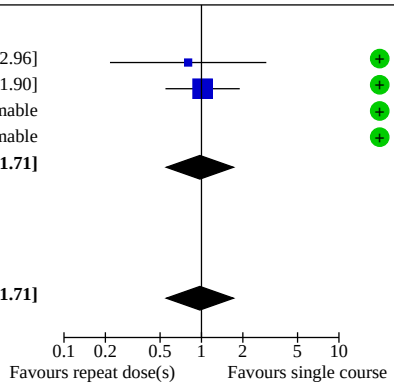


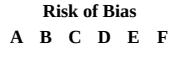


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.14. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 14: H3: Deafness/hearing impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
3.14.1 In all children						
Crowther 2006	4	521	5	521	20.6%	0.80 [0.22 , 2.96]
Murphy 2008	20	1069	19	1035	79.4%	1.02 [0.55 , 1.90]
Peltoniemi 2007	0	120	0	139		Not estimable
TEAMS 1999	0	59	0	64		Not estimable
Subtotal (95% CI)		**1769**		**1759**	**100.0%**	**0.97 [0.56 , 1.71]**
Total events:	24		24			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Total (95% CI)		**1769**		**1759**	**100.0%**	**0.97 [0.56 , 1.71]**
Total events:	24		24			
Heterogeneity: Chi² = 0.11, df = 1 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.09 (P = 0.93)						
Test for subgroup differences: Not applicable						

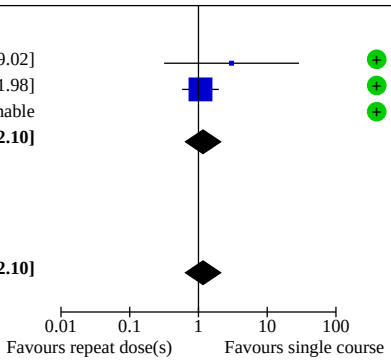




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.15. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 15: H4: Blindness/visual impairment at early childhood follow-up

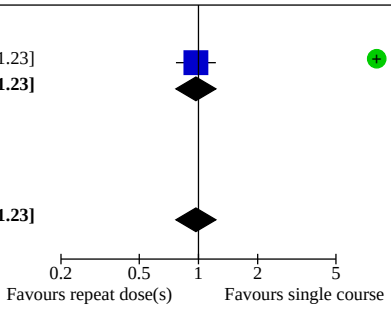
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.15.1 In all children							
Crowther 2006	3	521	1	526	4.9%	3.03 [0.32 , 29.02]	+ + + + + +
Murphy 2008	21	1069	19	1035	95.1%	1.07 [0.58 , 1.98]	+ + + + + +
TEAMS 1999	0	59	0	64		Not estimable	+ + ? + + ?
Subtotal (95% CI)		**1649**		**1625**	**100.0%**	**1.17 [0.65 , 2.10]**	
Total events:	24		20				
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Total (95% CI)		**1649**		**1625**	**100.0%**	**1.17 [0.65 , 2.10]**	
Total events:	24		20				
Heterogeneity: Chi² = 0.76, df = 1 (P = 0.38); I² = 0%							
Test for overall effect: Z = 0.51 (P = 0.61)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.16. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 16: H5: Hypertension at early childhood follow-up

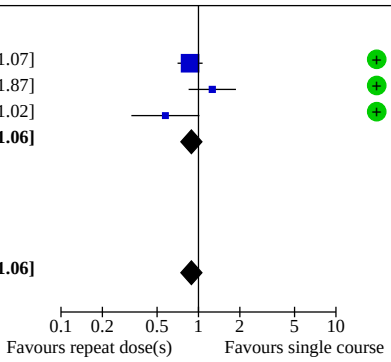
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.16.1 In all children							
Crowther 2006	92	301	103	327	100.0%	0.97 [0.77 , 1.23]	+ + ? + + ?
Subtotal (95% CI)		**301**		**327**	**100.0%**	**0.97 [0.77 , 1.23]**	
Total events:	92		103				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
Total (95% CI)		**301**		**327**	**100.0%**	**0.97 [0.77 , 1.23]**	
Total events:	92		103				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.25 (P = 0.80)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.17. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 17: H8: Asthma or recurrent wheeze at early childhood follow-up

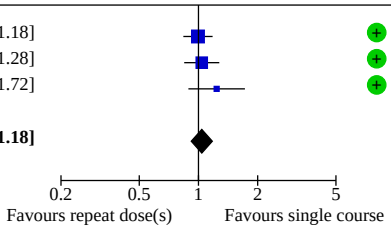
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
3.17.1 In all children							
Crowther 2006	122	527	142	533	70.1%	0.87 [0.70 , 1.07]	+ + + + + +
Peltoniemi 2007	37	120	34	139	15.6%	1.26 [0.85 , 1.87]	+ + ? ? + ?
Wapner 2006	17	206	28	195	14.3%	0.57 [0.33 , 1.02]	+ + + + ? ?
Subtotal (95% CI)		**853**		**867**	**100.0%**	**0.89 [0.74 , 1.06]**	
Total events:	176		204				
Heterogeneity: Chi² = 5.28, df = 2 (P = 0.07); I² = 62%							
Test for overall effect: Z = 1.32 (P = 0.19)							
Total (95% CI)		**853**		**867**	**100.0%**	**0.89 [0.74 , 1.06]**	
Total events:	176		204				
Heterogeneity: Chi² = 5.28, df = 2 (P = 0.07); I² = 62%							
Test for overall effect: Z = 1.32 (P = 0.19)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.18. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 18: H9: Any respiratory disease at early childhood follow-up

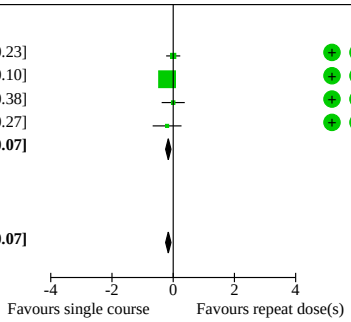
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	174	527	177	533	47.7%	0.99 [0.84 , 1.18]	+ + + ? + ?
Murphy 2008	161	1069	150	1035	41.3%	1.04 [0.85 , 1.28]	+ + + + + +
Peltoniemi 2007	47	120	44	139	11.0%	1.24 [0.89 , 1.72]	+ + ? ? + ?
Total (95% CI)		**1716**		**1707**	**100.0%**	**1.04 [0.92 , 1.18]**	
Total events:	382		371				
Heterogeneity: Chi² = 1.33, df = 2 (P = 0.52); I² = 0%							
Test for overall effect: Z = 0.62 (P = 0.54)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.19. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 19: N1i: Mean weight at early childhood follow-up (kg)

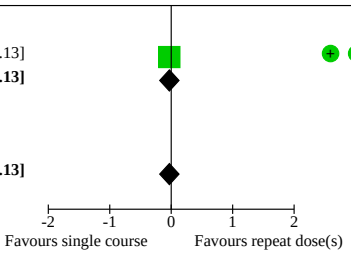
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.19.1 In all children									
Crowther 2006	12.6	1.9	520	12.6	1.9	527	14.4%	0.00 [-0.23 , 0.23]	+ + + + + +
Murphy 2008	11.94	1.14	1020	12.14	1.14	988	76.8%	-0.20 [-0.30 , -0.10]	+ + + + + +
Peltoniemi 2007	12.1	1.4	115	12.1	1.6	128	5.4%	0.00 [-0.38 , 0.38]	+ + ? + + ?
Wapner 2006	13.5	2.7	248	13.7	2.6	238	3.4%	-0.20 [-0.67 , 0.27]	+ + + + + +
Subtotal (95% CI)			**1903**			**1881**	**100.0%**	**-0.16 [-0.25 , -0.07]**	
Heterogeneity: Chi² = 3.19, df = 3 (P = 0.36); I² = 6%									
Test for overall effect: Z = 3.60 (P = 0.0003)									
Total (95% CI)			**1903**			**1881**	**100.0%**	**-0.16 [-0.25 , -0.07]**	
Heterogeneity: Chi² = 3.19, df = 3 (P = 0.36); I² = 6%									
Test for overall effect: Z = 3.60 (P = 0.0003)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.20. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 20: N1i: Mean weight Z score at early childhood follow-up

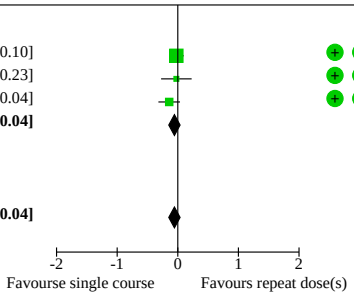
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.20.1 In all children									
Crowther 2006	-0.04	1.3	520	-0.01	1.29	527	100.0%	-0.03 [-0.19 , 0.13]	+ + + + + +
Subtotal (95% CI)			**520**			**527**	**100.0%**	**-0.03 [-0.19 , 0.13]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Total (95% CI)			**520**			**527**	**100.0%**	**-0.03 [-0.19 , 0.13]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.37 (P = 0.71)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.21. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 21: N1i: Mean weight adjusted for age at early childhood follow-up (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.21.1 In all children									
Crowther 2006 (1)	-0.04	1.3	520	-0.01	1.29	527	59.0%	-0.02 [-0.14 , 0.10]	+ + + + + +
Peltoniemi 2007 (2)	-5.2	7.9	115	-5	9	128	13.7%	-0.02 [-0.28 , 0.23]	+ + ? + + ?
Wapner 2006 (3)	49.5	31.8	248	54.1	33.1	238	27.3%	-0.14 [-0.32 , 0.04]	+ + + + + +
Subtotal (95% CI)			**883**			**893**	**100.0%**	**-0.06 [-0.15 , 0.04]**	
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%									
Test for overall effect: Z = 1.17 (P = 0.24)									
Total (95% CI)			**883**			**893**	**100.0%**	**-0.06 [-0.15 , 0.04]**	
Heterogeneity: Chi² = 1.23, df = 2 (P = 0.54); I² = 0%									
Test for overall effect: Z = 1.17 (P = 0.24)									
Test for subgroup differences: Not applicable									

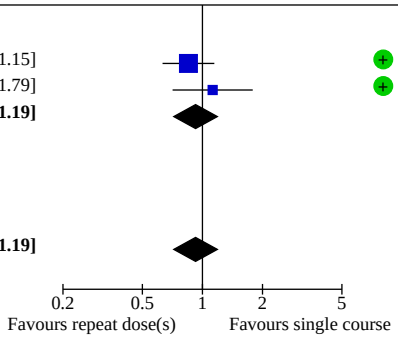


Footnotes
(1) Z score
(2) Relative weight as a percentage
(3) Weight centile

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.22. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 22: N1i: Weight small for age at early childhood follow-up

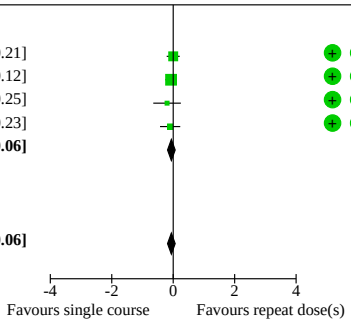
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.22.1 In all children							
Crowther 2006	68	520	81	527	70.6%	0.85 [0.63 , 1.15]	+ + + + + +
Wapner 2006	34	248	29	238	29.4%	1.13 [0.71 , 1.79]	+ + + + + +
Subtotal (95% CI)		**768**		**765**	**100.0%**	**0.92 [0.72 , 1.19]**	
Total events:	102		110				
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%							
Test for overall effect: Z = 0.62 (P = 0.54)							
Total (95% CI)		**768**		**765**	**100.0%**	**0.92 [0.72 , 1.19]**	
Total events:	102		110				
Heterogeneity: Chi² = 0.99, df = 1 (P = 0.32); I² = 0%							
Test for overall effect: Z = 0.62 (P = 0.54)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.23. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 23: N1ii: Mean head circumference at early childhood follow-up (cm)

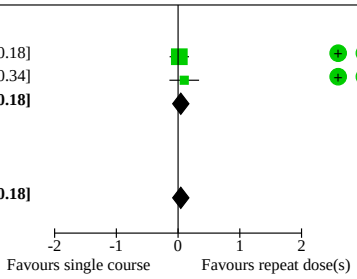
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.23.1 In all children									
Crowther 2006	48.9	1.7	520	48.9	1.8	527	34.2%	0.00 [-0.21 , 0.21]	+ + + + + +
Murphy 2008	48.18	2.14	1020	48.25	2.14	988	43.9%	-0.07 [-0.26 , 0.12]	+ + + + + +
Peltoniemi 2007	49.1	2	115	49.3	1.5	128	7.7%	-0.20 [-0.65 , 0.25]	+ + ? + + ?
Wapner 2006	49	1.9	248	49.1	1.8	238	14.2%	-0.10 [-0.43 , 0.23]	+ + + + + +
Subtotal (95% CI)			**1903**			**1881**	**100.0%**	**-0.06 [-0.18 , 0.06]**	
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%									
Test for overall effect: Z = 0.95 (P = 0.34)									
Total (95% CI)			**1903**			**1881**	**100.0%**	**-0.06 [-0.18 , 0.06]**	
Heterogeneity: Chi² = 0.75, df = 3 (P = 0.86); I² = 0%									
Test for overall effect: Z = 0.95 (P = 0.34)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.24. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 24: N1ii: Mean head circumference Z score at early childhood follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.24.1 In all children									
Crowther 2006	-0.74	1.26	520	-0.76	1.33	527	70.1%	0.02 [-0.14 , 0.18]	+ + + + + +
Peltoniemi 2007	0.1	1	115	0	0.9	128	29.9%	0.10 [-0.14 , 0.34]	+ + ? + + ?
Subtotal (95% CI)			**635**			**655**	**100.0%**	**0.04 [-0.09 , 0.18]**	
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%									
Test for overall effect: Z = 0.66 (P = 0.51)									
Total (95% CI)			**635**			**655**	**100.0%**	**0.04 [-0.09 , 0.18]**	
Heterogeneity: Chi² = 0.30, df = 1 (P = 0.58); I² = 0%									
Test for overall effect: Z = 0.66 (P = 0.51)									
Test for subgroup differences: Not applicable									



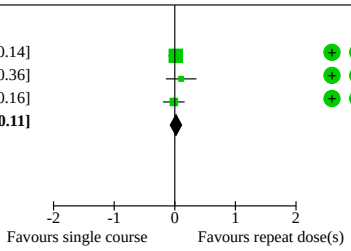
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.25. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 25: N1ii: Mean head circumference adjusted for age at early childhood follow-up (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI
3.25.1 In all babies								
Crowther 2006 (1)	-0.74	1.26	520	-0.76	1.33	527	59.0%	0.02 [-0.11 , 0.14]
Peltoniemi 2007 (1)	0.1	1	115	0	0.9	128	13.6%	0.11 [-0.15 , 0.36]
Wapner 2006 (2)	51.2	32.6	248	51.7	31.6	238	27.4%	-0.02 [-0.19 , 0.16]
Subtotal (95% CI)			**883**			**893**	**100.0%**	**0.02 [-0.07 , 0.11]**

Heterogeneity: Chi² = 0.60, df = 2 (P = 0.74); I² = 0%
Test for overall effect: Z = 0.40 (P = 0.69)

Test for subgroup differences: Not applicable



Footnotes
(1) Z score
(2) Head circumference centile

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

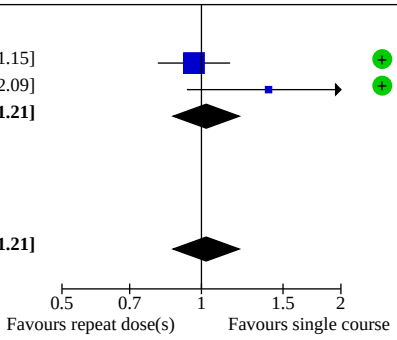
Analysis 3.26. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 26: N1ii: Head circumference small for age at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI
3.26.1 In all babies						
Crowther 2006	160	519	167	522	83.6%	0.96 [0.81 , 1.15]
Wapner 2006	48	248	33	238	16.4%	1.40 [0.93 , 2.09]
Subtotal (95% CI)		**767**		**760**	**100.0%**	**1.02 [0.87 , 1.21]**
Total events:	208		200			

Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.28 (P = 0.78)

Total (95% CI)		**767**		**760**	**100.0%**	**1.02 [0.87 , 1.21]**
Total events:	208		200			

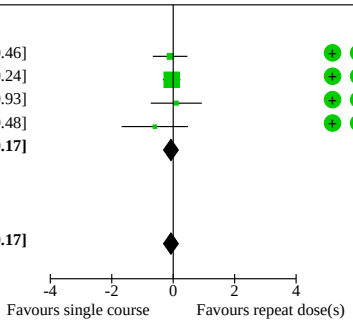
Heterogeneity: Chi² = 2.68, df = 1 (P = 0.10); I² = 63%
Test for overall effect: Z = 0.28 (P = 0.78)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.27. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 27: N1iii: Mean height at early childhood follow-up (cm)

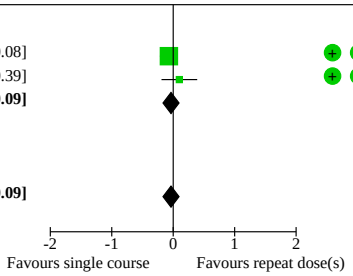
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.27.1 In all children									
Crowther 2006	87.6	4.6	520	87.7	4.7	527	18.0%	-0.10 [-0.66 , 0.46]	+ + + + + +
Murphy 2008	85.46	3.29	1020	85.51	3.29	988	68.8%	-0.05 [-0.34 , 0.24]	+ + + + + +
Peltoniemi 2007	87	3.1	115	86.9	3.5	128	8.3%	0.10 [-0.73 , 0.93]	+ + ? + + ?
Wapner 2006	90.5	6.4	248	91.1	5.7	238	4.9%	-0.60 [-1.68 , 0.48]	+ + + + + +
Subtotal (95% CI)			**1903**			**1881**	**100.0%**	**-0.07 [-0.31 , 0.17]**	
Heterogeneity: Chi² = 1.12, df = 3 (P = 0.77); I² = 0%									
Test for overall effect: Z = 0.60 (P = 0.55)									
Total (95% CI)			**1903**			**1881**	**100.0%**	**-0.07 [-0.31 , 0.17]**	
Heterogeneity: Chi² = 1.12, df = 3 (P = 0.77); I² = 0%									
Test for overall effect: Z = 0.60 (P = 0.55)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.28. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 28: N1iii: Height Z score at early childhood follow-up

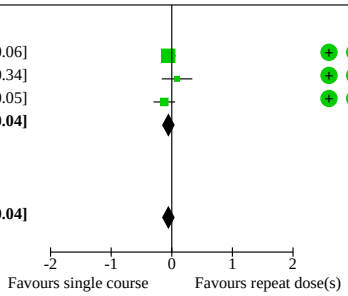
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.28.1 In all children									
Crowther 2006	0.01	1.17	520	0.08	1.24	527	79.8%	-0.07 [-0.22 , 0.08]	+ + + + + +
Peltoniemi 2007	-0.2	1.2	115	-0.3	1.1	128	20.2%	0.10 [-0.19 , 0.39]	+ + ? + + ?
Subtotal (95% CI)			**635**			**655**	**100.0%**	**-0.04 [-0.17 , 0.09]**	
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%									
Test for overall effect: Z = 0.54 (P = 0.59)									
Total (95% CI)			**635**			**655**	**100.0%**	**-0.04 [-0.17 , 0.09]**	
Heterogeneity: Chi² = 1.05, df = 1 (P = 0.31); I² = 5%									
Test for overall effect: Z = 0.54 (P = 0.59)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.29. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 29: N1iii: Mean height adjusted for age at early childhood follow-up (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.29.1 In all children									
Crowther 2006 (1)	0.01	1.17	520	0.08	1.24	527	59.0%	-0.06 [-0.18 , 0.06]	+ + + + + +
Peltoniemi 2007 (1)	-0.2	1.2	115	-0.3	1.1	128	13.6%	0.09 [-0.17 , 0.34]	+ + ? + + ?
Wapner 2006 (2)	48.6	30.5	248	52.3	29.2	238	27.3%	-0.12 [-0.30 , 0.05]	+ + + + + +
Subtotal (95% CI)			**883**			**893**	**100.0%**	**-0.06 [-0.15 , 0.04]**	
Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² = 0%									
Test for overall effect: Z = 1.18 (P = 0.24)									
Total (95% CI)			**883**			**893**	**100.0%**	**-0.06 [-0.15 , 0.04]**	
Heterogeneity: Chi² = 1.79, df = 2 (P = 0.41); I² = 0%									
Test for overall effect: Z = 1.18 (P = 0.24)									
Test for subgroup differences: Not applicable									

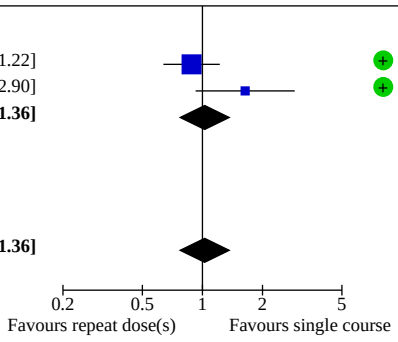


Footnotes
(1) Z score
(2) Height centile

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.30. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 30: N1iii: Height small for age at early childhood follow-up

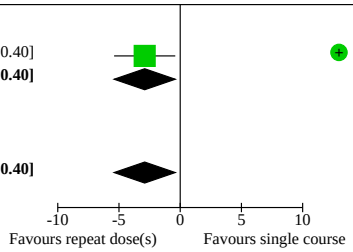
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio IV, Fixed, 95% CI	Risk of Bias A B C D E F
3.30.1 In all children							
Crowther 2006	60	520	68	520	75.6%	0.88 [0.64 , 1.22]	+ + + + + +
Wapner 2006	29	248	17	238	24.4%	1.64 [0.92 , 2.90]	+ + + + + +
Subtotal (95% CI)		**768**		**758**	**100.0%**	**1.03 [0.77 , 1.36]**	
Total events:	89		85				
Heterogeneity: Chi² = 3.39, df = 1 (P = 0.07); I² = 71%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Total (95% CI)		**768**		**758**	**100.0%**	**1.03 [0.77 , 1.36]**	
Total events:	89		85				
Heterogeneity: Chi² = 3.39, df = 1 (P = 0.07); I² = 71%							
Test for overall effect: Z = 0.18 (P = 0.86)							
Test for subgroup differences: Not applicable							

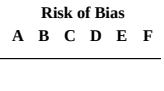


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.31. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 31: N3: Mean systolic blood pressure at early childhood follow-up (mmHg)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.31.1 In all children								
Wapner 2006	91.7	13.2	248	94.6	14.8	238	100.0%	-2.90 [-5.40 , -0.40]
Subtotal (95% CI)			**248**			**238**	**100.0%**	**-2.90 [-5.40 , -0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
Total (95% CI)			**248**			**238**	**100.0%**	**-2.90 [-5.40 , -0.40]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 2.28 (P = 0.02)								
Test for subgroup differences: Not applicable								

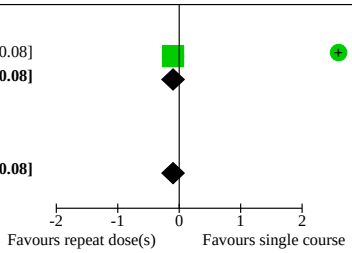


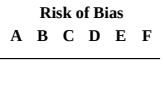


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.32. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 32: N3: Mean systolic blood pressure Z score at early childhood follow-up

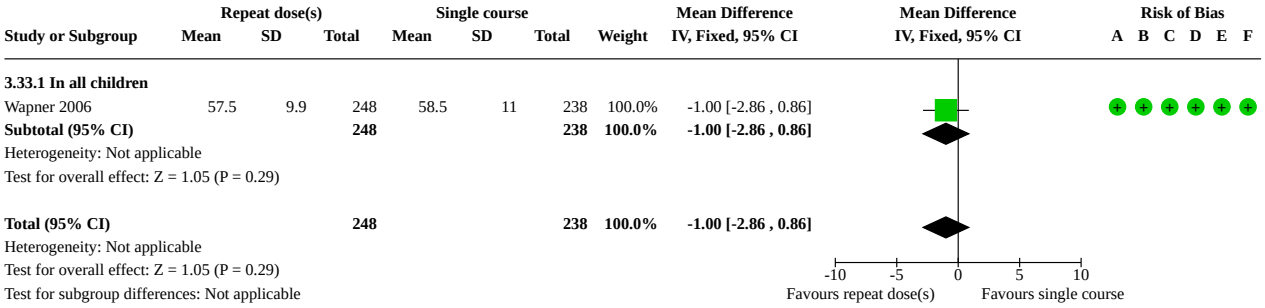
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
3.32.1 In all children								
Crowther 2006	0.2	1.2	327	0.3	1.2	345	100.0%	-0.10 [-0.28 , 0.08]
Subtotal (95% CI)			**327**			**345**	**100.0%**	**-0.10 [-0.28 , 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Total (95% CI)			**327**			**345**	**100.0%**	**-0.10 [-0.28 , 0.08]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 1.08 (P = 0.28)								
Test for subgroup differences: Not applicable								





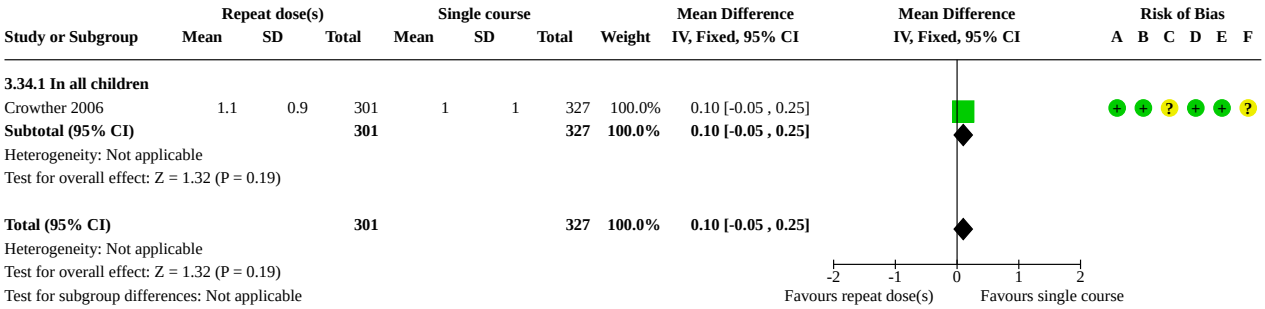
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.33. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 33: N3: Mean diastolic blood pressure at early childhood follow-up (mmHg)



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 3.34. Comparison 3: Repeat dose(s) of corticosteroids versus single course: outcomes for the child in early childhood (2 to < 5 years of age), Outcome 34: N3: Mean diastolic blood pressure Z score at early childhood follow-up



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 4. Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.1 D1: Total deaths (after randomisation) up to mid- to later childhood follow-up	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.26]
4.1.1 In all children	2	2874	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.69, 1.26]

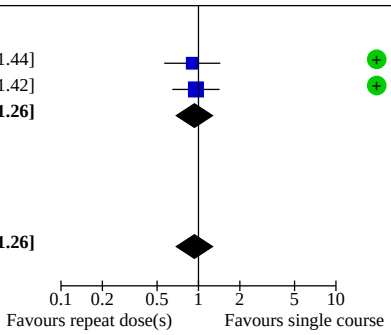
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.2 D2: Neurocognitive impairment at mid- to later childhood follow-up	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.29]
4.2.1 In all children	1	897	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.72, 1.29]
4.3 D3: Survival free of neurocognitive impairment at mid- to later childhood follow-up	1	963	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.08]
4.3.1 In all children	1	963	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.95, 1.08]
4.4 D4: Survival free of major neurocognitive impairment at mid- to later childhood follow-up	2		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
4.4.1 In all children	2	2682	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
4.5 D6: Cognitive impairment at mid- to later childhood follow-up	2	2504	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.22]
4.5.1 In all children	2	2504	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.81, 1.22]
4.6 D8: Cerebral palsy at mid- to later childhood follow-up	2	2622	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.43, 1.26]
4.6.1 In all children	2	2622	Risk Ratio (M-H, Fixed, 95% CI)	0.74 [0.43, 1.26]
4.7 I2: Blindness/visual impairment at mid- to later childhood follow-up	2	2532	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.79, 1.59]
4.7.1 In all children	2	2532	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.79, 1.59]
4.8 I3: Deafness/hearing impairment at mid- to later childhood follow-up	2	2532	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.77, 3.41]
4.8.1 In all children	2	2532	Risk Ratio (M-H, Fixed, 95% CI)	1.62 [0.77, 3.41]
4.9 I4: Abnormal child behaviour at mid- to later childhood follow-up	1	1615	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.75, 1.22]
4.10 I4: Child behaviour at mid- to later childhood follow-up (standardised mean difference)	2	2480	Std. Mean Difference (IV, Fixed, 95% CI)	-0.00 [-0.08, 0.08]
4.11 I5: Asthma or recurrent wheeze at mid- to later childhood follow-up	1	979	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]

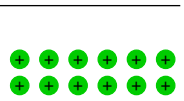
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.11.1 In all babies	1	979	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.85, 1.19]
4.12 I6: Any respiratory disease at mid- to later childhood follow-up	1	979	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.36, 1.72]
4.13 O1i: Mean weight at mid- to later childhood follow-up (kg)	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.62, 0.22]
4.13.1 In all children	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-0.62, 0.22]
4.14 O1i: Mean weight Z score at mid- to later childhood follow-up	1	940	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.23, 0.11]
4.14.1 In all children	1	940	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.23, 0.11]
4.15 O1ii: Mean head circumference at mid- to later childhood follow-up (cm)	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.36, 0.16]
4.15.1 In all children	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.10 [-0.36, 0.16]
4.16 O1ii: Head circumference Z score at mid- to later childhood follow-up	1	885	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.22, 0.14]
4.16.1 In all children	1	885	Mean Difference (IV, Fixed, 95% CI)	-0.04 [-0.22, 0.14]
4.17 O1iii: Mean height at mid- to later childhood follow-up (cm)	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.11, 0.31]
4.17.1 In all children	1	1635	Mean Difference (IV, Fixed, 95% CI)	-0.40 [-1.11, 0.31]
4.18 O1iii: Mean height Z score at mid- to later childhood follow-up	1	912	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.13, 0.17]
4.18.1 In all children	1	912	Mean Difference (IV, Fixed, 95% CI)	0.02 [-0.13, 0.17]
4.19 O2: BMI Z scores at mid- to later childhood follow-up	1	910	Mean Difference (IV, Fixed, 95% CI)	-0.13 [-0.30, 0.04]
4.20 O4: Body composition: total body fat-free mass at mid- to later childhood follow-up (kg)	1	185	Mean Difference (IV, Fixed, 95% CI)	-0.20 [-1.43, 1.03]
4.21 O5: Body composition: total body fat mass at mid- to later childhood follow-up (kg)	1	185	Mean Difference (IV, Fixed, 95% CI)	0.10 [-0.71, 0.91]
4.22 O6: Mean systolic blood pressure at mid- to later childhood follow-up (mmHg)	1	1635	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.06, 1.66]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
4.22.1 In all children	1	1635	Mean Difference (IV, Fixed, 95% CI)	0.30 [-1.06, 1.66]
4.23 O6: Mean diastolic blood pressure at mid- to later childhood follow-up (mmHg)	1	1635	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.46, 1.86]
4.23.1 In all children	1	1635	Mean Difference (IV, Fixed, 95% CI)	0.70 [-0.46, 1.86]
4.24 O6: Mean systolic blood pressure Z score at mid- to later childhood follow-up	1	848	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.06, 0.20]
4.24.1 In all children	1	848	Mean Difference (IV, Fixed, 95% CI)	0.07 [-0.06, 0.20]
4.25 O6: Mean diastolic blood pressure Z score at mid- to later childhood follow-up	1	848	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.25, 0.07]
4.25.1 In all children	1	848	Mean Difference (IV, Fixed, 95% CI)	-0.09 [-0.25, 0.07]
4.26 O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1 Z score	1	185	Mean Difference (IV, Fixed, 95% CI)	-0.06 [-0.34, 0.22]
4.27 O8: Measures of lung function at mid- to later childhood follow-up: mean FVC Z score	1	185	Mean Difference (IV, Fixed, 95% CI)	-0.18 [-0.49, 0.13]
4.28 O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1/FVC Z score	1	185	Mean Difference (IV, Fixed, 95% CI)	-0.19 [-0.44, 0.06]

Analysis 4.1. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 1: D1: Total deaths (after randomisation) up to mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.1.1 In all children						
Crowther 2006	31	568	35	578	42.2%	0.90 [0.56 , 1.44]
Murphy 2008	46	873	47	855	57.8%	0.96 [0.65 , 1.42]
Subtotal (95% CI)		**1441**		**1433**	**100.0%**	**0.93 [0.69 , 1.26]**
Total events:	77		82			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Total (95% CI)		**1441**		**1433**	**100.0%**	**0.93 [0.69 , 1.26]**
Total events:	77		82			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.84); I² = 0%						
Test for overall effect: Z = 0.44 (P = 0.66)						
Test for subgroup differences: Not applicable						

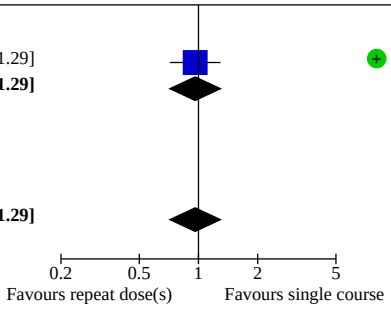


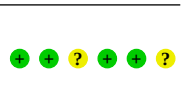


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.2. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 2: D2: Neurocognitive impairment at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.2.1 In all children						
Crowther 2006	72	448	75	449	100.0%	0.96 [0.72 , 1.29]
Subtotal (95% CI)		**448**		**449**	**100.0%**	**0.96 [0.72 , 1.29]**
Total events:	72		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**448**		**449**	**100.0%**	**0.96 [0.72 , 1.29]**
Total events:	72		75			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Test for subgroup differences: Not applicable						

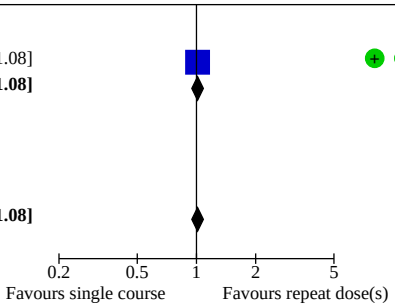




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.3. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 3: D3: Survival free of neurocognitive impairment at mid- to later childhood follow-up

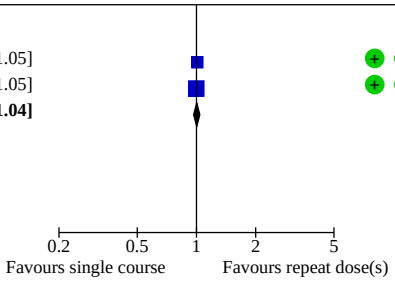
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
4.3.1 In all children							
Crowther 2006	375	479	374	484	100.0%	1.01 [0.95 , 1.08]	+ + ? + + ?
Subtotal (95% CI)		**479**		**484**	**100.0%**	**1.01 [0.95 , 1.08]**	
Total events:	375		374				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.38 (P = 0.70)							
Total (95% CI)		**479**		**484**	**100.0%**	**1.01 [0.95 , 1.08]**	
Total events:	375		374				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.38 (P = 0.70)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.4. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 4: D4: Survival free of major neurocognitive impairment at mid- to later childhood follow-up

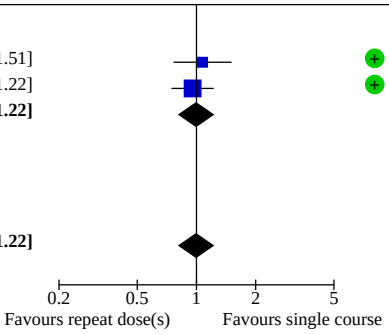
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
4.4.1 In all children							
Crowther 2006	437	479	437	484	40.2%	1.01 [0.97 , 1.05]	+ + ? + + ?
Murphy 2008	654	871	638	848	59.8%	1.00 [0.95 , 1.05]	+ + ? + + ?
Subtotal (95% CI)		**1350**		**1332**	**100.0%**	**1.00 [0.97 , 1.04]**	
Total events:	1091		1075				
Heterogeneity: $Chi^2 = 0.16$, df = 1 (P = 0.69); $I^2 = 0\%$							
Test for overall effect: Z = 0.16 (P = 0.87)							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.5. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 5: D6: Cognitive impairment at mid- to later childhood follow-up

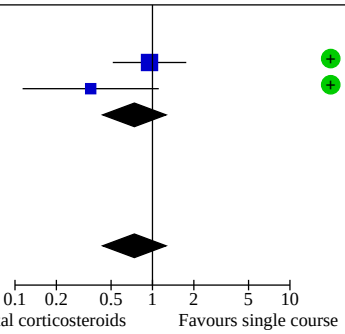
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.5.1 In all children						
Crowther 2006	60	444	56	445	33.5%	1.07 [0.76 , 1.51]
Murphy 2008	108	822	109	793	66.5%	0.96 [0.75 , 1.22]
Subtotal (95% CI)		**1266**		**1238**	**100.0%**	**1.00 [0.81 , 1.22]**
Total events:	168		165			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Total (95% CI)		**1266**		**1238**	**100.0%**	**1.00 [0.81 , 1.22]**
Total events:	168		165			
Heterogeneity: Chi² = 0.29, df = 1 (P = 0.59); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Not applicable						



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.6. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 6: D8: Cerebral palsy at mid- to later childhood follow-up

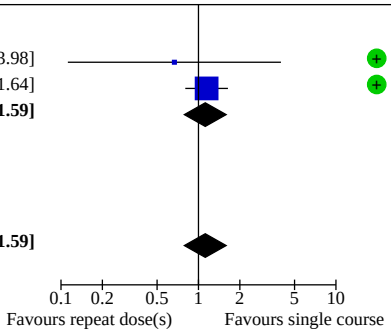
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.6.1 In all children						
Crowther 2006	19	493	20	494	64.2%	0.95 [0.51 , 1.76]
Murphy 2008	4	827	11	808	35.8%	0.36 [0.11 , 1.11]
Subtotal (95% CI)		**1320**		**1302**	**100.0%**	**0.74 [0.43 , 1.26]**
Total events:	23		31			
Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**1320**		**1302**	**100.0%**	**0.74 [0.43 , 1.26]**
Total events:	23		31			
Heterogeneity: Chi² = 2.24, df = 1 (P = 0.13); I² = 55%						
Test for overall effect: Z = 1.12 (P = 0.26)						
Test for subgroup differences: Not applicable						

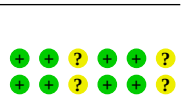


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.7. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 7: I2: Blindness/visual impairment at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.7.1 In all children						
Crowther 2006	2	448	3	449	5.4%	0.67 [0.11 , 3.98]
Murphy 2008	61	827	52	808	94.6%	1.15 [0.80 , 1.64]
Subtotal (95% CI)		**1275**		**1257**	**100.0%**	**1.12 [0.79 , 1.59]**
Total events:	63		55			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Total (95% CI)		**1275**		**1257**	**100.0%**	**1.12 [0.79 , 1.59]**
Total events:	63		55			
Heterogeneity: Chi² = 0.34, df = 1 (P = 0.56); I² = 0%						
Test for overall effect: Z = 0.64 (P = 0.52)						
Test for subgroup differences: Not applicable						

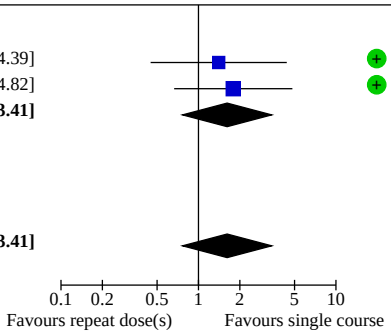




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.8. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 8: I3: Deafness/hearing impairment at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
4.8.1 In all children						
Crowther 2006	7	448	5	449	45.1%	1.40 [0.45 , 4.39]
Murphy 2008	11	827	6	808	54.9%	1.79 [0.67 , 4.82]
Subtotal (95% CI)		**1275**		**1257**	**100.0%**	**1.62 [0.77 , 3.41]**
Total events:	18		11			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Total (95% CI)		**1275**		**1257**	**100.0%**	**1.62 [0.77 , 3.41]**
Total events:	18		11			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 1.26 (P = 0.21)						
Test for subgroup differences: Not applicable						

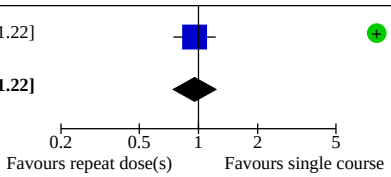


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.9. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 9: I4: Abnormal child behaviour at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Murphy 2008	108	822	109	793	100.0%	0.96 [0.75 , 1.22]		+ + ? + + ?
Total (95% CI)		**822**		**793**	**100.0%**	**0.96 [0.75 , 1.22]**		
Total events:	108		109					

Heterogeneity: Not applicable
Test for overall effect: Z = 0.36 (P = 0.72)
Test for subgroup differences: Not applicable

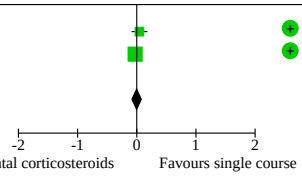


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.10. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 10: I4: Child behaviour at mid- to later childhood follow-up (standardised mean difference)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Std. Mean Difference IV, Fixed, 95% CI	Std. Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006 (1)	11	6.9	431	10.7	6.4	434	34.9%	0.05 [-0.09 , 0.18]		+ + ? + + ?
Murphy 2008 (2)	48.3	14.621977	822	48.7	14.36173	793	65.1%	-0.03 [-0.13 , 0.07]		+ + ? + + ?
Total (95% CI)			**1253**			**1227**	**100.0%**	**-0.00 [-0.08 , 0.08]**		

