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Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery (Review)

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[Intervention Review]

Timing of intravenous prophylactic antibiotics for preventing postpartum infectious morbidity in women undergoing cesarean delivery

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ABSTRACT

Background

Given the continued rise in cesarean birth rate and the increased risk of surgical site infections after cesarean birth compared with vaginal birth, effective interventions must be established for prevention of surgical site infections. Prophylactic intravenous (IV) antibiotic administration 60 minutes prior to skin incision is recommended for abdominal gynecologic surgery; however, administration of prophylactic antibiotics has traditionally been withheld until after neonatal umbilical cord clamping during cesarean delivery due to the concern for potential transfer of antibiotics to the neonate.

Objectives

To compare the effects of cesarean antibiotic prophylaxis administered preoperatively versus after neonatal cord clamp on postoperative infectious complications for both the mother and the neonate.

Search methods

We searched the Cochrane Pregnancy and Childbirth Group's Trials Register (1 March 2014) and reference lists of retrieved papers.

Selection criteria

Randomized controlled trials (RCTs) comparing maternal and neonatal outcomes following prophylactic antibiotics administered prior to skin incision versus after neonatal cord clamping during cesarean delivery. Cluster-RCTs were eligible for inclusion but none were identified. Quasi-RCT and trials using a cross-over design were not eligible for inclusion in this review. Studies published in abstract form only were eligible for inclusion if sufficient information was available in the report.

Data collection and analysis

At least two review authors independently assessed the studies for inclusion, assessed risk of bias, abstracted data and checked entries for accuracy. We assessed the quality of evidence using the GRADE approach.

Main results

We included 10 studies (12 trial reports) from which 5041 women contributed data for the primary outcome. The overall risk of bias was low.

When comparing prophylactic intravenous (IV) antibiotic administration in women undergoing cesarean delivery, there was a reduction in composite maternal infectious morbidity (risk ratio (RR) 0.57, 95% confidence interval (CI) 0.45 to 0.72, high quality evidence), which was specifically due to the reduction in endometritis (RR 0.54, 95% CI 0.36 to 0.79, high quality evidence) and wound infection (RR 0.59, 95% CI 0.44 to 0.81, high quality evidence) in those that received antibiotics preoperatively as compared to those who received antibiotics after neonatal cord clamping. There were no clear differences in neonatal sepsis (RR 0.76, 95% CI 0.51 to 1.13, moderate quality evidence).

There were no clear differences for other maternal outcomes such as urinary tract infection (UTI), cystitis and pyelonephritis (moderate quality evidence), respiratory infection (low quality evidence), or any neonatal outcomes. Maternal side effects were not reported in the included studies.

The quality of the evidence using GRADE was high for composite morbidity, endomyometritis, wound infection and neonatal intensive care unit admission, moderate for UTI/cystitis/pyelonephritis and neonatal sepsis, and low for maternal respiratory infection.

Authors' conclusions

Based on high quality evidence from studies whose overall risk of bias is low, intravenous prophylactic antibiotics for cesarean administered preoperatively significantly decreases the incidence of composite maternal postpartum infectious morbidity as compared with administration after cord clamp. There were no clear differences in adverse neonatal outcomes reported. Women undergoing cesarean delivery should receive antibiotic prophylaxis preoperatively to reduce maternal infectious morbidities. Further research may be needed to elucidate short- and long-term adverse effects for neonates.

PLAIN LANGUAGE SUMMARY

When should antibiotics be given to prevent infectious complications after cesarean birth?

People who undergo surgery are at risk of developing infections, which complicate their recovery. In order to prevent these infections and reduce complications, antibiotics are sometimes given as a preventative (or prophylactic) treatment. The antibiotics are generally given approximately 60 minutes before the operation so that adequate tissue concentrations are reached before the skin is cut. For cesarean deliveries however, the effect of the antibiotic on the baby has to be considered, and for this reason antibiotics have been administered to women after the baby's umbilical cord is clamped. This may not allow for adequate tissue penetration in the mother for the prevention of surgery-related infections; additionally deferring antibiotics may not benefit the newborn.

This review of randomized controlled studies looked at the different timing options for administration of prophylactic antibiotics to prevent infectious complications in women undergoing cesarean delivery. We compared preoperative administration to administration after the cord had been clamped.

The review includes 10 studies (with data from 5041 women). The studies were at a low risk of bias. Antibiotics given to women before cesarean delivery nearly halved the risks of combined infections (43%), endometritis (46%), and wound infection (41%) compared to giving the antibiotics after clamping of the baby's umbilical. Other maternal infections such as urinary or lung infections were no different between the two groups of women, nor were adverse effects in newborns. High quality evidence shows that preoperative intravenous antibiotic administration decreases postpartum infections and is, therefore, beneficial for the mother. Maternal side effects were not consistently reported. Numbers were limited with respect to information on newborns and any adverse outcomes. Further research may be needed to determine adverse effects on the babies.

Summary of findings for the main comparison. Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping

Prophylactic antibiotics for preventing postpartum infectious morbidity in women and infants after cesarean delivery

Population: women undergoing cesarean delivery.
Settings: eight trials were conducted in developed countries: seven from US, one from Austria. Five trials were conducted in developing countries: two trials from India, one trial each from Egypt, South Africa and Turkey.
Intervention: prophylactic intravenous antibiotic administration for cesarean birth administered prior to skin incision versus after neonatal umbilical cord clamping.

Outcomes	Illustrative comparative risks* (95% CI)		Relative effect (95% CI)	No of Participants (studies)	Quality of the evidence (GRADE)	Comments
	Assumed risk	Corresponding risk				
	Control	Maternal and neonatal postpartum infectious morbidity				
Maternal composite morbidity	**Study population**		**RR 0.67** (0.54 to 0.82)	5041 (10 studies)	⊕⊕⊕⊕ **high**	
	85 per 1000	**57 per 1000** (46 to 70)				
	Moderate					
	97 per 1000	**65 per 1000** (52 to 80)				
Maternal endomyometritis	**Study population**		**RR 0.54** (0.36 to 0.79)	5041 (10 studies)	⊕⊕⊕⊕ **high**	
	28 per 1000	**15 per 1000** (10 to 22)				
	Moderate					
	26 per 1000	**14 per 1000** (9 to 21)				
Maternal wound Infection	**Study population**		**RR 0.59** (0.44 to 0.81)	5041 (10 studies)	⊕⊕⊕⊕ **high**	
	41 per 1000	**24 per 1000** (17 to 33)				

	Moderate				
	51 per 1000	**30 per 1000** (22 to 41)			
Maternal UTI/cystitis/pyelonephritis	**Study population**		**RR 1.02** (0.65 to 1.59)	4001 (8 studies)	⊕⊕⊕⊖ **moderate** [1]
	18 per 1000	**18 per 1000** (12 to 29)			
	Moderate				
	13 per 1000	**13 per 1000** (8 to 21)			
Maternal respiratory infection (pneumonia)	**Study population**		**RR 2.3** (0.34 to 15.45)	1158 (2 studies)	⊕⊕⊖⊖ **low** [2]
	2 per 1000	**4 per 1000** (1 to 27)			
	Moderate				
	0 per 1000	**0 per 1000** (0 to 0)			
Neonatal sepsis	**Study population**		**RR 0.76** (0.51 to 1.13)	2907 (5 studies)	⊕⊕⊕⊖ **moderate** [1]
	37 per 1000	**28 per 1000** (19 to 42)			
	Moderate				
	40 per 1000	**30 per 1000** (20 to 45)			
Neonatal ICU admission	**Study population**		**RR 0.91** (0.74 to 1.13)	3708 (6 studies)	⊕⊕⊕⊕ **high**
	86 per 1000	**78 per 1000** (64 to 97)			
	Moderate				
	71 per 1000	**65 per 1000**			

		(53 to 80)			

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (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 quality: further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: we are very uncertain about the estimate.

[1] Wide confidence interval crossing the line of no effect.
[2] Wide confidence interval crossing the line of no effect, few events and small sample size.

BACKGROUND

Description of the condition

Cesarean birth is one of the most common surgical procedures performed worldwide. Internationally, 46 countries are noted to have cesarean delivery rates greater than 20%. Of these 46, China and Brazil account for almost 50% of total cesarean births (Gibbons 2012). The World Health Organization (WHO) Multicountry Survey on Maternal and Newborn Health survey conducted in 29 countries showed the overall rate of cesarean delivery was 28.6%, and the coverage of prophylactic antibiotics for cesarean birth was 87.3%, globally (Souza 2013). Worldwide, infectious morbidity consisting primarily of endomyometritis and wound infection occurs in approximately 5% to 10% of cesarean births (Henderson 1995; Olsen 2008; Opoien 2007; Yokoe 2001). As the cesarean birth rate continues to rise in most developed countries, postpartum infectious morbidity will become an even more significant problem. Therefore, measures aimed at decreasing postpartum infectious morbidity are an important area of focus.

Surgical site infections are the most common nosocomial infections among surgical patients, accounting for about 23% of all such infections from the data reported to the National Healthcare Safety Network (NHSN) in the United States during 2009 to 2010 (Sievert 2013). A prospective multicenter cohort study conducted in England reported that 9.6% of women in the study developed a postsurgical infection after cesarean delivery (Wloch 2012). Infectious complications after cesarean birth include, but are not limited to, wound infection, endomyometritis, urinary tract infection, pelvic abscess, septic shock, septic pelvic thrombophlebitis, necrotizing fasciitis, and pneumonia.

The risk of postpartum infection after cesarean birth is nearly five-fold that of vaginal birth (Leth 2009). Many interventions have been studied in an attempt to decrease the incidence of surgical site infections after cesarean birth including prophylactic antibiotics, surgical hand antisepsis, skin preparation methods, surgical techniques, closure of subcutaneous fat, subcutaneous drain placement, and postoperative surveillance (Barwolff 2006; Dahlke 2013; Edi-Osagie 1998; Hellums 2007; Lorenz 1988; Magann 1993; Starr 2005; Ventolini 2004).

Description of the intervention

In 2008, the WHO established a 'Safe Surgery Saves Lives' campaign. An intraoperative surgical checklist was developed to reduce post-surgical infection as well as other associated morbidities. This checklist acknowledged the evidence-based value of prophylactic antibiotic administration 60 minutes prior to skin incision (Soar 2009).

The obstetric population poses a unique challenge for antibiotic prophylaxis as there is known transplacental delivery of antibiotics to the fetus. Traditionally, the administration of prophylactic antibiotics has been withheld until after neonatal umbilical cord clamping during cesarean birth in order to avoid transfer of antibiotics to the fetus. The theoretical concerns of neonatal antibiotic exposure include the masking of neonatal infection, interference with sepsis workup and the selection of antibiotic-resistant bacterial strains in both neonatal colonization and infection (Cunningham 1983). Due to these theoretical risks, the Centers for Disease Control and Prevention's 'Guideline for Prevention of Surgical Site Infection, 1999' stated with high level evidence, that for high-risk cesarean birth, prophylactic antimicrobial agents should be given immediately after umbilical cord clamping, rather than preoperatively (Mangram 1999).

How the intervention might work

The general surgery tenet of antibiotic prophylaxis was born out of animal studies that demonstrated maximum suppression of infection when adequate tissue antibiotic levels were present at the time of microbial contamination (Burke 1961). These findings were confirmed in clinical practice: less surgical-wound infections were noted when antibiotics were administered within two hours before skin incision as compared to when antibiotics were administered postoperatively (Classen 1992). One of the most commonly used antibiotics for cesarean birth is cefazolin. Pharmacokinetic studies of cefazolin demonstrate that mean inhibiting concentration levels for group B streptococcus are attained in maternal, fetal and amniotic fluid samples within 30 minutes of administration (Fiore 2001). It has also been demonstrated that bactericidal levels against group B streptococcus are achieved in maternal, fetal and amniotic fluid samples within five minutes of ampicillin administration (Bloom 1996).

Why it is important to do this review

The benefit of using prophylactic antibiotics in order to prevent surgical site and other infections has been demonstrated in the obstetric literature. A 2010 Cochrane review concluded that antibiotic prophylaxis, as compared to no prophylaxis, was associated with a reduction in the incidence of febrile morbidity, wound infection, endomyometritis and other serious maternal infectious complications (Smaill 2010). This prior review stated that data were insufficient to compare timing of antibiotic administration.

Several recent studies have evaluated timing of the administration of prophylactic antibiotics, specifically administration prior to skin incision versus after neonatal umbilical cord clamping. A meta-analysis comparing the administration of prophylactic antibiotics prior to skin incision versus after clamping of the umbilical cord concluded that pre-incision antibiotic prophylaxis for cesarean birth not only decreased the incidence of postpartum endomyometritis and total infectious morbidity, but also did not adversely affect neonatal outcomes (Costantine 2008). Several institutions have evaluated the impact of protocol changes in the timing of perioperative antibiotic administration on postoperative infectious complications, and have found decreased infectious complications with antibiotics given prior to skin incision compared to after cord clamping (Kaimal 2008; Owens 2009).

In response to the recent attention on the timing of prophylactic antibiotics in cesarean birth, the American College of Obstetricians and Gynecologists (ACOG) recommended antimicrobial prophylaxis for all cesarean births, and further stated that prophylaxis should be administered within 60 minutes of the start of the cesarean delivery (ACOG 2010). These recommendations are consistent with recommendations from the National Surgical Infection Prevention Project (Bratzler 2005).

Given the continued rise in cesarean birth rate and the relatively high risk of surgical site infections after cesarean birth as compared to other surgical procedures (NNIS System 2004), measures must

be taken to prevent surgical site infections. Prior Cochrane reviews have looked at the maternal morbidity associated in relation to administration of prophylactic antibiotics at time of cesarean delivery (Smaill 2010) and various antibiotic regimens for cesarean delivery (Hopkins 1999). This review will focus on studies comparing antibiotic prophylaxis administered prior to skin incision compared with administration after umbilical cord clamping for cesarean birth. We will compare infectious morbidity and address the concern for neonatal harm.