Heterogeneity: Chi² = 0.74, df = 1 (P = 0.39); I² = 0%
Test for overall effect: Z = 0.06 (P = 0.96)
Test for subgroup differences: Not applicable

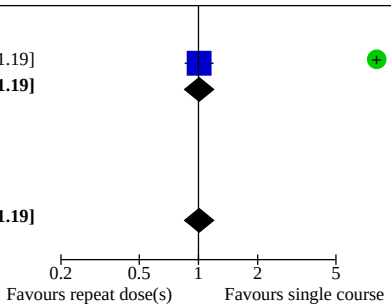


Footnotes
(1) Crowther 2006 used Strengths and difficulties questionnaire.
(2) Murphy 2008 used the Child behaviour checklist 1.5-5years.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.11. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 11: I5: Asthma or recurrent wheeze at mid- to later childhood follow-up

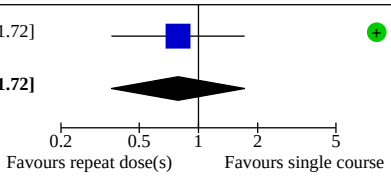
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
4.11.1 In all babies								
Crowther 2006	174	489	173	490	100.0%	1.01 [0.85 , 1.19]		+ + + + + +
Subtotal (95% CI)		**489**		**490**	**100.0%**	**1.01 [0.85 , 1.19]**		
Total events:	174		173					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
Total (95% CI)		**489**		**490**	**100.0%**	**1.01 [0.85 , 1.19]**		
Total events:	174		173					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.09 (P = 0.93)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.12. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 12: I6: Any respiratory disease at mid- to later childhood follow-up

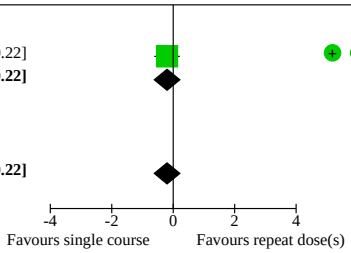
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	11	489	14	490	100.0%	0.79 [0.36 , 1.72]		+ + + - + -
Total (95% CI)		**489**		**490**	**100.0%**	**0.79 [0.36 , 1.72]**		
Total events:	11		14					
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.60 (P = 0.55)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.13. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 13: O1i: Mean weight at mid- to later childhood follow-up (kg)

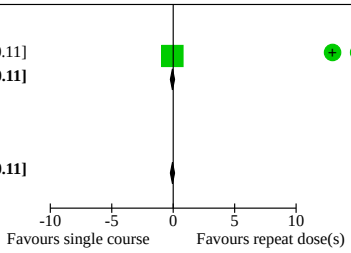
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.13.1 In all children								
Murphy 2008	19.3	4.3	827	19.5	4.3	808	100.0%	-0.20 [-0.62 , 0.22]
Subtotal (95% CI)			**827**			**808**	**100.0%**	**-0.20 [-0.62 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.94 (P = 0.35)								
Total (95% CI)			**827**			**808**	**100.0%**	**-0.20 [-0.62 , 0.22]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.94 (P = 0.35)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.14. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 14: O1i: Mean weight Z score at mid- to later childhood follow-up

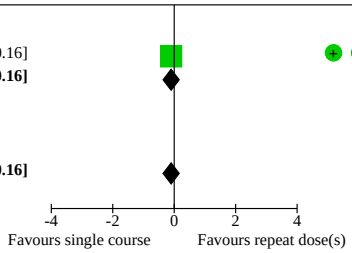
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI
4.14.1 In all children								
Crowther 2006	0.12	1.27	475	0.18	1.36	465	100.0%	-0.06 [-0.23 , 0.11]
Subtotal (95% CI)			**475**			**465**	**100.0%**	**-0.06 [-0.23 , 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
Total (95% CI)			**475**			**465**	**100.0%**	**-0.06 [-0.23 , 0.11]**
Heterogeneity: Not applicable								
Test for overall effect: Z = 0.70 (P = 0.48)								
Test for subgroup differences: Not applicable								



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.15. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 15: O1ii: Mean head circumference at mid- to later childhood follow-up (cm)

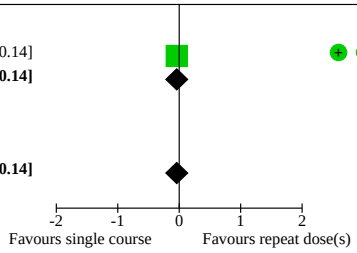
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.15.1 In all children									
Murphy 2008	51.1	2.6	827	51.2	2.8	808	100.0%	-0.10 [-0.36 , 0.16]	+ + ? + + ?
Subtotal (95% CI)			**827**			**808**	**100.0%**	**-0.10 [-0.36 , 0.16]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.75 (P = 0.45)									
Total (95% CI)			**827**			**808**	**100.0%**	**-0.10 [-0.36 , 0.16]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.75 (P = 0.45)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

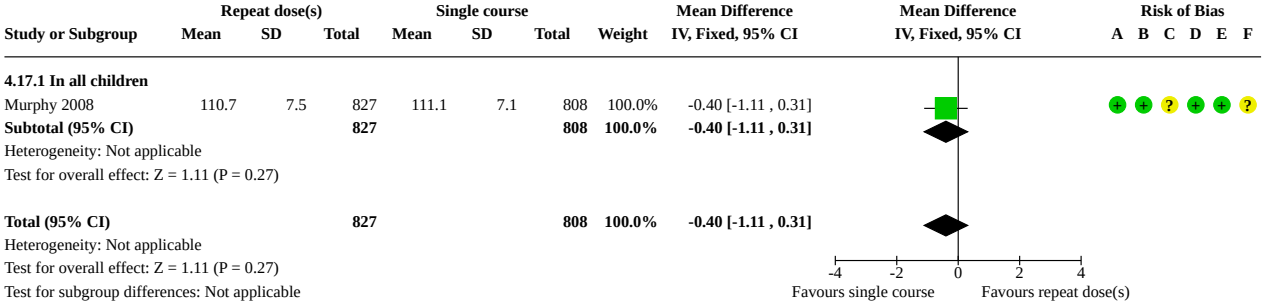
Analysis 4.16. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 16: O1ii: Head circumference Z score at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.16.1 In all children									
Crowther 2006	-0.49	1.33	442	-0.45	1.36	443	100.0%	-0.04 [-0.22 , 0.14]	+ + ? + + ?
Subtotal (95% CI)			**442**			**443**	**100.0%**	**-0.04 [-0.22 , 0.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.44 (P = 0.66)									
Total (95% CI)			**442**			**443**	**100.0%**	**-0.04 [-0.22 , 0.14]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.44 (P = 0.66)									
Test for subgroup differences: Not applicable									



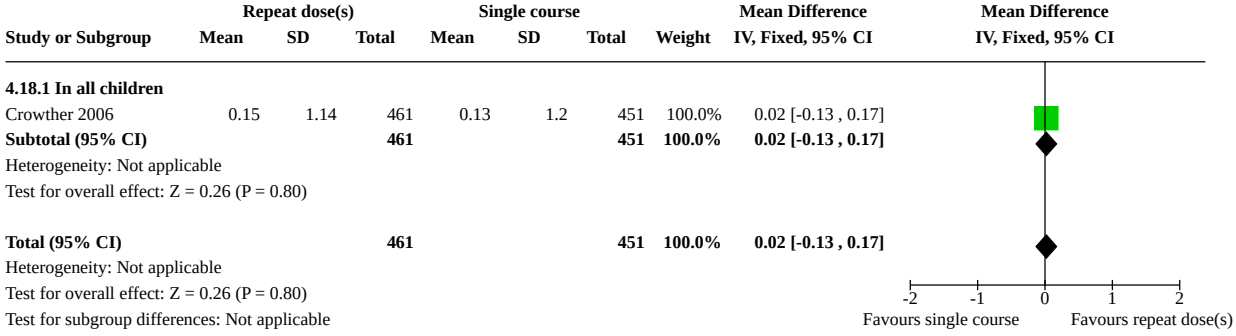
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.17. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 17: O1iii: Mean height at mid- to later childhood follow-up (cm)

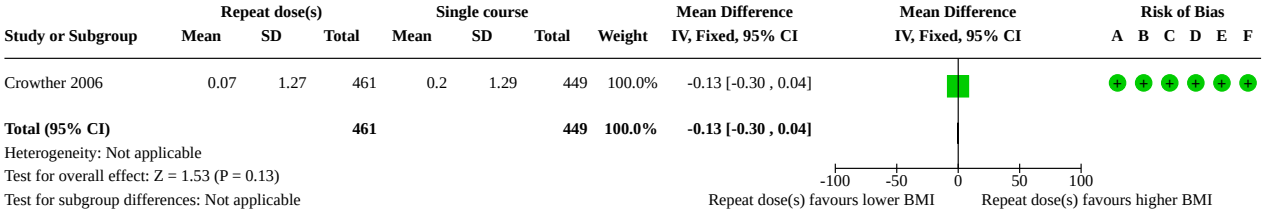


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.18. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 18: O1iii: Mean height Z score at mid- to later childhood follow-up



Analysis 4.19. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 19: O2: BMI Z scores at mid- to later childhood follow-up

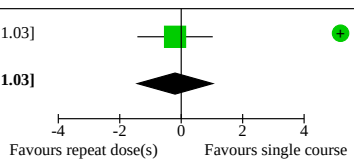


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.20. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 20: O4: Body composition: total body fat-free mass at mid- to later childhood follow-up (kg)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006 (1)	19.3	4.4	91	19.5	4.1	94	100.0%	-0.20 [-1.43 , 1.03]	+ + ? + ? ?
Total (95% CI)			**91**			**94**	**100.0%**	**-0.20 [-1.43 , 1.03]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.32 (P = 0.75)
Test for subgroup differences: Not applicable



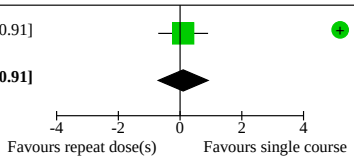
Footnotes
(1) Calculated mean and SD. Aged 6-8years.

Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.21. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 21: O5: Body composition: total body fat mass at mid- to later childhood follow-up (kg)

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	4.2	2.8	91	4.1	2.8	94	100.0%	0.10 [-0.71 , 0.91]	+ + ? + + ?
Total (95% CI)			**91**			**94**	**100.0%**	**0.10 [-0.71 , 0.91]**	

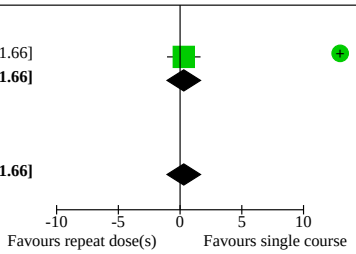
Heterogeneity: Not applicable
Test for overall effect: Z = 0.24 (P = 0.81)
Test for subgroup differences: Not applicable



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.22. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 22: O6: Mean systolic blood pressure at mid- to later childhood follow-up (mmHg)

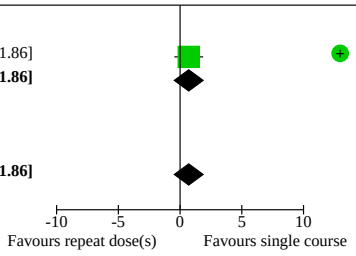
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.22.1 In all children										
Murphy 2008	98.5	14.1	827	98.2	13.9	808	100.0%	0.30 [-1.06 , 1.66]		+ + ? + + ?
Subtotal (95% CI)			**827**			**808**	**100.0%**	**0.30 [-1.06 , 1.66]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.43 (P = 0.66)										
Total (95% CI)			**827**			**808**	**100.0%**	**0.30 [-1.06 , 1.66]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 0.43 (P = 0.66)										
Test for subgroup differences: Not applicable										



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.23. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 23: O6: Mean diastolic blood pressure at mid- to later childhood follow-up (mmHg)

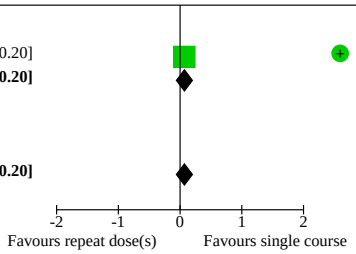
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.23.1 In all children										
Murphy 2008	61	11.5	827	60.3	12.5	808	100.0%	0.70 [-0.46 , 1.86]		+ + ? + + ?
Subtotal (95% CI)			**827**			**808**	**100.0%**	**0.70 [-0.46 , 1.86]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.18 (P = 0.24)										
Total (95% CI)			**827**			**808**	**100.0%**	**0.70 [-0.46 , 1.86]**		
Heterogeneity: Not applicable										
Test for overall effect: Z = 1.18 (P = 0.24)										
Test for subgroup differences: Not applicable										



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.24. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 24: O6: Mean systolic blood pressure Z score at mid- to later childhood follow-up

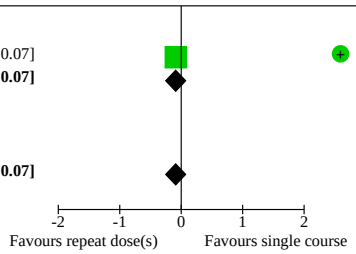
Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.24.1 In all children									
Crowther 2006	-0.26	0.97	423	-0.33	0.96	425	100.0%	0.07 [-0.06 , 0.20]	+ + ? + + ?
Subtotal (95% CI)			**423**			**425**	**100.0%**	**0.07 [-0.06 , 0.20]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.06 (P = 0.29)									
Total (95% CI)			**423**			**425**	**100.0%**	**0.07 [-0.06 , 0.20]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.06 (P = 0.29)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.25. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 25: O6: Mean diastolic blood pressure Z score at mid- to later childhood follow-up

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
4.25.1 In all children									
Crowther 2006	-1.14	1.21	423	-1.05	1.2	425	100.0%	-0.09 [-0.25 , 0.07]	+ + ? + + ?
Subtotal (95% CI)			**423**			**425**	**100.0%**	**-0.09 [-0.25 , 0.07]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.09 (P = 0.28)									
Total (95% CI)			**423**			**425**	**100.0%**	**-0.09 [-0.25 , 0.07]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 1.09 (P = 0.28)									
Test for subgroup differences: Not applicable									

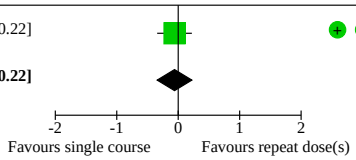


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.26. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 26: O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1 Z score

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	-0.04	0.94	98	0.02	1.01	87	100.0%	-0.06 [-0.34 , 0.22]	+ + - + + -
Total (95% CI)			**98**			**87**	**100.0%**	**-0.06 [-0.34 , 0.22]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 0.42 (P = 0.68)
Test for subgroup differences: Not applicable

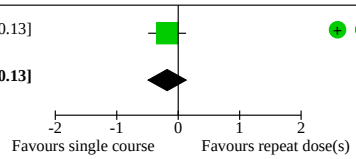


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.27. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 27: O8: Measures of lung function at mid- to later childhood follow-up: mean FVC Z score

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	-0.92	1.1	98	-0.74	1.04	87	100.0%	-0.18 [-0.49 , 0.13]	+ + - + + -
Total (95% CI)			**98**			**87**	**100.0%**	**-0.18 [-0.49 , 0.13]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.14 (P = 0.25)
Test for subgroup differences: Not applicable

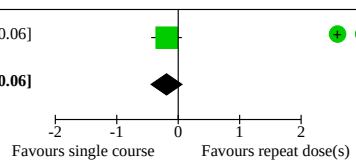


Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 4.28. Comparison 4: Repeat dose(s) of prenatal corticosteroids versus single course: outcomes for the child in mid- to later childhood (5 to < 18 years of age), Outcome 28: O8: Measures of lung function at mid- to later childhood follow-up: mean FEV_1/FVC Z score

Study or Subgroup	Repeat dose(s) Mean	SD	Total	Single course Mean	SD	Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
Crowther 2006	-1.54	0.85	98	-1.35	0.88	87	100.0%	-0.19 [-0.44 , 0.06]	+ + - + + -
Total (95% CI)			**98**			**87**	**100.0%**	**-0.19 [-0.44 , 0.06]**	

Heterogeneity: Not applicable
Test for overall effect: Z = 1.49 (P = 0.14)
Test for subgroup differences: Not applicable



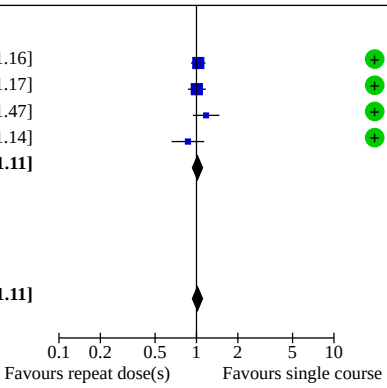
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

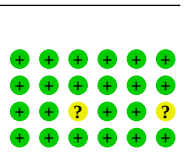
Comparison 6. Repeat dose(s) of corticosteroids versus single course: outcomes for health services

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
6.1 K1: Hospital re-admission by early childhood follow-up	4	3824	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
6.1.1 In all children	4	3824	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.93, 1.11]
6.2 K1: Hospital re-admission by mid to later childhood follow-up	1	980	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.80, 1.52]
6.2.1 In all children	1	980	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.80, 1.52]
6.3 Q2: Length of postnatal hospitalisation for the woman (days)	1	483	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.22, 0.22]
6.3.1 For all women	1	483	Mean Difference (IV, Fixed, 95% CI)	0.00 [-0.22, 0.22]
6.4 Q4: Length of infant hospitalisation (days)	3	1733	Mean Difference (IV, Fixed, 95% CI)	0.18 [-2.60, 2.96]

Analysis 6.1. Comparison 6: Repeat dose(s) of corticosteroids versus single course: outcomes for health services, Outcome 1: K1: Hospital re-admission by early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
6.1.1 In all children						
Crowther 2006	266	527	261	533	39.5%	1.03 [0.91 , 1.16]
Murphy 2008	266	1069	256	1035	39.6%	1.01 [0.87 , 1.17]
Peltoniemi 2007	71	120	70	139	9.9%	1.17 [0.94 , 1.47]
Wapner 2006	65	206	71	195	11.1%	0.87 [0.66 , 1.14]
Subtotal (95% CI)		**1922**		**1902**	**100.0%**	**1.02 [0.93 , 1.11]**
Total events:	668		658			
Heterogeneity: Chi² = 3.00, df = 3 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Total (95% CI)		**1922**		**1902**	**100.0%**	**1.02 [0.93 , 1.11]**
Total events:	668		658			
Heterogeneity: Chi² = 3.00, df = 3 (P = 0.39); I² = 0%						
Test for overall effect: Z = 0.39 (P = 0.70)						
Test for subgroup differences: Not applicable						

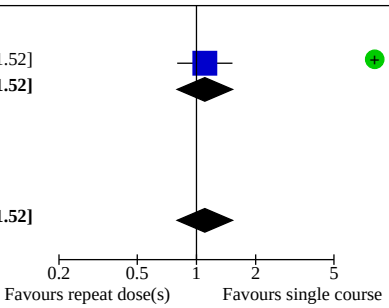




Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.2. Comparison 6: Repeat dose(s) of corticosteroids versus single course: outcomes for health services, Outcome 2: K1: Hospital re-admission by mid to later childhood follow-up

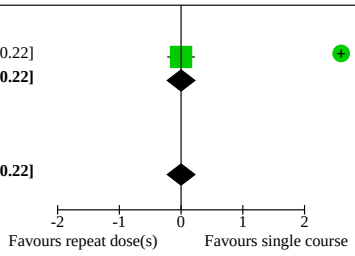
Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
6.2.1 In all children							
Crowther 2006	67	489	61	491	100.0%	1.10 [0.80 , 1.52]	+ + + - + -
Subtotal (95% CI)		**489**		**491**	**100.0%**	**1.10 [0.80 , 1.52]**	
Total events:	67		61				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.59 (P = 0.55)							
Total (95% CI)		**489**		**491**	**100.0%**	**1.10 [0.80 , 1.52]**	
Total events:	67		61				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.59 (P = 0.55)							
Test for subgroup differences: Not applicable							



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

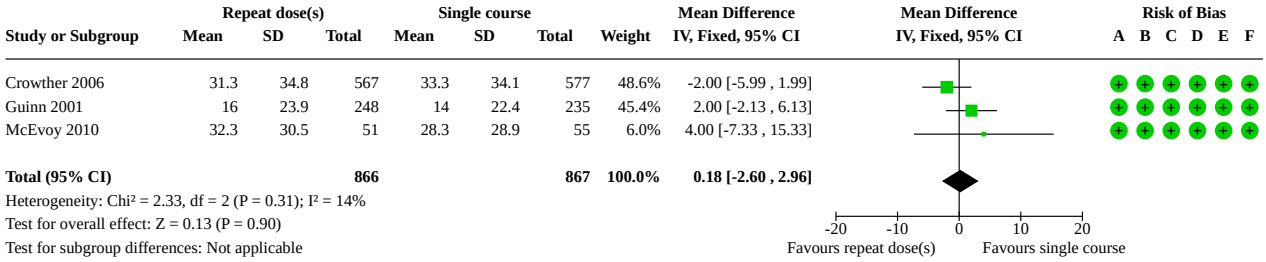
Analysis 6.3. Comparison 6: Repeat dose(s) of corticosteroids versus single course: outcomes for health services, Outcome 3: Q2: Length of postnatal hospitalisation for the woman (days)

Study or Subgroup	Repeat dose(s) Mean	Repeat dose(s) SD	Repeat dose(s) Total	Single course Mean	Single course SD	Single course Total	Weight	Mean Difference IV, Fixed, 95% CI	Risk of Bias A B C D E F
6.3.1 For all women									
Guinn 2001	2.6	1.2	248	2.6	1.3	235	100.0%	0.00 [-0.22 , 0.22]	+ + + + + +
Subtotal (95% CI)			**248**			**235**	**100.0%**	**0.00 [-0.22 , 0.22]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
Total (95% CI)			**248**			**235**	**100.0%**	**0.00 [-0.22 , 0.22]**	
Heterogeneity: Not applicable									
Test for overall effect: Z = 0.00 (P = 1.00)									
Test for subgroup differences: Not applicable									



Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 6.4. Comparison 6: Repeat dose(s) of corticosteroids versus single course: outcomes for health services, Outcome 4: Q4: Length of infant hospitalisation (days)



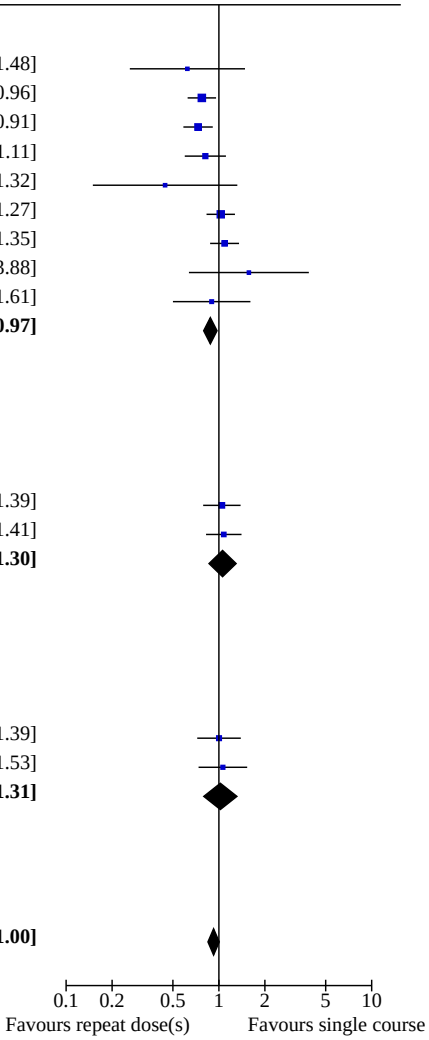
Risk of bias legend
(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Comparison 7. Subgroup analysis for the number of babies in utero

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
7.1 A12: Composite serious outcome (variously defined)	9	8373	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.85, 1.00]
7.1.1 A12: Composite serious outcome (variously defined); intention to treat analysis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
7.1.2 In babies from singleton pregnancies	2	1646	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.86, 1.30]
7.1.3 In babies from multiple pregnancies	2	991	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.31]
7.2 C3: Survival free of neurodevelopmental impairment at early childhood follow-up	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.03]
7.2.1 In babies from singleton pregnancies	1	1333	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.96, 1.05]
7.2.2 In babies from multiple pregnancies	1	771	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.94, 1.05]

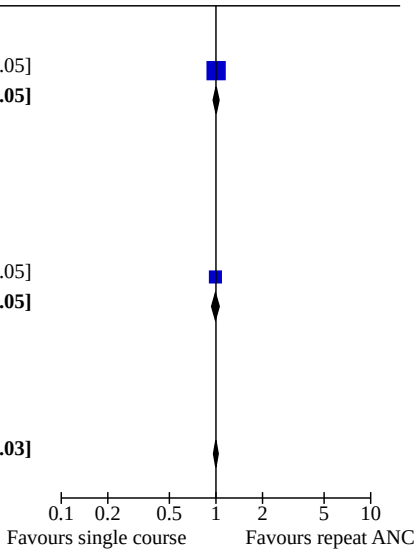
Analysis 7.1. Comparison 7: Subgroup analysis for the number of babies in utero, Outcome 1: A12: Composite serious outcome (variously defined)

Study or Subgroup	Repeat ANC Events	Repeat ANC Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.1.1 A12: Composite serious outcome (variously defined); intention to treat analysis						
Aghajafari 2002	4	9	5	7	0.7%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	18.0%	0.77 [0.62 , 0.96]
Garite 2009	88	289	120	288	14.6%	0.73 [0.59 , 0.91]
Guinn 2001	56	256	66	246	8.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.1%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	17.5%	1.03 [0.83 , 1.27]
Peltoniemi 2007	83	160	80	168	9.5%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	0.8%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	2.7%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2879**		**2857**	**73.0%**	**0.88 [0.80 , 0.97]**
Total events:	530		602			
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%						
Test for overall effect: Z = 2.51 (P = 0.01)						
7.1.2 In babies from singleton pregnancies						
Murphy 2008	88	739	83	729	10.1%	1.05 [0.79 , 1.39]
Peltoniemi 2007	53	93	45	85	5.7%	1.08 [0.82 , 1.41]
Subtotal (95% CI)		**832**		**814**	**15.8%**	**1.06 [0.86 , 1.30]**
Total events:	141		128			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
7.1.3 In babies from multiple pregnancies						
Murphy 2008	62	427	60	414	7.4%	1.00 [0.72 , 1.39]
Peltoniemi 2007	30	67	35	83	3.8%	1.06 [0.74 , 1.53]
Subtotal (95% CI)		**494**		**497**	**11.2%**	**1.02 [0.80 , 1.31]**
Total events:	92		95			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
Total (95% CI)		**4205**		**4168**	**100.0%**	**0.92 [0.85 , 1.00]**
Total events:	763		825			
Heterogeneity: Chi² = 17.40, df = 12 (P = 0.14); I² = 31%						
Test for overall effect: Z = 1.85 (P = 0.06)						
Test for subgroup differences: Chi² = 3.24, df = 2 (P = 0.20), I² = 38.3%						



Analysis 7.2. Comparison 7: Subgroup analysis for the number of babies in utero, Outcome 2: C3: Survival free of neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
7.2.1 In babies from singleton pregnancies						
Murphy 2008	582	675	566	658	63.2%	1.00 [0.96 , 1.05]
Subtotal (95% CI)		**675**		**658**	**63.2%**	**1.00 [0.96 , 1.05]**
Total events:	582		566			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
7.2.2 In babies from multiple pregnancies						
Murphy 2008	339	394	327	377	36.8%	0.99 [0.94 , 1.05]
Subtotal (95% CI)		**394**		**377**	**36.8%**	**0.99 [0.94 , 1.05]**
Total events:	339		327			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.28 (P = 0.78)						
Total (95% CI)		**1069**		**1035**	**100.0%**	**1.00 [0.96 , 1.03]**
Total events:	921		893			
Heterogeneity: Chi^2 = 0.08, df = 1 (P = 0.77); I^2 = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
Test for subgroup differences: Chi^2 = 0.08, df = 1 (P = 0.77), I^2 = 0%						



Comparison 8. Subgroup analysis for the planned number of repeat courses of corticosteroids to be given

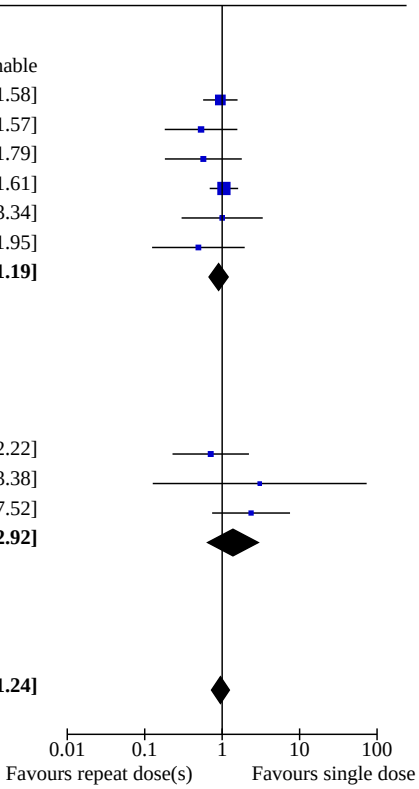
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.1 A1: Fetal or neonatal or infant death (< 1 year of age)	10	5849	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.24]
8.1.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	7	4831	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.68, 1.19]
8.1.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.38 [0.65, 2.92]
8.2 A2: Fetal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
8.2.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	4	1740	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.57]
8.2.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.14, 7.23]
8.3 A3: Neonatal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.61, 1.31]
8.3.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	4	1740	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.23]
8.3.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.36 [0.58, 3.19]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.4 A5: Respiratory distress syndrome	9	3540	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
8.4.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	6	2522	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.71, 0.91]
8.4.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.72, 0.98]
8.5 A6: Severe respiratory distress syndrome	5	3809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
8.5.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	4	3481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.09]
8.5.2 In babies planned for only 1 repeat course of prenatal corticosteroids	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.94, 1.60]
8.6 A7: Severe lung disease	6	4955	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
8.6.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	5	4627	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.63, 0.89]
8.6.2 In babies planned for only 1 repeat course of prenatal corticosteroids	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.94, 1.60]
8.7 A8: Chronic lung disease	9	5661	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.22]
8.7.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	6	4643	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.19]
8.7.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	1018	Risk Ratio (M-H, Fixed, 95% CI)	1.20 [0.80, 1.82]
8.8 A9: Severe Intraventricular haemorrhage (grade 3 or 4)	7	5066	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
8.8.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	5	4161	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.53, 1.79]
8.8.2 In babies planned for only 1 repeat course of prenatal corticosteroids	2	905	Risk Ratio (M-H, Fixed, 95% CI)	1.53 [0.63, 3.71]
8.9 A10: Intraventricular haemorrhage	6	3223	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
8.9.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	4	2318	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.24]
8.9.2 In babies planned for only 1 repeat course of prenatal corticosteroids	2	905	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.69, 1.42]

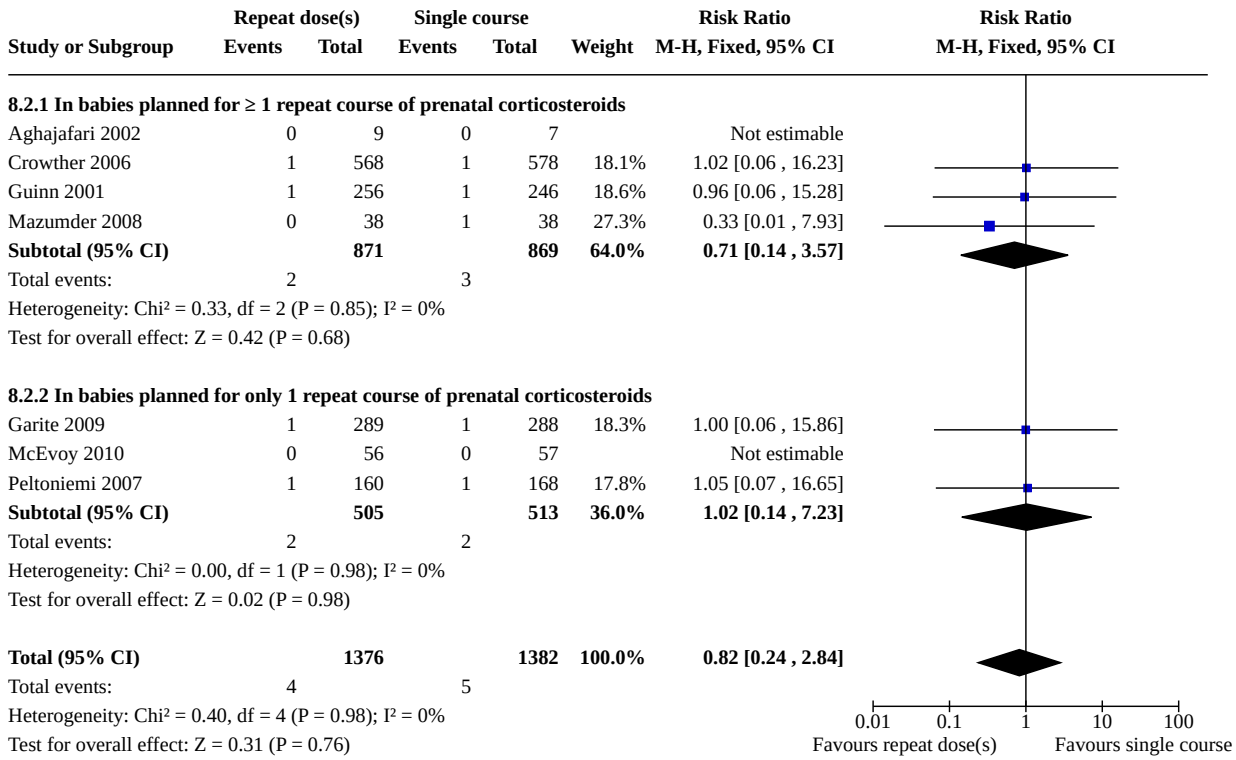
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
8.10 A11: Necrotising enterocolitis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.22]
8.10.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	7	4831	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.61, 1.39]
8.10.2 In babies planned for only 1 repeat course of prenatal corticosteroids	2	905	Risk Ratio (M-H, Fixed, 95% CI)	0.60 [0.27, 1.37]
8.11 A12: Composite serious outcome (variously defined)	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
8.11.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	7	4831	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.78, 1.00]
8.11.2 In babies planned for only 1 repeat course of prenatal corticosteroids	2	905	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]
8.12 B2: Maternal sepsis	8	4666	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.39]
8.12.1 For women planned for ≥ 1 repeat course of prenatal corticosteroids	7	4417	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.89, 1.36]
8.12.2 For women planned for only 1 repeat course of prenatal corticosteroids	1	249	Risk Ratio (M-H, Fixed, 95% CI)	1.57 [0.80, 3.10]
8.13 B3: Caesarean section	8	4266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
8.13.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	5	3495	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [1.00, 1.13]
8.13.2 In babies planned for only 1 repeat course of prenatal corticosteroids	3	771	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.83, 1.03]
8.14 C1: Total deaths (after randomisation) up to early childhood follow-up	5	4565	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]
8.14.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	4	4237	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.32]
8.14.2 In babies planned for only 1 repeat course of prenatal corticosteroids	1	328	Risk Ratio (M-H, Fixed, 95% CI)	2.31 [0.82, 6.50]
8.15 C4: Survival free of major neurodevelopmental impairment at early childhood follow-up	3	1816	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]
8.15.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids	2	1559	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.07]
8.15.2 In babies planned for only 1 repeat course of prenatal corticosteroids	1	257	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.95, 1.01]

Analysis 8.1. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 1: A1: Fetal or neonatal or infant death (< 1 year of age)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.1.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	27	568	29	578	26.7%	0.95 [0.57 , 1.58]
Guinn 2001	5	256	9	246	8.5%	0.53 [0.18 , 1.57]
Mazumder 2008	4	38	7	38	6.5%	0.57 [0.18 , 1.79]
Murphy 2008	43	1166	40	1143	37.5%	1.05 [0.69 , 1.61]
TEAMS 1999	5	94	5	94	4.6%	1.00 [0.30 , 3.34]
Wapner 2006	3	299	6	295	5.6%	0.49 [0.12 , 1.95]
Subtotal (95% CI)		**2430**		**2401**	**89.4%**	**0.90 [0.68 , 1.19]**
Total events:	87		96			
Heterogeneity: Chi² = 2.84, df = 5 (P = 0.72); I² = 0%						
Test for overall effect: Z = 0.73 (P = 0.46)						
8.1.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	5	289	7	288	6.5%	0.71 [0.23 , 2.22]
McEvoy 2010	1	56	0	57	0.5%	3.05 [0.13 , 73.38]
Peltoniemi 2007	9	160	4	168	3.6%	2.36 [0.74 , 7.52]
Subtotal (95% CI)		**505**		**513**	**10.6%**	**1.38 [0.65 , 2.92]**
Total events:	15		11			
Heterogeneity: Chi² = 2.37, df = 2 (P = 0.31); I² = 16%						
Test for overall effect: Z = 0.84 (P = 0.40)						
Total (95% CI)		**2935**		**2914**	**100.0%**	**0.95 [0.73 , 1.24]**
Total events:	102		107			
Heterogeneity: Chi² = 6.11, df = 8 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: Chi² = 1.09, df = 1 (P = 0.30), I² = 8.0%						

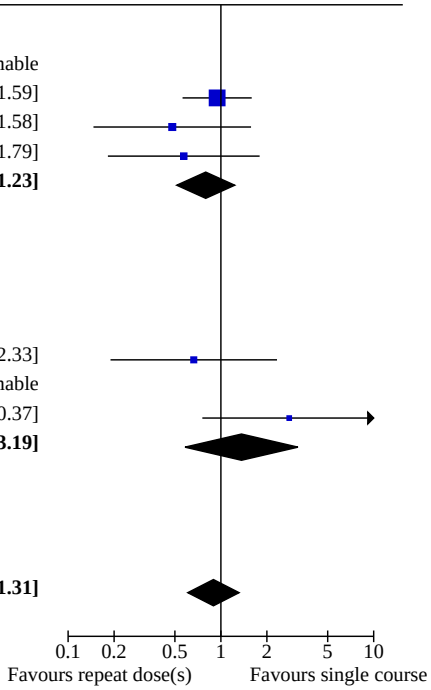


Analysis 8.2. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 2: A2: Fetal death



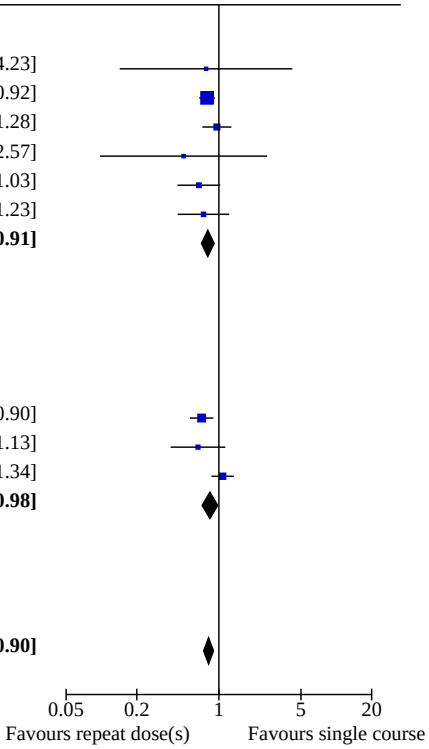
Analysis 8.3. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 3: A3: Neonatal death

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.3.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	26	568	28	578	53.5%	0.94 [0.56 , 1.59]
Guinn 2001	4	256	8	246	15.7%	0.48 [0.15 , 1.58]
Mazumder 2008	4	38	7	38	13.5%	0.57 [0.18 , 1.79]
Subtotal (95% CI)		**871**		**869**	**82.8%**	**0.80 [0.51 , 1.23]**
Total events:	34		43			
Heterogeneity: Chi² = 1.43, df = 2 (P = 0.49); I² = 0%						
Test for overall effect: Z = 1.03 (P = 0.30)						
8.3.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	4	289	6	288	11.6%	0.66 [0.19 , 2.33]
McEvoy 2010	0	56	0	57		Not estimable
Peltoniemi 2007	8	160	3	168	5.6%	2.80 [0.76 , 10.37]
Subtotal (95% CI)		**505**		**513**	**17.2%**	**1.36 [0.58 , 3.19]**
Total events:	12		9			
Heterogeneity: Chi² = 2.42, df = 1 (P = 0.12); I² = 59%						
Test for overall effect: Z = 0.71 (P = 0.47)						
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.89 [0.61 , 1.31]**
Total events:	46		52			
Heterogeneity: Chi² = 4.82, df = 4 (P = 0.31); I² = 17%						
Test for overall effect: Z = 0.57 (P = 0.57)						
Test for subgroup differences: Chi² = 1.22, df = 1 (P = 0.27), I² = 18.0%						