OBJECTIVES

To assess the differences in infectious morbidity for mother and neonate when prophylactic cesarean antibiotics are administered preoperatively versus after neonatal cord clamping.

METHODS

Criteria for considering studies for this review

Types of studies

Only randomized controlled trials were included. We excluded quasi-randomized studies.

Abstracts were included if they provided sufficient information to make an assessment of methodologic quality, i.e., information allows for completion of at least some of the domains within the 'Risk of bias' tables. We attempted to contact authors of such manuscripts before deciding to exclude a study on these grounds.

Types of participants

Pregnant women who have undergone cesarean delivery and received prophylactic antibiotics.

Types of interventions

Prophylactic intravenous (IV) antibiotic administration for cesarean birth 0 to 30 and 30 to 60 minutes prior to skin incision versus prophylactic antibiotic administration for cesarean birth after neonatal umbilical cord clamping. We planned to exclude studies of women who received antibiotics after skin incision but before cord clamping.

Types of outcome measures

Primary outcomes

Composite maternal postpartum infectious morbidity (including serious infectious complications such as sepsis (including septic shock), endomyometritis, wound infection, or death attributed to infection). Though not pre-specified in the protocol, we stratified composite morbidity by whether 1 g or 2 g of cephalosporin were administered.

Secondary outcomes

Maternal

1. Maternal mortality.

2. Maternal postpartum infection (the following are as defined by the individual trials):

- endomyometritis (though not pre-specified in the protocol, we stratified endomyometritis by whether 1 g or 2 g of cephalosporin were administered);
- wound infection (though not pre-specified in the protocol, we stratified wound infection by whether 1 g or 2 g of cephalosporin were administered);
- urinary tract infection (UTI), cystitis and pyelonephritis;
- sepsis, including septic shock;
- pelvic abscess;
- septic pelvic thrombophlebitis;
- respiratory infection (e.g. pneumonia);
- length of hospital stay (days);
- Intensive care unit (ICU) admission;
- cost of antibiotics;
- antibiotic-related adverse events (e.g. anaphylaxis);
- febrile illness.

3. Placental transfer of antibiotics

4. Breastfeeding

Neonatal outcomes

1. Neonatal mortality.

2. Neonatal morbidity (the following are as defined by the individual trials):

- sepsis;
- neonatal sepsis workup;
- infection with resistant organism;
- infection (other);
- admission to ICU;
- length of ICU stay (days);
- neonatal antibiotic treatment;
- febrile illness.

Search methods for identification of studies

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

Electronic searches

We contacted the Trials Search Co-ordinator to search the Cochrane Pregnancy and Childbirth Group's Trials Register (1 March 2014).

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

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

Details of the search strategies for CENTRAL, MEDLINE and Embase, the list of handsearched journals and conference proceedings, and the list of journals reviewed via the current awareness service can

be found in the 'Specialized Register' section within the editorial information about the Cochrane Pregnancy and Childbirth Group.

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

Searching other resources

We searched reference lists of retrieved studies.

We did not apply any language or date restrictions.

Data collection and analysis

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

Selection of studies

At least two review authors independently assessed for inclusion all the potential studies we identified as a result of the search strategy. We resolved any disagreement through discussion with the whole group.

Data extraction and management

We designed a form to abstract data. For eligible studies, two review authors independently abstracted the data using the agreed form. We resolved discrepancies through group discussion. We entered data into Review Manager software (RevMan 2014) and checked for accuracy.

When information regarding any of the above was unclear, we attempted to contact authors of the original reports to provide further details.

Assessment of risk of bias in included studies

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

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

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

We assessed the method as:

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

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

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

We assessed the methods as:

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

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

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

We assessed the methods as:

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

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

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

We have assessed methods used to blind outcome assessment as:

- low, high or unclear risk of bias.

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

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

We assessed methods as:

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

(5) Selective reporting (checking for reporting bias)

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

We assessed the methods as:

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

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

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

(7) Overall risk of bias

We made explicit judgements about whether studies were at high risk of bias, according to the criteria given in the *Handbook* (Higgins 2011). With reference to (1) to (6) above, we planned to assess the likely magnitude and direction of the bias and whether we considered it is likely to impact on the findings. However, as overall methodologic quality was considered low risk, sensitivity analyses were not undertaken. In future updates, we will explore the impact of the level of bias through undertaking sensitivity analyses - see Sensitivity analysis.

The quality of the evidence was assessed using the GRADE approach (Schunemann 2009) in order to assess the quality of the body of evidence relating to the following key outcomes for the main comparison.

1. Composite morbidity
2. Endomyometritis
3. Wound infection
4. Urinary tract infection (UTI)/cystitis/pyelonephritis
5. Respiratory infections (e.g. pneumonia)
6. Neonatal sepsis
7. Neonatal ICU admission

GRADEprofiler (GRADE 2008) was used to import data from Review Manager 5.3 (RevMan 2014) in order to create 'Summary of findings' tables. A summary of the intervention effect and a measure of quality for each of the above outcomes were produced using the GRADE approach. The GRADE approach uses five considerations (study limitations, consistency of effect, imprecision, indirectness and publication bias) to assess the quality of the body of evidence for each outcome. The evidence can be downgraded from 'high quality' by one level for serious (or by two levels for very serious) limitations, depending on assessments for risk of bias, indirectness of evidence, serious inconsistency, imprecision of effect estimates or potential publication bias.

Measures of treatment effect

Dichotomous data

For dichotomous data, we presented results as summary risk ratio with 95% confidence intervals.

Continuous data

For continuous data, we used the mean difference if outcomes are measured in the same way between trials. If necessary, we planned to use the standardized mean difference to combine trials that measured the same outcome, but used different methods.

Unit of analysis issues

We did not identify any cluster-randomized trials, but we would include cluster-randomized trials along with individually-randomized trials in the analysis in future updates, if identified. We will adjust their sample size using the methods described in the *Handbook* using an estimate of the intracluster correlation co-efficient (ICC) derived from the trial (if possible), from a similar trial or from a study of a similar population. If we use ICCs from other sources, we will report this and conduct sensitivity analyses to investigate the effect of variation in the ICC. If we identify cluster-randomized trials, we plan to synthesize the relevant information. We will consider it reasonable to combine the results from both if there is little heterogeneity between the study designs and the interaction between the effect of intervention and the choice of randomization unit is considered to be unlikely. We will also acknowledge heterogeneity in the randomization unit and perform a sensitivity analysis to investigate the effects of the randomization unit.

We did not include cross-over trials.

Dealing with missing data

For included studies, we noted levels of attrition. In a subsequent update of this review, we will include a sensitivity analysis excluding poor quality studies with high levels of attrition.

For all outcomes, analyses were carried out, as far as possible, on an intention-to-treat basis, i.e. we attempted to include all participants randomized to each group in the analyses. The denominator for each outcome in each trial was the number randomized minus any participants whose outcomes were known to be missing.