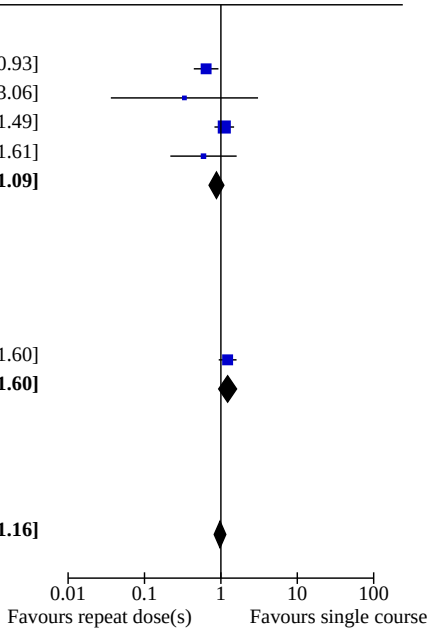
Analysis 8.4. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 4: A5: Respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.4.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14 , 4.23]
Crowther 2006	186	568	239	578	39.5%	0.79 [0.68 , 0.92]
Guinn 2001	69	256	69	246	11.7%	0.96 [0.72 , 1.28]
Mazumder 2008	2	38	4	38	0.7%	0.50 [0.10 , 2.57]
TEAMS 1999	25	94	37	94	6.2%	0.68 [0.44 , 1.03]
Wapner 2006	24	299	32	295	5.4%	0.74 [0.45 , 1.23]
Subtotal (95% CI)		**1264**		**1258**	**63.8%**	**0.80 [0.71 , 0.91]**
Total events:	308		383			
Heterogeneity: Chi² = 2.64, df = 5 (P = 0.76); I² = 0%						
Test for overall effect: Z = 3.44 (P = 0.0006)						
8.4.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	83	289	116	288	19.4%	0.71 [0.57 , 0.90]
McEvoy 2010	15	56	23	57	3.8%	0.66 [0.39 , 1.13]
Peltoniemi 2007	82	160	80	168	13.0%	1.08 [0.86 , 1.34]
Subtotal (95% CI)		**505**		**513**	**36.2%**	**0.84 [0.72 , 0.98]**
Total events:	180		219			
Heterogeneity: Chi² = 7.63, df = 2 (P = 0.02); I² = 74%						
Test for overall effect: Z = 2.26 (P = 0.02)						
Total (95% CI)		**1769**		**1771**	**100.0%**	**0.82 [0.74 , 0.90]**
Total events:	488		602			
Heterogeneity: Chi² = 10.71, df = 8 (P = 0.22); I² = 25%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Test for subgroup differences: Chi² = 0.17, df = 1 (P = 0.68), I² = 0%						



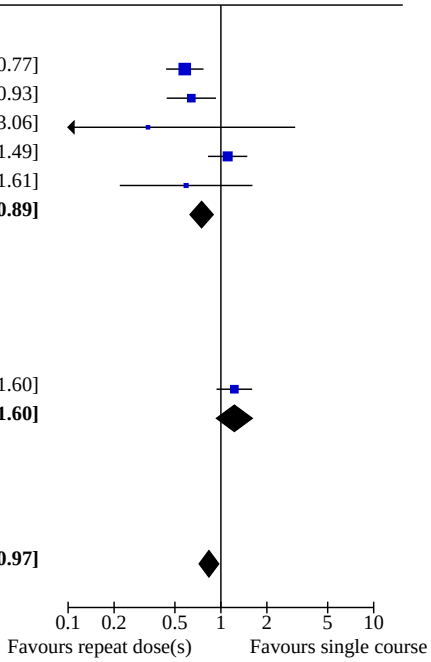
Analysis 8.5. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 5: A6: Severe respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.5.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Guinn 2001	38	256	57	246	28.0%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	1.4%	0.33 [0.04 , 3.06]
Murphy 2008	87	1166	77	1143	37.5%	1.11 [0.82 , 1.49]
Wapner 2006	6	299	10	295	4.9%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**1759**		**1722**	**71.8%**	**0.87 [0.70 , 1.09]**
Total events:	132		147			
Heterogeneity: Chi² = 6.47, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 1.18 (P = 0.24)						
8.5.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Peltoniemi 2007	70	160	60	168	28.2%	1.23 [0.94 , 1.60]
Subtotal (95% CI)		**160**		**168**	**28.2%**	**1.23 [0.94 , 1.60]**
Total events:	70		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**1919**		**1890**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	202		207			
Heterogeneity: Chi² = 10.28, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Test for subgroup differences: Chi² = 3.58, df = 1 (P = 0.06), I² = 72.1%						

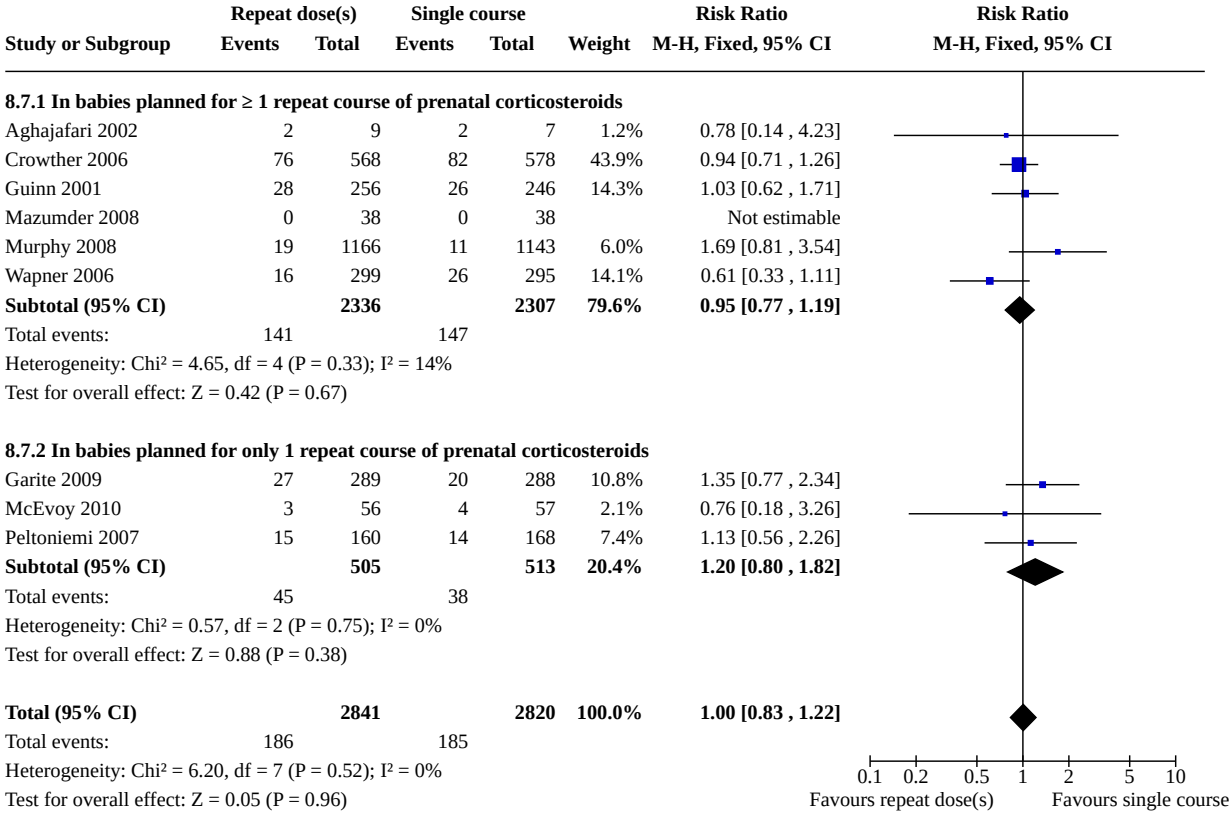


Analysis 8.6. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 6: A7: Severe lung disease

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.6.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Crowther 2006	65	568	114	578	35.3%	0.58 [0.44 , 0.77]
Guinn 2001	38	256	57	246	18.1%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	0.9%	0.33 [0.04 , 3.06]
Murphy 2008	87	1166	77	1143	24.3%	1.11 [0.82 , 1.49]
Wapner 2006	6	299	10	295	3.1%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**2327**		**2300**	**81.7%**	**0.75 [0.63 , 0.89]**
Total events:	197		261			
Heterogeneity: Chi² = 11.28, df = 4 (P = 0.02); I² = 65%						
Test for overall effect: Z = 3.28 (P = 0.001)						
8.6.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Peltoniemi 2007	70	160	60	168	18.3%	1.23 [0.94 , 1.60]
Subtotal (95% CI)		**160**		**168**	**18.3%**	**1.23 [0.94 , 1.60]**
Total events:	70		60			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.48 (P = 0.14)						
Total (95% CI)		**2487**		**2468**	**100.0%**	**0.83 [0.72 , 0.97]**
Total events:	267		321			
Heterogeneity: Chi² = 20.83, df = 5 (P = 0.0009); I² = 76%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Chi² = 9.16, df = 1 (P = 0.002), I² = 89.1%						

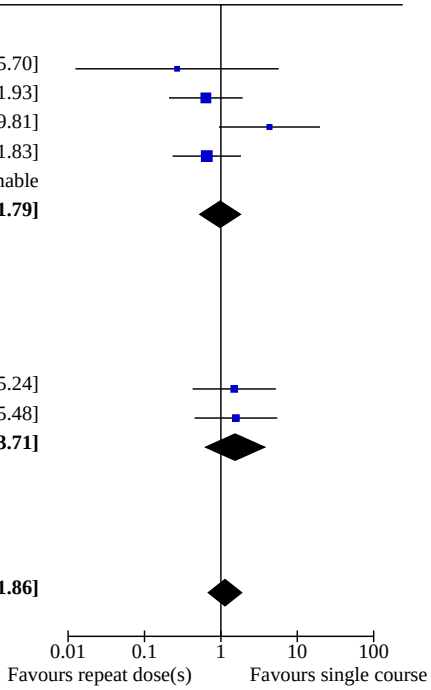


Analysis 8.7. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 7: A8: Chronic lung disease

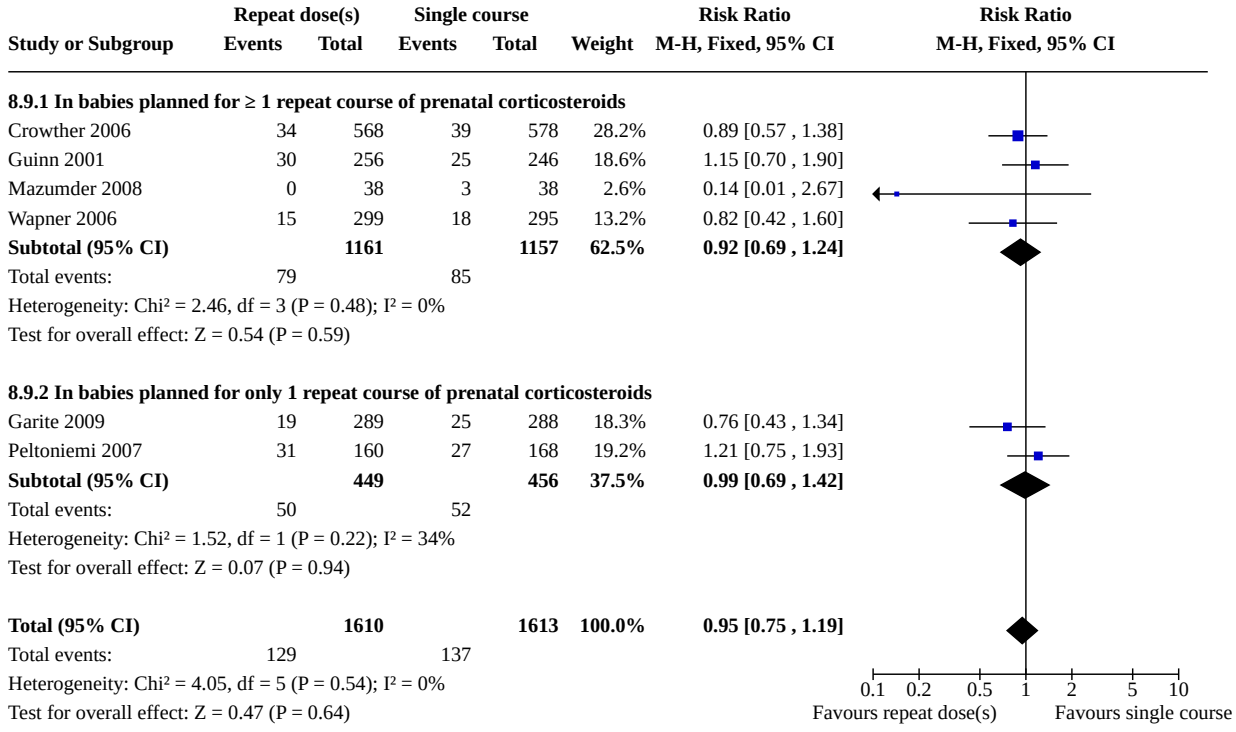


Analysis 8.8. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 8: A9: Severe Intraventricular haemorrhage (grade 3 or 4)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.8.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	0	9	1	7	5.8%	0.27 [0.01 , 5.70]
Crowther 2006	5	568	8	578	27.7%	0.64 [0.21 , 1.93]
Guinn 2001	9	256	2	246	7.1%	4.32 [0.94 , 19.81]
Murphy 2008	6	1166	9	1143	31.7%	0.65 [0.23 , 1.83]
TEAMS 1999	0	94	0	94		Not estimable
Subtotal (95% CI)		**2093**		**2068**	**72.4%**	**0.98 [0.53 , 1.79]**
Total events:	20		20			
Heterogeneity: Chi² = 5.52, df = 3 (P = 0.14); I² = 46%						
Test for overall effect: Z = 0.08 (P = 0.94)						
8.8.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	6	289	4	288	14.0%	1.49 [0.43 , 5.24]
Peltoniemi 2007	6	160	4	168	13.6%	1.57 [0.45 , 5.48]
Subtotal (95% CI)		**449**		**456**	**27.6%**	**1.53 [0.63 , 3.71]**
Total events:	12		8			
Heterogeneity: Chi² = 0.00, df = 1 (P = 0.95); I² = 0%						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**2542**		**2524**	**100.0%**	**1.13 [0.69 , 1.86]**
Total events:	32		28			
Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.68, df = 1 (P = 0.41), I² = 0%						

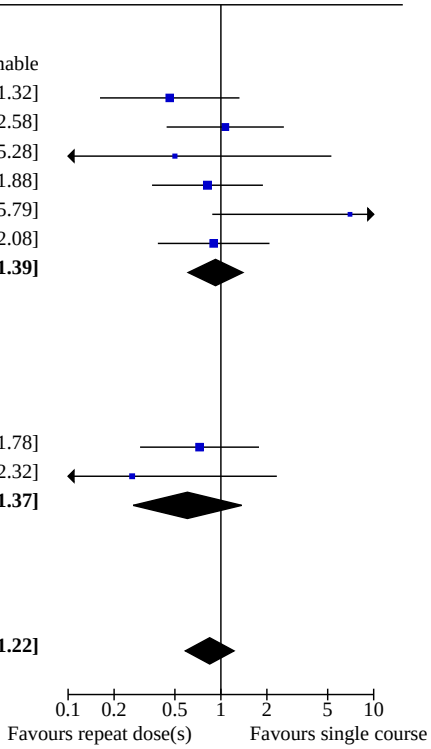


Analysis 8.9. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 9: A10: Intraventricular haemorrhage



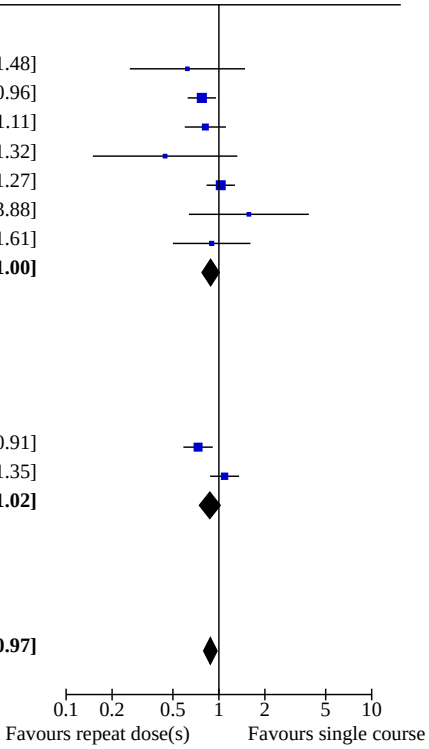
Analysis 8.10. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 10: A11: Necrotising enterocolitis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.10.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	5	568	11	578	17.8%	0.46 [0.16 , 1.32]
Guinn 2001	10	256	9	246	15.0%	1.07 [0.44 , 2.58]
Mazumder 2008	1	38	2	38	3.3%	0.50 [0.05 , 5.28]
Murphy 2008	10	1166	12	1143	19.8%	0.82 [0.35 , 1.88]
TEAMS 1999	7	94	1	94	1.6%	7.00 [0.88 , 55.79]
Wapner 2006	10	299	11	295	18.1%	0.90 [0.39 , 2.08]
Subtotal (95% CI)		**2430**		**2401**	**75.6%**	**0.92 [0.61 , 1.39]**
Total events:	43		46			
Heterogeneity: Chi² = 5.77, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 0.39 (P = 0.70)						
8.10.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	8	289	11	288	18.0%	0.72 [0.30 , 1.78]
Peltoniemi 2007	1	160	4	168	6.4%	0.26 [0.03 , 2.32]
Subtotal (95% CI)		**449**		**456**	**24.4%**	**0.60 [0.27 , 1.37]**
Total events:	9		15			
Heterogeneity: Chi² = 0.72, df = 1 (P = 0.40); I² = 0%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.84 [0.59 , 1.22]**
Total events:	52		61			
Heterogeneity: Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 0.82, df = 1 (P = 0.36), I² = 0%						

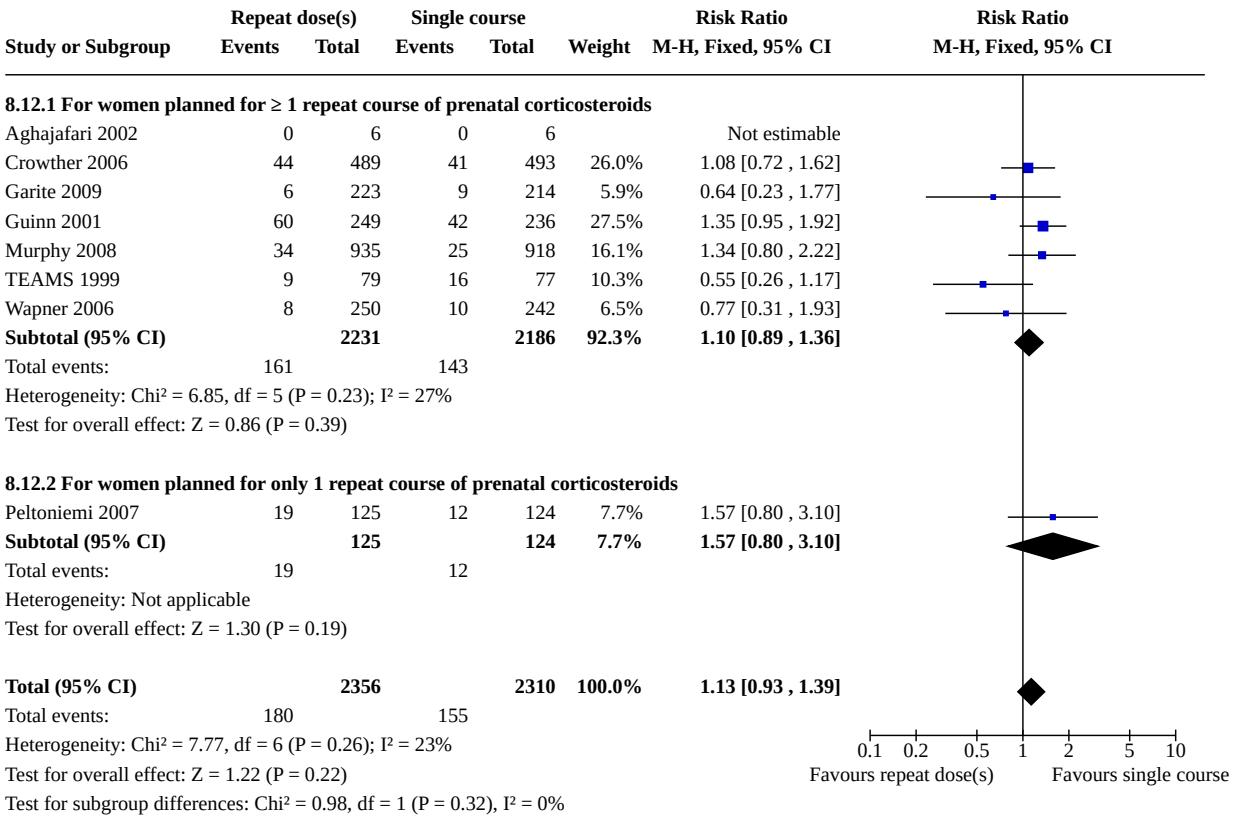


Analysis 8.11. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 11: A12: Composite serious outcome (variously defined)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.11.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.5%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	24.0%	1.03 [0.83 , 1.27]
TEAMS 1999	11	94	7	94	1.2%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	3.7%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2430**		**2401**	**67.1%**	**0.88 [0.78 , 1.00]**
Total events:	359		402			
Heterogeneity: Chi² = 7.39, df = 6 (P = 0.29); I² = 19%						
Test for overall effect: Z = 1.90 (P = 0.06)						
8.11.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	88	289	120	288	20.0%	0.73 [0.59 , 0.91]
Peltoniemi 2007	83	160	80	168	13.0%	1.09 [0.88 , 1.35]
Subtotal (95% CI)		**449**		**456**	**32.9%**	**0.87 [0.75 , 1.02]**
Total events:	171		200			
Heterogeneity: Chi² = 6.46, df = 1 (P = 0.01); I² = 85%						
Test for overall effect: Z = 1.72 (P = 0.08)						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.88 [0.80 , 0.97]**
Total events:	530		602			
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Chi² = 0.01, df = 1 (P = 0.91), I² = 0%						

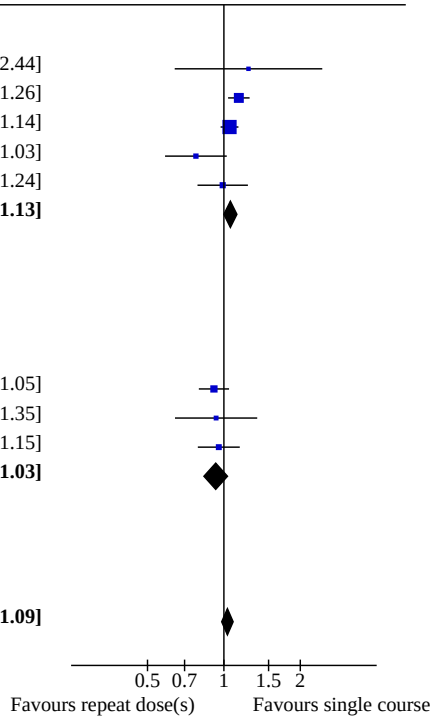


Analysis 8.12. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 12: B2: Maternal sepsis



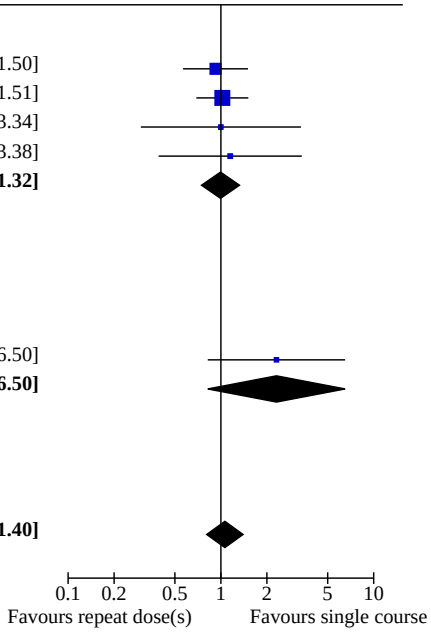
Analysis 8.13. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 13: B3: Caesarean section

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.13.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Aghajafari 2002	5	6	4	6	0.3%	1.25 [0.64 , 2.44]
Crowther 2006	326	489	287	493	24.0%	1.15 [1.04 , 1.26]
Murphy 2008	537	935	501	918	42.4%	1.05 [0.97 , 1.14]
TEAMS 1999	39	79	49	77	4.2%	0.78 [0.59 , 1.03]
Wapner 2006	93	250	91	242	7.8%	0.99 [0.79 , 1.24]
Subtotal (95% CI)		**1759**		**1736**	**78.7%**	**1.06 [1.00 , 1.13]**
Total events:	1000		932			
Heterogeneity: Chi² = 7.79, df = 4 (P = 0.10); I² = 49%						
Test for overall effect: Z = 1.95 (P = 0.05)						
8.13.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Garite 2009	139	223	146	214	12.5%	0.91 [0.80 , 1.05]
McEvoy 2010	24	44	24	41	2.1%	0.93 [0.64 , 1.35]
Peltoniemi 2007	77	125	80	124	6.7%	0.95 [0.79 , 1.15]
Subtotal (95% CI)		**392**		**379**	**21.3%**	**0.93 [0.83 , 1.03]**
Total events:	240		250			
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 1.36 (P = 0.17)						
Total (95% CI)		**2151**		**2115**	**100.0%**	**1.03 [0.98 , 1.09]**
Total events:	1240		1182			
Heterogeneity: Chi² = 13.00, df = 7 (P = 0.07); I² = 46%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 4.58, df = 1 (P = 0.03), I² = 78.1%						



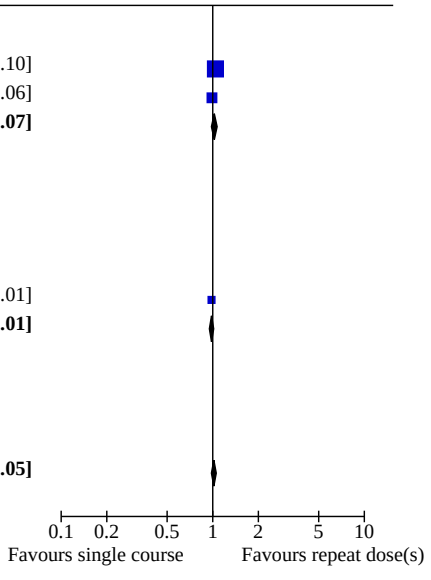
Analysis 8.14. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 14: C1: Total deaths (after randomisation) up to early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.14.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Crowther 2006	29	568	32	578	33.4%	0.92 [0.57 , 1.50]
Murphy 2008	49	1166	47	1143	49.9%	1.02 [0.69 , 1.51]
TEAMS 1999	5	94	5	94	5.3%	1.00 [0.30 , 3.34]
Wapner 2006	7	299	6	295	6.4%	1.15 [0.39 , 3.38]
Subtotal (95% CI)		**2127**		**2110**	**94.9%**	**0.99 [0.75 , 1.32]**
Total events:	90		90			
Heterogeneity: Chi² = 0.18, df = 3 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.04 (P = 0.97)						
8.14.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Peltoniemi 2007	11	160	5	168	5.1%	2.31 [0.82 , 6.50]
Subtotal (95% CI)		**160**		**168**	**5.1%**	**2.31 [0.82 , 6.50]**
Total events:	11		5			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.59 (P = 0.11)						
Total (95% CI)		**2287**		**2278**	**100.0%**	**1.06 [0.81 , 1.40]**
Total events:	101		95			
Heterogeneity: Chi² = 2.55, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 2.37, df = 1 (P = 0.12), I² = 57.8%						



Analysis 8.15. Comparison 8: Subgroup analysis for the planned number of repeat courses of corticosteroids to be given, Outcome 15: C4: Survival free of major neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
8.15.1 In babies planned for ≥ 1 repeat course of prenatal corticosteroids						
Crowther 2006	442	524	434	536	55.3%	1.04 [0.99 , 1.10]
Wapner 2006	222	255	215	244	28.3%	0.99 [0.92 , 1.06]
Subtotal (95% CI)		**779**		**780**	**83.7%**	**1.02 [0.98 , 1.07]**
Total events:	664		649			
Heterogeneity: Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 1.06 (P = 0.29)						
8.15.2 In babies planned for only 1 repeat course of prenatal corticosteroids						
Peltoniemi 2007	115	118	138	139	16.3%	0.98 [0.95 , 1.01]
Subtotal (95% CI)		**118**		**139**	**16.3%**	**0.98 [0.95 , 1.01]**
Total events:	115		138			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.12 (P = 0.26)						
Total (95% CI)		**897**		**919**	**100.0%**	**1.02 [0.98 , 1.05]**
Total events:	779		787			
Heterogeneity: Chi² = 5.98, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 2.33, df = 1 (P = 0.13), I² = 57.0%						



Comparison 9. Subgroup analysis for planned interval between corticosteroid treatments

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.1 A1: Fetal or neonatal or infant death (< 1 year of age)	10	5849	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.24]
9.1.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	7	2850	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.62, 1.28]
9.1.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.1.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2999	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.52]
9.2 A2: Fetal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]
9.2.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2068	Risk Ratio (M-H, Fixed, 95% CI)	0.78 [0.19, 3.15]
9.2.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.2.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	690	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.86]
9.3 A3: Neonatal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
9.3.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2068	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.62, 1.39]
9.3.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.3.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	690	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.27, 2.61]
9.4 A5: Respiratory distress syndrome	9	3540	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
9.4.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	7	2850	Risk Ratio (M-H, Fixed, 95% CI)	0.85 [0.76, 0.95]
9.4.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.4.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	690	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.57, 0.87]
9.5 A6: Severe respiratory distress syndrome	5	3809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
9.5.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	4	1500	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.72, 1.10]
9.5.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.5.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2309	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.49]
9.6 A7: Severe lung disease	6	4955	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
9.6.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2646	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.63, 0.89]
9.6.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.6.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2309	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.49]
9.7 A8: Chronic lung disease	9	5661	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.22]
9.7.1 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.7.2 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	6	2662	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.14]
9.7.3 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.7.4 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2999	Risk Ratio (M-H, Fixed, 95% CI)	1.39 [0.91, 2.12]
9.8 A9: Severe intraventricular haemorrhage (grade 3 or 4)	7	5066	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
9.8.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2180	Risk Ratio (M-H, Fixed, 95% CI)	1.32 [0.69, 2.53]

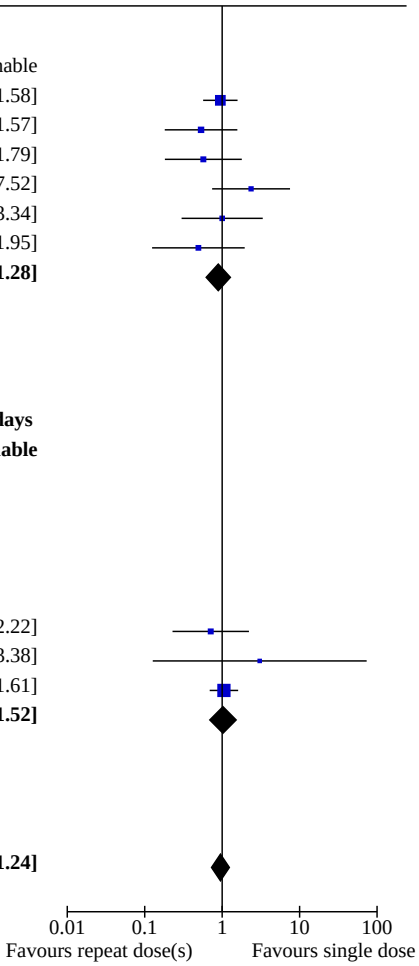
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.8.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.8.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2886	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.42, 1.99]
9.9 A10: Intraventricular haemorrhage	6	3223	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
9.9.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	2646	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.77, 1.27]
9.9.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.9.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	577	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.43, 1.34]
9.10 A11: Necrotising enterocolitis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.22]
9.10.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	7	2850	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.56, 1.40]
9.10.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.10.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2886	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.42, 1.42]
9.11 A12: Composite serious outcome (variously defined)	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
9.11.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	7	2850	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 0.99]
9.11.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.11.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2886	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
9.12 B2: Maternal sepsis	8	4666	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.39]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.12.1 For women treated with repeat corticosteroids at a minimum interval of 7 days or less	6	2376	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.90, 1.42]
9.12.2 For women treated with repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.12.3 For women treated with repeat corticosteroids at a minimum interval of 14 days or more	2	2290	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.73, 1.80]
9.13 B3: Caesarean section	8	4266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
9.13.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	5	1891	Risk Ratio (M-H, Fixed, 95% CI)	1.05 [0.97, 1.14]
9.13.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.13.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	3	2375	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.95, 1.09]
9.14 C1: Total deaths after randomisation up to early childhood follow-up	5	4565	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]
9.14.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	4	2256	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.75, 1.61]
9.14.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.14.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2309	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.69, 1.51]
9.15 C2: Neurodevelopmental impairment at early childhood follow-up	4	3616	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.10]
9.15.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	3	1608	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.82, 1.10]
9.15.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.15.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2008	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.77, 1.32]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
9.16 C3: Survival free of neurodevelopmental impairment at early childhood follow-up	4	3845	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]
9.16.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	3	1741	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.96, 1.09]
9.16.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.16.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2104	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.03]
9.17 C5: Cerebral palsy at early childhood follow-up	5	3923	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
9.17.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	4	1915	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.68, 1.85]
9.17.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.17.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	2008	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.53, 1.62]
9.18 C6: Developmental delay or intellectual impairment at early childhood follow-up (any)	4	3581	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.84, 1.09]
9.18.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	3	1680	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.81, 1.09]
9.18.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
9.18.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	1	1901	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.75, 1.32]

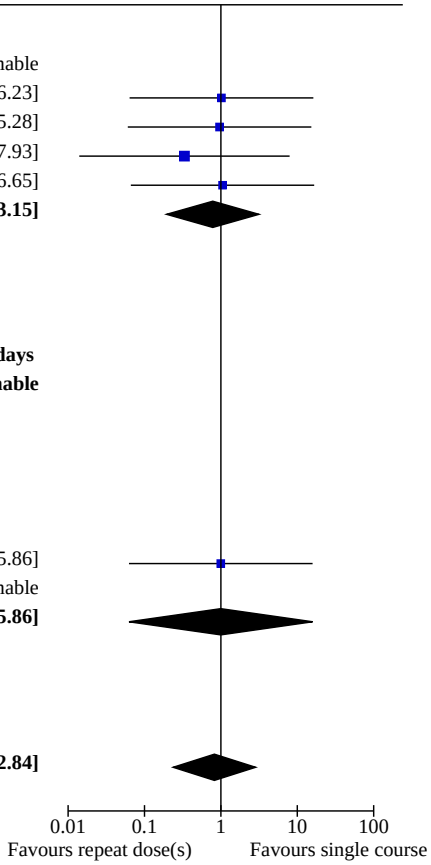
Analysis 9.1. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 1: A1: Fetal or neonatal or infant death (< 1 year of age)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.1.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	27	568	29	578	26.7%	0.95 [0.57 , 1.58]
Guinn 2001	5	256	9	246	8.5%	0.53 [0.18 , 1.57]
Mazumder 2008	4	38	7	38	6.5%	0.57 [0.18 , 1.79]
Peltoniemi 2007	9	160	4	168	3.6%	2.36 [0.74 , 7.52]
TEAMS 1999	5	94	5	94	4.6%	1.00 [0.30 , 3.34]
Wapner 2006	3	299	6	295	5.6%	0.49 [0.12 , 1.95]
Subtotal (95% CI)		**1424**		**1426**	**55.5%**	**0.89 [0.62 , 1.28]**
Total events:	53		60			
Heterogeneity: Chi² = 4.97, df = 5 (P = 0.42); I² = 0%						
Test for overall effect: Z = 0.63 (P = 0.53)						
9.1.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.1.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	5	289	7	288	6.5%	0.71 [0.23 , 2.22]
McEvoy 2010	1	56	0	57	0.5%	3.05 [0.13 , 73.38]
Murphy 2008	43	1166	40	1143	37.5%	1.05 [0.69 , 1.61]
Subtotal (95% CI)		**1511**		**1488**	**44.5%**	**1.02 [0.69 , 1.52]**
Total events:	49		47			
Heterogeneity: Chi² = 0.86, df = 2 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.12 (P = 0.90)						
Total (95% CI)		**2935**		**2914**	**100.0%**	**0.95 [0.73 , 1.24]**
Total events:	102		107			
Heterogeneity: Chi² = 6.11, df = 8 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: Chi² = 0.27, df = 1 (P = 0.61), I² = 0%						



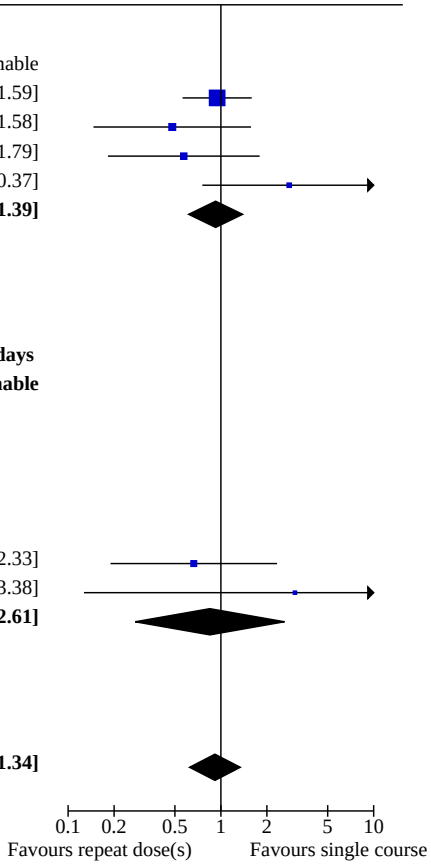
Analysis 9.2. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 2: A2: Fetal death

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.2.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	1	568	1	578	18.1%	1.02 [0.06 , 16.23]
Guinn 2001	1	256	1	246	18.6%	0.96 [0.06 , 15.28]
Mazumder 2008	0	38	1	38	27.3%	0.33 [0.01 , 7.93]
Peltoniemi 2007	1	160	1	168	17.8%	1.05 [0.07 , 16.65]
Subtotal (95% CI)		**1031**		**1037**	**81.7%**	**0.78 [0.19 , 3.15]**
Total events:	3		4			
Heterogeneity: Chi² = 0.38, df = 3 (P = 0.94); I² = 0%						
Test for overall effect: Z = 0.34 (P = 0.73)						
9.2.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.2.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	1	289	1	288	18.3%	1.00 [0.06 , 15.86]
McEvoy 2010	0	56	0	57		Not estimable
Subtotal (95% CI)		**345**		**345**	**18.3%**	**1.00 [0.06 , 15.86]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.00 (P = 1.00)						
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.82 [0.24 , 2.84]**
Total events:	4		5			
Heterogeneity: Chi² = 0.40, df = 4 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.31 (P = 0.76)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.88), I² = 0%						



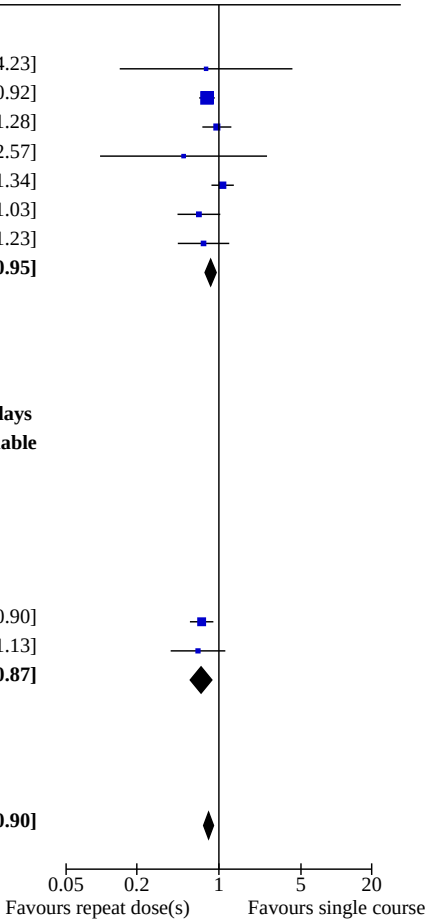
Analysis 9.3. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 3: A3: Neonatal death

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.3.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	26	568	28	578	53.0%	0.94 [0.56 , 1.59]
Guinn 2001	4	256	8	246	15.6%	0.48 [0.15 , 1.58]
Mazumder 2008	4	38	7	38	13.4%	0.57 [0.18 , 1.79]
Peltoniemi 2007	8	160	3	168	5.6%	2.80 [0.76 , 10.37]
Subtotal (95% CI)		**1031**		**1037**	**87.6%**	**0.92 [0.62 , 1.39]**
Total events:	42		46			
Heterogeneity: Chi² = 4.61, df = 3 (P = 0.20); I² = 35%						
Test for overall effect: Z = 0.38 (P = 0.70)						
9.3.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.3.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	4	289	6	288	11.5%	0.66 [0.19 , 2.33]
McEvoy 2010	1	56	0	57	0.9%	3.05 [0.13 , 73.38]
Subtotal (95% CI)		**345**		**345**	**12.4%**	**0.85 [0.27 , 2.61]**
Total events:	5		6			
Heterogeneity: Chi² = 0.77, df = 1 (P = 0.38); I² = 0%						
Test for overall effect: Z = 0.29 (P = 0.77)						
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.91 [0.62 , 1.34]**
Total events:	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Chi² = 0.02, df = 1 (P = 0.89), I² = 0%						



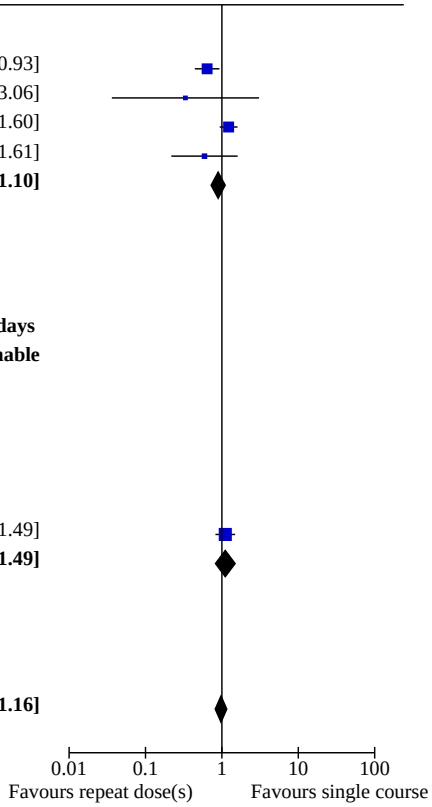
Analysis 9.4. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 4: A5: Respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.4.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14 , 4.23]
Crowther 2006	186	568	239	578	39.5%	0.79 [0.68 , 0.92]
Guinn 2001	69	256	69	246	11.7%	0.96 [0.72 , 1.28]
Mazumder 2008	2	38	4	38	0.7%	0.50 [0.10 , 2.57]
Peltoniemi 2007	82	160	80	168	13.0%	1.08 [0.86 , 1.34]
TEAMS 1999	25	94	37	94	6.2%	0.68 [0.44 , 1.03]
Wapner 2006	24	299	32	295	5.4%	0.74 [0.45 , 1.23]
Subtotal (95% CI)		**1424**		**1426**	**76.8%**	**0.85 [0.76 , 0.95]**
Total events:	390		463			
Heterogeneity: Chi² = 7.85, df = 6 (P = 0.25); I² = 24%						
Test for overall effect: Z = 2.93 (P = 0.003)						
9.4.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.4.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	83	289	116	288	19.4%	0.71 [0.57 , 0.90]
McEvoy 2010	15	56	23	57	3.8%	0.66 [0.39 , 1.13]
Subtotal (95% CI)		**345**		**345**	**23.2%**	**0.70 [0.57 , 0.87]**
Total events:	98		139			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 3.25 (P = 0.001)						
Total (95% CI)		**1769**		**1771**	**100.0%**	**0.82 [0.74 , 0.90]**
Total events:	488		602			
Heterogeneity: Chi² = 10.71, df = 8 (P = 0.22); I² = 25%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Test for subgroup differences: Chi² = 2.40, df = 1 (P = 0.12), I² = 58.3%						



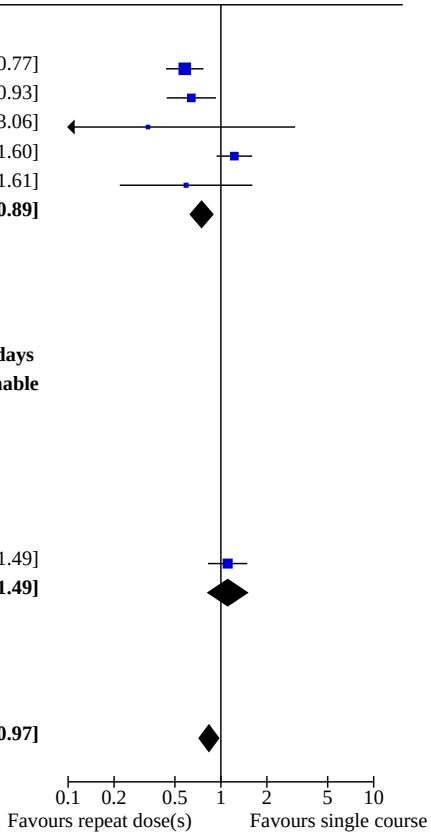
Analysis 9.5. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 5: A6: Severe respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.5.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Guinn 2001	38	256	57	246	28.0%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	1.4%	0.33 [0.04 , 3.06]
Peltoniemi 2007	70	160	60	168	28.2%	1.23 [0.94 , 1.60]
Wapner 2006	6	299	10	295	4.9%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**753**		**747**	**62.5%**	**0.89 [0.72 , 1.10]**
Total events:	115		130			
Heterogeneity: Chi² = 9.81, df = 3 (P = 0.02); I² = 69%						
Test for overall effect: Z = 1.04 (P = 0.30)						
9.5.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.5.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	87	1166	77	1143	37.5%	1.11 [0.82 , 1.49]
Subtotal (95% CI)		**1166**		**1143**	**37.5%**	**1.11 [0.82 , 1.49]**
Total events:	87		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**1919**		**1890**	**100.0%**	**0.97 [0.82 , 1.16]**
Total events:	202		207			
Heterogeneity: Chi² = 10.28, df = 4 (P = 0.04); I² = 61%						
Test for overall effect: Z = 0.30 (P = 0.76)						
Test for subgroup differences: Chi² = 1.34, df = 1 (P = 0.25), I² = 25.4%						



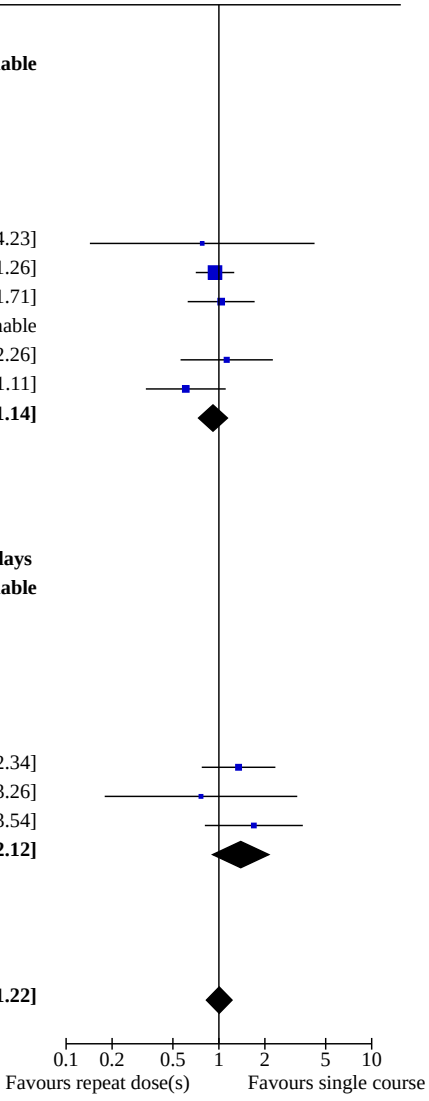
Analysis 9.6. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 6: A7: Severe lung disease

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.6.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	65	568	114	578	35.3%	0.58 [0.44 , 0.77]
Guinn 2001	38	256	57	246	18.1%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	0.9%	0.33 [0.04 , 3.06]
Peltoniemi 2007	70	160	60	168	18.3%	1.23 [0.94 , 1.60]
Wapner 2006	6	299	10	295	3.1%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**1321**		**1325**	**75.7%**	**0.75 [0.63 , 0.89]**
Total events:	180		244			
Heterogeneity: Chi² = 17.50, df = 4 (P = 0.002); I² = 77%						
Test for overall effect: Z = 3.37 (P = 0.0008)						
9.6.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.6.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	87	1166	77	1143	24.3%	1.11 [0.82 , 1.49]
Subtotal (95% CI)		**1166**		**1143**	**24.3%**	**1.11 [0.82 , 1.49]**
Total events:	87		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
Total (95% CI)		**2487**		**2468**	**100.0%**	**0.83 [0.72 , 0.97]**
Total events:	267		321			
Heterogeneity: Chi² = 20.83, df = 5 (P = 0.0009); I² = 76%						
Test for overall effect: Z = 2.41 (P = 0.02)						
Test for subgroup differences: Chi² = 5.11, df = 1 (P = 0.02), I² = 80.4%						



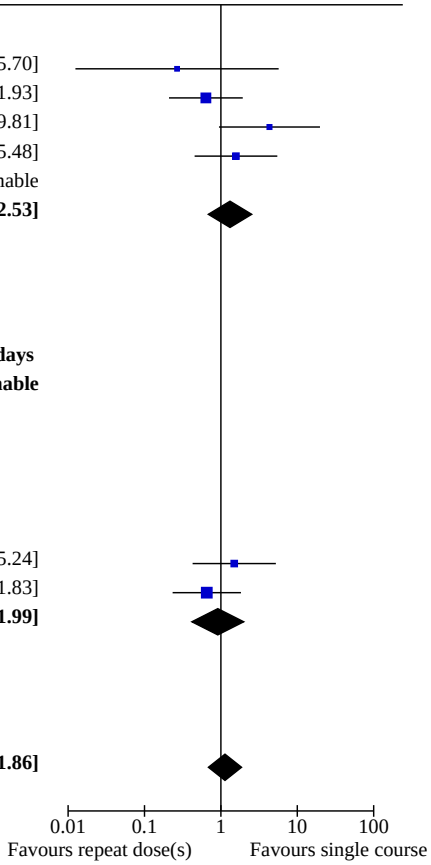
Analysis 9.7. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 7: A8: Chronic lung disease

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.7.1 In babies where pregnancy complicated by preterm prelabour rupture of membranes						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.7.2 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	2	9	2	7	1.2%	0.78 [0.14 , 4.23]
Crowther 2006	76	568	82	578	43.9%	0.94 [0.71 , 1.26]
Guinn 2001	28	256	26	246	14.3%	1.03 [0.62 , 1.71]
Mazumder 2008	0	38	0	38		Not estimable
Peltoniemi 2007	15	160	14	168	7.4%	1.13 [0.56 , 2.26]
Wapner 2006	16	299	26	295	14.1%	0.61 [0.33 , 1.11]
Subtotal (95% CI)		**1330**		**1332**	**81.0%**	**0.91 [0.74 , 1.14]**
Total events:	137		150			
Heterogeneity: $Chi^2 = 2.43$, df = 4 (P = 0.66); $I^2 = 0\%$						
Test for overall effect: Z = 0.80 (P = 0.42)						
9.7.3 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.7.4 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	27	289	20	288	10.8%	1.35 [0.77 , 2.34]
McEvoy 2010	3	56	4	57	2.1%	0.76 [0.18 , 3.26]
Murphy 2008	19	1166	11	1143	6.0%	1.69 [0.81 , 3.54]
Subtotal (95% CI)		**1511**		**1488**	**19.0%**	**1.39 [0.91 , 2.12]**
Total events:	49		35			
Heterogeneity: $Chi^2 = 0.94$, df = 2 (P = 0.62); $I^2 = 0\%$						
Test for overall effect: Z = 1.53 (P = 0.13)						
Total (95% CI)		**2841**		**2820**	**100.0%**	**1.00 [0.83 , 1.22]**
Total events:	186		185			
Heterogeneity: $Chi^2 = 6.20$, df = 7 (P = 0.52); $I^2 = 0\%$						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: $Chi^2 = 2.98$, df = 1 (P = 0.08), $I^2 = 66.4\%$						



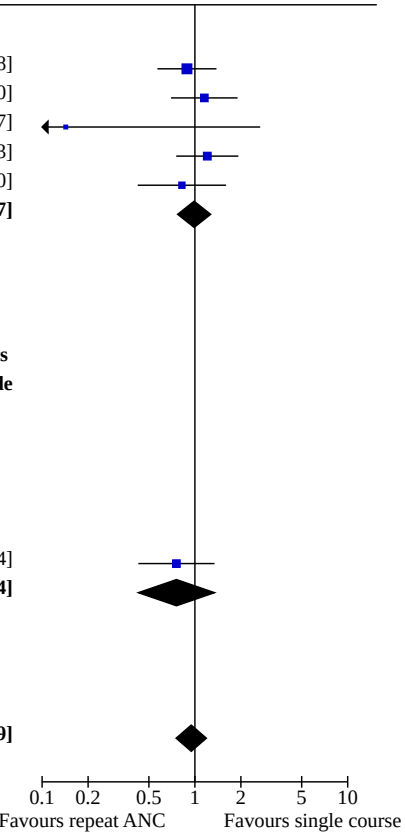
Analysis 9.8. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 8: A9: Severe intraventricular haemorrhage (grade 3 or 4)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.8.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	9	1	7	5.8%	0.27 [0.01 , 5.70]
Crowther 2006	5	568	8	578	27.7%	0.64 [0.21 , 1.93]
Guinn 2001	9	256	2	246	7.1%	4.32 [0.94 , 19.81]
Peltoniemi 2007	6	160	4	168	13.6%	1.57 [0.45 , 5.48]
TEAMS 1999	0	94	0	94		Not estimable
Subtotal (95% CI)		**1087**		**1093**	**54.3%**	**1.32 [0.69 , 2.53]**
Total events:	20		15			
Heterogeneity: Chi² = 5.11, df = 3 (P = 0.16); I² = 41%						
Test for overall effect: Z = 0.83 (P = 0.41)						
9.8.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.8.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	6	289	4	288	14.0%	1.49 [0.43 , 5.24]
Murphy 2008	6	1166	9	1143	31.7%	0.65 [0.23 , 1.83]
Subtotal (95% CI)		**1455**		**1431**	**45.7%**	**0.91 [0.42 , 1.99]**
Total events:	12		13			
Heterogeneity: Chi² = 1.00, df = 1 (P = 0.32); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.81)						
Total (95% CI)		**2542**		**2524**	**100.0%**	**1.13 [0.69 , 1.86]**
Total events:	32		28			
Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%						



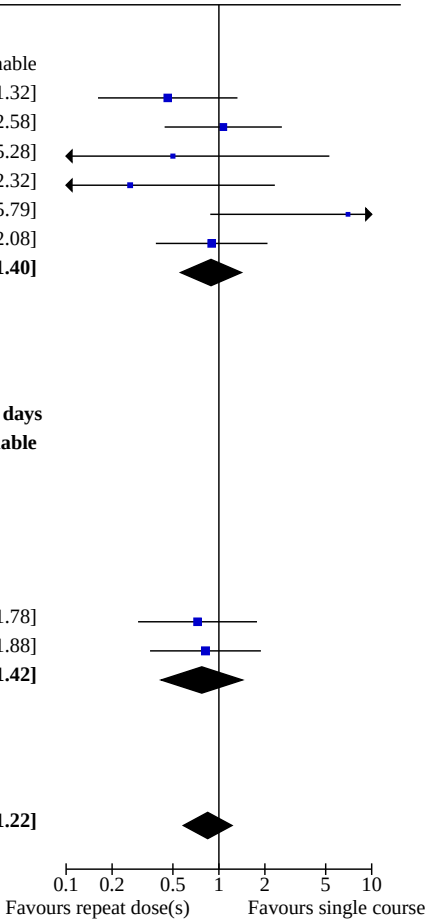
Analysis 9.9. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 9: A10: Intraventricular haemorrhage

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.9.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	34	568	39	578	28.2%	0.89 [0.57 , 1.38]
Guinn 2001	30	256	25	246	18.6%	1.15 [0.70 , 1.90]
Mazumder 2008	0	38	3	38	2.6%	0.14 [0.01 , 2.67]
Peltoniemi 2007	31	160	27	168	19.2%	1.21 [0.75 , 1.93]
Wapner 2006	15	299	18	295	13.2%	0.82 [0.42 , 1.60]
Subtotal (95% CI)		**1321**		**1325**	**81.7%**	**0.99 [0.77 , 1.27]**
Total events:	110		112			
Heterogeneity: Chi² = 3.25, df = 4 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.09 (P = 0.93)						
9.9.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.9.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	19	289	25	288	18.3%	0.76 [0.43 , 1.34]
Subtotal (95% CI)		**289**		**288**	**18.3%**	**0.76 [0.43 , 1.34]**
Total events:	19		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.95 (P = 0.34)						
Total (95% CI)		**1610**		**1613**	**100.0%**	**0.95 [0.75 , 1.19]**
Total events:	129		137			
Heterogeneity: Chi² = 4.05, df = 5 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						



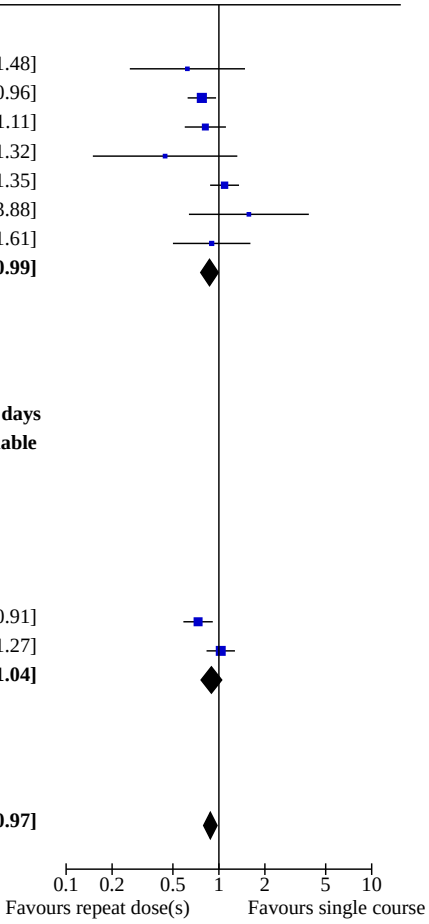
Analysis 9.10. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 10: A11: Necrotising enterocolitis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.10.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	9	0	7		Not estimable
Crowther 2006	5	568	11	578	17.8%	0.46 [0.16 , 1.32]
Guinn 2001	10	256	9	246	15.0%	1.07 [0.44 , 2.58]
Mazumder 2008	1	38	2	38	3.3%	0.50 [0.05 , 5.28]
Peltoniemi 2007	1	160	4	168	6.4%	0.26 [0.03 , 2.32]
TEAMS 1999	7	94	1	94	1.6%	7.00 [0.88 , 55.79]
Wapner 2006	10	299	11	295	18.1%	0.90 [0.39 , 2.08]
Subtotal (95% CI)		**1424**		**1426**	**62.2%**	**0.89 [0.56 , 1.40]**
Total events:	34		38			
Heterogeneity: Chi² = 6.88, df = 5 (P = 0.23); I² = 27%						
Test for overall effect: Z = 0.51 (P = 0.61)						
9.10.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.10.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	8	289	11	288	18.0%	0.72 [0.30 , 1.78]
Murphy 2008	10	1166	12	1143	19.8%	0.82 [0.35 , 1.88]
Subtotal (95% CI)		**1455**		**1431**	**37.8%**	**0.77 [0.42 , 1.42]**
Total events:	18		23			
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.83 (P = 0.41)						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.84 [0.59 , 1.22]**
Total events:	52		61			
Heterogeneity: Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



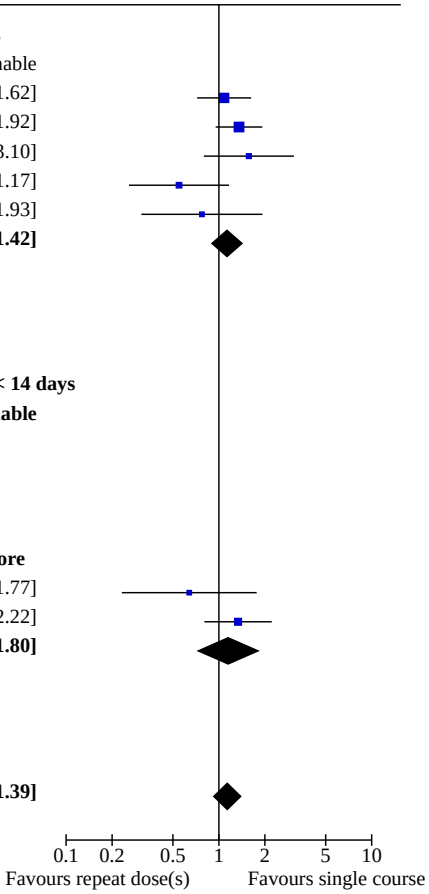
Analysis 9.11. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 11: A12: Composite serious outcome (variously defined)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.11.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.5%	0.44 [0.15 , 1.32]
Peltoniemi 2007	83	160	80	168	13.0%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	1.2%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	3.7%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**1424**		**1426**	**56.1%**	**0.87 [0.76 , 0.99]**
Total events:	292		339			
Heterogeneity: Chi² = 9.14, df = 6 (P = 0.17); I² = 34%						
Test for overall effect: Z = 2.10 (P = 0.04)						
9.11.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.11.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	88	289	120	288	20.0%	0.73 [0.59 , 0.91]
Murphy 2008	150	1166	143	1143	24.0%	1.03 [0.83 , 1.27]
Subtotal (95% CI)		**1455**		**1431**	**43.9%**	**0.89 [0.76 , 1.04]**
Total events:	238		263			
Heterogeneity: Chi² = 4.82, df = 1 (P = 0.03); I² = 79%						
Test for overall effect: Z = 1.43 (P = 0.15)						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.88 [0.80 , 0.97]**
Total events:	530		602			
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%						
Test for overall effect: Z = 2.51 (P = 0.01)						
Test for subgroup differences: Chi² = 0.08, df = 1 (P = 0.78), I² = 0%						



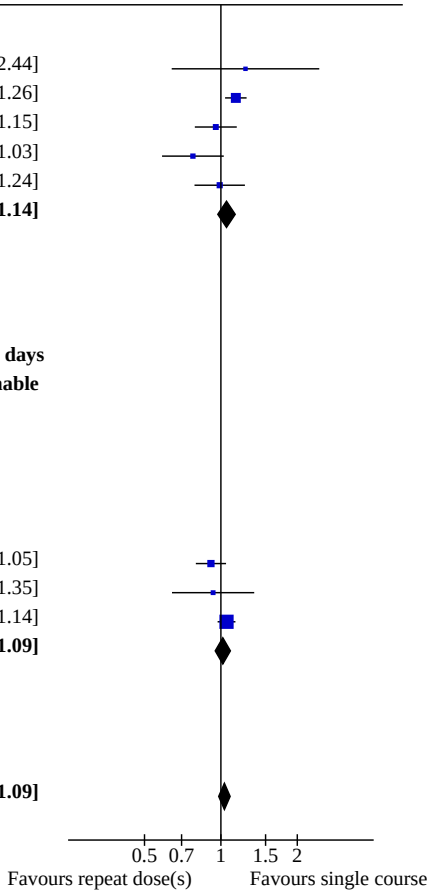
Analysis 9.12. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 12: B2: Maternal sepsis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.12.1 For women treated with repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	0	6	0	6		Not estimable
Crowther 2006	44	489	41	493	26.0%	1.08 [0.72 , 1.62]
Guinn 2001	60	249	42	236	27.5%	1.35 [0.95 , 1.92]
Peltoniemi 2007	19	125	12	124	7.7%	1.57 [0.80 , 3.10]
TEAMS 1999	9	79	16	77	10.3%	0.55 [0.26 , 1.17]
Wapner 2006	8	250	10	242	6.5%	0.77 [0.31 , 1.93]
Subtotal (95% CI)		**1198**		**1178**	**78.1%**	**1.13 [0.90 , 1.42]**
Total events:	140		121			
Heterogeneity: Chi² = 6.16, df = 4 (P = 0.19); I² = 35%						
Test for overall effect: Z = 1.06 (P = 0.29)						
9.12.2 For women treated with repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.12.3 For women treated with repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	6	223	9	214	5.9%	0.64 [0.23 , 1.77]
Murphy 2008	34	935	25	918	16.1%	1.34 [0.80 , 2.22]
Subtotal (95% CI)		**1158**		**1132**	**21.9%**	**1.15 [0.73 , 1.80]**
Total events:	40		34			
Heterogeneity: Chi² = 1.61, df = 1 (P = 0.20); I² = 38%						
Test for overall effect: Z = 0.61 (P = 0.54)						
Total (95% CI)		**2356**		**2310**	**100.0%**	**1.13 [0.93 , 1.39]**
Total events:	180		155			
Heterogeneity: Chi² = 7.77, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 0.00, df = 1 (P = 0.95), I² = 0%						



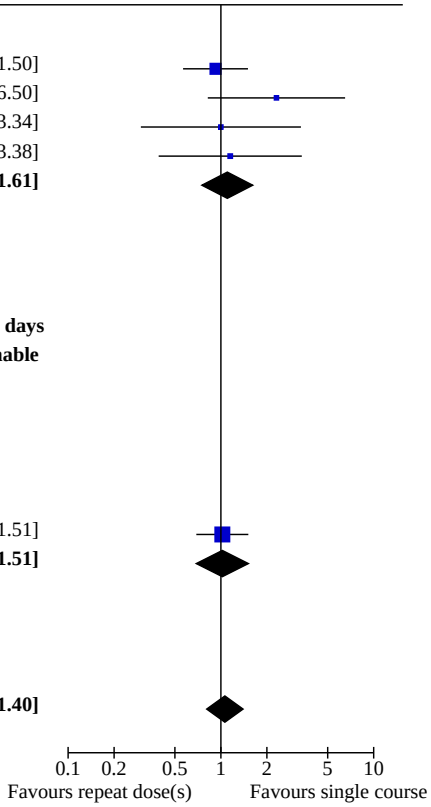
Analysis 9.13. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 13: B3: Caesarean section

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.13.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	5	6	4	6	0.3%	1.25 [0.64 , 2.44]
Crowther 2006	326	489	287	493	24.0%	1.15 [1.04 , 1.26]
Peltoniemi 2007	77	125	80	124	6.7%	0.95 [0.79 , 1.15]
TEAMS 1999	39	79	49	77	4.2%	0.78 [0.59 , 1.03]
Wapner 2006	93	250	91	242	7.8%	0.99 [0.79 , 1.24]
Subtotal (95% CI)		**949**		**942**	**43.0%**	**1.05 [0.97 , 1.14]**
Total events:	540		511			
Heterogeneity: Chi² = 8.98, df = 4 (P = 0.06); I² = 55%						
Test for overall effect: Z = 1.27 (P = 0.21)						
9.13.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.13.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Garite 2009	139	223	146	214	12.5%	0.91 [0.80 , 1.05]
McEvoy 2010	24	44	24	41	2.1%	0.93 [0.64 , 1.35]
Murphy 2008	537	935	501	918	42.4%	1.05 [0.97 , 1.14]
Subtotal (95% CI)		**1202**		**1173**	**57.0%**	**1.02 [0.95 , 1.09]**
Total events:	700		671			
Heterogeneity: Chi² = 3.25, df = 2 (P = 0.20); I² = 39%						
Test for overall effect: Z = 0.50 (P = 0.62)						
Total (95% CI)		**2151**		**2115**	**100.0%**	**1.03 [0.98 , 1.09]**
Total events:	1240		1182			
Heterogeneity: Chi² = 13.00, df = 7 (P = 0.07); I² = 46%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 0.39, df = 1 (P = 0.53), I² = 0%						



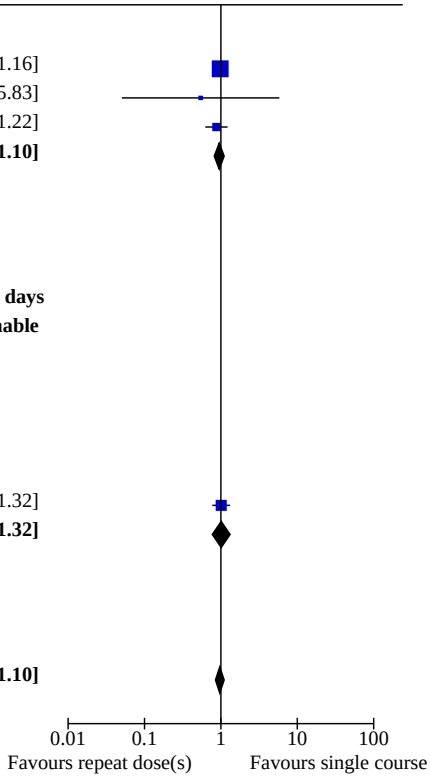
Analysis 9.14. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 14: C1: Total deaths after randomisation up to early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.14.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	29	568	32	578	33.4%	0.92 [0.57 , 1.50]
Peltoniemi 2007	11	160	5	168	5.1%	2.31 [0.82 , 6.50]
TEAMS 1999	5	94	5	94	5.3%	1.00 [0.30 , 3.34]
Wapner 2006	7	299	6	295	6.4%	1.15 [0.39 , 3.38]
Subtotal (95% CI)		**1121**		**1135**	**50.1%**	**1.10 [0.75 , 1.61]**
Total events:	52		48			
Heterogeneity: Chi² = 2.51, df = 3 (P = 0.47); I² = 0%						
Test for overall effect: Z = 0.50 (P = 0.62)						
9.14.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.14.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	49	1166	47	1143	49.9%	1.02 [0.69 , 1.51]
Subtotal (95% CI)		**1166**		**1143**	**49.9%**	**1.02 [0.69 , 1.51]**
Total events:	49		47			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.11 (P = 0.91)						
Total (95% CI)		**2287**		**2278**	**100.0%**	**1.06 [0.81 , 1.40]**
Total events:	101		95			
Heterogeneity: Chi² = 2.55, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 0.07, df = 1 (P = 0.79), I² = 0%						



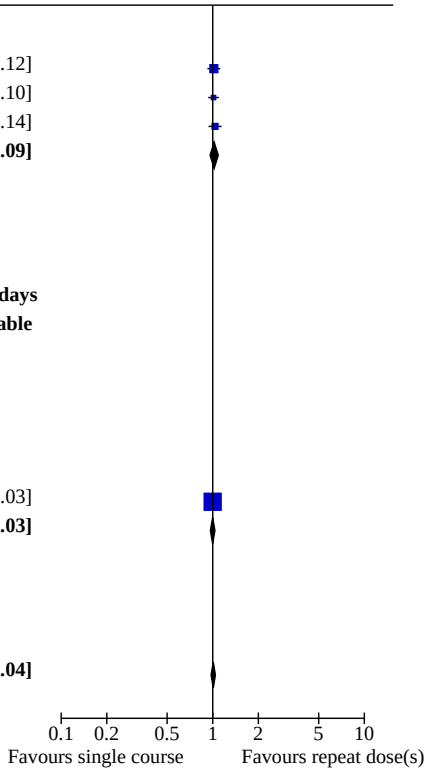
Analysis 9.15. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 15: C2: Neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.15.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	175	495	182	504	53.7%	0.98 [0.83 , 1.16]
TEAMS 1999	1	59	2	64	0.6%	0.54 [0.05 , 5.83]
Wapner 2006	51	248	56	238	17.0%	0.87 [0.63 , 1.22]
Subtotal (95% CI)		**802**		**806**	**71.3%**	**0.95 [0.82 , 1.10]**
Total events:	227		240			
Heterogeneity: Chi² = 0.58, df = 2 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
9.15.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.15.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	99	1020	95	988	28.7%	1.01 [0.77 , 1.32]
Subtotal (95% CI)		**1020**		**988**	**28.7%**	**1.01 [0.77 , 1.32]**
Total events:	99		95			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.07 (P = 0.95)						
Total (95% CI)		**1822**		**1794**	**100.0%**	**0.97 [0.85 , 1.10]**
Total events:	326		335			
Heterogeneity: Chi² = 0.70, df = 3 (P = 0.87); I² = 0%						
Test for overall effect: Z = 0.49 (P = 0.62)						
Test for subgroup differences: Chi² = 0.15, df = 1 (P = 0.70), I² = 0%						



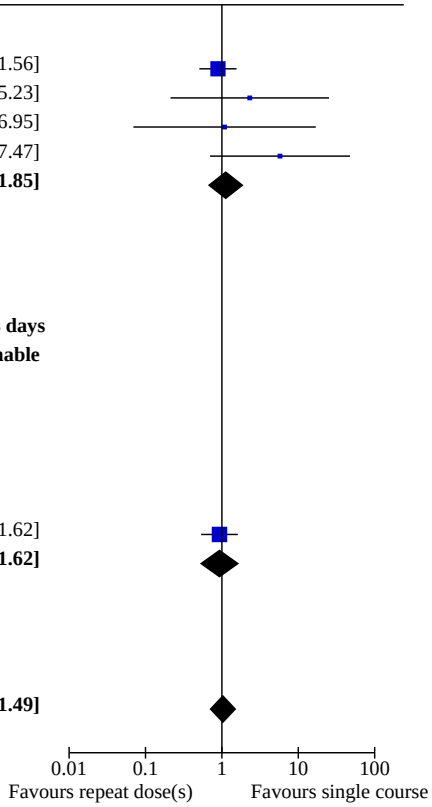
Analysis 9.16. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 16: C3: Survival free of neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.16.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	320	524	322	536	21.3%	1.02 [0.92 , 1.12]
TEAMS 1999	85	91	84	91	5.6%	1.01 [0.93 , 1.10]
Wapner 2006	197	255	182	244	12.4%	1.04 [0.94 , 1.14]
Subtotal (95% CI)		**870**		**871**	**39.3%**	**1.02 [0.96 , 1.09]**
Total events:	602		588			
Heterogeneity: Chi² = 0.14, df = 2 (P = 0.93); I² = 0%						
Test for overall effect: Z = 0.68 (P = 0.49)						
9.16.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.16.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	921	1069	893	1035	60.7%	1.00 [0.97 , 1.03]
Subtotal (95% CI)		**1069**		**1035**	**60.7%**	**1.00 [0.97 , 1.03]**
Total events:	921		893			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.08 (P = 0.93)						
Total (95% CI)		**1939**		**1906**	**100.0%**	**1.01 [0.98 , 1.04]**
Total events:	1523		1481			
Heterogeneity: Chi² = 0.61, df = 3 (P = 0.89); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: Chi² = 0.41, df = 1 (P = 0.52), I² = 0%						

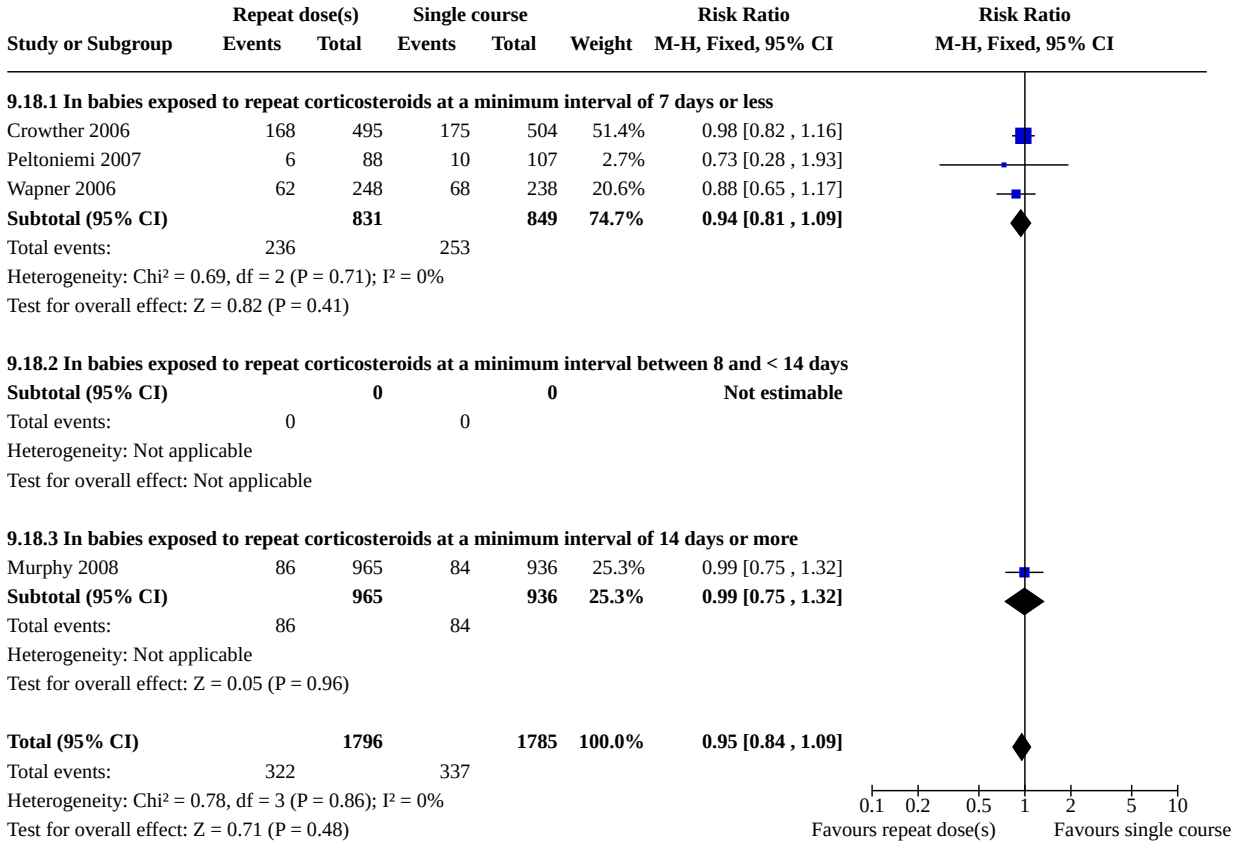


Analysis 9.17. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 17: C5: Cerebral palsy at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
9.17.1 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Crowther 2006	22	521	25	526	46.8%	0.89 [0.51 , 1.56]
Peltoniemi 2007	2	120	1	139	1.7%	2.32 [0.21 , 25.23]
TEAMS 1999	1	59	1	64	1.8%	1.08 [0.07 , 16.95]
Wapner 2006	6	248	1	238	1.9%	5.76 [0.70 , 47.47]
Subtotal (95% CI)		**948**		**967**	**52.2%**	**1.12 [0.68 , 1.85]**
Total events:	31		28			
Heterogeneity: Chi² = 3.33, df = 3 (P = 0.34); I² = 10%						
Test for overall effect: Z = 0.45 (P = 0.65)						
9.17.2 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.17.3 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more						
Murphy 2008	24	1020	25	988	47.8%	0.93 [0.53 , 1.62]
Subtotal (95% CI)		**1020**		**988**	**47.8%**	**0.93 [0.53 , 1.62]**
Total events:	24		25			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.26 (P = 0.80)						
Total (95% CI)		**1968**		**1955**	**100.0%**	**1.03 [0.71 , 1.49]**
Total events:	55		53			
Heterogeneity: Chi² = 3.40, df = 4 (P = 0.49); I² = 0%						
Test for overall effect: Z = 0.16 (P = 0.88)						
Test for subgroup differences: Chi² = 0.24, df = 1 (P = 0.62), I² = 0%						



Analysis 9.18. Comparison 9: Subgroup analysis for planned interval between corticosteroid treatments, Outcome 18: C6: Developmental delay or intellectual impairment at early childhood follow-up (any)



Comparison 10. Subgroup analysis for the planned dose of corticosteroid given per treatment

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.1 A1: Fetal or neonatal or infant death (< 1 year of age)	10	5849	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.73, 1.24]
10.1.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.77]
10.1.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	8	4375	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.21]
10.1.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.2 A2: Fetal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.24, 2.84]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.2.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.15, 7.31]
10.2.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	5	1284	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.14, 3.55]
10.2.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.3 A3: Neonatal death	7	2758	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.62, 1.34]
10.3.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.70, 1.80]
10.3.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	5	1284	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.32, 1.20]
10.3.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.4 A5: Respiratory distress syndrome	9	3540	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.74, 0.90]
10.4.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.76, 0.98]
10.4.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	7	2066	Risk Ratio (M-H, Fixed, 95% CI)	0.77 [0.66, 0.89]
10.4.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.5 A6: Severe respiratory distress syndrome	5	3809	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.82, 1.16]
10.5.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	1	328	Risk Ratio (M-H, Fixed, 95% CI)	1.22 [0.94, 1.60]
10.5.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	4	3481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.09]
10.5.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.6 A7: Severe lung disease	6	4955	Risk Ratio (M-H, Fixed, 95% CI)	0.83 [0.72, 0.97]
10.6.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.66, 0.97]
10.6.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	4	3481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.09]
10.6.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.7 A8: Chronic lung disease	9	5661	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.83, 1.22]
10.7.1 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.74, 1.27]
10.7.2 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent	7	4187	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.79, 1.38]
10.7.3 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.8 A9: Severe intraventricular haemorrhage (grade 3 or 4)	7	5066	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.69, 1.86]
10.8.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.42, 2.12]
10.8.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	5	3592	Risk Ratio (M-H, Fixed, 95% CI)	1.26 [0.67, 2.38]
10.8.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.9 A10: Intraventricular haemorrhage	6	3223	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.75, 1.19]
10.9.1 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.74, 1.40]
10.9.2 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent	4	1749	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.64, 1.22]