Assessment of heterogeneity

We assessed statistical heterogeneity in each meta-analysis using the Tau^2, I^2 and Chi^2 statistics. We regarded heterogeneity as substantial if an I^2 was greater than 30% and either a Tau^2 was greater than zero, or there was a low P value (less than 0.10) in the Chi^2 test for heterogeneity.

Assessment of reporting biases

As there were 10 studies in the meta-analysis for the primary outcome, we investigated reporting biases (such as publication bias) using a funnel plot. We assessed funnel plot asymmetry visually. If asymmetry is suggested by a visual assessment in the future update, we will perform exploratory analyses to investigate it.

Data synthesis

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

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

Subgroup analysis and investigation of heterogeneity

Substantial heterogeneity was not present, therefore we did not perform subgroup analyses in relation to heterogeneity. In future updates, if we identify substantial heterogeneity, we will perform subgroup analyses for composite maternal infectious morbidity based on:

1. cesarean as compared to labor: laboring versus non-laboring (i.e. prelabor);
2. cesarean performed in presence of chorioamnionitis with treatment versus without treatment;
3. cesarean performed on women who have received antibiotic prophylaxis for other indications (e.g. Group*Beta Streptococcus*) versus those without antibiotic treatment for any other indication;
4. timing of antibiotics prior to skin incision (e.g. less than 30 minutes to skin incision versus greater than 30 minutes prior to skin incision).

We considered whether an overall summary was meaningful and used random-effects analysis to produce it. We assessed subgroup differences based on dose of cephalosporin (1 g versus 2 g) by interaction tests available within RevMan (RevMan 2014). Interaction test results are reported, along with the Chi^2 statistic, P value, and I^2 value.

Sensitivity analysis

We planned to carry out sensitivity analysis for the primary outcomes by restricting our analysis to trials assessed as having a low risk of bias for the domain attrition bias; if > 30% of participants were lost to follow-up, these studies would have been excluded from sensitivity analyses. This was not necessary because none of the studies were assessed as having a high risk of bias. Planned sensitivity analysis will be conducted in future updates of this review, if appropriate.

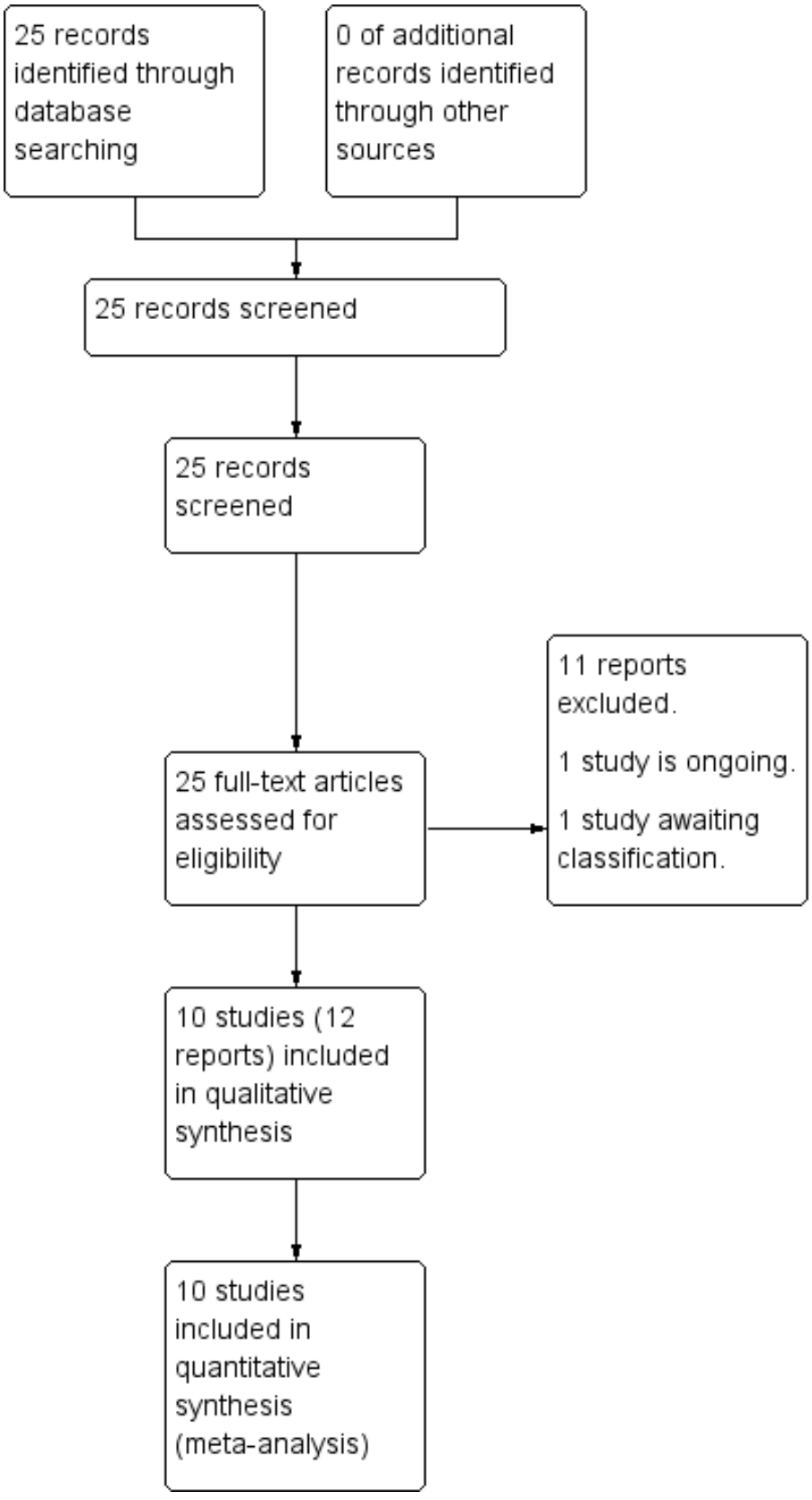
RESULTS

Description of studies

Results of the search

The search of the Cochrane Pregnancy and Childbirth Group's Register retrieved 25 reports (see: Figure 1). Ten studies (12 trial reports) were included with 5041 women contributing data to the primary outcome. Eleven trials were excluded. One study is awaiting classification (Pevzner 2009). One study is ongoing (Zhang 2012) (see Characteristics of ongoing studies).

Figure 1. Study flow diagram.



Included studies

Ten trials met our inclusion criteria and contributed data on the 5041 women they enrolled for the primary outcome of composite infectious morbidity: 2531 received antibiotics preoperatively and 2510 received antibiotics after cord clamp.

For detailed information on all studies, see Characteristics of included studies tables.

Participants

Most studies described characteristics of the women who were included and excluded in detail. Most studies included women with non-emergent or elective cesarean delivery at term (some studies included from 24 weeks estimated gestational age, others included from 34 or 36 weeks of gestation). Several studies excluded women with obstetric complications, while other studies only excluded women with infection at enrolment or allergy to antibiotics.

Settings

Eight trials were conducted in developed countries, seven from the United States of America and one from Austria. Five trials were performed in developing countries, with two trials from India and one trial each from Egypt, South Africa and Turkey.

Interventions

Antibiotics for prophylaxis were administered intravenously either before the incision versus after clamping of the neonatal umbilical cord. Studies administered antibiotics before incision at various time frames with the vast majority ranging from 15 to 60 minutes.

The antimicrobial agents used included a first generation cephalosporin (cefazolin 1 g or 2 g) in seven trials (Kandil 2014 (2 g); Macones 2012 (1 g); Sullivan 2007 (1 g); Thigpen 2005 (2 g); Wax 1997 (1 g); Witt 2011 (2 g); Yildirim 2009 (1 g)). The remaining three trials used a third generation cephalosporin (ceftriaxone 1 g or 2 g) (Bhattacharjee 2013 (2 g); Francis 2013 (2 g); Kalaranjini 2013 (1 g)). Clindamycin was typically the agent of choice for women who had known allergy to cephalosporins.

Outcomes

The primary outcome was a composite of maternal postpartum infectious morbidities including septic shock, endometritis, wound infection, or death attributed to infection. However, these were defined individually by the trialists.

The clinical criteria listed to define endometritis and urinary tract infection were remarkably consistent across trials. Wound infection was usually a clinical diagnosis and generally included induration, erythema, cellulitis or various degrees of drainage. Duration of maternal hospital stay and neonatal ICU length of stay were included when reported.

Two studies reported on septic pelvic thrombophlebitis, though there were no occurrences (Kalaranjini 2013; Yildirim 2009). One study (Kalaranjini 2013) reported on septic shock and maternal death, though there were no occurrences. None of the included studies reported on ICU admission, cost of antibiotics, antibiotic-related adverse events, placental transfer of antibiotics, breastfeeding or neonatal mortality.

Excluded studies

Seven trials were excluded from analysis as antibiotic administrations were not limited to preoperative versus post-cord clamp: women continued to receive antibiotics postoperatively in five (De Palma 1980; Gordon 1979; Gul 1999; Nokiani 2009; Tassi 1987) and single dose was compared to multiple day regimens in two (van Beekhuizen 2008; Van Velzen 2009). One study was excluded as antibiotics were given preoperatively and postoperatively, but were not given at neonatal cord clamp (Xu 1997). One study was excluded because it was not a randomized controlled trial (Cunningham 1983). Three studies published in abstract form did not provide sufficient information: two were excluded (Rodriguez 1990; Seton 1996) and one (Pevzner 2009) is awaiting classification pending publication of the final manuscript.

(Please refer to Characteristics of excluded studies for further details).

Risk of bias in included studies

The overall methodological quality of the trials 10 trials that contributed data towards the analysis was considered low risk of bias (see Figure 2; Figure 3).

Figure 2. 'Risk of bias. graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