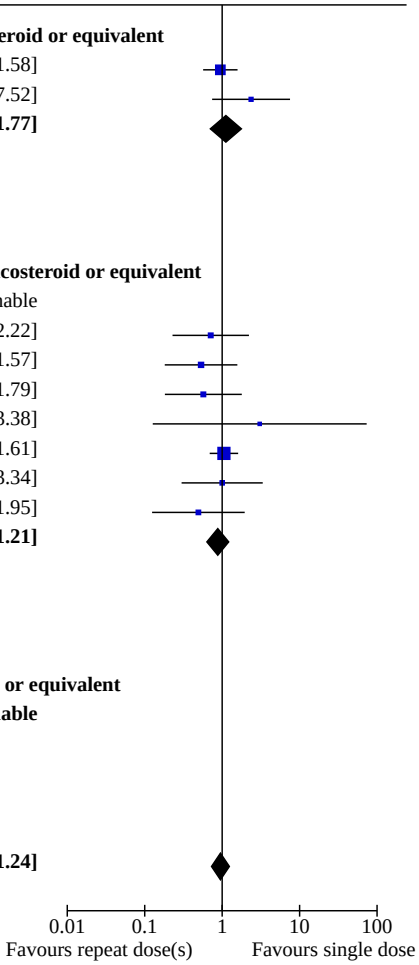
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.9.3 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.10 A11: Necrotising enterocolitis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.59, 1.22]
10.10.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.41 [0.16, 1.05]
10.10.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	7	4262	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.66, 1.47]
10.10.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.11 A12: Composite serious outcome (variously defined)	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
10.11.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.03]
10.11.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	7	4262	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.00]
10.11.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.12 B2: Maternal sepsis	8	4666	Risk Ratio (M-H, Fixed, 95% CI)	1.13 [0.93, 1.39]
10.12.1 For women treated where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1231	Risk Ratio (M-H, Fixed, 95% CI)	1.19 [0.84, 1.69]
10.12.2 For women where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	6	3435	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [0.86, 1.42]
10.12.3 For women where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.13 B3: Caesarean section	8	4266	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.09]
10.13.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1231	Risk Ratio (M-H, Fixed, 95% CI)	1.10 [1.01, 1.20]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.13.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	6	3035	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.94, 1.07]
10.13.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.14 C1: Total deaths after randomisation up to early childhood follow-up	5	4565	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.81, 1.40]
10.14.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.72, 1.71]
10.14.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	3	3091	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.73, 1.47]
10.14.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.15 C2: Neurodevelopmental impairment at early childhood follow-up	4	3616	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.85, 1.10]
10.15.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	1	999	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.83, 1.16]
10.15.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	3	2617	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.17]
10.15.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.16 C3: Survival free of neurodevelopmental impairment at early childhood follow-up	4	3845	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.98, 1.04]
10.16.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.92, 1.12]
10.16.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	3	2785	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.97, 1.04]
10.16.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.17 C4: Survival free of major neurodevelopmental impairment at early childhood follow-up	3	1816	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.05]

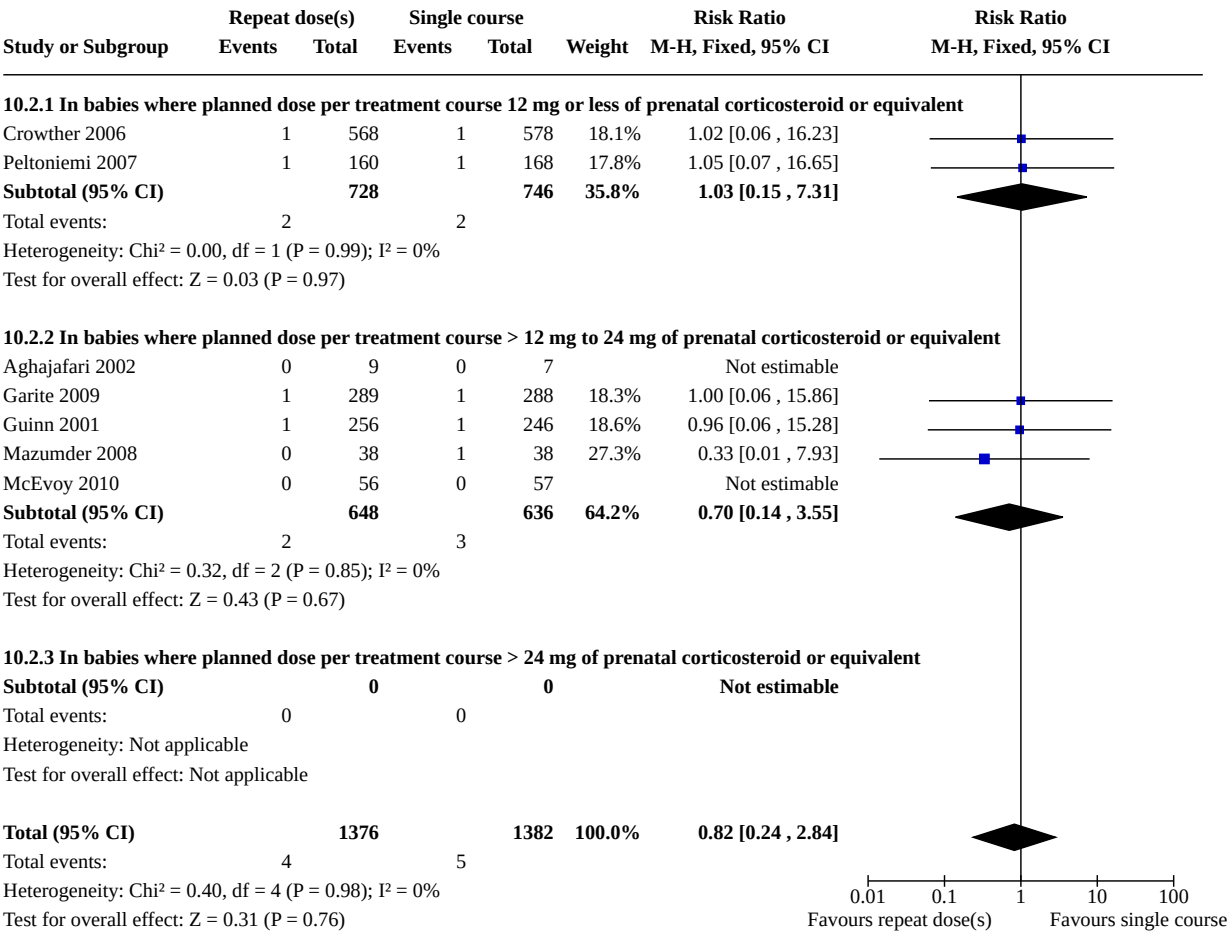
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
10.17.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1317	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.98, 1.07]
10.17.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.06]
10.17.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.18 C5: Cerebral palsy at early childhood follow-up	5	3923	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.71, 1.49]
10.18.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1306	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.55, 1.62]
10.18.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	3	2617	Risk Ratio (M-H, Fixed, 95% CI)	1.12 [0.67, 1.86]
10.18.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
10.19 C6: Developmental delay or intellectual impairment at early childhood follow-up (any)	4	3581	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.09]
10.19.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1194	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.81, 1.14]
10.19.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	2	2387	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.17]
10.19.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Analysis 10.1. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 1: A1: Fetal or neonatal or infant death (< 1 year of age)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.1.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	27	568	29	578	26.7%	0.95 [0.57 , 1.58]
Peltoniemi 2007	9	160	4	168	3.6%	2.36 [0.74 , 7.52]
Subtotal (95% CI)		**728**		**746**	**30.3%**	**1.12 [0.70 , 1.77]**
Total events:	36		33			
Heterogeneity: Chi² = 2.01, df = 1 (P = 0.16); I² = 50%						
Test for overall effect: Z = 0.47 (P = 0.64)						
10.1.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Garite 2009	5	289	7	288	6.5%	0.71 [0.23 , 2.22]
Guinn 2001	5	256	9	246	8.5%	0.53 [0.18 , 1.57]
Mazumder 2008	4	38	7	38	6.5%	0.57 [0.18 , 1.79]
McEvoy 2010	1	56	0	57	0.5%	3.05 [0.13 , 73.38]
Murphy 2008	43	1166	40	1143	37.5%	1.05 [0.69 , 1.61]
TEAMS 1999	5	94	5	94	4.6%	1.00 [0.30 , 3.34]
Wapner 2006	3	299	6	295	5.6%	0.49 [0.12 , 1.95]
Subtotal (95% CI)		**2207**		**2168**	**69.7%**	**0.88 [0.64 , 1.21]**
Total events:	66		74			
Heterogeneity: Chi² = 3.51, df = 6 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.79 (P = 0.43)						
10.1.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2935**		**2914**	**100.0%**	**0.95 [0.73 , 1.24]**
Total events:	102		107			
Heterogeneity: Chi² = 6.11, df = 8 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.38 (P = 0.71)						
Test for subgroup differences: Chi² = 0.70, df = 1 (P = 0.40), I² = 0%						

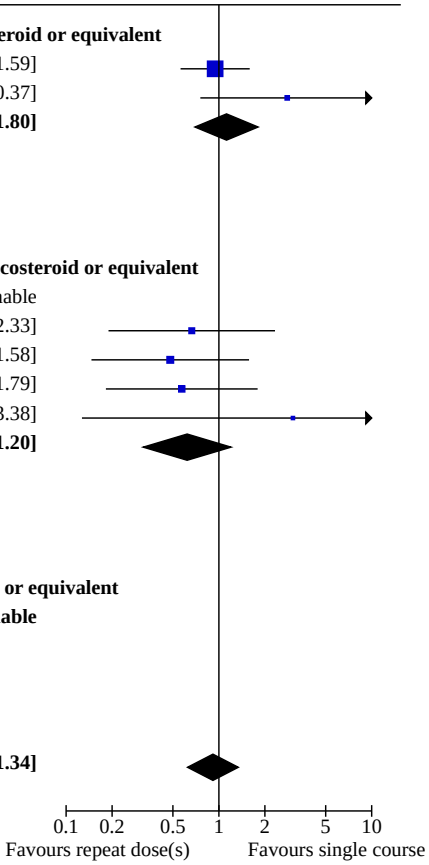


Analysis 10.2. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 2: A2: Fetal death



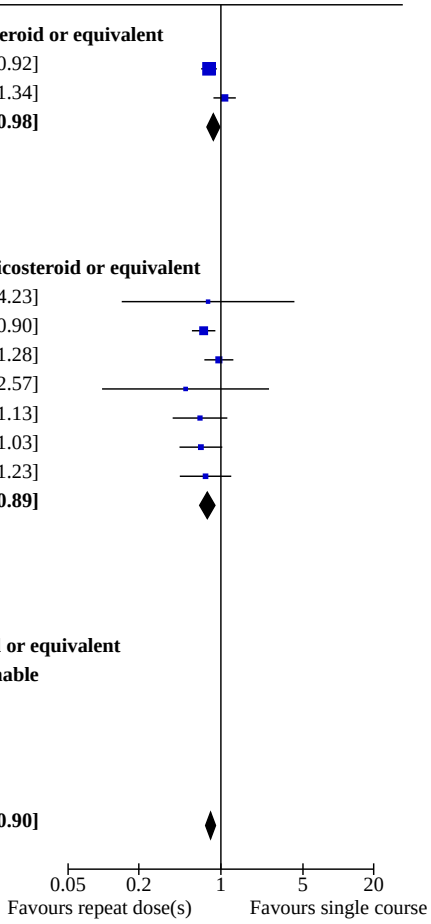
Analysis 10.3. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 3: A3: Neonatal death

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.3.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	26	568	28	578	53.0%	0.94 [0.56 , 1.59]
Peltoniemi 2007	8	160	3	168	5.6%	2.80 [0.76 , 10.37]
Subtotal (95% CI)		**728**		**746**	**58.6%**	**1.12 [0.70 , 1.80]**
Total events:	34		31			
Heterogeneity: Chi² = 2.29, df = 1 (P = 0.13); I² = 56%						
Test for overall effect: Z = 0.47 (P = 0.64)						
10.3.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Garite 2009	4	289	6	288	11.5%	0.66 [0.19 , 2.33]
Guinn 2001	4	256	8	246	15.6%	0.48 [0.15 , 1.58]
Mazumder 2008	4	38	7	38	13.4%	0.57 [0.18 , 1.79]
McEvoy 2010	1	56	0	57	0.9%	3.05 [0.13 , 73.38]
Subtotal (95% CI)		**648**		**636**	**41.4%**	**0.62 [0.32 , 1.20]**
Total events:	13		21			
Heterogeneity: Chi² = 1.17, df = 3 (P = 0.76); I² = 0%						
Test for overall effect: Z = 1.42 (P = 0.16)						
10.3.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1376**		**1382**	**100.0%**	**0.91 [0.62 , 1.34]**
Total events:	47		52			
Heterogeneity: Chi² = 5.40, df = 5 (P = 0.37); I² = 7%						
Test for overall effect: Z = 0.46 (P = 0.64)						
Test for subgroup differences: Chi² = 2.04, df = 1 (P = 0.15), I² = 51.0%						

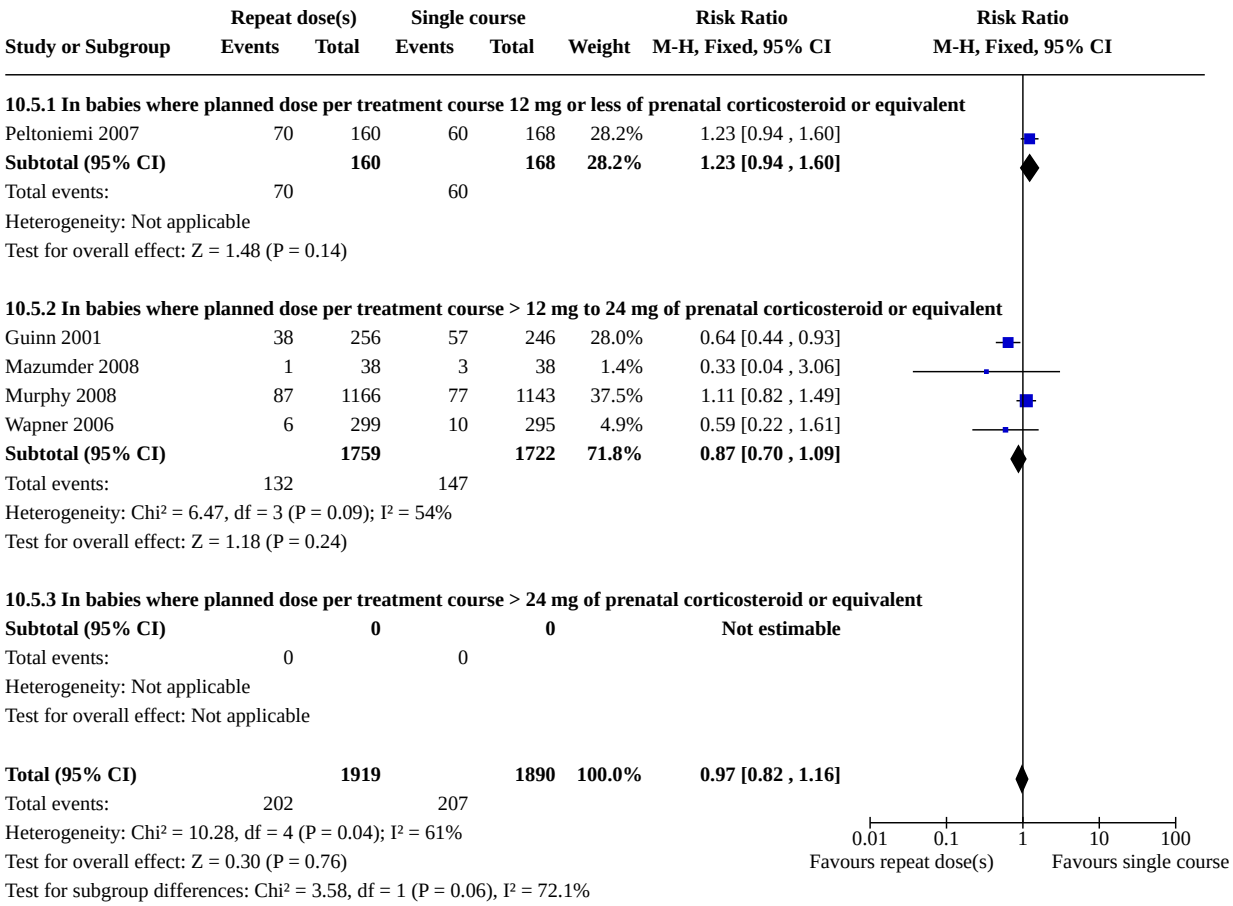


Analysis 10.4. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 4: A5: Respiratory distress syndrome

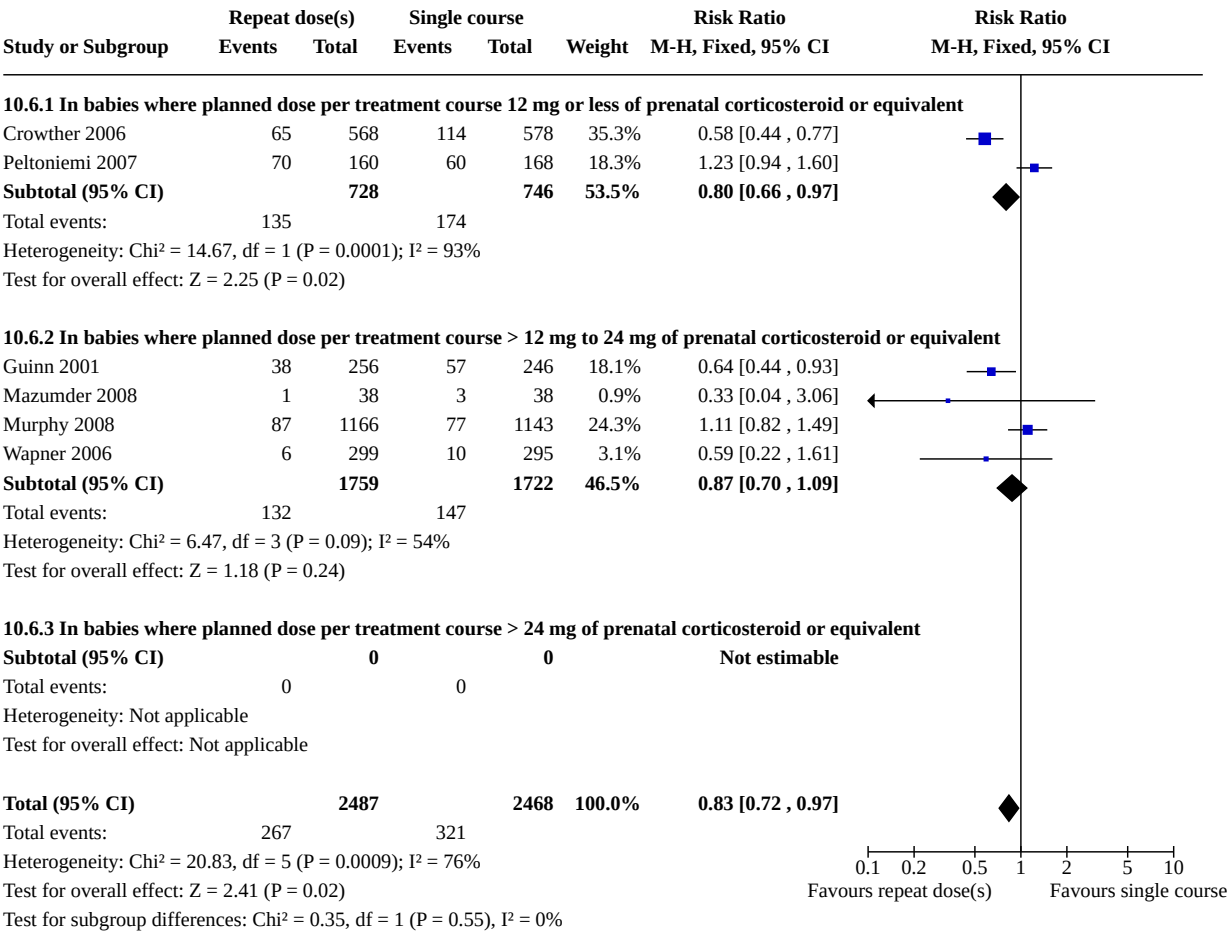
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.4.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	186	568	239	578	39.5%	0.79 [0.68 , 0.92]
Peltoniemi 2007	82	160	80	168	13.0%	1.08 [0.86 , 1.34]
Subtotal (95% CI)		**728**		**746**	**52.5%**	**0.86 [0.76 , 0.98]**
Total events:	268		319			
Heterogeneity: Chi² = 5.12, df = 1 (P = 0.02); I² = 80%						
Test for overall effect: Z = 2.31 (P = 0.02)						
10.4.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	2	9	2	7	0.4%	0.78 [0.14 , 4.23]
Garite 2009	83	289	116	288	19.4%	0.71 [0.57 , 0.90]
Guinn 2001	69	256	69	246	11.7%	0.96 [0.72 , 1.28]
Mazumder 2008	2	38	4	38	0.7%	0.50 [0.10 , 2.57]
McEvoy 2010	15	56	23	57	3.8%	0.66 [0.39 , 1.13]
TEAMS 1999	25	94	37	94	6.2%	0.68 [0.44 , 1.03]
Wapner 2006	24	299	32	295	5.4%	0.74 [0.45 , 1.23]
Subtotal (95% CI)		**1041**		**1025**	**47.5%**	**0.77 [0.66 , 0.89]**
Total events:	220		283			
Heterogeneity: Chi² = 3.72, df = 6 (P = 0.71); I² = 0%						
Test for overall effect: Z = 3.50 (P = 0.0005)						
10.4.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1769**		**1771**	**100.0%**	**0.82 [0.74 , 0.90]**
Total events:	488		602			
Heterogeneity: Chi² = 10.71, df = 8 (P = 0.22); I² = 25%						
Test for overall effect: Z = 4.12 (P < 0.0001)						
Test for subgroup differences: Chi² = 1.42, df = 1 (P = 0.23), I² = 29.5%						



Analysis 10.5. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 5: A6: Severe respiratory distress syndrome

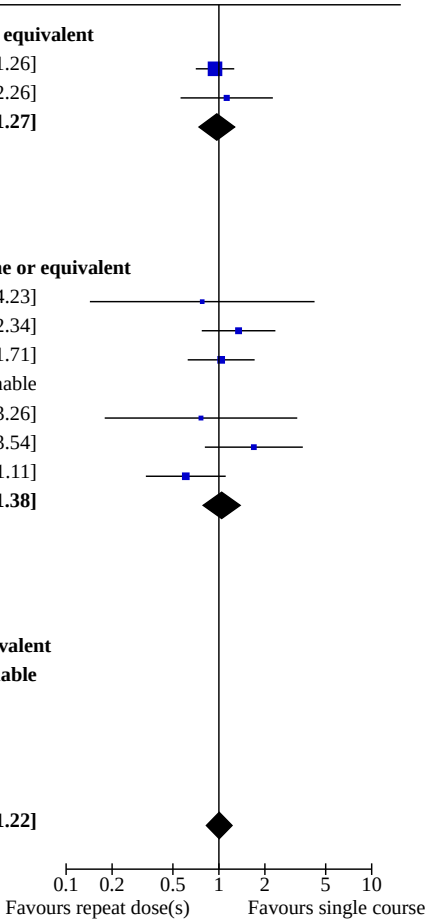


Analysis 10.6. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 6: A7: Severe lung disease



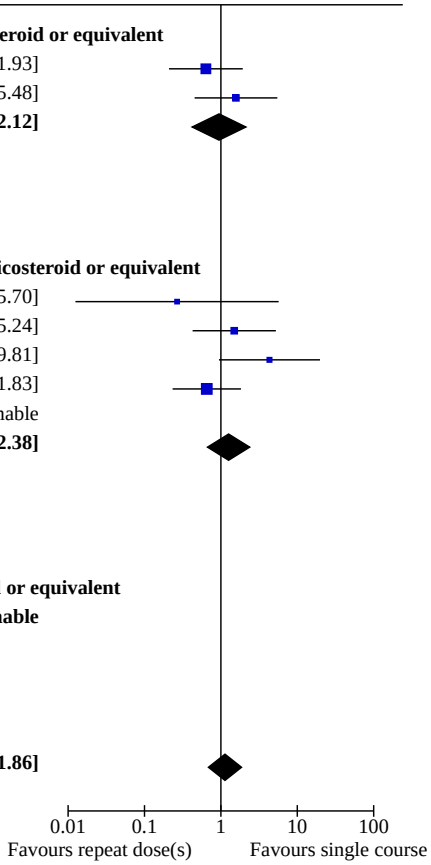
Analysis 10.7. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 7: A8: Chronic lung disease

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.7.1 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent						
Crowther 2006	76	568	82	578	43.9%	0.94 [0.71 , 1.26]
Peltoniemi 2007	15	160	14	168	7.4%	1.13 [0.56 , 2.26]
Subtotal (95% CI)		**728**		**746**	**51.3%**	**0.97 [0.74 , 1.27]**
Total events:	91		96			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 0.23 (P = 0.82)						
10.7.2 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent						
Aghajafari 2002	2	9	2	7	1.2%	0.78 [0.14 , 4.23]
Garite 2009	27	289	20	288	10.8%	1.35 [0.77 , 2.34]
Guinn 2001	28	256	26	246	14.3%	1.03 [0.62 , 1.71]
Mazumder 2008	0	38	0	38		Not estimable
McEvoy 2010	3	56	4	57	2.1%	0.76 [0.18 , 3.26]
Murphy 2008	19	1166	11	1143	6.0%	1.69 [0.81 , 3.54]
Wapner 2006	16	299	26	295	14.1%	0.61 [0.33 , 1.11]
Subtotal (95% CI)		**2113**		**2074**	**48.7%**	**1.04 [0.79 , 1.38]**
Total events:	95		89			
Heterogeneity: Chi² = 5.87, df = 5 (P = 0.32); I² = 15%						
Test for overall effect: Z = 0.29 (P = 0.77)						
10.7.3 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2841**		**2820**	**100.0%**	**1.00 [0.83 , 1.22]**
Total events:	186		185			
Heterogeneity: Chi² = 6.20, df = 7 (P = 0.52); I² = 0%						
Test for overall effect: Z = 0.05 (P = 0.96)						
Test for subgroup differences: Chi² = 0.14, df = 1 (P = 0.71), I² = 0%						



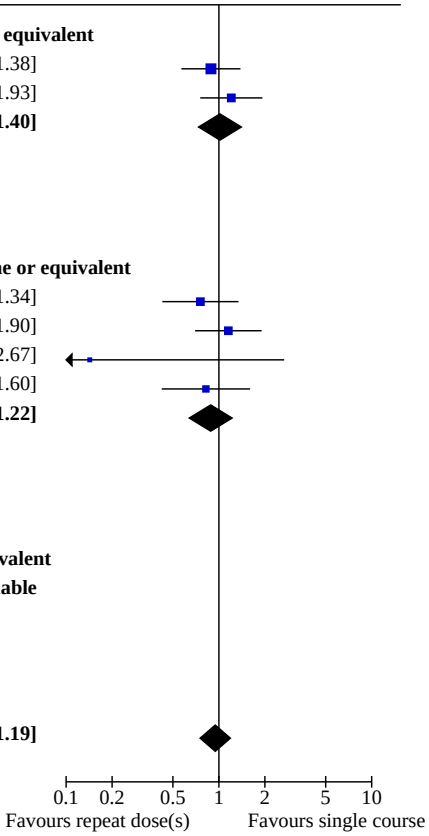
Analysis 10.8. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 8: A9: Severe intraventricular haemorrhage (grade 3 or 4)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.8.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	5	568	8	578	27.7%	0.64 [0.21 , 1.93]
Peltoniemi 2007	6	160	4	168	13.6%	1.57 [0.45 , 5.48]
Subtotal (95% CI)		**728**		**746**	**41.3%**	**0.95 [0.42 , 2.12]**
Total events:	11		12			
Heterogeneity: Chi² = 1.13, df = 1 (P = 0.29); I² = 12%						
Test for overall effect: Z = 0.14 (P = 0.89)						
10.8.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	1	7	5.8%	0.27 [0.01 , 5.70]
Garite 2009	6	289	4	288	14.0%	1.49 [0.43 , 5.24]
Guinn 2001	9	256	2	246	7.1%	4.32 [0.94 , 19.81]
Murphy 2008	6	1166	9	1143	31.7%	0.65 [0.23 , 1.83]
TEAMS 1999	0	94	0	94		Not estimable
Subtotal (95% CI)		**1814**		**1778**	**58.7%**	**1.26 [0.67 , 2.38]**
Total events:	21		16			
Heterogeneity: Chi² = 5.14, df = 3 (P = 0.16); I² = 42%						
Test for overall effect: Z = 0.72 (P = 0.47)						
10.8.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2542**		**2524**	**100.0%**	**1.13 [0.69 , 1.86]**
Total events:	32		28			
Heterogeneity: Chi² = 6.42, df = 5 (P = 0.27); I² = 22%						
Test for overall effect: Z = 0.48 (P = 0.63)						
Test for subgroup differences: Chi² = 0.30, df = 1 (P = 0.58), I² = 0%						



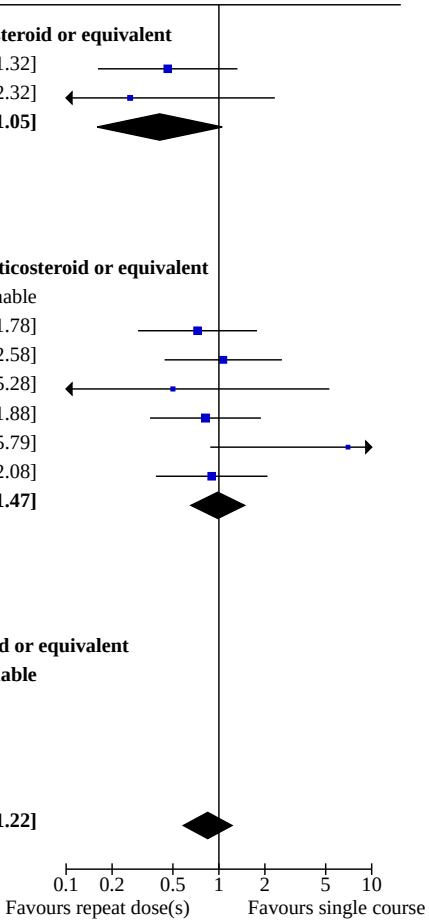
Analysis 10.9. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 9: A10: Intraventricular haemorrhage

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.9.1 In babies where planned dose per treatment course 12 mg or less of betamethasone or equivalent						
Crowther 2006	34	568	39	578	28.2%	0.89 [0.57 , 1.38]
Peltoniemi 2007	31	160	27	168	19.2%	1.21 [0.75 , 1.93]
Subtotal (95% CI)		**728**		**746**	**47.4%**	**1.02 [0.74 , 1.40]**
Total events:	65		66			
Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); I² = 0%						
Test for overall effect: Z = 0.10 (P = 0.92)						
10.9.2 In babies where planned dose per treatment course > 12 mg to 24 mg of betamethasone or equivalent						
Garite 2009	19	289	25	288	18.3%	0.76 [0.43 , 1.34]
Guinn 2001	30	256	25	246	18.6%	1.15 [0.70 , 1.90]
Mazumder 2008	0	38	3	38	2.6%	0.14 [0.01 , 2.67]
Wapner 2006	15	299	18	295	13.2%	0.82 [0.42 , 1.60]
Subtotal (95% CI)		**882**		**867**	**52.6%**	**0.88 [0.64 , 1.22]**
Total events:	64		71			
Heterogeneity: Chi² = 2.89, df = 3 (P = 0.41); I² = 0%						
Test for overall effect: Z = 0.75 (P = 0.45)						
10.9.3 In babies where planned dose per treatment course > 24 mg of betamethasone or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1610**		**1613**	**100.0%**	**0.95 [0.75 , 1.19]**
Total events:	129		137			
Heterogeneity: Chi² = 4.05, df = 5 (P = 0.54); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: Chi² = 0.36, df = 1 (P = 0.55), I² = 0%						

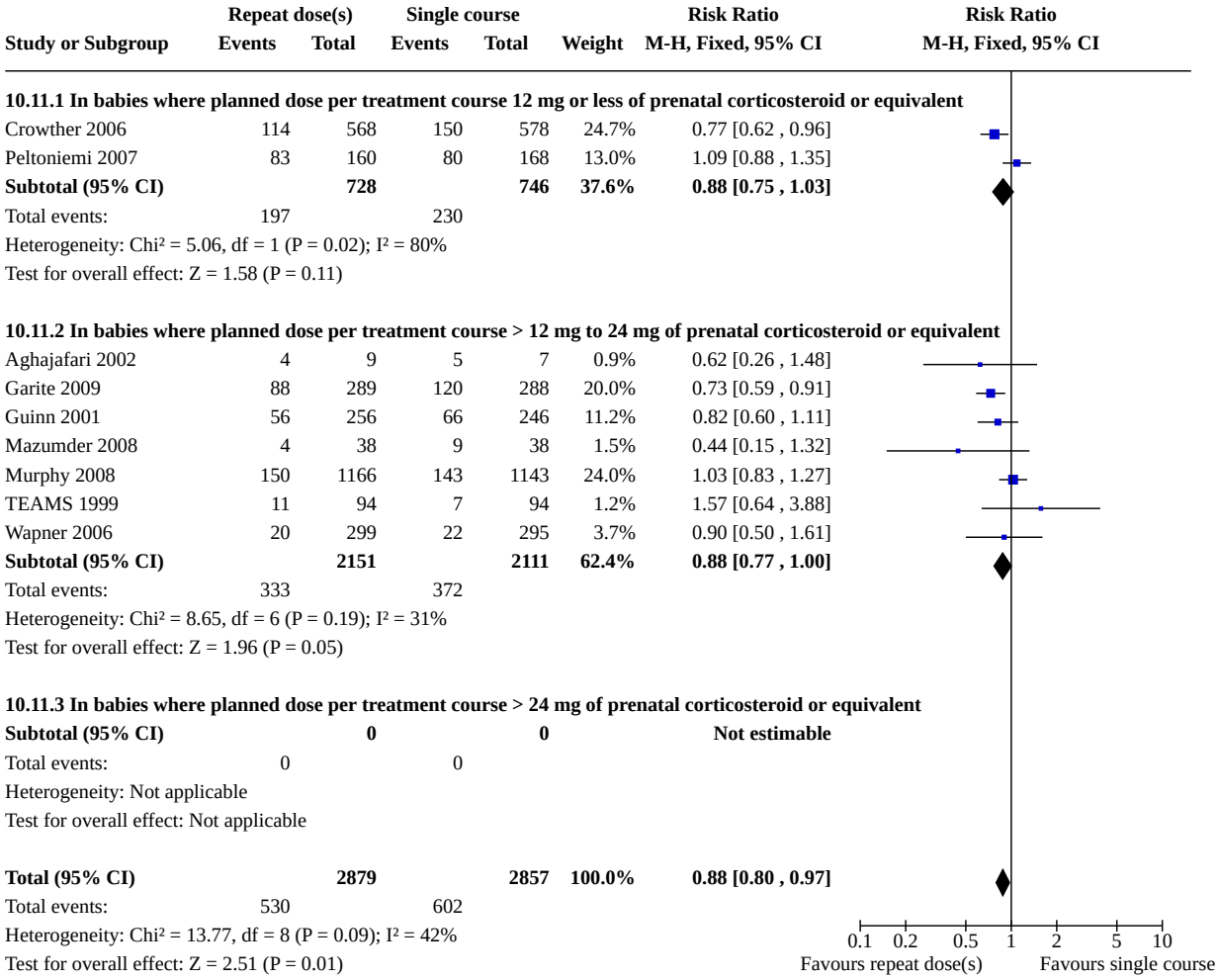


Analysis 10.10. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 10: A11: Necrotising enterocolitis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.10.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	5	568	11	578	17.8%	0.46 [0.16 , 1.32]
Peltoniemi 2007	1	160	4	168	6.4%	0.26 [0.03 , 2.32]
Subtotal (95% CI)		**728**		**746**	**24.2%**	**0.41 [0.16 , 1.05]**
Total events:	6		15			
Heterogeneity: Chi² = 0.21, df = 1 (P = 0.65); I² = 0%						
Test for overall effect: Z = 1.86 (P = 0.06)						
10.10.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Garite 2009	8	289	11	288	18.0%	0.72 [0.30 , 1.78]
Guinn 2001	10	256	9	246	15.0%	1.07 [0.44 , 2.58]
Mazumder 2008	1	38	2	38	3.3%	0.50 [0.05 , 5.28]
Murphy 2008	10	1166	12	1143	19.8%	0.82 [0.35 , 1.88]
TEAMS 1999	7	94	1	94	1.6%	7.00 [0.88 , 55.79]
Wapner 2006	10	299	11	295	18.1%	0.90 [0.39 , 2.08]
Subtotal (95% CI)		**2151**		**2111**	**75.8%**	**0.98 [0.66 , 1.47]**
Total events:	46		46			
Heterogeneity: Chi² = 4.46, df = 5 (P = 0.48); I² = 0%						
Test for overall effect: Z = 0.08 (P = 0.93)						
10.10.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2879**		**2857**	**100.0%**	**0.84 [0.59 , 1.22]**
Total events:	52		61			
Heterogeneity: Chi² = 6.95, df = 7 (P = 0.43); I² = 0%						
Test for overall effect: Z = 0.90 (P = 0.37)						
Test for subgroup differences: Chi² = 2.80, df = 1 (P = 0.09), I² = 64.3%						

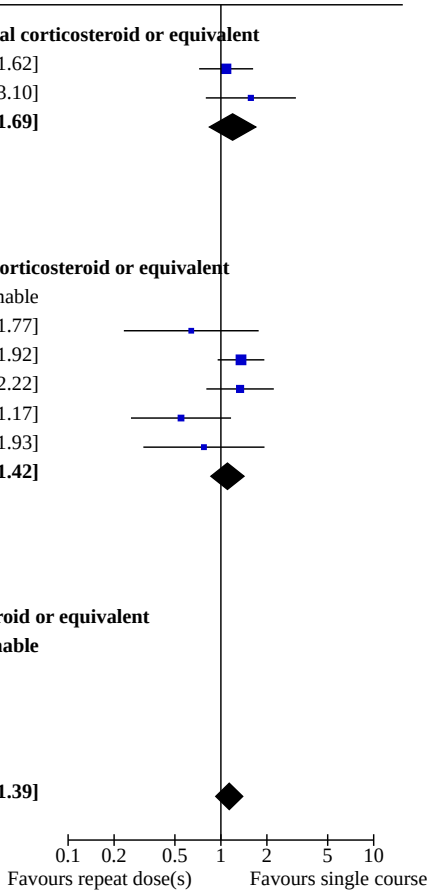


Analysis 10.11. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 11: A12: Composite serious outcome (variously defined)



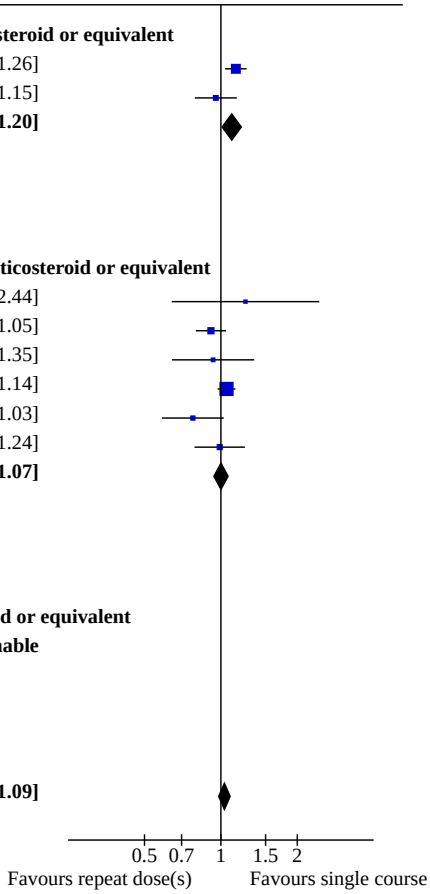
Analysis 10.12. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 12: B2: Maternal sepsis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.12.1 For women treated where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	44	489	41	493	26.0%	1.08 [0.72 , 1.62]
Peltoniemi 2007	19	125	12	124	7.7%	1.57 [0.80 , 3.10]
Subtotal (95% CI)		**614**		**617**	**33.7%**	**1.19 [0.84 , 1.69]**
Total events:	63		53			
Heterogeneity: Chi² = 0.85, df = 1 (P = 0.36); I² = 0%						
Test for overall effect: Z = 1.00 (P = 0.32)						
10.12.2 For women where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	6	0	6		Not estimable
Garite 2009	6	223	9	214	5.9%	0.64 [0.23 , 1.77]
Guinn 2001	60	249	42	236	27.5%	1.35 [0.95 , 1.92]
Murphy 2008	34	935	25	918	16.1%	1.34 [0.80 , 2.22]
TEAMS 1999	9	79	16	77	10.3%	0.55 [0.26 , 1.17]
Wapner 2006	8	250	10	242	6.5%	0.77 [0.31 , 1.93]
Subtotal (95% CI)		**1742**		**1693**	**66.3%**	**1.10 [0.86 , 1.42]**
Total events:	117		102			
Heterogeneity: Chi² = 6.83, df = 4 (P = 0.15); I² = 41%						
Test for overall effect: Z = 0.78 (P = 0.44)						
10.12.3 For women where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2356**		**2310**	**100.0%**	**1.13 [0.93 , 1.39]**
Total events:	180		155			
Heterogeneity: Chi² = 7.77, df = 6 (P = 0.26); I² = 23%						
Test for overall effect: Z = 1.22 (P = 0.22)						
Test for subgroup differences: Chi² = 0.13, df = 1 (P = 0.72), I² = 0%						



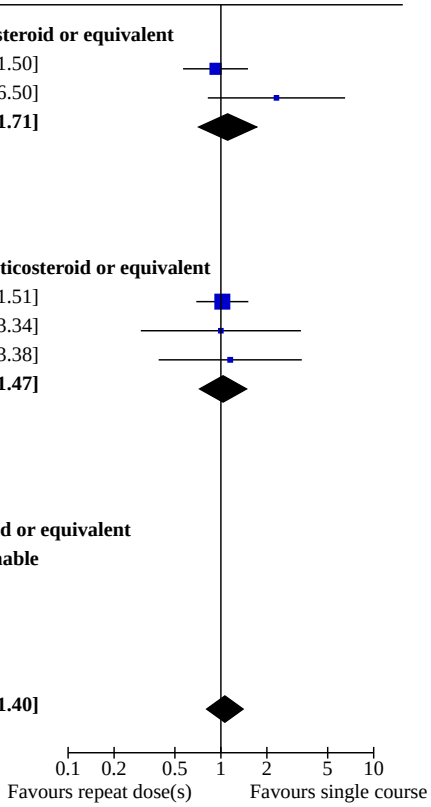
Analysis 10.13. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 13: B3: Caesarean section