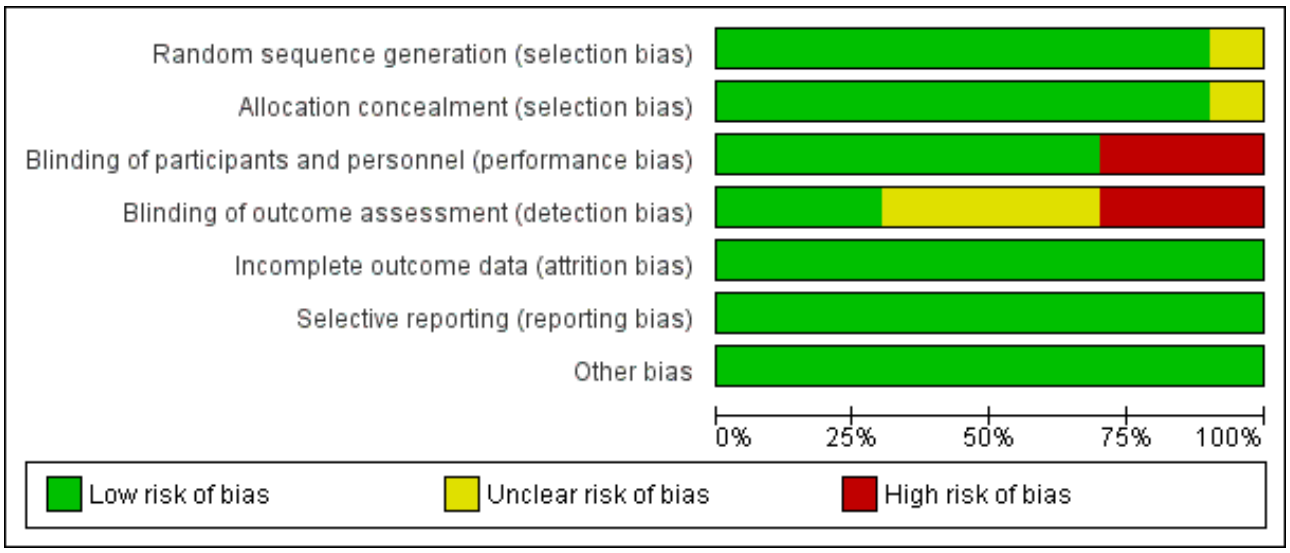
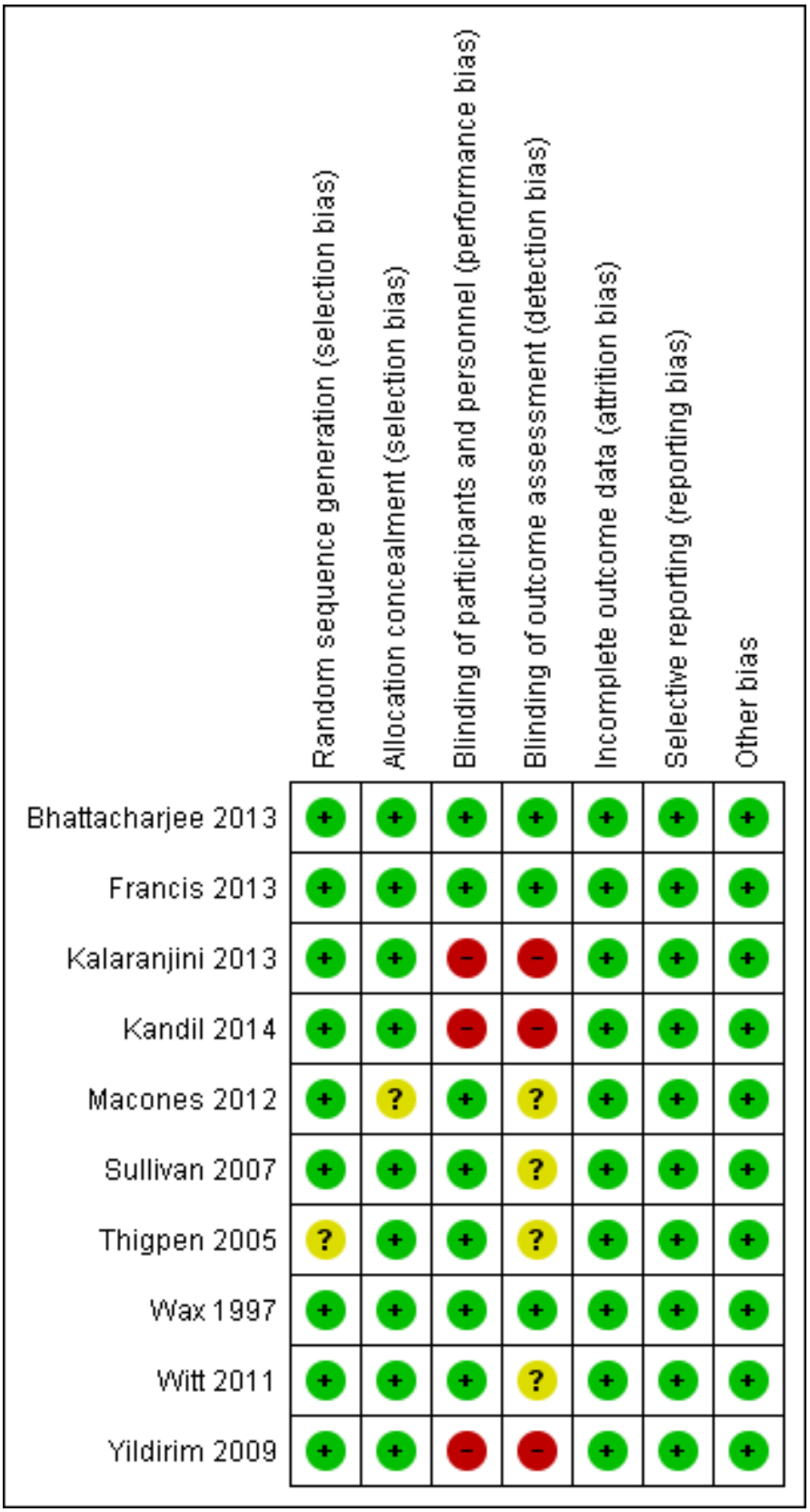
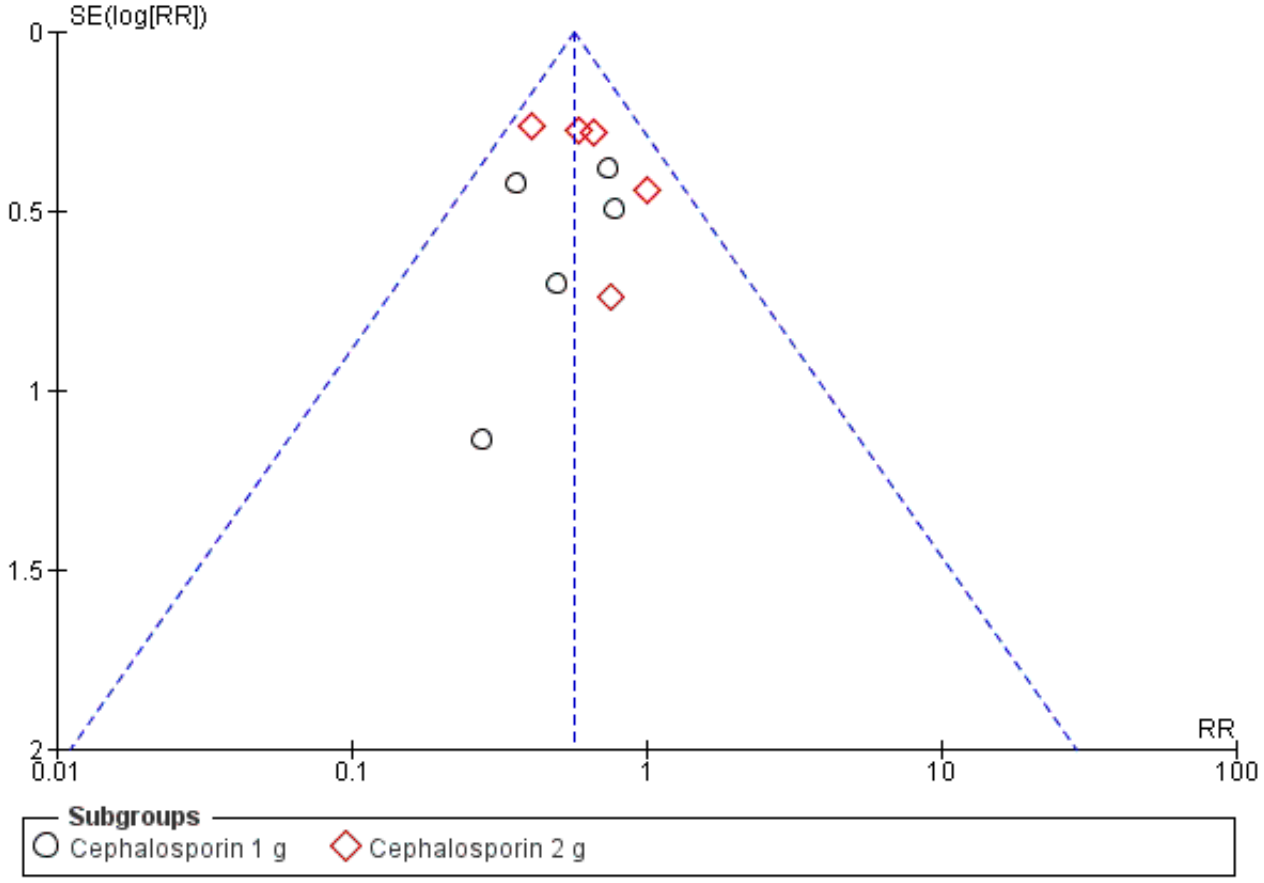


Figure 3. 'Risk of bias' summary: review authors' judgements about each risk of bias item for each included study.



There was no serious publication bias in the primary outcome due to the large number of women in the symmetrical part of the funnel plot (Figure 4).

Figure 4. Funnel plot of comparison: 1 Maternal postpartum infectious morbidity, outcome: 1.1 Composite morbidity (as defined by trials).



Allocation

The studies used various methods of randomization, e.g. computer-generated (Bhattacharjee 2013; Wax 1997), cards shuffled (Kandil 2014), and random number tables (Sullivan 2007), all of which were judged as low risk, except for Thigpen 2005 which was judged as unclear risk as it was only mentioned that randomization was performed by pharmacy personnel.

Four studies used sealed envelopes for allocation concealment (Bhattacharjee 2013; Kalaranjini 2013; Kandil 2014; Yildirim 2009) and five had pharmacy or nursing staff provide the antibiotics (Francis 2013; Sullivan 2007; Thigpen 2005; Wax 1997; Witt 2011). Macones 2012 does not mention method of allocation concealment.

Blinding

Seven trials were adequately blinded in regards to participants as well as providers, and therefore, deemed to have a low risk of performance bias. Three studies did not report performance bias but we suspect (from the study methods) that no blinding occurred and therefore categorized them as high risk of bias (Kalaranjini 2013; Kandil 2014; Yildirim 2009) for both blinding domains.