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.13.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	326	489	287	493	24.0%	1.15 [1.04 , 1.26]
Peltoniemi 2007	77	125	80	124	6.7%	0.95 [0.79 , 1.15]
Subtotal (95% CI)		**614**		**617**	**30.7%**	**1.10 [1.01 , 1.20]**
Total events:	403		367			
Heterogeneity: Chi² = 2.78, df = 1 (P = 0.10); I² = 64%						
Test for overall effect: Z = 2.22 (P = 0.03)						
10.13.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Aghajafari 2002	5	6	4	6	0.3%	1.25 [0.64 , 2.44]
Garite 2009	139	223	146	214	12.5%	0.91 [0.80 , 1.05]
McEvoy 2010	24	44	24	41	2.1%	0.93 [0.64 , 1.35]
Murphy 2008	537	935	501	918	42.4%	1.05 [0.97 , 1.14]
TEAMS 1999	39	79	49	77	4.2%	0.78 [0.59 , 1.03]
Wapner 2006	93	250	91	242	7.8%	0.99 [0.79 , 1.24]
Subtotal (95% CI)		**1537**		**1498**	**69.3%**	**1.00 [0.94 , 1.07]**
Total events:	837		815			
Heterogeneity: Chi² = 6.94, df = 5 (P = 0.23); I² = 28%						
Test for overall effect: Z = 0.03 (P = 0.98)						
10.13.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2151**		**2115**	**100.0%**	**1.03 [0.98 , 1.09]**
Total events:	1240		1182			
Heterogeneity: Chi² = 13.00, df = 7 (P = 0.07); I² = 46%						
Test for overall effect: Z = 1.21 (P = 0.23)						
Test for subgroup differences: Chi² = 3.13, df = 1 (P = 0.08), I² = 68.0%						



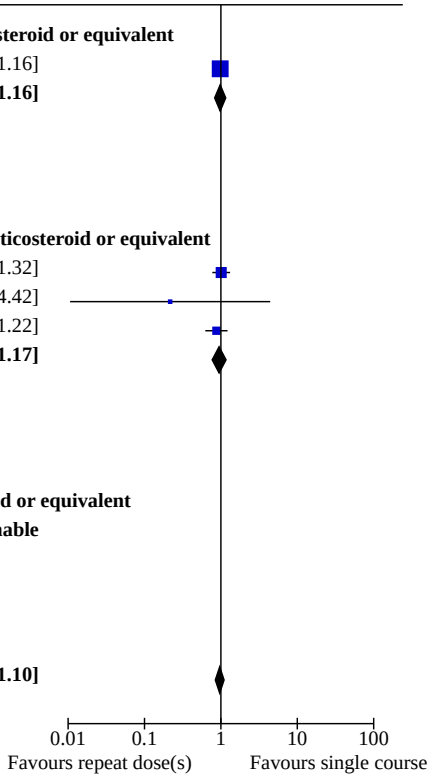
Analysis 10.14. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 14: C1: Total deaths after randomisation up to early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.14.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	29	568	32	578	33.4%	0.92 [0.57 , 1.50]
Peltoniemi 2007	11	160	5	168	5.1%	2.31 [0.82 , 6.50]
Subtotal (95% CI)		**728**		**746**	**38.5%**	**1.11 [0.72 , 1.71]**
Total events:	40		37			
Heterogeneity: Chi² = 2.48, df = 1 (P = 0.12); I² = 60%						
Test for overall effect: Z = 0.46 (P = 0.65)						
10.14.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Murphy 2008	49	1166	47	1143	49.9%	1.02 [0.69 , 1.51]
TEAMS 1999	5	94	5	94	5.3%	1.00 [0.30 , 3.34]
Wapner 2006	7	299	6	295	6.4%	1.15 [0.39 , 3.38]
Subtotal (95% CI)		**1559**		**1532**	**61.5%**	**1.03 [0.73 , 1.47]**
Total events:	61		58			
Heterogeneity: Chi² = 0.04, df = 2 (P = 0.98); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.85)						
10.14.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2287**		**2278**	**100.0%**	**1.06 [0.81 , 1.40]**
Total events:	101		95			
Heterogeneity: Chi² = 2.55, df = 4 (P = 0.63); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.67)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



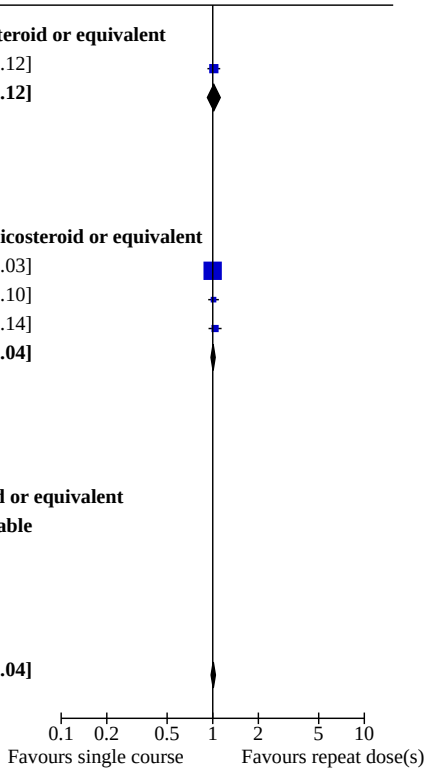
Analysis 10.15. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 15: C2: Neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.15.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	175	495	182	504	53.6%	0.98 [0.83 , 1.16]
Subtotal (95% CI)		**495**		**504**	**53.6%**	**0.98 [0.83 , 1.16]**
Total events:	175		182			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.25 (P = 0.80)						
10.15.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Murphy 2008	99	1020	95	988	28.7%	1.01 [0.77 , 1.32]
TEAMS 1999	0	59	2	64	0.7%	0.22 [0.01 , 4.42]
Wapner 2006	51	248	56	238	17.0%	0.87 [0.63 , 1.22]
Subtotal (95% CI)		**1327**		**1290**	**46.4%**	**0.95 [0.77 , 1.17]**
Total events:	150		153			
Heterogeneity: Chi² = 1.36, df = 2 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.51 (P = 0.61)						
10.15.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1822**		**1794**	**100.0%**	**0.96 [0.85 , 1.10]**
Total events:	325		335			
Heterogeneity: Chi² = 1.42, df = 3 (P = 0.70); I² = 0%						
Test for overall effect: Z = 0.54 (P = 0.59)						
Test for subgroup differences: Chi² = 0.06, df = 1 (P = 0.81), I² = 0%						



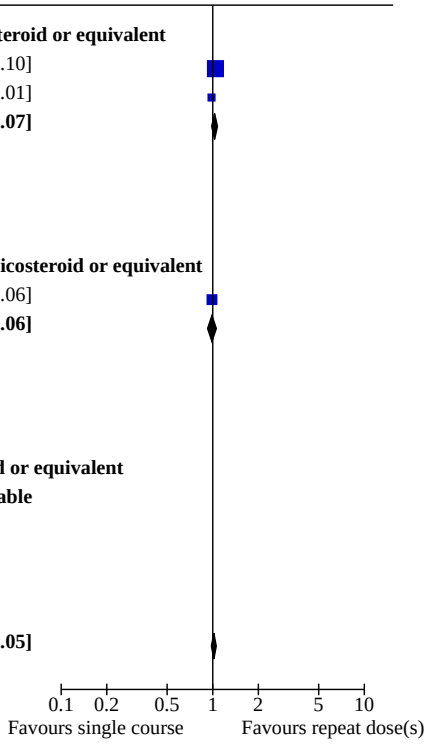
Analysis 10.16. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 16: C3: Survival free of neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.16.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	320	524	322	536	21.3%	1.02 [0.92 , 1.12]
Subtotal (95% CI)		**524**		**536**	**21.3%**	**1.02 [0.92 , 1.12]**
Total events:	320		322			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.33 (P = 0.74)						
10.16.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Murphy 2008	921	1069	893	1035	60.7%	1.00 [0.97 , 1.03]
TEAMS 1999	85	91	84	91	5.6%	1.01 [0.93 , 1.10]
Wapner 2006	197	255	182	244	12.4%	1.04 [0.94 , 1.14]
Subtotal (95% CI)		**1415**		**1370**	**78.7%**	**1.01 [0.97 , 1.04]**
Total events:	1203		1159			
Heterogeneity: $Chi^2 = 0.52$, df = 2 (P = 0.77); $I^2 = 0\%$						
Test for overall effect: Z = 0.34 (P = 0.74)						
10.16.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1939**		**1906**	**100.0%**	**1.01 [0.98 , 1.04]**
Total events:	1523		1481			
Heterogeneity: $Chi^2 = 0.61$, df = 3 (P = 0.89); $I^2 = 0\%$						
Test for overall effect: Z = 0.47 (P = 0.64)						
Test for subgroup differences: $Chi^2 = 0.05$, df = 1 (P = 0.83), $I^2 = 0\%$						

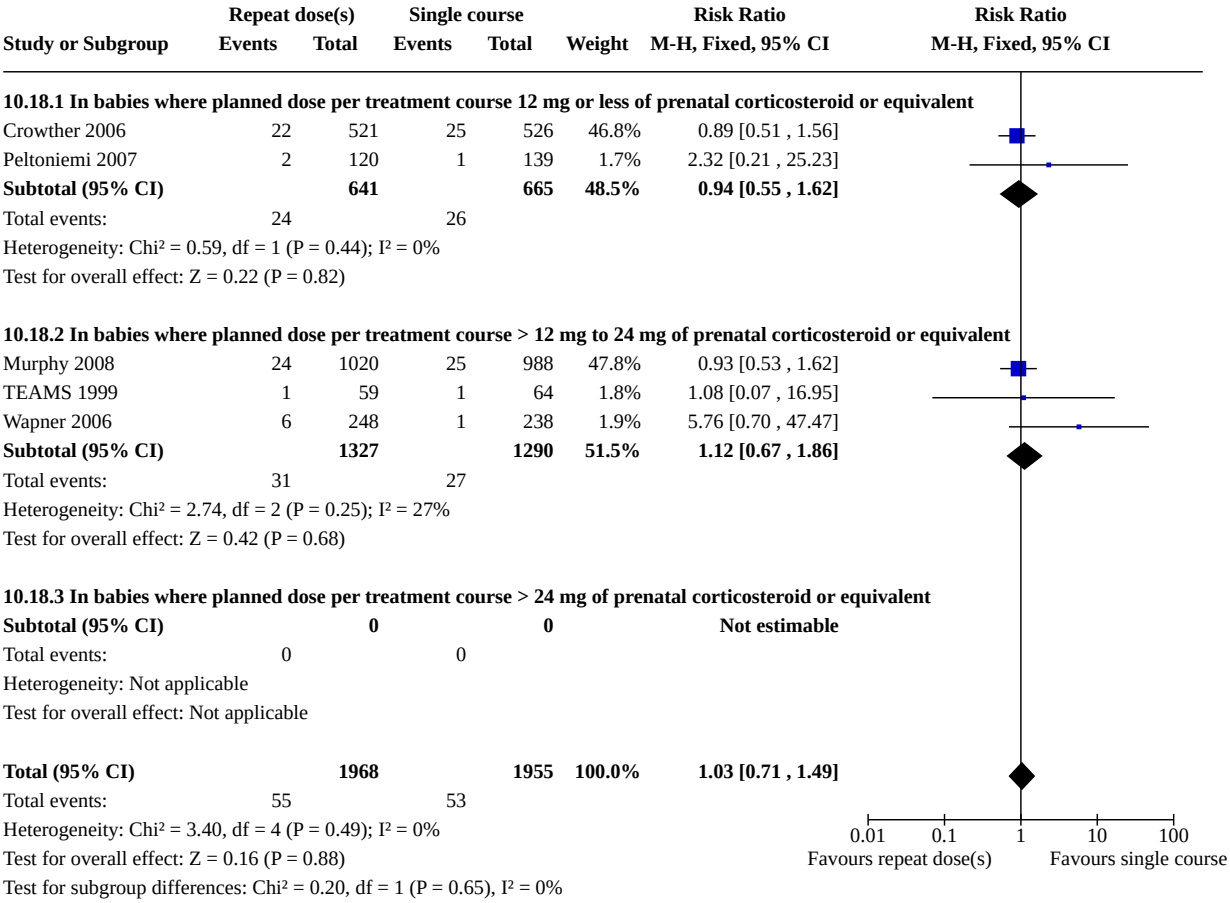


Analysis 10.17. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 17: C4: Survival free of major neurodevelopmental impairment at early childhood follow-up

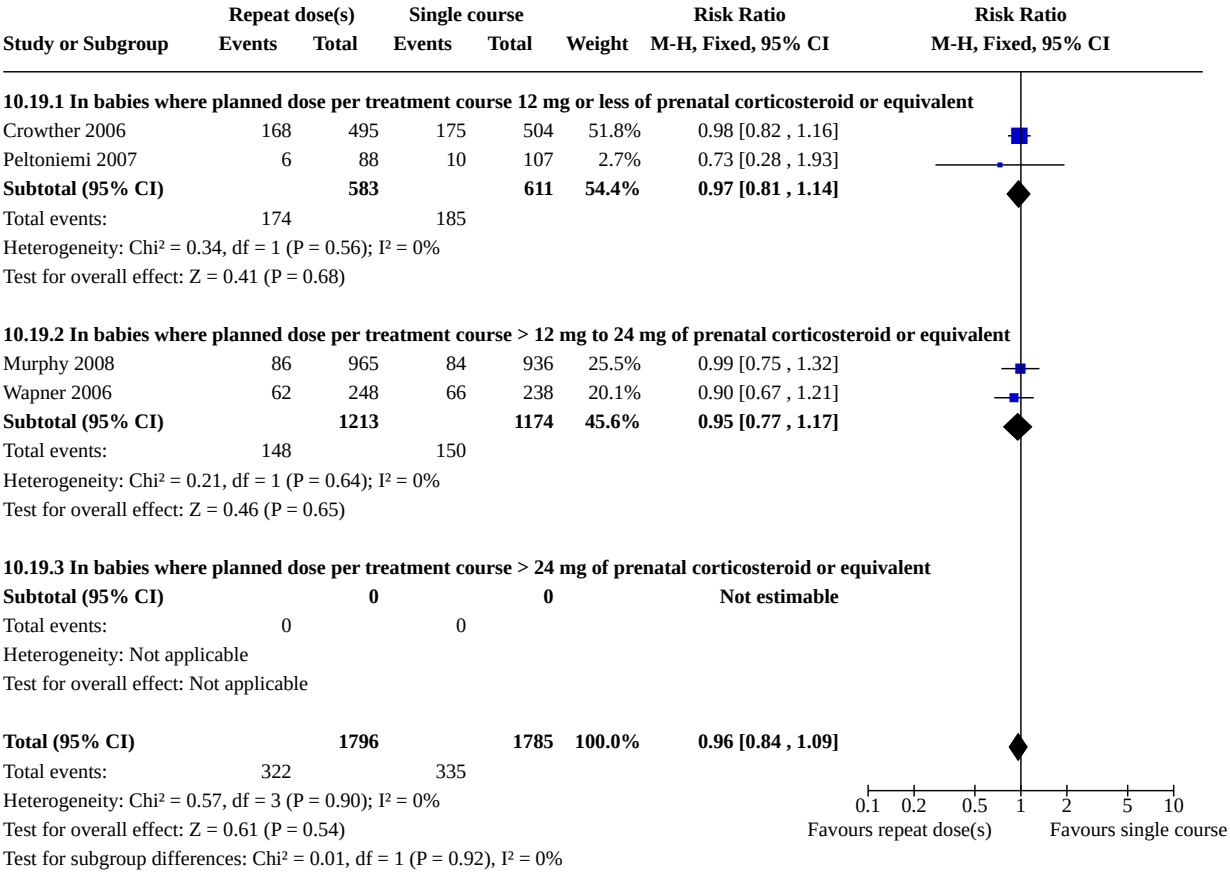
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
10.17.1 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent						
Crowther 2006	442	524	434	536	55.3%	1.04 [0.99 , 1.10]
Peltoniemi 2007	115	118	138	139	16.3%	0.98 [0.95 , 1.01]
Subtotal (95% CI)		**642**		**675**	**71.7%**	**1.03 [0.98 , 1.07]**
Total events:	557		572			
Heterogeneity: Chi² = 8.03, df = 1 (P = 0.005); I² = 88%						
Test for overall effect: Z = 1.25 (P = 0.21)						
10.17.2 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent						
Wapner 2006	222	255	215	244	28.3%	0.99 [0.92 , 1.06]
Subtotal (95% CI)		**255**		**244**	**28.3%**	**0.99 [0.92 , 1.06]**
Total events:	222		215			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
10.17.3 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**897**		**919**	**100.0%**	**1.02 [0.98 , 1.05]**
Total events:	779		787			
Heterogeneity: Chi² = 5.98, df = 2 (P = 0.05); I² = 67%						
Test for overall effect: Z = 0.89 (P = 0.37)						
Test for subgroup differences: Chi² = 0.97, df = 1 (P = 0.32), I² = 0%						



Analysis 10.18. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 18: C5: Cerebral palsy at early childhood follow-up



Analysis 10.19. Comparison 10: Subgroup analysis for the planned dose of corticosteroid given per treatment , Outcome 19: C6: Developmental delay or intellectual impairment at early childhood follow-up (any)



Comparison 11. Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.1 A1: Fetal or neonatal or infant death (< 1 year of age)	7	4756	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.68, 1.21]
11.1.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.73, 1.40]
11.1.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	5	1301	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.31, 1.14]
11.1.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.2 A2: Fetal death	4	1740	Risk Ratio (M-H, Fixed, 95% CI)	0.71 [0.14, 3.57]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.2.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.06, 16.23]
11.2.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	3	594	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.08, 4.42]
11.2.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.3 A3: Neonatal death	4	1740	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.51, 1.23]
11.3.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.56, 1.59]
11.3.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	3	594	Risk Ratio (M-H, Fixed, 95% CI)	0.52 [0.23, 1.19]
11.3.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.4 A5: Respiratory distress syndrome	5	2334	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.72, 0.93]
11.4.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.68, 0.92]
11.4.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.69, 1.12]
11.4.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.5 A6: Severe respiratory distress syndrome	4	3481	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.70, 1.09]
11.5.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	1	2309	Risk Ratio (M-H, Fixed, 95% CI)	1.11 [0.82, 1.49]
11.5.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	3	1172	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.88]
11.5.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.6 A7: Severe lung disease	5	4627	Risk Ratio (M-H, Fixed, 95% CI)	0.75 [0.63, 0.89]
11.6.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.80 [0.65, 0.97]
11.6.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	3	1172	Risk Ratio (M-H, Fixed, 95% CI)	0.62 [0.44, 0.88]
11.6.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.7 A8: Chronic lung disease	6	4641	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.77, 1.19]
11.7.1 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	1.03 [0.79, 1.35]
11.7.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent	4	1186	Risk Ratio (M-H, Fixed, 95% CI)	0.82 [0.56, 1.19]
11.7.3 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.8 A9: Severe intraventricular haemorrhage (grade 3 or 4)	4	3973	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.53, 1.79]
11.8.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.30, 1.37]
11.8.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	2	518	Risk Ratio (M-H, Fixed, 95% CI)	2.50 [0.76, 8.22]
11.8.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.9 A10: Intraventricular haemorrhage	4	2318	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.24]
11.9.1 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent	1	1146	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.57, 1.38]
11.9.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of betamethasone or equivalent	3	1172	Risk Ratio (M-H, Fixed, 95% CI)	0.95 [0.64, 1.41]

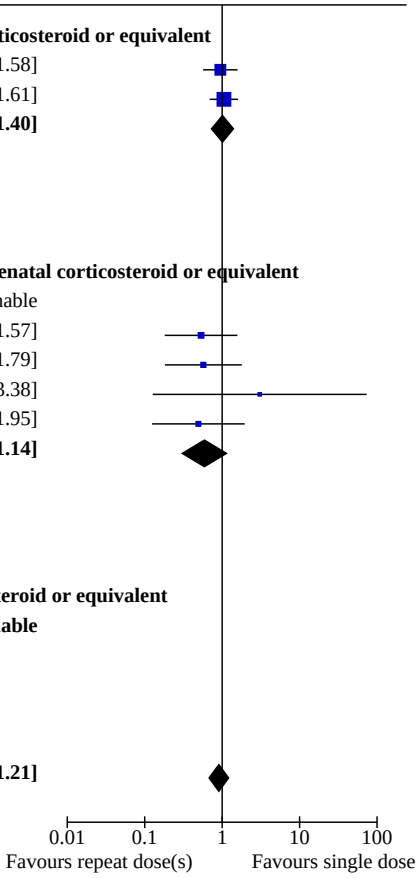
Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.9.3 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.10 A11: Necrotising enterocolitis	6	4643	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.51, 1.22]
11.10.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.65 [0.34, 1.24]
11.10.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.68]
11.10.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.11 A12: Composite serious outcome (variously defined)	6	4643	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 0.99]
11.11.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
11.11.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.02]
11.11.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.12 B2: Maternal sepsis	5	3824	Risk Ratio (M-H, Fixed, 95% CI)	1.21 [0.96, 1.52]
11.12.1 For women where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	2835	Risk Ratio (M-H, Fixed, 95% CI)	1.18 [0.86, 1.62]
11.12.2 For women where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	3	989	Risk Ratio (M-H, Fixed, 95% CI)	1.24 [0.90, 1.73]
11.12.3 For women where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.13 B3: Caesarean section	4	3339	Risk Ratio (M-H, Fixed, 95% CI)	1.08 [1.01, 1.14]
11.13.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	2835	Risk Ratio (M-H, Fixed, 95% CI)	1.09 [1.02, 1.16]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.13.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	2	504	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.80, 1.25]
11.13.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.14 C1: Total deaths after randomisation up to early childhood follow-up	3	4049	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.74, 1.33]
11.14.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.72, 1.33]
11.14.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	594	Risk Ratio (M-H, Fixed, 95% CI)	1.15 [0.39, 3.38]
11.14.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.15 C2: Neurodevelopmental impairment at early childhood follow-up	3	3493	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.85, 1.11]
11.15.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3007	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.86, 1.14]
11.15.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	486	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.63, 1.22]
11.15.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.16 C3: Survival free of neurodevelopmental impairment at early childhood follow-up	3	3663	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.97, 1.04]
11.16.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3164	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.97, 1.04]
11.16.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	499	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.94, 1.14]
11.16.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.17 C4: Survival free of major neurodevelopmental impairment at early childhood follow-up	2	1559	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.98, 1.07]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
11.17.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	1	1060	Risk Ratio (M-H, Fixed, 95% CI)	1.04 [0.99, 1.10]
11.17.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	499	Risk Ratio (M-H, Fixed, 95% CI)	0.99 [0.92, 1.06]
11.17.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.18 C5: Cerebral palsy at early childhood follow-up	3	3541	Risk Ratio (M-H, Fixed, 95% CI)	1.01 [0.69, 1.47]
11.18.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3055	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.61, 1.35]
11.18.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	486	Risk Ratio (M-H, Fixed, 95% CI)	5.76 [0.70, 47.47]
11.18.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
11.19 C6: Developmental delay or intellectual impairment at early childhood follow-up (any)	3	3386	Risk Ratio (M-H, Fixed, 95% CI)	0.96 [0.84, 1.10]
11.19.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	2900	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.85, 1.14]
11.19.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	1	486	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.65, 1.17]
11.19.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable

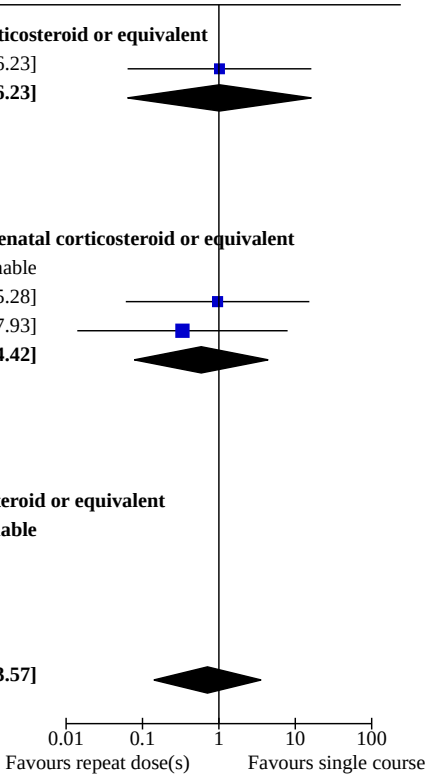
Analysis 11.1. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 1: A1: Fetal or neonatal or infant death (< 1 year of age)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.1.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	27	568	29	578	31.3%	0.95 [0.57 , 1.58]
Murphy 2008	43	1166	40	1143	44.0%	1.05 [0.69 , 1.61]
Subtotal (95% CI)		**1734**		**1721**	**75.3%**	**1.01 [0.73 , 1.40]**
Total events:	70		69			
Heterogeneity: Chi² = 0.10, df = 1 (P = 0.75); I² = 0%						
Test for overall effect: Z = 0.06 (P = 0.95)						
11.1.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Guinn 2001	5	256	9	246	10.0%	0.53 [0.18 , 1.57]
Mazumder 2008	4	38	7	38	7.6%	0.57 [0.18 , 1.79]
McEvoy 2010	1	56	0	57	0.5%	3.05 [0.13 , 73.38]
Wapner 2006	3	299	6	295	6.6%	0.49 [0.12 , 1.95]
Subtotal (95% CI)		**658**		**643**	**24.7%**	**0.59 [0.31 , 1.14]**
Total events:	13		22			
Heterogeneity: Chi² = 1.13, df = 3 (P = 0.77); I² = 0%						
Test for overall effect: Z = 1.58 (P = 0.11)						
11.1.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2392**		**2364**	**100.0%**	**0.91 [0.68 , 1.21]**
Total events:	83		91			
Heterogeneity: Chi² = 3.38, df = 5 (P = 0.64); I² = 0%						
Test for overall effect: Z = 0.67 (P = 0.50)						
Test for subgroup differences: Chi² = 2.07, df = 1 (P = 0.15), I² = 51.8%						

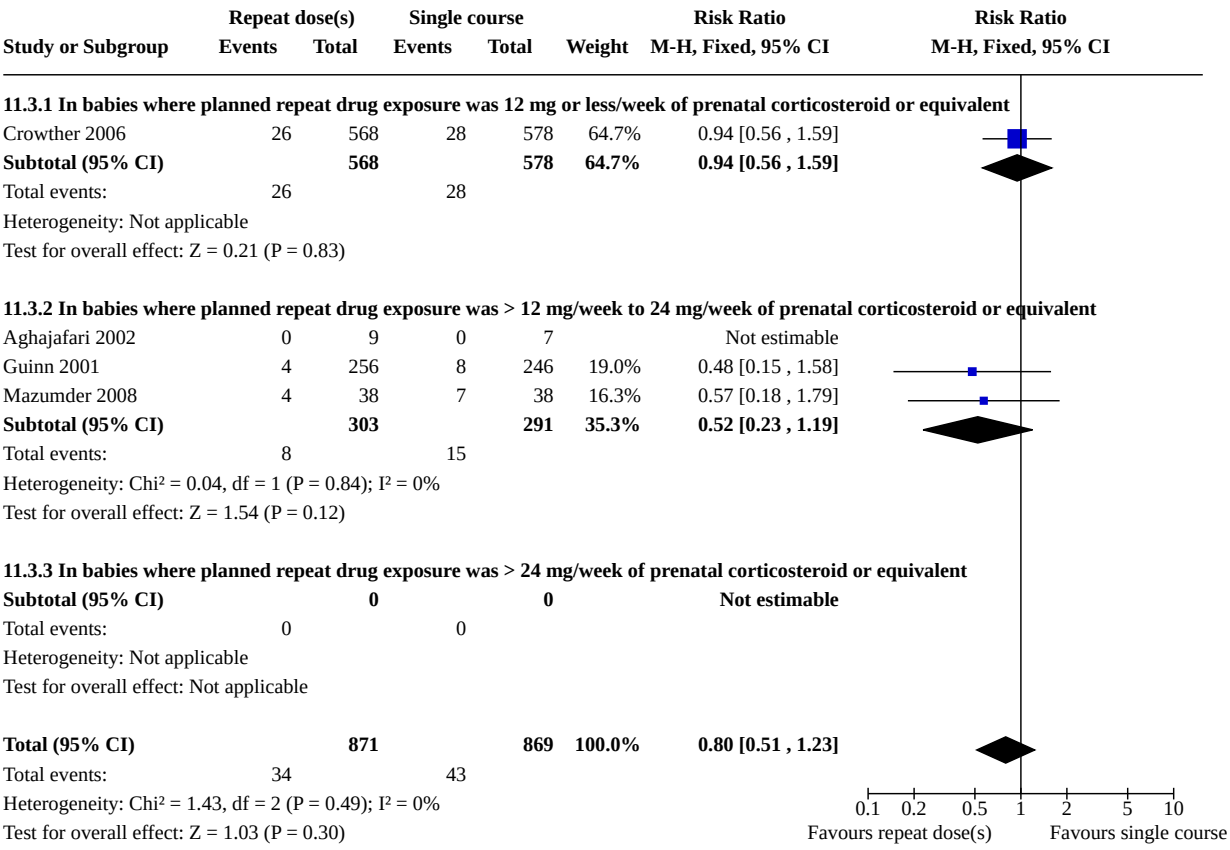


Analysis 11.2. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 2: A2: Fetal death

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.2.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	1	568	1	578	28.2%	1.02 [0.06 , 16.23]
Subtotal (95% CI)		**568**		**578**	**28.2%**	**1.02 [0.06 , 16.23]**
Total events:	1		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						
11.2.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Guinn 2001	1	256	1	246	29.0%	0.96 [0.06 , 15.28]
Mazumder 2008	0	38	1	38	42.7%	0.33 [0.01 , 7.93]
Subtotal (95% CI)		**303**		**291**	**71.8%**	**0.59 [0.08 , 4.42]**
Total events:	1		2			
Heterogeneity: Chi² = 0.24, df = 1 (P = 0.62); I² = 0%						
Test for overall effect: Z = 0.52 (P = 0.61)						
11.2.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**871**		**869**	**100.0%**	**0.71 [0.14 , 3.57]**
Total events:	2		3			
Heterogeneity: Chi² = 0.33, df = 2 (P = 0.85); I² = 0%						
Test for overall effect: Z = 0.42 (P = 0.68)						
Test for subgroup differences: Chi² = 0.10, df = 1 (P = 0.75), I² = 0%						

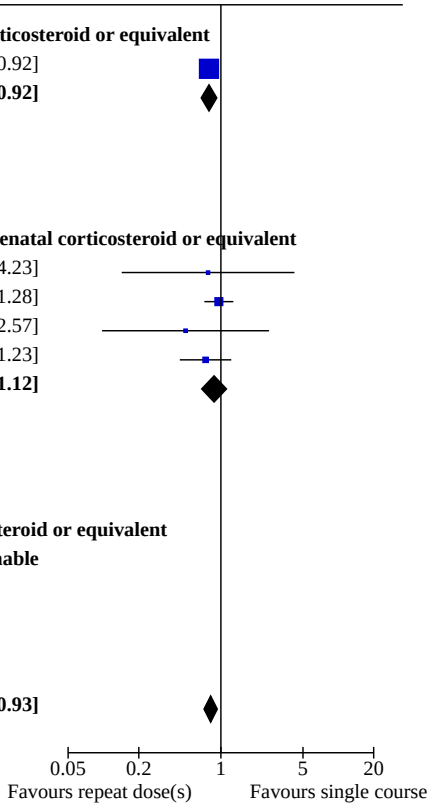


Analysis 11.3. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 3: A3: Neonatal death



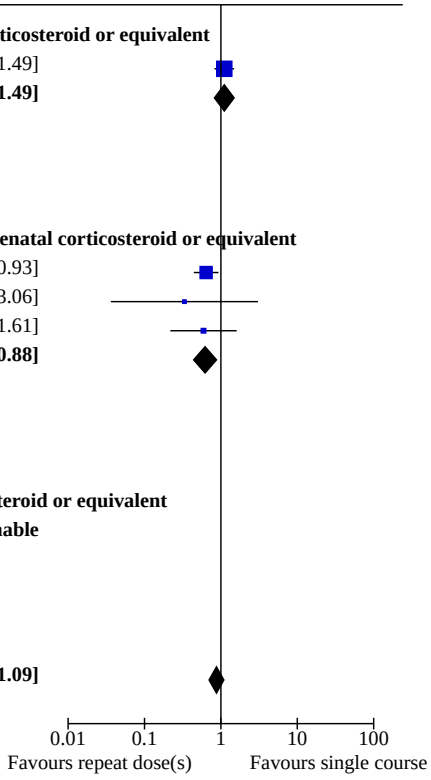
Analysis 11.4. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 4: A5: Respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.4.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	186	568	239	578	68.5%	0.79 [0.68 , 0.92]
Subtotal (95% CI)		**568**		**578**	**68.5%**	**0.79 [0.68 , 0.92]**
Total events:	186		239			
Heterogeneity: Not applicable						
Test for overall effect: Z = 2.99 (P = 0.003)						
11.4.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	2	9	2	7	0.7%	0.78 [0.14 , 4.23]
Guinn 2001	69	256	69	246	20.4%	0.96 [0.72 , 1.28]
Mazumder 2008	2	38	4	38	1.2%	0.50 [0.10 , 2.57]
Wapner 2006	24	299	32	295	9.3%	0.74 [0.45 , 1.23]
Subtotal (95% CI)		**602**		**586**	**31.5%**	**0.87 [0.69 , 1.12]**
Total events:	97		107			
Heterogeneity: Chi^2 = 1.31, df = 3 (P = 0.73); I^2 = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
11.4.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1170**		**1164**	**100.0%**	**0.82 [0.72 , 0.93]**
Total events:	283		346			
Heterogeneity: Chi^2 = 1.91, df = 4 (P = 0.75); I^2 = 0%						
Test for overall effect: Z = 3.03 (P = 0.002)						
Test for subgroup differences: Chi^2 = 0.46, df = 1 (P = 0.50), I^2 = 0%						



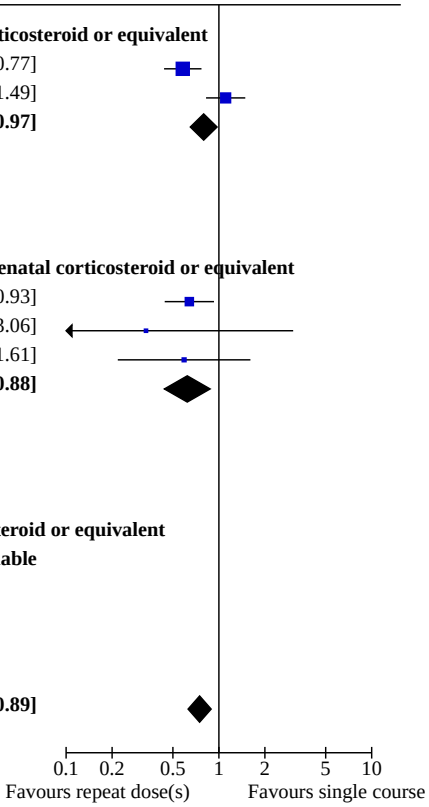
Analysis 11.5. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 5: A6: Severe respiratory distress syndrome

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.5.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Murphy 2008	87	1166	77	1143	52.2%	1.11 [0.82 , 1.49]
Subtotal (95% CI)		**1166**		**1143**	**52.2%**	**1.11 [0.82 , 1.49]**
Total events:	87		77			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.68 (P = 0.50)						
11.5.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Guinn 2001	38	256	57	246	39.0%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	2.0%	0.33 [0.04 , 3.06]
Wapner 2006	6	299	10	295	6.8%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**593**		**579**	**47.8%**	**0.62 [0.44 , 0.88]**
Total events:	45		70			
Heterogeneity: Chi² = 0.34, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						
11.5.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1759**		**1722**	**100.0%**	**0.87 [0.70 , 1.09]**
Total events:	132		147			
Heterogeneity: Chi² = 6.47, df = 3 (P = 0.09); I² = 54%						
Test for overall effect: Z = 1.18 (P = 0.24)						
Test for subgroup differences: Chi² = 6.25, df = 1 (P = 0.01), I² = 84.0%						



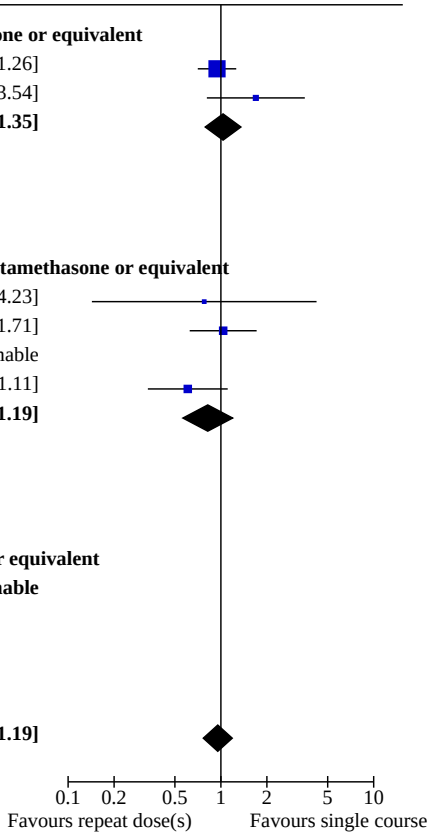
Analysis 11.6. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 6: A7: Severe lung disease

Study or Subgroup	Repeat dose(s) Events	Repeat dose(s) Total	Single course Events	Single course Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.6.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	65	568	114	578	43.1%	0.58 [0.44 , 0.77]
Murphy 2008	87	1166	77	1143	29.7%	1.11 [0.82 , 1.49]
Subtotal (95% CI)		**1734**		**1721**	**72.8%**	**0.80 [0.65 , 0.97]**
Total events:	152		191			
Heterogeneity: Chi² = 9.63, df = 1 (P = 0.002); I² = 90%						
Test for overall effect: Z = 2.23 (P = 0.03)						
11.6.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Guinn 2001	38	256	57	246	22.2%	0.64 [0.44 , 0.93]
Mazumder 2008	1	38	3	38	1.1%	0.33 [0.04 , 3.06]
Wapner 2006	6	299	10	295	3.8%	0.59 [0.22 , 1.61]
Subtotal (95% CI)		**593**		**579**	**27.2%**	**0.62 [0.44 , 0.88]**
Total events:	45		70			
Heterogeneity: Chi² = 0.34, df = 2 (P = 0.84); I² = 0%						
Test for overall effect: Z = 2.71 (P = 0.007)						
11.6.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2327**		**2300**	**100.0%**	**0.75 [0.63 , 0.89]**
Total events:	197		261			
Heterogeneity: Chi² = 11.28, df = 4 (P = 0.02); I² = 65%						
Test for overall effect: Z = 3.28 (P = 0.001)						
Test for subgroup differences: Chi² = 1.48, df = 1 (P = 0.22), I² = 32.4%						

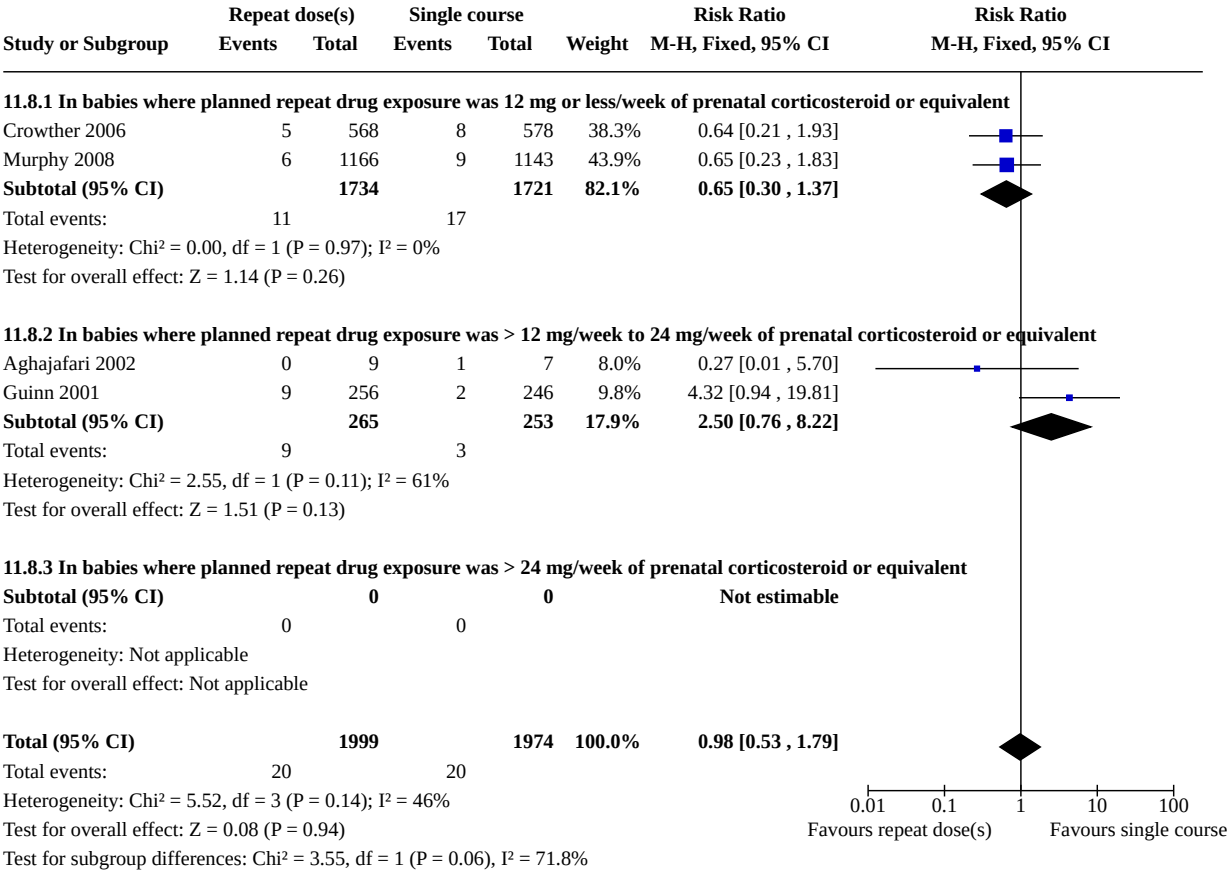


Analysis 11.7. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 7: A8: Chronic lung disease