Four trials did not clearly report detection bias and we were unable to infer the potential for bias from the methods, so it was judged to be unclear risk (Macones 2012; Sullivan 2007; Thigpen 2005; Witt 2011). Three trials that described blinding of outcome assessment and were categorized as low risk of bias (Bhattacharjee 2013; Francis 2013; Wax 1997). Kalaranjini 2013; Yildirim 2009; and Kandil 2014 were again deemed high risk of bias as no mention was made in the associated text about detection bias and we suspect that no blinding occurred.

Incomplete outcome data

All 10 studies reported that all women who were initially randomized were included in the analysis; loss to follow-up was low and typically reasons were provided.

Selective reporting

We found the reporting bias to be low risk as the primary outcomes were stated in the study methods of all 10 studies.

Other potential sources of bias

No other potential sources of bias were identified in the 10 trials.

Effects of interventions

See: **Summary of findings for the main comparison** Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping

The overall risk of bias was low. The quality of the evidence using GRADE was high for composite morbidity, endomyometritis, wound infection and neonatal intensive care unit admission, moderate for UTI/cystitis/pyelonephritis and neonatal sepsis, and low for maternal respiratory infection.

1. Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes) - Analyses 1.1 to 1.10

Primary outcomes

Composite morbidity (as defined by trials)

There were significant reductions in composite morbidity (as defined by trials) for women who received antibiotics preoperatively as compared to those who received antibiotics after cord clamp (risk ratio (RR) 0.57; 95% confidence interval (CI) 0.45 to 0.72, 10 trials, 5041 women, high quality evidence) (Analysis 1.1). An interaction test for subgroup differences (1 g versus 2 g of cephalosporin) found no clear difference between studies using 1g of cephalosporin and those using 2 g of cephalosporin ($Chi^2 = 0.02$, $df = 1$ ($P = 0.88$); $I^2 = 0\%$).

Secondary outcomes (maternal)

There were significant reductions in **endomyometritis** (RR 0.54; 95% CI 0.36 to 0.79, 10 trials, 5041 women, high quality evidence (Analysis 1.2); **wound infection** (RR 0.59; 95% CI 0.44 to 0.81, 10 trials, 5041 women, high quality evidence (Analysis 1.3)) and **length of hospital stay** (mean difference (MD) -0.17; 95% CI -0.30 to -0.04, two trials, 1342 women (Analysis 1.7)) in women who received antibiotics preoperatively as compared to those who received antibiotics after cord clamp.

An interaction test for subgroup differences (1 g versus 2 g of cephalosporin) found no clear difference between studies for endometritis ($Chi^2 = 0.10$, ($P = 0.75$); $I^2 = 0\%$) or wound infections ($Chi^2 = 0.08$, ($P = 0.78$); $I^2 = 0\%$).

There were no clear differences in occurrence of **UTI/cystitis/pyelonephritis** (RR 1.02; 95% CI 0.65 to 1.59, eight trials, 4001 women, moderate quality evidence (Analysis 1.4)); **pelvic abscesses** (RR 1.00; 95% CI 0.06 to 15.97, one trial, 741 women (Analysis 1.5)); **respiratory infections (e.g. pneumonia)** (RR 2.30; 95% CI 0.34 to 15.45, four trials, 1849 women, low quality evidence (Analysis 1.6)); or **febrile illness** (RR 0.93; 95% CI 0.63 to 1.35, four trials, 2650 women (Analysis 1.8)) between the groups.

Two studies reported on septic pelvic thrombophlebitis, though there were no occurrences (Kalaranjini 2013; Yildirim 2009); so RR could not be calculated. One study (Kalaranjini 2013) reported on septic shock and maternal death, though there were no occurrences; so RR could not be calculated. None of the included studies reported on ICU admission, cost of antibiotics, antibiotic-related adverse events, placental transfer of antibiotics, breastfeeding or neonatal mortality.

2. Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes) - Analyses 2.1 to 2.8

Secondary outcomes

There were no clear differences for any of the neonatal outcomes when comparing preoperative administration of antibiotics to administration after cord clamp: **neonatal sepsis** (RR 0.76; 95% CI 0.51 to 1.13, five trials, 2907 neonates, moderate quality evidence (Analysis 2.1)); **neonatal sepsis work up** (RR 0.92; 95% CI 0.69 to 1.23, four trials, 1170 neonates) (Analysis 2.2)); **infection with a resistant organism** (RR 0.70; 95% CI 0.12 to 4.14, one trial, 379 neonates (Analysis 2.3)); **infection (other)** (RR 0.93; 95% CI 0.52 to 1.64, one trial, 302 neonates (Analysis 2.4)); **ICU admission** (RR 0.91; 95% CI 0.74 to 1.13, six trials, 3708 neonates (Analysis 2.5));**ICU length of stay (days)** (MD -0.07; 95% CI -2.60 to 2.46, three trials, 1731 neonates, random-effects, $Tau^2 = 4.07$; $I^2 = 97\%$ (Analysis 2.6)); **neonatal antibiotic treatment** (RR 0.84; 95% CI 0.12 to 5.68, one trial, 90 neonates (Analysis 2.7)); and febrile illness (RR 0.67; 95% CI 0.28 to 1.62, one trial, 953 neonates (Analysis 2.8)).

Among the included studies, no data were available for the neonatal outcome of mortality.

DISCUSSION

Summary of main results

This review included 10 trials of 5041 women who received prophylactic antibiotic administration for cesarean birth prior to skin incision versus after neonatal umbilical cord clamping to assess which is superior in preventing postpartum infectious morbidity.

Those who received antibiotics preoperatively were 43% less likely to have infectious morbidity as compared to those who received antibiotics after neonatal cord clamping. Those who received antibiotics preoperatively were 46% and 41% less likely to have endomyometritis and wound infection, respectively, as compared to those who received antibiotics after neonatal cord clamping.

Although a significant difference was noted in the hospital length of stay favoring preoperative antibiotics, the difference is unlikely to be of clinical significance. For other maternal infections such as UTI, pelvic abscess, respiratory infection (pneumonia), febrile illness, and fever showed no differences. There were no clear differences in neonatal outcomes regardless of when antibiotics were administered (Summary of findings for the main comparison).

Overall completeness and applicability of evidence

The included trials enrolled 5041 women from six (developing and developed) countries from 1990 to 2013. Overall, the trials in this review were of reasonably sound methodology and the results were generally consistent across the trials.

Prophylactic administration of antibiotics for cesarean delivery given prior to skin incision was more effective in preventing infectious morbidity (specifically, endomyometritis and wound infection) than when antibiotics were given after neonatal cord clamp.

Some secondary outcomes were not (or rarely) reported: septic pelvic thrombophlebitis, septic shock, maternal death, pelvic abscess, hospital length of stay, ICU admission, cost of antibiotics, antibiotic-related adverse events, placental transfer of antibiotics, breastfeeding. Maternal side effects were not reported (or might not have been collected consistently across trials) in the included studies; however, all the studies consistently reported on wound infection and endomyometritis,which are included in the composite primary outcome. Neonatal outcomes were not consistently reported from all trials, although no evidence of adverse effects were found regardless of timing of antibiotic administration. No study reported on neonatal mortality.