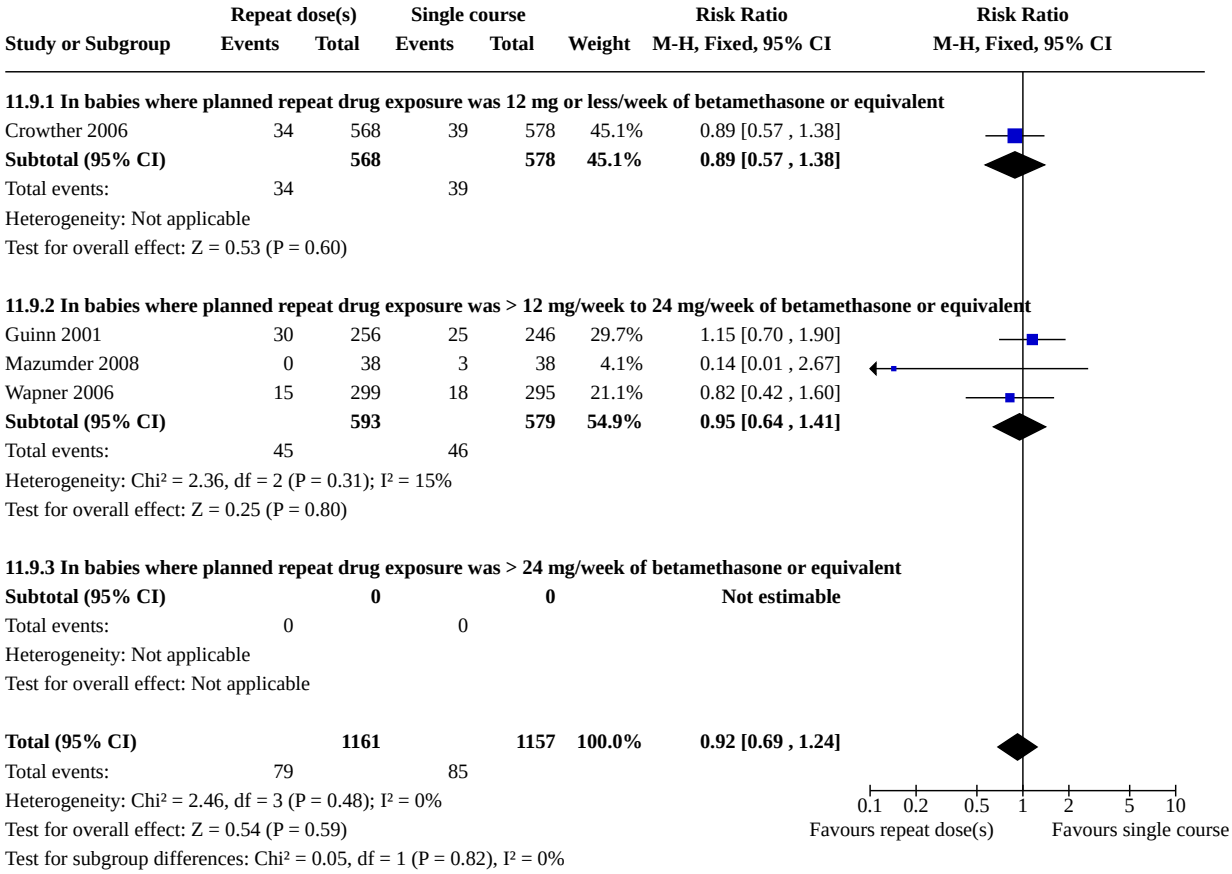
Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.7.1 In babies where planned repeat drug exposure was 12 mg or less/week of betamethasone or equivalent						
Crowther 2006	76	568	82	578	55.2%	0.94 [0.71 , 1.26]
Murphy 2008	19	1166	11	1143	7.5%	1.69 [0.81 , 3.54]
Subtotal (95% CI)		**1734**		**1721**	**62.7%**	**1.03 [0.79 , 1.35]**
Total events:	95		93			
Heterogeneity: Chi² = 2.10, df = 1 (P = 0.15); I² = 52%						
Test for overall effect: Z = 0.24 (P = 0.81)						
11.7.2 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	1.5%	0.78 [0.14 , 4.23]
Guinn 2001	28	256	26	246	18.0%	1.03 [0.62 , 1.71]
Mazumder 2008	0	37	0	37		Not estimable
Wapner 2006	16	299	26	295	17.8%	0.61 [0.33 , 1.11]
Subtotal (95% CI)		**601**		**585**	**37.3%**	**0.82 [0.56 , 1.19]**
Total events:	46		54			
Heterogeneity: Chi² = 1.78, df = 2 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.04 (P = 0.30)						
11.7.3 In babies where planned repeat drug exposure was > 24 mg/week of betamethasone or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2335**		**2306**	**100.0%**	**0.95 [0.77 , 1.19]**
Total events:	141		147			
Heterogeneity: Chi² = 4.65, df = 4 (P = 0.33); I² = 14%						
Test for overall effect: Z = 0.42 (P = 0.67)						
Test for subgroup differences: Chi² = 0.96, df = 1 (P = 0.33), I² = 0%						



Analysis 11.8. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 8: A9: Severe intraventricular haemorrhage (grade 3 or 4)

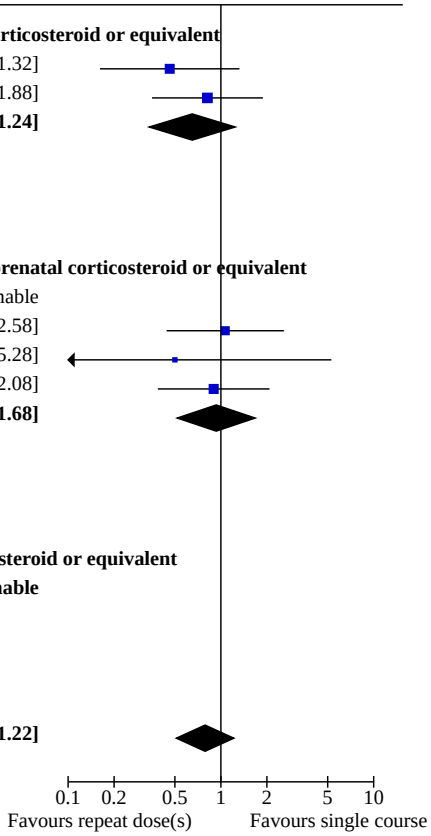


Analysis 11.9. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 9: A10: Intraventricular haemorrhage



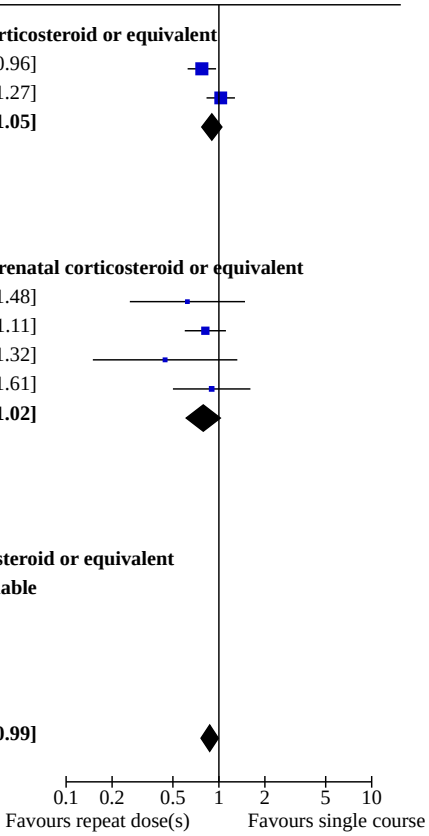
Analysis 11.10. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 10: A11: Necrotising enterocolitis

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.10.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	5	568	11	578	24.1%	0.46 [0.16 , 1.32]
Murphy 2008	10	1166	12	1143	26.8%	0.82 [0.35 , 1.88]
Subtotal (95% CI)		**1734**		**1721**	**50.9%**	**0.65 [0.34 , 1.24]**
Total events:	15		23			
Heterogeneity: Chi² = 0.69, df = 1 (P = 0.41); I² = 0%						
Test for overall effect: Z = 1.31 (P = 0.19)						
11.10.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	0	9	0	7		Not estimable
Guinn 2001	10	256	9	246	20.3%	1.07 [0.44 , 2.58]
Mazumder 2008	1	38	2	38	4.4%	0.50 [0.05 , 5.28]
Wapner 2006	10	299	11	295	24.5%	0.90 [0.39 , 2.08]
Subtotal (95% CI)		**602**		**586**	**49.1%**	**0.93 [0.52 , 1.68]**
Total events:	21		22			
Heterogeneity: Chi² = 0.37, df = 2 (P = 0.83); I² = 0%						
Test for overall effect: Z = 0.24 (P = 0.81)						
11.10.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2336**		**2307**	**100.0%**	**0.79 [0.51 , 1.22]**
Total events:	36		45			
Heterogeneity: Chi² = 1.68, df = 4 (P = 0.79); I² = 0%						
Test for overall effect: Z = 1.08 (P = 0.28)						
Test for subgroup differences: Chi² = 0.66, df = 1 (P = 0.42), I² = 0%						

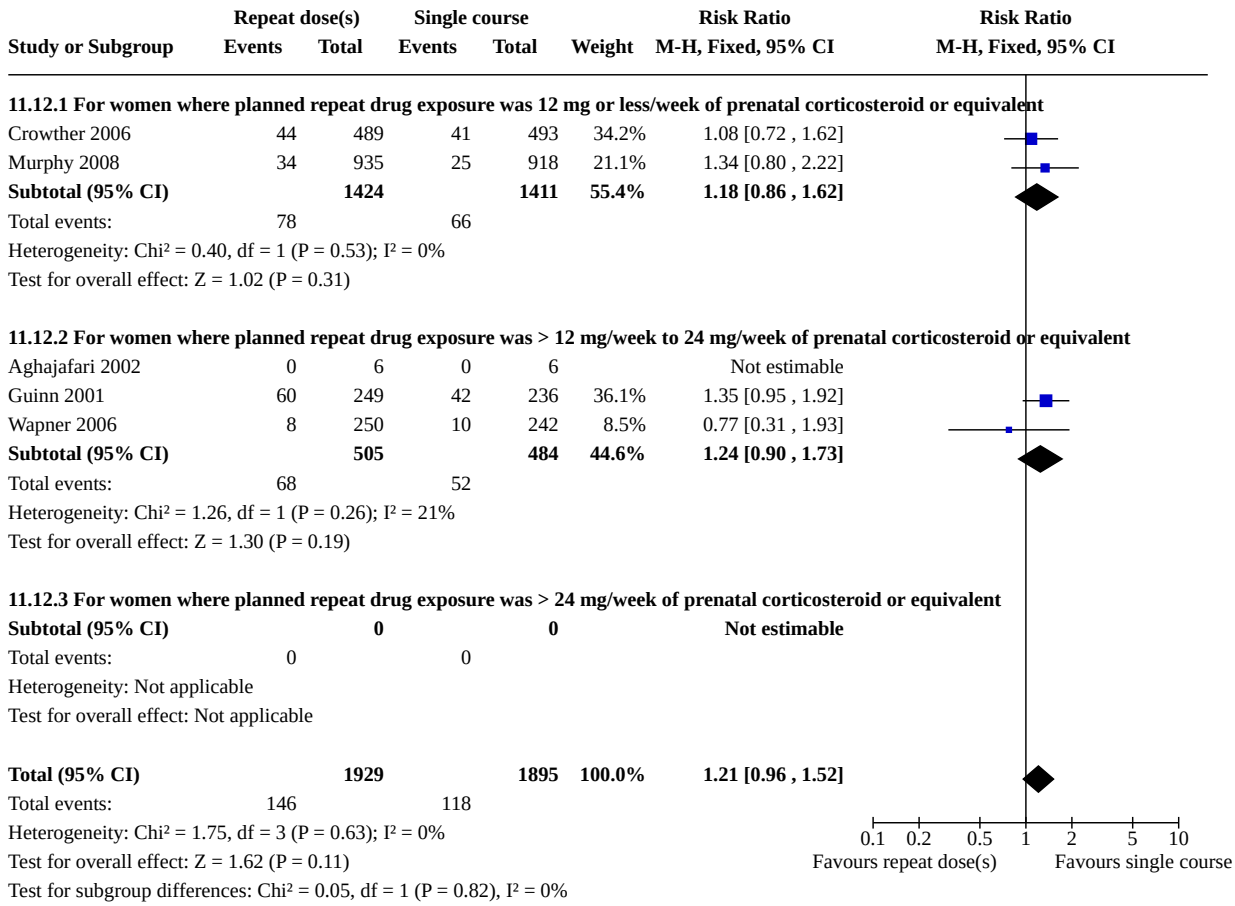


Analysis 11.11. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 11: A12: Composite serious outcome (variously defined)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.11.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	114	568	150	578	37.4%	0.77 [0.62 , 0.96]
Murphy 2008	150	1166	143	1143	36.4%	1.03 [0.83 , 1.27]
Subtotal (95% CI)		**1734**		**1721**	**73.8%**	**0.90 [0.77 , 1.05]**
Total events:	264		293			
Heterogeneity: Chi² = 3.41, df = 1 (P = 0.06); I² = 71%						
Test for overall effect: Z = 1.38 (P = 0.17)						
11.11.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	4	9	5	7	1.4%	0.62 [0.26 , 1.48]
Guinn 2001	56	256	66	246	16.9%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	2.3%	0.44 [0.15 , 1.32]
Wapner 2006	20	299	22	295	5.6%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**602**		**586**	**26.2%**	**0.79 [0.61 , 1.02]**
Total events:	84		102			
Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%						
Test for overall effect: Z = 1.80 (P = 0.07)						
11.11.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**2336**		**2307**	**100.0%**	**0.87 [0.76 , 0.99]**
Total events:	348		395			
Heterogeneity: Chi² = 5.72, df = 5 (P = 0.33); I² = 13%						
Test for overall effect: Z = 2.09 (P = 0.04)						
Test for subgroup differences: Chi² = 0.72, df = 1 (P = 0.40), I² = 0%						

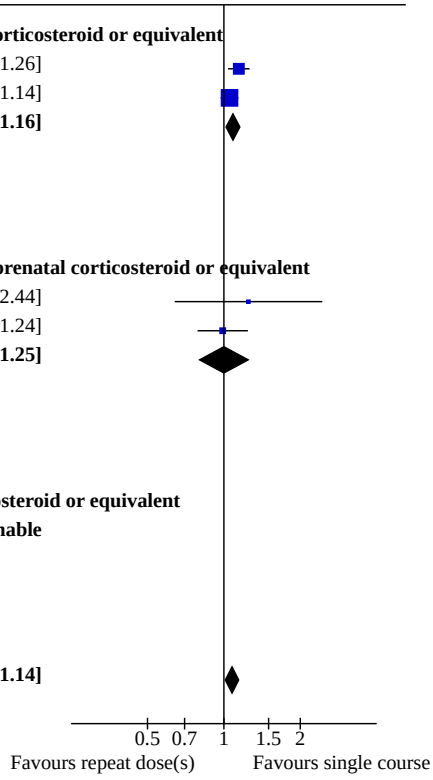


Analysis 11.12. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 12: B2: Maternal sepsis

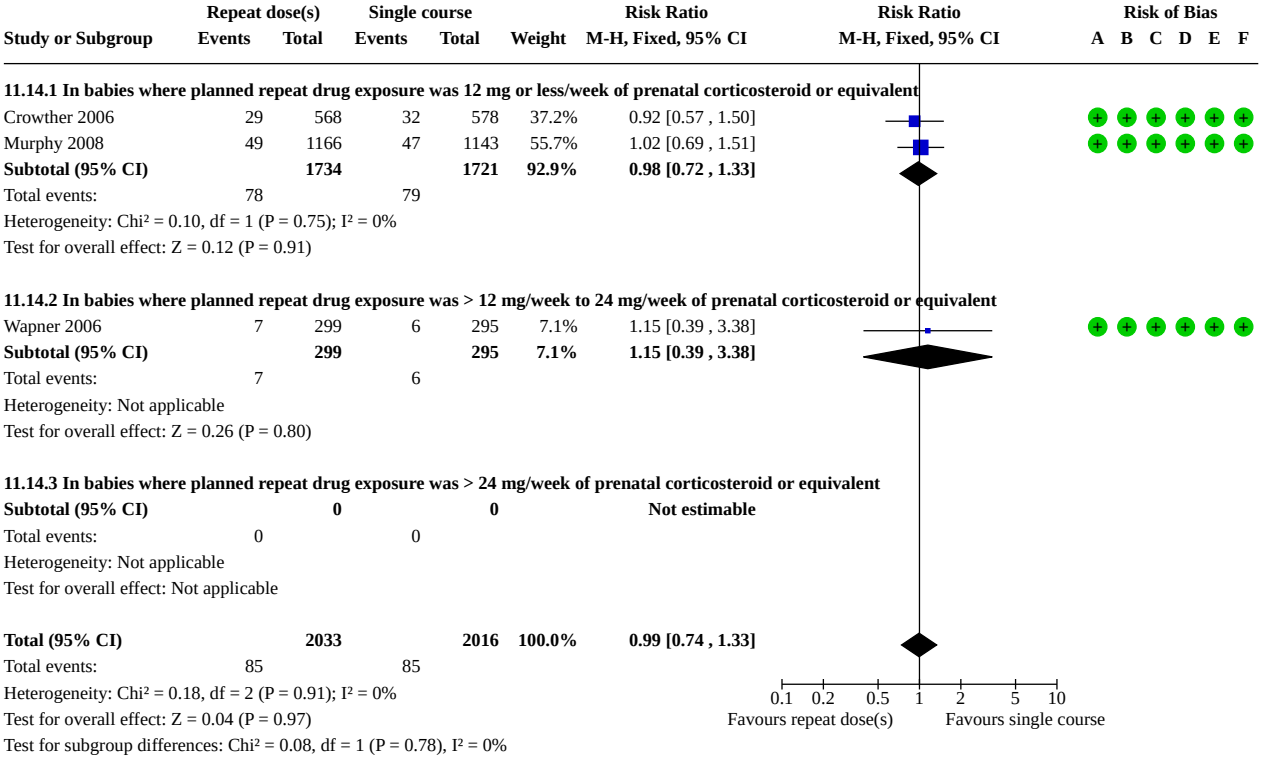


Analysis 11.13. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 13: B3: Caesarean section

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.13.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	326	489	287	493	32.2%	1.15 [1.04 , 1.26]
Murphy 2008	537	935	501	918	56.9%	1.05 [0.97 , 1.14]
Subtotal (95% CI)		**1424**		**1411**	**89.1%**	**1.09 [1.02 , 1.16]**
Total events:	863		788			
Heterogeneity: Chi² = 1.72, df = 1 (P = 0.19); I² = 42%						
Test for overall effect: Z = 2.59 (P = 0.010)						
11.13.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Aghajafari 2002	5	6	4	6	0.5%	1.25 [0.64 , 2.44]
Wapner 2006	93	250	91	242	10.4%	0.99 [0.79 , 1.24]
Subtotal (95% CI)		**256**		**248**	**10.9%**	**1.00 [0.80 , 1.25]**
Total events:	98		95			
Heterogeneity: Chi² = 0.44, df = 1 (P = 0.51); I² = 0%						
Test for overall effect: Z = 0.00 (P = 1.00)						
11.13.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1680**		**1659**	**100.0%**	**1.08 [1.01 , 1.14]**
Total events:	961		883			
Heterogeneity: Chi² = 2.56, df = 3 (P = 0.46); I² = 0%						
Test for overall effect: Z = 2.39 (P = 0.02)						
Test for subgroup differences: Chi² = 0.50, df = 1 (P = 0.48), I² = 0%						



Analysis 11.14. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 14: C1: Total deaths after randomisation up to early childhood follow-up

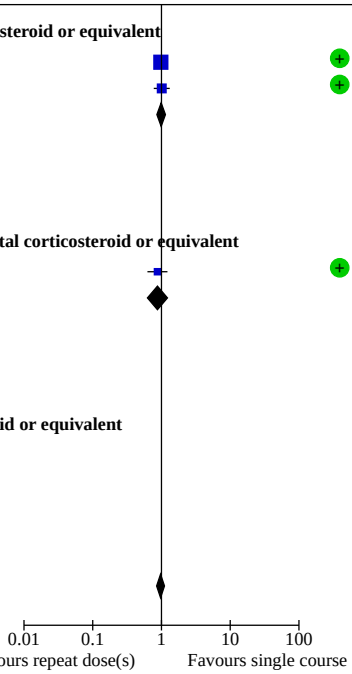


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

Analysis 11.15. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 15: C2: Neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI	Risk of Bias A B C D E F
11.15.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent							
Crowther 2006	175	495	182	504	54.0%	0.98 [0.83 , 1.16]	+ + + + + +
Murphy 2008	99	1020	95	988	28.9%	1.01 [0.77 , 1.32]	+ + + + + +
Subtotal (95% CI)		**1515**		**1492**	**82.9%**	**0.99 [0.86 , 1.14]**	
Total events:	274		277				
Heterogeneity: Chi² = 0.04, df = 1 (P = 0.85); I² = 0%							
Test for overall effect: Z = 0.14 (P = 0.89)							
11.15.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent							
Wapner 2006	51	248	56	238	17.1%	0.87 [0.63 , 1.22]	+ + ? + + ?
Subtotal (95% CI)		**248**		**238**	**17.1%**	**0.87 [0.63 , 1.22]**	
Total events:	51		56				
Heterogeneity: Not applicable							
Test for overall effect: Z = 0.79 (P = 0.43)							
11.15.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent							
Subtotal (95% CI)		**0**		**0**		**Not estimable**	
Total events:	0		0				
Heterogeneity: Not applicable							
Test for overall effect: Not applicable							
Total (95% CI)		**1763**		**1730**	**100.0%**	**0.97 [0.85 , 1.11]**	
Total events:	325		333				
Heterogeneity: Chi² = 0.47, df = 2 (P = 0.79); I² = 0%							
Test for overall effect: Z = 0.46 (P = 0.65)							
Test for subgroup differences: Chi² = 0.45, df = 1 (P = 0.50), I² = 0%							

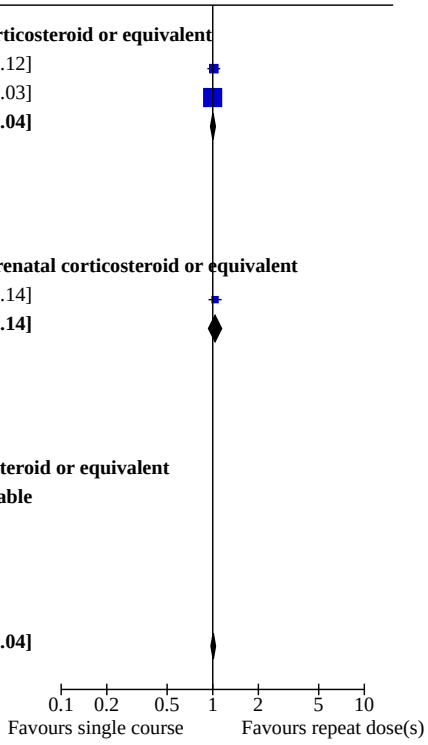


Risk of bias legend

(A) Bias arising from the randomization process
(B) Bias due to deviations from intended interventions
(C) Bias due to missing outcome data
(D) Bias in measurement of the outcome
(E) Bias in selection of the reported result
(F) Overall bias

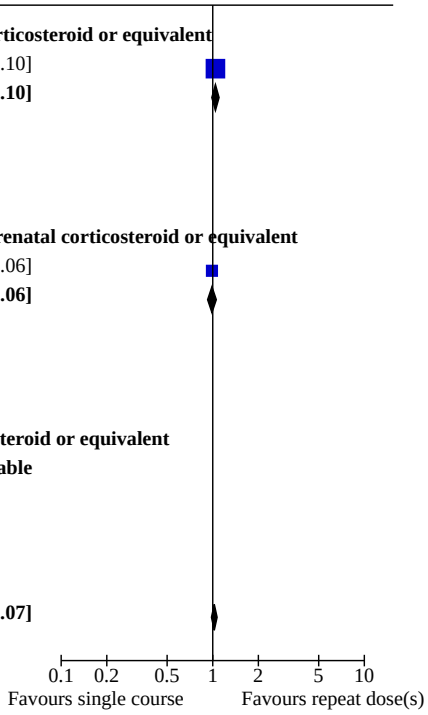
Analysis 11.16. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 16: C3: Survival free of neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.16.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	320	524	322	536	22.5%	1.02 [0.92 , 1.12]
Murphy 2008	921	1069	893	1035	64.3%	1.00 [0.97 , 1.03]
Subtotal (95% CI)		**1593**		**1571**	**86.8%**	**1.00 [0.97 , 1.04]**
Total events:	1241		1215			
Heterogeneity: Chi² = 0.14, df = 1 (P = 0.71); I² = 0%						
Test for overall effect: Z = 0.18 (P = 0.86)						
11.16.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Wapner 2006	197	255	182	244	13.2%	1.04 [0.94 , 1.14]
Subtotal (95% CI)		**255**		**244**	**13.2%**	**1.04 [0.94 , 1.14]**
Total events:	197		182			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.70 (P = 0.49)						
11.16.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1848**		**1815**	**100.0%**	**1.01 [0.97 , 1.04]**
Total events:	1438		1397			
Heterogeneity: Chi² = 0.59, df = 2 (P = 0.74); I² = 0%						
Test for overall effect: Z = 0.43 (P = 0.66)						
Test for subgroup differences: Chi² = 0.35, df = 1 (P = 0.55), I² = 0%						



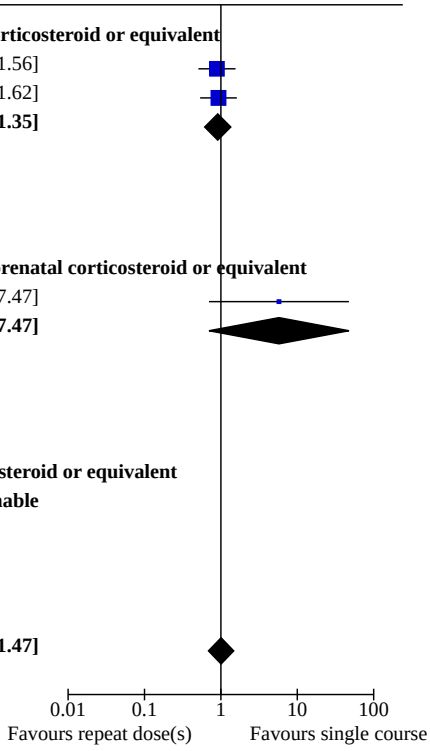
Analysis 11.17. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 17: C4: Survival free of major neurodevelopmental impairment at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.17.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	442	524	434	536	66.1%	1.04 [0.99 , 1.10]
Subtotal (95% CI)		**524**		**536**	**66.1%**	**1.04 [0.99 , 1.10]**
Total events:	442		434			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.45 (P = 0.15)						
11.17.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Wapner 2006	222	255	215	244	33.9%	0.99 [0.92 , 1.06]
Subtotal (95% CI)		**255**		**244**	**33.9%**	**0.99 [0.92 , 1.06]**
Total events:	222		215			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.36 (P = 0.72)						
11.17.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**779**		**780**	**100.0%**	**1.02 [0.98 , 1.07]**
Total events:	664		649			
Heterogeneity: Chi² = 1.49, df = 1 (P = 0.22); I² = 33%						
Test for overall effect: Z = 1.06 (P = 0.29)						
Test for subgroup differences: Chi² = 1.45, df = 1 (P = 0.23), I² = 31.3%						

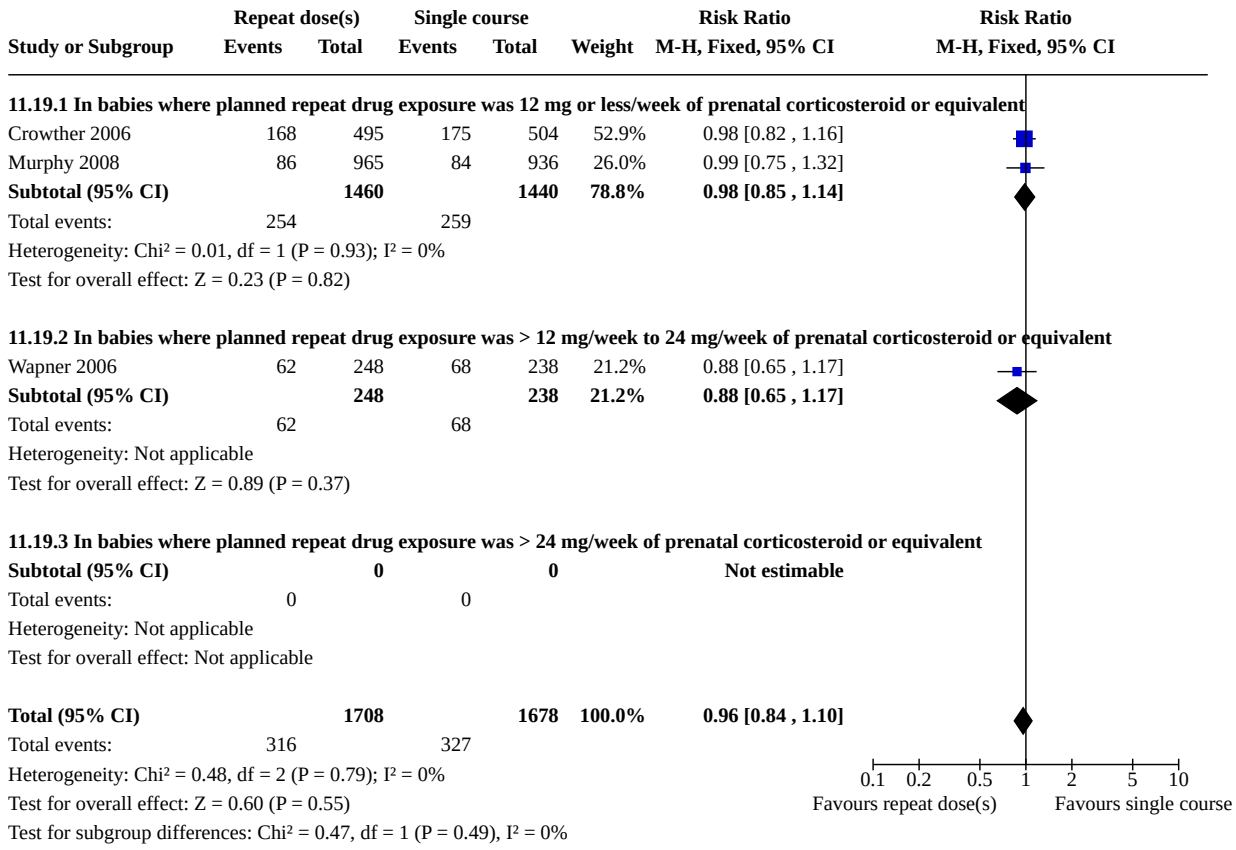


Analysis 11.18. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 18: C5: Cerebral palsy at early childhood follow-up

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
11.18.1 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent						
Crowther 2006	22	521	25	526	48.5%	0.89 [0.51 , 1.56]
Murphy 2008	24	1020	25	988	49.5%	0.93 [0.53 , 1.62]
Subtotal (95% CI)		**1541**		**1514**	**98.0%**	**0.91 [0.61 , 1.35]**
Total events:	46		50			
Heterogeneity: Chi² = 0.01, df = 1 (P = 0.91); I² = 0%						
Test for overall effect: Z = 0.47 (P = 0.64)						
11.18.2 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent						
Wapner 2006	6	248	1	238	2.0%	5.76 [0.70 , 47.47]
Subtotal (95% CI)		**248**		**238**	**2.0%**	**5.76 [0.70 , 47.47]**
Total events:	6		1			
Heterogeneity: Not applicable						
Test for overall effect: Z = 1.63 (P = 0.10)						
11.18.3 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**1789**		**1752**	**100.0%**	**1.01 [0.69 , 1.47]**
Total events:	52		51			
Heterogeneity: Chi² = 2.89, df = 2 (P = 0.24); I² = 31%						
Test for overall effect: Z = 0.03 (P = 0.98)						
Test for subgroup differences: Chi² = 2.84, df = 1 (P = 0.09), I² = 64.8%						



Analysis 11.19. Comparison 11: Subgroup analysis for the planned dose of repeat dose of corticosteroid drug exposure/week, Outcome 19: C6: Developmental delay or intellectual impairment at early childhood follow-up (any)



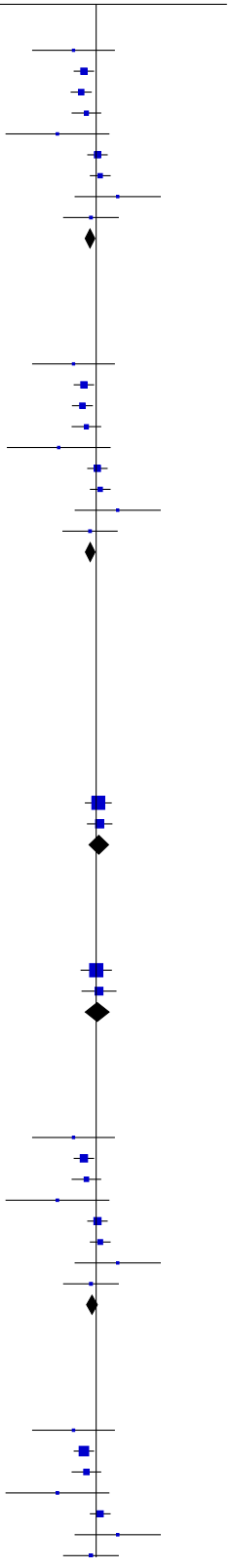
Comparison 12. Subgroup analysis for the gestational age at which the first repeat treatment was given

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1 A12: Composite serious outcome (variously defined)	9		Risk Ratio (M-H, Fixed, 95% CI)	Subtotals only
12.1.1 A12: Composite serious outcome (variously defined); intention to treat analysis	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.97]
12.1.2 A12: Composite serious outcome (variously defined); per protocol analysis	9	5599	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.80, 0.98]
12.1.3 In babies where pregnancy complicated by preterm prelabour rupture of membranes	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1.4 In babies from singleton pregnancies	2	1646	Risk Ratio (M-H, Fixed, 95% CI)	1.06 [0.86, 1.30]
12.1.5 In babies from multiple pregnancies	2	991	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.80, 1.31]
12.1.6 In babies exposed to repeat corticosteroids as betamethasone	8	5159	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.82, 1.03]

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
12.1.7 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less	7	2850	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.76, 0.99]
12.1.8 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1.9 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more	2	2886	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.76, 1.04]
12.1.10 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent	2	1474	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.75, 1.03]
12.1.11 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent	7	4262	Risk Ratio (M-H, Fixed, 95% CI)	0.88 [0.77, 1.00]
12.1.12 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1.13 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent	2	3455	Risk Ratio (M-H, Fixed, 95% CI)	0.90 [0.77, 1.05]
12.1.14 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent	4	1188	Risk Ratio (M-H, Fixed, 95% CI)	0.79 [0.61, 1.02]
12.1.15 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent	0	0	Risk Ratio (M-H, Fixed, 95% CI)	Not estimable
12.1.16 In babies where prenatal corticosteroid was administered intramuscularly	9	5736	Risk Ratio (M-H, Fixed, 95% CI)	0.86 [0.78, 0.95]
12.1.17 In babies given their first repeat course at less than 28 completed weeks' gestational age	1	181	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.71, 1.41]
12.1.18 In babies planned for one repeat course of prenatal corticosteroids	2	905	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.75, 1.02]

Analysis 12.1. Comparison 12: Subgroup analysis for the gestational age at which the first repeat treatment was given, Outcome 1: A12: Composite serious outcome (variously defined)

Study or Subgroup	Repeat dose(s) Events	Total	Single course Events	Total	Weight	Risk Ratio M-H, Fixed, 95% CI
12.1.1 A12: Composite serious outcome (variously defined); intention to treat analysis						
Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]
Garite 2009	88	289	120	288	20.0%	0.73 [0.59 , 0.91]
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.5%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	24.0%	1.03 [0.83 , 1.27]
Peltoniemi 2007	83	160	80	168	13.0%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	1.2%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	3.7%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2879**		**2857**	**100.0%**	**0.88 [0.80 , 0.97]**
Total events:	530		602			
Heterogeneity: Chi² = 13.77, df = 8 (P = 0.09); I² = 42%						
Test for overall effect: Z = 2.51 (P = 0.01)						
12.1.2 A12: Composite serious outcome (variously defined); per protocol analysis						
Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]
Crowther 2006	114	567	150	577	24.7%	0.77 [0.62 , 0.96]
Garite 2009	88	276	120	282	19.7%	0.75 [0.60 , 0.93]
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	37	9	38	1.5%	0.46 [0.15 , 1.35]
Murphy 2008	150	1164	143	1140	24.0%	1.03 [0.83 , 1.27]
Peltoniemi 2007	83	159	80	167	13.0%	1.09 [0.88 , 1.35]
TEAMS 1999	11	91	7	91	1.2%	1.57 [0.64 , 3.87]
Wapner 2006	20	250	22	242	3.7%	0.88 [0.49 , 1.57]
Subtotal (95% CI)		**2809**		**2790**	**100.0%**	**0.88 [0.80 , 0.98]**
Total events:	530		602			
Heterogeneity: Chi² = 13.01, df = 8 (P = 0.11); I² = 39%						
Test for overall effect: Z = 2.44 (P = 0.01)						
12.1.3 In babies where pregnancy complicated by preterm prelabour rupture of membranes						
Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
12.1.4 In babies from singleton pregnancies						
Murphy 2008	88	739	83	729	64.0%	1.05 [0.79 , 1.39]
Peltoniemi 2007	53	93	45	85	36.0%	1.08 [0.82 , 1.41]
Subtotal (95% CI)		**832**		**814**	**100.0%**	**1.06 [0.86 , 1.30]**
Total events:	141		128			
Heterogeneity: Chi² = 0.02, df = 1 (P = 0.88); I² = 0%						
Test for overall effect: Z = 0.53 (P = 0.59)						
12.1.5 In babies from multiple pregnancies						
Murphy 2008	62	427	60	414	66.1%	1.00 [0.72 , 1.39]
Peltoniemi 2007	30	67	35	83	33.9%	1.06 [0.74 , 1.53]
Subtotal (95% CI)		**494**		**497**	**100.0%**	**1.02 [0.80 , 1.31]**
Total events:	92		95			
Heterogeneity: Chi² = 0.06, df = 1 (P = 0.81); I² = 0%						
Test for overall effect: Z = 0.17 (P = 0.86)						
12.1.6 In babies exposed to repeat corticosteroids as betamethasone						
Aghajafari 2002	4	9	5	7	1.2%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	30.8%	0.77 [0.62 , 0.96]
Guinn 2001	56	256	66	246	14.0%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.9%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	29.9%	1.03 [0.83 , 1.27]
Peltoniemi 2007	83	160	80	168	16.2%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	1.5%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	4.6%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2590**		**2569**	**100.0%**	**0.92 [0.82 , 1.03]**
Total events:	442		482			
Heterogeneity: Chi² = 10.33, df = 7 (P = 0.17); I² = 32%						
Test for overall effect: Z = 1.52 (P = 0.13)						
12.1.7 In babies exposed to repeat corticosteroids at a minimum interval of 7 days or less						
Aghajafari 2002	4	9	5	7	1.7%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	44.0%	0.77 [0.62 , 0.96]
Guinn 2001	56	256	66	246	19.9%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	2.7%	0.44 [0.15 , 1.32]
Peltoniemi 2007	83	160	80	168	23.1%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	2.1%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	6.6%	0.90 [0.50 , 1.61]



Analysis 12.1. (Continued)

Peltoniemi 2007	83	160	80	168	23.1%	1.09 [0.88 , 1.35]
TEAMS 1999	11	94	7	94	2.1%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	6.6%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**1424**		**1426**	**100.0%**	**0.87 [0.76 , 0.99]**
Total events:	292		339			

Heterogeneity: Chi² = 9.14, df = 6 (P = 0.17); I² = 34%
Test for overall effect: Z = 2.10 (P = 0.04)

12.1.8 In babies exposed to repeat corticosteroids at a minimum interval between 8 and < 14 days

Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

12.1.9 In babies exposed to repeat corticosteroids at a minimum interval of 14 days or more

Garite 2009	88	289	120	288	45.4%	0.73 [0.59 , 0.91]
Murphy 2008	150	1166	143	1143	54.6%	1.03 [0.83 , 1.27]
Subtotal (95% CI)		**1455**		**1431**	**100.0%**	**0.89 [0.76 , 1.04]**
Total events:	238		263			

Heterogeneity: Chi² = 4.82, df = 1 (P = 0.03); I² = 79%
Test for overall effect: Z = 1.43 (P = 0.15)

12.1.10 In babies where planned dose per treatment course 12 mg or less of prenatal corticosteroid or equivalent

Crowther 2006	114	568	150	578	65.6%	0.77 [0.62 , 0.96]
Peltoniemi 2007	83	160	80	168	34.4%	1.09 [0.88 , 1.35]
Subtotal (95% CI)		**728**		**746**	**100.0%**	**0.88 [0.75 , 1.03]**
Total events:	197		230			

Heterogeneity: Chi² = 5.06, df = 1 (P = 0.02); I² = 80%
Test for overall effect: Z = 1.58 (P = 0.11)

12.1.11 In babies where planned dose per treatment course > 12 mg to 24 mg of prenatal corticosteroid or equivalent

Aghajafari 2002	4	9	5	7	1.5%	0.62 [0.26 , 1.48]
Garite 2009	88	289	120	288	32.0%	0.73 [0.59 , 0.91]
Guinn 2001	56	256	66	246	17.9%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	2.4%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	38.4%	1.03 [0.83 , 1.27]
TEAMS 1999	11	94	7	94	1.9%	1.57 [0.64 , 3.88]
Wapner 2006	20	299	22	295	5.9%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2151**		**2111**	**100.0%**	**0.88 [0.77 , 1.00]**
Total events:	333		372			

Heterogeneity: Chi² = 8.65, df = 6 (P = 0.19); I² = 31%
Test for overall effect: Z = 1.96 (P = 0.05)

12.1.12 In babies where planned dose per treatment course > 24 mg of prenatal corticosteroid or equivalent

Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

12.1.13 In babies where planned repeat drug exposure was 12 mg or less/week of prenatal corticosteroid or equivalent

Crowther 2006	114	568	150	578	50.7%	0.77 [0.62 , 0.96]
Murphy 2008	150	1166	143	1143	49.3%	1.03 [0.83 , 1.27]
Subtotal (95% CI)		**1734**		**1721**	**100.0%**	**0.90 [0.77 , 1.05]**
Total events:	264		293			

Heterogeneity: Chi² = 3.41, df = 1 (P = 0.06); I² = 71%
Test for overall effect: Z = 1.38 (P = 0.17)

12.1.14 In babies where planned repeat drug exposure was > 12 mg/week to 24 mg/week of prenatal corticosteroid or equivalent

Aghajafari 2002	4	9	5	7	5.4%	0.62 [0.26 , 1.48]
Guinn 2001	56	256	66	246	64.7%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	8.6%	0.44 [0.15 , 1.32]
Wapner 2006	20	299	22	295	21.3%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**602**		**586**	**100.0%**	**0.79 [0.61 , 1.02]**
Total events:	84		102			

Heterogeneity: Chi² = 1.58, df = 3 (P = 0.66); I² = 0%
Test for overall effect: Z = 1.80 (P = 0.07)

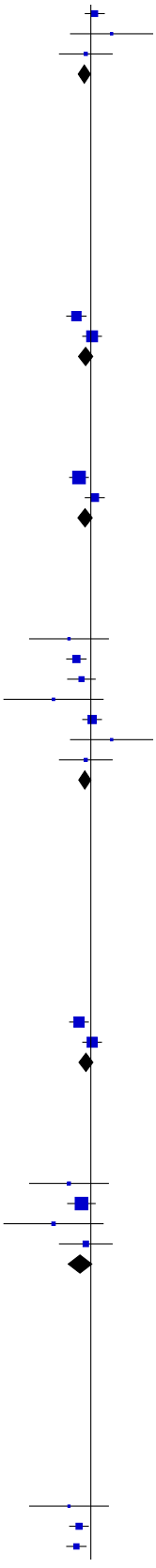
12.1.15 In babies where planned repeat drug exposure was > 24 mg/week of prenatal corticosteroid or equivalent

Subtotal (95% CI)		**0**		**0**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable

12.1.16 In babies where prenatal corticosteroid was administered intramuscularly

Aghajafari 2002	4	9	5	7	0.9%	0.62 [0.26 , 1.48]
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]
Garite 2009	88	289	120	288	19.9%	0.73 [0.59 , 0.91]



Analysis 12.1. (Continued)

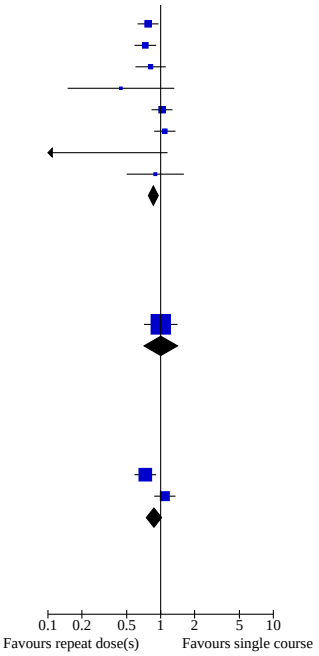
Crowther 2006	114	568	150	578	24.7%	0.77 [0.62 , 0.96]
Garite 2009	88	289	120	288	19.9%	0.73 [0.59 , 0.91]
Guinn 2001	56	256	66	246	11.2%	0.82 [0.60 , 1.11]
Mazumder 2008	4	38	9	38	1.5%	0.44 [0.15 , 1.32]
Murphy 2008	150	1166	143	1143	24.0%	1.03 [0.83 , 1.27]
Peltoniemi 2007	83	160	80	168	12.9%	1.09 [0.88 , 1.35]
TEAMS 1999	0	94	7	94	1.2%	0.07 [0.00 , 1.15]
Wapner 2006	20	299	22	295	3.7%	0.90 [0.50 , 1.61]
Subtotal (95% CI)		**2879**		**2857**	**100.0%**	**0.86 [0.78 , 0.95]**
Total events:	519		602			
Heterogeneity: Chi² = 15.39, df = 8 (P = 0.05); I² = 48%						
Test for overall effect: Z = 2.91 (P = 0.004)						

12.1.17 In babies given their first repeat course at less than 28 completed weeks' gestational age

Guinn 2001	37	88	39	93	100.0%	1.00 [0.71 , 1.41]
Subtotal (95% CI)		**88**		**93**	**100.0%**	**1.00 [0.71 , 1.41]**
Total events:	37		39			
Heterogeneity: Not applicable						
Test for overall effect: Z = 0.01 (P = 0.99)						

12.1.18 In babies planned for one repeat course of prenatal corticosteroids

Garite 2009	88	289	120	288	60.6%	0.73 [0.59 , 0.91]
Peltoniemi 2007	83	160	80	168	39.4%	1.09 [0.88 , 1.35]
Subtotal (95% CI)		**449**		**456**	**100.0%**	**0.87 [0.75 , 1.02]**
Total events:	171		200			
Heterogeneity: Chi² = 6.46, df = 1 (P = 0.01); I² = 85%						
Test for overall effect: Z = 1.72 (P = 0.08)						



ADDITIONAL TABLES

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant

Secondary outcome	Certainty of evidence	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Comments
Gestational age at birth ≥ 37 weeks	Low	Not serious	Serious	Serious	Serious	Undetected	Downgraded 1 level due to indirectness as participants in the trials varied markedly in their gestational age at entry, limiting the generalisability of this finding. Downgraded 1 level due to inconsistency of effect as evidenced by moderate statistical heterogeneity.
Gestational age at birth < 37 weeks	Low	Not serious	Serious	Not serious	Serious	Undetected	Downgraded 1 level due to indirectness as participants in the trials varied markedly in their gestational age at entry, limiting the generalisability of this finding. Downgraded 1 level due to inconsistency of effect as evidenced by moderate statistical heterogeneity.
Gestational age at birth < 34 weeks	Moderate	Not serious	Not serious	Not serious	Serious	Undetected	Downgraded 1 level due to indirectness as participants in the trials varied markedly in their gestational age at entry, limiting the generalisability of this finding.
Gestational age at birth < 28 weeks	Low	Not serious	Not serious	Serious	Serious	Undetected	Downgraded 1 level due to indirectness as participants in the trials varied markedly in their gestational age at entry, limiting the generalisability of this finding. Downgraded 1 level due to imprecision (95% CI including possible benefit and harm).
Mean gestational age at birth	Moderate	Not serious	Not serious	Not serious	Serious	Undetected	Downgraded 1 level due to indirectness as participants in the trials varied markedly in their gestational age at entry, limiting the generalisability of this finding.
Mean birthweight	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/10 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean birthweight adjusted for gestational age	High	Not serious	Not serious	Not serious	Not serious	Undetected	—

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant *(Continued)*

Interval between trial entry and birth	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded due to imprecision due to an inadequate sample size for this outcome.
Small for gestational age	High	Not serious	Not serious	Not serious	Not serious	Undetected	2/7 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean length at birth	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/6 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean length at birth adjusted for gestational age	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Mean head circumference at birth	High	Not serious	Not serious	Not serious	Not serious	Undetected	2/10 trials had risk of bias (1 some concerns and 1 high risk). Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean head circumference Z score at birth	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Mean weight at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings. Not downgraded for inconsistency, as the degree of statistical heterogeneity was small, measured across only 2 studies with similar results.
Mean weight Z score at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean length at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant *(Continued)*

Mean length Z score at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean head circumference at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean head circumference Z score at primary hospital discharge	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/2 trials had some concerns for risk of bias. Limiting the analysis to trials at low risk of bias did not markedly alter the findings.
Mean weight at infant follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Of 2 trials, 1 had some concerns of risk of bias and 1 had high risk of bias. Downgraded for imprecision due to an inadequate sample size for this outcome.
Mean weight Z score at infant follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	The only included trial had high risk of bias. Downgraded for imprecision as the 95% CI included marked increase and marked decrease in Z score.
Mean length at infant follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Of 2 trials, 1 had some concerns of risk of bias and 1 had high risk of bias. Downgraded for imprecision due to inadequate sample size for this outcome.
Mean length Z score at primary infant follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	The only included trial had high risk of bias. Downgraded for imprecision as the 95% CI included marked increase and marked decrease in Z score.
Mean head circumference at infant follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Of 2 trials, 1 had some concerns of risk of bias and 1 had high risk of bias. Downgraded for imprecision as the number of infants was too small for confident conclusions regarding this outcome.
Mean head circumference Z	Very low	Very serious	Not serious	Serious	Not serious	Undetected	The only included trial had high risk of bias. Downgraded for imprecision as the 95%

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant *(Continued)*

score at infant follow-up							CI included marked increase and marked decrease in Z score.
Admission to neonatal intensive care unit	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Proven neonatal infection while in the neonatal intensive care unit	High	Not serious	Not serious	Not serious	Not serious	Undetected	2/8 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings.
Early systemic neonatal infection	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/4 trials had high risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings.
Late systemic neonatal infection	Low	Not serious	Not serious	Very Serious	Not serious	Undetected	1/2 trials had high risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings. Downgraded for imprecision due to small numbers of events with a limited sample size and wide 95% CI including benefit and marked harm.
Retinopathy of prematurity	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	2/8 trials had some concerns and 1 had high risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings. Downgraded for imprecision due to a 95% CI including benefit and harm.
Periventricular leukomalacia	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	1/8 trials had some concerns and 1 had high risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings. Downgraded for imprecision due to a wide 95% CI including marked benefit and harm.
Neonatal encephalopathy	Very low	Very serious	Not serious	Very serious	Not serious	Undetected	Downgraded 2 levels as the only trial reporting this outcome had high risk of bias for lack of blinding and subjective outcome measurement. Downgraded 2 levels for imprecision due to small numbers of events with a small sample

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant *(Continued)*

							size and a wide 95% CI including marked benefit and marked harm.
Patent ductus arteriosus	Low	Very Serious	Not serious	Not serious	Not serious	Undetected	1/7 trials had some concerns and 1 had high risk of bias. Limiting the analysis to trials at low risk of bias changed the findings.
Use of respiratory support	High	Not serious	Not serious	Not serious	Not serious	Undetected	
Use of invasive respiratory support	Moderate	Not serious	Serious	Not serious	Not serious	Undetected	1/6 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings. Downgraded for inconsistency as evidenced by marked statistical heterogeneity, possibly related to different types of invasive respiratory support in use.
Duration of invasive respiratory support	Moderate	Not serious	Serious	Not serious	Not serious	Undetected	Downgraded for inconsistency as evidenced by marked statistical heterogeneity, possibly related to different types of invasive respiratory support in use.
Use of non-invasive respiratory support	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/3 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings.
Duration of non-invasive respiratory support	Low	Not serious	Not serious	Very serious	Not serious	Undetected	Downgraded 2 levels for imprecision due to small sample size and a wide 95% CI including benefit and minimal harm.
Use of oxygen supplementation	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Duration of oxygen supplementation	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision due to a 95% CI including benefit and harm.
Use of surfactant	Moderate	Not serious	Serious	Not serious	Not serious	Undetected	2/10 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings.

Table 1. GRADE certainty of evidence assessments for secondary outcomes for the fetus/neonate/infant *(Continued)*

							Downgraded for Inconsistency as evidenced by marked statistical heterogeneity.
Use of nitric oxide for respiratory support	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision due to a 95% CI including marked benefit and harm.
Use of postnatal corticosteroids	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision due to a 95% CI including benefit and marked harm.
Use of inotropic support	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Air leak syndrome	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	1/4 trials had some concerns of risk of bias. Limiting the analysis to trials at low risk of bias did not markedly change the findings. Downgraded for imprecision due to a 95% CI including marked benefit and marked harm.
Apgar score < 7 at 5 minutes	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded due to imprecision due to a 95% CI including marked benefit and harm.
Cardiac hypertrophy	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded for risk of bias as the only trial reporting data for this outcome had some concerns regarding missing outcome data.
Measures of hypothalamic-pituitary-adrenal axis function	Very low	Serious	Serious	Serious	Not serious	Undetected	Both trials had some concerns of risk of bias for this outcome. Downgraded for inconsistency as different measures had different findings. Downgraded for imprecision as all measures except cord blood cortisol had inadequate sample size.

CI: confidence interval.

Table 2. GRADE certainty of evidence assessments for secondary outcomes for the woman

Secondary outcome	Certainty of evidence	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Comments

Table 2. GRADE certainty of evidence assessments for secondary outcomes for the woman *(Continued)*

Puerperal sepsis	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and marked harm.
Chorioamnionitis during labour	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and marked harm.
Endometritis	Low	Not serious	Serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and marked harm. Downgraded for inconsistency as evidenced by marked statistical heterogeneity.
Pyrexia after trial entry requiring the use of antibiotics	Low	Not serious	Not serious	Very Serious	Not serious	Undetected	Downgraded 2 levels for imprecision as 95% CI included both marked benefit and harm and data were from a single trial of limited size.
Postpartum haemorrhage	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as the number of events was too low for a reliable effect estimate.
Postnatal pyrexia	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both marked benefit and harm.
Preterm prelabour rupture of the membranes after trial entry	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both marked benefit and harm.
Mode of birth: vaginal birth	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Hypertension	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both possible benefit and harm.
Glucose intolerance	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	1/2 trials had some concerns of risk of bias but limiting the analysis to low-risk trials only did not markedly change the findings. Downgraded for imprecision as 95% CI included both benefit and marked harm.
Postnatal depression	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded 1 level for imprecision as 95% CI included both benefit and harm.

Table 2. GRADE certainty of evidence assessments for secondary outcomes for the woman *(Continued)*

Local injection site adverse effects	Low	Not serious	Very serious	Not serious	Not serious	Undetected	Downgraded 2 levels for inconsistency due to severe heterogeneity.
Insomnia after treatment	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/4 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not markedly change the findings.
Gastrointestinal adverse effects of treatment	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as the number of events was too low and the study size too small for a reliable effect estimate.

CI: confidence interval.

Table 3. GRADE certainty of evidence assessments for secondary outcomes for the child in early childhood (aged two to less than five years)

Secondary outcome	Certainty of evidence	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Comments
Child behaviour	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	1/3 trials reporting data for this outcome had some concerns of risk of bias for missing data. Not downgraded for inconsistency as clearly different methods of measurement were used. Downgraded for imprecision as 2/3 trials had 95% CIs that included both marked harm and either benefit or no effect.
Motor impairment	Moderate	Not serious	Serious	Not serious	Not serious	Undetected	1/2 trials had some risks of bias but limiting the analysis to low risk of bias trials did not change the findings. Downgraded for inconsistency as evidenced by statistical heterogeneity.
Deafness/hearing impairment	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	2/4 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings. Downgraded for imprecision as 95% CI included both marked benefit and marked harm.
Blindness/visual impairment	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	1/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings. Downgraded for impreci-

Table 3. GRADE certainty of evidence assessments for secondary outcomes for the child in early childhood (aged two to less than five years) *(Continued)*

							sion as 95% CI included both marked benefit and marked harm.
Mean weight at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/4 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Weight for age at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Low weight for age	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and possible harm.
Mean height at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/4 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Height for age at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Short for age	Low	Not serious	Serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and marked harm. Downgraded for inconsistency as evidenced by marked heterogeneity.
Mean head circumference at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/4 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Head circumference for age at early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	1/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.
Small head circumference for age	Moderate	Not serious	Serious	Not serious	Not serious	Undetected	Downgraded for inconsistency as evidenced by marked heterogeneity.

Table 3. GRADE certainty of evidence assessments for secondary outcomes for the child in early childhood (aged two to less than five years) *(Continued)*

Mean systolic blood pressure	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Systolic blood pressure Z score	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded for risk of bias as the only included trial had some concerns for risk of bias.
Mean diastolic blood pressure	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Diastolic blood pressure Z score	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded for risk of bias as the only included trial had some concerns for risk of bias.
Hypertension	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded for risk of bias as the only included trial had some concerns for risk of bias.
Asthma or recurrent wheeze	Moderate	Not serious	Serious	Serious	Not serious	Undetected	2/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings. Downgraded for inconsistency as evidenced by marked heterogeneity. Downgraded for imprecision as 95% CI included both benefit and possible harm.
Any respiratory disease	High	Not serious	Not serious	Not serious	Not serious	Undetected	2/3 trials had some concerns of risk of bias but limiting the analysis to low-risk trials did not change the findings.

CI: confidence interval.

Table 4. GRADE certainty of evidence assessments for secondary outcomes for the child in mid- to late childhood (aged five to less than 18 years)

Secondary outcome	Certainty of evidence	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Comments
Child behaviour	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as both trials had some concerns of risk of bias due to missing data.
Deafness/hearing impairment	Low	Serious	Not serious	Serious	Not serious	Undetected	Downgraded 1 level as both trials had some concerns of risk of bias due to missing data.

Table 4. GRADE certainty of evidence assessments for secondary outcomes for the child in mid- to late childhood (aged five to less than 18 years) *(Continued)*

							Downgraded for imprecision as the 95% CI included both benefit and marked harm.
Blindness/visual impairment	Low	Serious	Not serious	Serious	Not serious	Undetected	Downgraded 1 level as both trials had some concerns of risk of bias due to missing data. Downgraded for imprecision as the 95% CI included both benefit and marked harm.
Mean weight	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Mean weight Z score	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Mean height	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Mean height Z score	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Mean head circumference	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Mean head circumference Z score	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Body mass index Z score	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Mean systolic blood pressure	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Mean systolic blood pressure Z score	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Mean diastolic blood pressure	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.

Table 4. GRADE certainty of evidence assessments for secondary outcomes for the child in mid- to late childhood (aged five to less than 18 years) *(Continued)*

Mean diastolic blood pressure Z score	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Forced expiratory volume in 1 second (FEV_1) Z score	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Downgraded 2 levels as the only included trial had high risk of bias due to missing data. Downgraded 1 level for imprecision as 95% CI included both benefit and harm.
Forced vital capacity (FVC) Z score	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Downgraded 2 levels as the only included trial had high risk of bias due to missing data. Downgraded 1 level for imprecision as 95% CI included both benefit and harm.
FEV_1/FVC ratio Z score	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Downgraded 2 levels as the only included trial had high risk of bias due to missing data. Downgraded 1 level for imprecision as 95% CI included both benefit and harm.
Asthma or recurrent wheeze	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Any respiratory disease	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Downgraded 2 levels as the only included trial had high risk of bias due to missing data. Downgraded 1 level for imprecision as 95% CI included both benefit and harm.
Measures of insulin and glucose homeostasis	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Measures of hypothalamic-pituitary-adrenal (HPA) axis function	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.
Body composition	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.

Table 4. GRADE certainty of evidence assessments for secondary outcomes for the child in mid- to late childhood (aged five to less than 18 years) *(Continued)*

Bone density	Moderate	Serious	Not serious	Not serious	Not serious	Undetected	Downgraded 1 level as the only included trial had some concerns of risk of bias due to missing data.

CI: confidence interval.

Table 5. GRADE certainty of evidence assessments for secondary outcomes for health services

Secondary outcome	Certainty of evidence	Risk of bias	Inconsistency	Imprecision	Indirectness	Publication bias	Comments
Length of postnatal hospitalisation for the woman	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Length of infant hospitalisation	Moderate	Not serious	Not serious	Serious	Not serious	Undetected	Downgraded for imprecision as 95% CI included both benefit and harm.
Hospital re-admission by early childhood follow-up	High	Not serious	Not serious	Not serious	Not serious	Undetected	—
Hospital re-admission by mid- to late childhood follow-up	Very low	Very serious	Not serious	Serious	Not serious	Undetected	Downgraded 2 levels for risk of bias as the only study included was at high risk of bias due to outcome measurement. Downgraded for imprecision as 95% CI included both benefit and marked harm.

CI: confidence interval.

APPENDICES

Appendix 1. Search methods for ICTRP and ClinicalTrials.gov

ICTRP

(Each line was run separately and run 'with all synonyms')

corticosteroids AND premature

corticosteroids AND preterm

steroids AND premature

steroids AND preterm

ClinicalTrials.gov

Advanced search

Interventional Studies | Preterm Labor | Corticosteroid

Interventional Studies | Preterm Labor | Steroids

FEEDBACK

Murphy, July 2012

Summary

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

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

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

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

The table below shows the summary statistic for the mean difference in birth weight at early childhood follow-up with and without the MACS data. When MACS data are included, the difference in birth weight between the two groups is statistically significant..

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

	Mean Difference in Weight	Variance of Mean Difference	Lower Limit	Upper Limit	P value

Summary without MACS	-0.0297	0.0086	-0.2114	0.1520	0.7488
Summary with MACS	-0.2003	0.0046	-0.3327	-0.0678	0.0030

The long term impact of weighing less in early childhood is not known. Nevertheless, that repeated doses of antenatal corticosteroids have adverse effects on growth is worrisome in that it signifies the potential for repeated doses to cause harm.

Follow-up studies have thus far been reassuring, demonstrating no difference in death or neurologic impairment in early childhood. However, we should not be falsely reassured by these studies. The long-term follow-up studies have limited power to rule out the effect of repeated doses of antenatal corticosteroids on infrequent adverse events. Thus, finding no difference in long-term outcome does not necessarily prove safety. We are reminded of the RCTs of postnatal corticosteroid treatment which initially demonstrated short term benefits and then over time, with the completion of long-term studies, demonstrated the potential for harm.[2]

4. We believe that the findings of short term neonatal benefits from repeated courses of antenatal corticosteroids are important. However, given the adverse effect of antenatal corticosteroids on birth weight and weight at early childhood follow-up, and the uncertain effect on long term outcomes, we believe that the conclusions and recommendations for clinical practice in this review should be more cautious than they currently are. We would suggest the review authors consider a statement such as “Although the short term neonatal benefits of repeated courses of antenatal corticosteroids support their use, long-term benefits have not been demonstrated and long-term adverse effects have not been ruled out. The adverse effect of repeated doses of antenatal corticosteroids on birth weight and weight at early childhood follow-up is a concern. Caution should therefore be exercised to ensure that only those women who are at particularly high risk of very early preterm birth are offered treatment with repeated courses of antenatal corticosteroids.”

References

1. Asztalos EV, Murphy KE, Hannah ME, Willan AR, Matthews SG, Ohlsson A, et al. Multiple courses of antenatal corticosteroids for preterm birth study: 2-year outcomes. *Pediatrics* 2010;**126**:e1045-e1055.

2. Halliday HL, Ehrenkranz RA, Doyle LW. Early (<8 days) postnatal corticosteroids for preventing chronic lung disease in preterm infants. Cochran Database of Sys Rev 2010, Issue 5.

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

[Feedback received from Kellie E Murphy, 5 July 2012]

Reply

Many thanks to the authors of the Multiple courses of Antenatal Corticosteroids for preterm birth Study (MACS).

1. The MACS trial reported on the outcome of 'severe respiratory distress syndrome'. The authors query why the data from MACS were only included in the outcome for 'severe lung disease' rather than RDS (any).

We do not feel that it would be appropriate to combine data from trials reporting respiratory distress syndrome (mild or severe) with severe RDS. This is likely to result in significant heterogeneity and therefore we chose to report data for RDS and severe lung disease as separate outcomes. If the authors of the MACS trial can provide data for RDS (any) we would certainly be willing to add it to the appropriate analysis.

2. The authors of the MACS trial query the labelling of the outcome 'severe lung disease'.

This outcome was selected by the review authors and is defined in the review protocol.

3. The authors of the MACS trial query why their data for anthropometric assessments at 18 to 24 months were not included in the meta-analysis.

Data were not included as SD's were not available in the trial report. We acknowledge that the author of this report was Asztalos 2008, however Cochrane methodology requires that it is the primary trial that is cited in the text. The reference to Asztalos can be found in the reference section of this review. In order to enter data in to the statistical programme we require mean values for each group with the associated standard deviation or standard error. If the authors of the MACS trial can provide us with the mean and standard deviations for the treatment and the control groups with the numbers of children in each group we will certainly be willing to add these data to the appropriate analyses.

4. The authors of the MACS trial query the conclusions of the review.

The review authors consider the conclusions and both the clinical and research recommendations to be appropriate summaries of the available evidence.

Contributors

Caroline Crowther

WHAT'S NEW

Date	Event	Description
26 January 2021	New citation required and conclusions have changed	The updated review includes data from one an additional trial, with a total of 11 trials now included. Additional data now suggests that repeat doses of corticosteroids are associated with an increase in small for gestational age. In the last update, there was no increase identified.
26 January 2021	New search has been performed	Search updated with 48 additional reports. A total of 63 reports were assessed for this update (15 from awaiting classification in last published version plus 48 reports from updated searches).

HISTORY

Protocol first published: Issue 4, 2002
Review first published: Issue 3, 2003

Date	Event	Description
5 January 2015	New search has been performed	Search updated and two new trials excluded (Bontis 2011; Romejko-Wolniewicz 2013).
5 January 2015	New citation required but conclusions have not changed	There are no changes to the conclusions of this review.
24 July 2012	Feedback has been incorporated	Comments from Kellie Murphy added - see Feedback 1.
18 July 2011	Amended	Corrected reference error - Ashworth 2006 amended to read Ashwood 2006.
18 April 2011	New citation required and conclusions have changed	Conclusions are now stronger; early benefit now without evidence of longer term harm. Two additional authors joined the review team (C McKinlay and P Middleton).
31 March 2011	New search has been performed	Search updated in March 2011 and data from five new trials added (Garite 2009; Mazumder 2008; McEvoy 2010; Murphy 2008; Peltoniemi 2007). Published longer term follow-up in early childhood now included for four trials (Crowther 2006; Murphy 2008; Peltoniemi 2007; Wapner 2006) and information on follow up for one further trial added (Mazumder 2008).

Date	Event	Description
		Acknowledgement of unpublished information provided on caesarean section by Emeritus Professor Thomas Garite for the Garite 2009 trial.
20 September 2008	Amended	Converted to new review format.
11 May 2007	New search has been performed	Search updated in November 2006 and data from two trials now published added (Crowther 2006; Wapner 2006). We updated the search just before submission for publication and identified the published report for the previously listed Peltoniemi ongoing study. We have added it to the ' Studies awaiting assessment' section and will consider it for inclusion in the next update (Peltoniemi 2007).

CONTRIBUTIONS OF AUTHORS

For this 2021 updated, all authors contributed to updating the protocol.

AW, CM, JH, CAC assessed identified studies for eligibility.

AW and one additional author (CAC, JEH, CM or PM) performed data extraction, trustworthiness assessments and risk of bias assessments for each trial.

AW prepared the risk of bias tables from these assessments.

AW prepared the first draft.

All authors commented on subsequent drafts and approved the final version.

Previous versions and protocol

CAC and JEH prepared the original protocol published in 2000.

CAC wrote the draft of the original review, and both CAC and JEH commented on subsequent drafts and prepared the previous updates.

For the 2011 and 2015 updates, CAC prepared the first draft; CAC, CM and PM prepared the risk of bias tables, CAC and CM assessed identified studies for eligibility and CAC, CM and PM extracted data for the included trials.

All authors commented on subsequent drafts and approved the final version.

DECLARATIONS OF INTEREST

AW: reports working as a health professional but in an unrelated area (as an Endocrinology advanced trainee).

CM: reports previously publishing on repeat prenatal corticosteroids, being an investigator in the six- to eight-year follow-up studies of the Australasian Collaborative Trial of Repeat Doses of Corticosteroid for the Prevention of Neonatal Respiratory Disease (Crowther 2006), and working as a health professional for Counties Manukau Health.

PM: reports being an Editor for Cochrane Pregnancy and Childbirth, but was not involved in the editorial process for this review.

JH: reports giving multiple lectures and publishing review articles which relate to the material included in this review, none directly reporting the contents of the review. Investigator in the two-year and six- to eight-year follow-up studies of the Australasian Collaborative Trial of Repeat Doses of Corticosteroid for the Prevention of Neonatal Respiratory Disease (Crowther 2006). Funding for the ACTORDS follow-up studies was updated received from: the National Health and Medical Research Council of Australia; Channel 7 Research Foundation, South Australia; the Women's and Children's Research Foundation, Adelaide, South Australia; Discipline of Obstetrics and Gynaecology, University of Adelaide, South Australia; Health Research Council of New Zealand; Auckland Medical Research Foundation, New Zealand. None of the funding bodies had any role in the conduct of the study, analysis or decision to publish.

CAC: reports being the lead investigator for the Australasian Collaborative Trial of Repeat Doses of Corticosteroid for the Prevention of Neonatal Respiratory Disease and subsequent follow-up studies (Crowther 2006).

SOURCES OF SUPPORT

Internal sources

- South Australian Health and Medical Research Institute, Australia

  Salary support for PM
- Liggins Institute, The University of Auckland, New Zealand

  Salary support for CC, JH, CMcK

External sources

- Aotearoa Foundation, USA

  Scholarship support for AW
- National Institute for Health Research, UK

  NIHR Programme of centrally-managed pregnancy and childbirth systematic reviews of priority to the NHS and users of the NHS:10/4001/02 (2015 update)
- World Health Organization (WHO) and the UNDP-UNFPA-UNICEF-WHO-World Bank Special Programme of Research, Development and Research Training in Human Reproduction (HRP), Switzerland

  This review is supported by funding to Cochrane Pregnancy and Childbirth (University of Liverpool) (2021 update)

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Previous review and updates

Amendments made to the protocol for the 2011 update that clarified the longer-term health outcomes: total deaths added under outcomes for the child and the child as an adult; survival free of any disability and survival free of major disability added under primary outcomes for the child and for the child as an adult. In addition: periventricular haemorrhage changed to intraventricular haemorrhage; small-for-gestational age, intraventricular haemorrhage, intraventricular haemorrhage grade 3 or 4 and periventricular leukomalacia moved to secondary outcomes for the infant; "However defined by authors" added to the definitions of the following outcomes: necrotising enterocolitis, patent ductus arteriosus, retinopathy of prematurity and early systemic neonatal infection.

In the 2015 update, the prespecified groups for subgroup analysis were edited to describe specific populations of interest and methods were updated according to current Cochrane Pregnancy and Childbirth Group standard methods text (2015). An additional search of ClinicalTrials.gov, the WHO International Clinical Trials Registry Platform (ICTRP) for ongoing and unpublished studies was performed.

2021 update

We made the following changes for the 2021 update.

Revised the outcome measures

Grouped primary and secondary outcomes into those for the woman, the child as a fetus/neonate/infant, the child in early (two to less than five years of age) and mid- to late childhood (five to less than 18 years of age) and the child as an adult (greater than 18 years of age).

Added the following primary outcomes **for the fetus/neonate/infant.**

- Infant death (less than one year of age).
- Severe respiratory distress syndrome (however defined by authors).
- Severe intraventricular haemorrhage (grade 3 or 4) (moved from secondary outcomes).
- Necrotising enterocolitis (however defined by authors) (moved from secondary outcomes).

Added the following secondary outcomes **for the fetus/neonate/infant.**

- Birthweight (moved from primary outcomes).
- Late systemic neonatal infection (48 hours or greater after birth or however defined by authors).
- Neonatal encephalopathy (however defined by authors).
- Pulmonary hypertension (however defined by authors).
- Duration of inotropic support.
- Measures of renal function (however reported by authors).
- Feed tolerance (time to full feed tolerance, number of feed interruptions or however defined by authors).

Removed the following secondary outcomes **for the fetus/neonate/infant.**

- Placental weight.
- Skin-fold thickness at birth, at primary hospital discharge and at infant follow-up.
- Placental weight.
- Neonatal blood pressure.
- Developmental delay at infant follow-up (moved to primary outcomes for the child in early childhood (aged two to less than five years)).

"Measures of HPA axis function (however assessed by authors)" has replaced "HPA axis suppression". "The use of respiratory support (mechanical ventilation or continuous positive airways pressure (CPAP), or both)" and "duration of respiratory support" have been clarified as "Use of respiratory support (any respiratory support including invasive (via an endotracheal tube) or non-invasive modalities or however defined by authors)". Use and duration of "mechanical ventilation" have been replaced with use and duration of "use of invasive respiratory support (any respiratory support via an endotracheal tube or however defined by authors)". Use and duration of "CPAP" have been replaced with "Duration of non-invasive respiratory support (any form of respiratory support that does not require an endotracheal tube including any non-invasive ventilation, CPAP and high or low flow gases or however defined by authors)".

Added the following primary outcomes **for the woman.**

- Maternal sepsis (any of chorioamnionitis during labour, endometritis, pyrexia after trial entry requiring the use of antibiotics, puerperal sepsis, intrapartum fever requiring the use of antibiotics, postnatal pyrexia or however defined by authors).

"Adverse effects of corticosteroid" has been clarified with the following text "including gastrointestinal upset, insomnia, local injection site adverse effects (pain, bruising, haematoma or infection at the injection site)".

Removed the following primary outcomes **for the woman.**

- Puerperal sepsis (however defined by authors) (moved to secondary outcomes).
- Chorioamnionitis during labour (however defined by authors) (moved to secondary outcomes).

Added the following secondary outcomes **for the woman.**

- Puerperal sepsis (however defined by authors) (moved to secondary outcomes).
- Chorioamnionitis during labour (however defined by authors) (moved to secondary outcomes).
- Endometritis (however defined by authors).

Removed the following secondary outcomes **for the woman.**

- Length of labour.
- Parenting stress.
- Adverse drug reaction.

Added the following secondary outcomes for **the child in early childhood (two to less than five years of age).**

- Obesity/overweight.
- Hypertension (however defined by authors).
- Chronic lung disease of infancy (however defined by authors).
- Asthma or recurrent wheeze (however defined by authors).
- Measure of insulin and glucose homeostasis (however defined by authors).
- Measures of lipid profile (however defined by authors).
- Body composition (lean body mass corrected for height, fat mass corrected for height or however defined by authors).

Removed the following secondary outcomes for **the child in early childhood (two to less than five years of age).**

- Skin fold thickness at childhood follow-up.
- Learning difficulties.
- Dyslipidaemia.
- Composite serious outcome.
- Insulin sensitivity.

Developmental outcomes have been revised. "Survival free of any disability" has been replaced by "neurodevelopmental impairment at age two to less than five years", "survival free of major disability" by "survival free of neurodevelopmental impairment at age two to less than five years" and "disability at childhood follow-up" by and "survival free of major neurodevelopmental impairment at age two to less

than years". "Developmental delay" and "intellectual impairment" have been replaced by "developmental delay or intellectual impairment at age two to less than five years".

The following primary outcomes have been added **for the child in mid- to late childhood (five to less than 18 years).**

- Total deaths (after randomisation).
- Neurocognitive impairment at age five to less than 18 years (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment), or cerebral palsy, or however defined by authors).
- Survival free of neurocognitive impairment at age five to less than 18 (none of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), executive dysfunction, learning difficulties, motor impairment (mild or major impairment by appropriate mode of assessment) cerebral palsy, or however defined by authors).
- Survival free of major neurocognitive impairment at age five to less than 18 years (none of: moderate or severe intellectual impairment (developmental quotient or intelligence quotient more than two SD below the mean), major motor impairment, moderate or severe cerebral palsy, blindness (corrected visual acuity worse than 6/60 in the better eye) or deafness (hearing loss requiring amplification or worse), or however defined by authors).
- Motor impairment at age five to less than 18 years (categorised as nil, mild impairment, major impairment by appropriate mode of assessment or however defined by authors).
- Cognitive impairment at age five to less than 18 years (categorised as mild (one SD below the mean), moderate (two SDs below the mean) or severe (three SDs below the mean) by an appropriate rating scale, or however defined by authors).
- Educational achievement (however defined by authors).
- Cerebral palsy (categorised as nil, mild, moderate or severe using an appropriate scale or however defined by authors).
- Hypertension (however defined by authors).

Added the following secondary outcomes **for the child in mid- to late childhood (five to less than 18 years).**

- Child behaviour (however defined by authors).
- Deafness/hearing impairment (however defined by authors).
- Blindness/visual impairment (however defined by authors).
- Growth assessments (weight, head circumference, height).
- BMI.
- Obesity/overweight.
- Blood pressure (systolic, diastolic, mean arterial).
- Measures of lung function (however defined by authors).
- Asthma or recurrent wheeze (however defined by authors).
- Respiratory disease (however defined by authors).
- Measure of insulin and glucose homeostasis (however defined by authors).
- Lipid profile (however reported by authors).
- Measures of HPA axis function (however defined by authors).
- Bone density (however assessed by authors).
- Body composition (lean body mass (fat free mass) for height, fat mass for height or however defined by authors).

Added the following primary outcomes **for the child as an adult (greater than 18 years).**

- Neurodevelopmental disability at age 18 years or greater (any of: visual impairment, hearing impairment, intellectual impairment (developmental quotient or intelligence quotient more than one SD below the mean), cerebral palsy, or however defined by authors).
- Cardiovascular disease (including diagnosis of ischaemic heart disease, cerebrovascular disease, heart failure or however defined by authors).
- Cardiovascular death (ischaemic heart disease, stroke, arrhythmia or heart failure as cause of death or however defined by authors).
- Type 2 diabetes mellitus (however defined by authors).
- Glucose intolerance (however defined by authors).
- Obesity/overweight (however defined by authors).
- Hypertension (however defined by authors).

Removed the following primary outcomes **for the child as an adult (greater than 18 years).**

- Survival free of any disability (however defined by authors).

- Survival free of major disability (however defined by authors).
- Disability at adult follow-up (developmental delay or intellectual impairment, blindness, deafness, or cerebral palsy, however defined by authors).
- Major sensorineural disability (defined as any of legal blindness, sensorineural deafness requiring hearing aids, moderate or severe cerebral palsy, or developmental delay or intellectual impairment (defined as developmental quotient or intelligence quotient more than two SDs below mean)).
- Composite serious outcome (however defined by authors).

Added the following secondary outcomes **for the child as an adult (aged 18 years or greater).**

- Educational achievement (however defined by authors).
- Prediabetes (however defined by authors).
- Mental health disorders (however defined by authors).
- Diagnosis of depression (however defined by authors).
- Diagnosis of bipolar affective disorder (however defined by authors).
- Diagnosis of anxiety disorder (however defined by authors).
- Ischaemic heart disease (however defined by authors).
- Stroke (however defined by authors).
- Heart failure.
- Blindness/visual impairment (however defined by authors).
- Deafness/hearing impairment (however defined by authors).
- Measure of insulin and glucose homeostasis (however defined by authors).

Removed the following secondary outcomes **for the child as an adult (aged 18 years or greater).**

- Insulin sensitivity.
- Skin-fold thickness in later life.
- Blindness.
- Deafness.
- Insulin sensitivity.

Assessment of all eligible studies

Incorporated an assessment of scientific integrity (trustworthiness) as described in Selection of studies.

Risk of bias

Used the RoB 2 tool to assess risk of bias at the outcome level and replaced study level assessments as described in Assessment of risk of bias in included studies.

Sensitivity analyses

Modified planned sensitivity analyses to reflect changes in the risk of bias assessment and now state "Where overall risk of bias was assessed as 'high risk' or 'some concerns' for a study outcome, we explored this by sensitivity analysis excluding these studies".

Clinical subgroups for subgroup analysis

Removed "The number of repeat courses of corticosteroids actually given" from the list of clinical subgroups for subgroup analysis because it is a postrandomisation categorisation.

Unit of analysis

Included a comment on the unit of analysis. Changed the denominator for neonatal outcomes from live births to fetuses alive at randomisation.

Summary of findings tables

Included GRADE summary of findings tables to summarise the key outcomes for each group (for the fetus/neonate/infant, the woman, the child in early childhood (aged two to less than five years), the child in mid- to late childhood (aged five to less than 18 years) and the child as an adult (aged 18 years or greater).

INDEX TERMS

Medical Subject Headings (MeSH)

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

MeSH check words

Female; Humans; Infant, Newborn; Pregnancy