The lack of consistent reporting of neonatal outcomes is certainly a limitation of this review. Although the primary outcome of composite maternal morbidity is well represented, the lack of neonatal data within several of the included studies creates an artificial separation of the effects of antibiotics on the maternal/fetal diad. Additionally, no maternal deaths or ICU admissions were noted in any of the studies.

Quality of the evidence

The quality of the evidence using GRADE was high for composite morbidity, endomyometritis, wound infection and neonatal ICU admission. UTI/cystitis/pyelonephritis and neonatal sepsis were moderate for quality of the evidence, downgraded one due to wide confidence interval crossing the line of no effect. Maternal respiratory infection (pneumonia) was considered to be of low quality of evidence due to wide confidence intervals crossing the line of no effect, few events and small sample size (Summary of findings for the main comparison).

Potential biases in the review process

We followed to the Cochrane Pregnancy and Childbirth Group search strategies and review process. Two review authors conducted the study selection, data collection independently to avoid potential biases, and we are not aware of any potential bias in the review process.

Agreements and disagreements with other studies or reviews

There are two reviews that examined maternal and neonatal infectious morbidity in women undergoing cesarean delivery receiving preoperative prophylaxis compared with those receiving intraoperative administration (Baaqeel 2013; Costantine 2008). Costantine 2008 included three trials. Baaqeel 2013 included six trials. Our review includes 10 trials. Overall, the results of our review are in agreement with the previous reviews. All three reviews found that preoperative administration of antibiotics lead to a significant decrease in endomyometritis and total maternal infectious morbidity. Additionally, all three reviews found no significant differences in neonatal sepsis or neonatal ICU admission. In contrast, this review was able to demonstrate a significant decrease in wound infection when women received preoperative antibiotics, whereas the previous two reviews were only able to demonstrate a non-significant trend towards decrease in wound infection. Other outcomes of the two previous reviews (including maternal febrile morbidity and neonatal morbidity) were found to have non-significant reductions which was consistent with this review.

AUTHORS' CONCLUSIONS

Implications for practice

Cesarean antibiotic prophylaxis administered preoperatively significantly reduced the incidence of maternal infection especially endomyometritis and wound infection compared with administration of antibiotics after neonatal umbilical cord clamping (based on high quality evidence with an overall low risk of bias). There were no adverse neonatal outcomes detected.

Implications for research

The current evidence supports preoperative prophylactic antibiotic administration to decrease infectious morbidity after cesarean section, especially endometritis and wound infection. There is not enough information regarding genitourinary infections, pelvic abscess occurrence, respiratory infections or febrile illness to show whether administration preoperatively is superior to administration of antibiotics after cord clamp. Additional research may be able to provide further insight into adverse effects for neonates. We were not able to determine whether there is a specific time frame preoperatively that is preferred, for example, 30 to 60 minutes versus within 30 minutes.

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As part of the pre-publication editorial process, this review has been commented on by two peers (an editor and referee who is external to the editorial team), a member of the Pregnancy and Childbirth Group's international panel of consumers and the Group's Statistical Adviser.

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Smaill FM, Gyte GM. Antibiotic prophylaxis versus no prophylaxis for preventing infection after cesarean section. *Cochrane Database of Systematic Reviews* 2010, Issue 1. [DOI: 10.1002/14651858.CD007482.pub2]

Soar 2009

Soar J, Peyton J, Leonard M, Pullyblank AM. Surgical safety checklists. *BMJ* 2009;**338**:b220.

Souza 2013

Souza JP, Gülmezoglu AM, Vogel J, Carroli G, Lumbiganon P, Qureshi Z, et al. Moving beyond essential interventions for reduction of maternal mortality (the WHO Multicountry Survey on Maternal and Newborn Health): a cross-sectional study. *Lancet* 2013;**381**(9879):1747-55.

Starr 2005

Starr RB, Zurawski J, Ismail M. Preoperative vaginal preparation with povidone-iodine and the risk of postcesarean endometritis. *Obstetrics & Gynecology* 2005;**105**(5 Pt 1):1024-6.

Ventolini 2004

Ventolini G, Neiger R, McKenna D. Decreasing infectious morbidity in cesarean delivery by changing gloves. *Journal of Reproductive Medicine* 2004;**49**(1):13-6.

Wloch 2012

Wloch C, Wilson J, Lamagni T, Harrington P, Charlett A, Sheridan E. Risk factors for surgical site infection following caesarean section in England: results from a multicentre cohort study. *BJOG: An International Journal of Obstetrics & Gynaecology* 2012;**119**(11):1324-33. [DOI: 10.1111/j.1471-0528.2012.03452.x]

Yokoe 2001

Yokoe DS, Christiansen CL, Johnson R, Sands KE, Livingston J, Shtatland ES, et al. Epidemiology of and surveillance for postpartum infections. *Emerging Infectious Diseases* 2001;**7**:837-41.

* Indicates the major publication for the study

CHARACTERISTICS OF STUDIES

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

Bhattacharjee 2013

Methods	Randomized controlled trial.
Participants	953 pregnant women, more than 34 weeks of gestation, requiring cesarean deliveries. Excluded:obstetric complications (pre-eclampsia, antepartum hemorrhage, etc), renal disease, heart disease, diabetes mellitus, febrile during or prior to screening, ruptured membranes with or without antibiotic prophylaxis, any exposure to antibiotic during past 1 week, obstetrical indication for emergency cesarean delivery during labor, penicillin or cephalosporin allergy.
Interventions	Group A received prophylactic single-dose intravenous antibiotic (2 g ceftriaxone mixed with 10 mL) prior to incision and intravenous placebo (10 mL water) after cord clamp (n = 476). Group B received intravenous placebo (10 mL water) prior to incision and intravenous ceftriaxone 2 g in 10 mL after cord clamp (n = 477).
Outcomes	Primary outcome: postoperative maternal infectious morbidity. Secondary outcomes: neonatal complications, postoperative hospital stay of mother and stay of neonates at NICU (days).
Notes	July 2010 to December 2011, at 2 teaching hospitals in West Bengal India.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"A computer-generated randomisation sequence" was used.
Allocation concealment (selection bias)	Low risk	"The allocation was concealed in sealed, sequentially numbered, brown envelopes (opaque), which had been prepared by the statistician of each centre and handed over to the sister-in-charge of the operation theatre" was used.

Bhattacharjee 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	Low risk	"The drugs were supplied in small sealed bags", "Both vials were identical", conducted double-blinded manner.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	"Postoperative follow-up was done by resident doctors who were blinded to the patients' and babies' identity." Outcome assessor was blinded.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All the women randomized included in the analysis (intention-to-treat analysis), however, the number of women who completed the intervention group was n = 458 (96.2%), and in the control group was n = 456 (95.6%).
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Francis 2013

Methods	Randomized controlled trial.
Participants	896 women undergoing non-emergent cesarean delivery including women with ruptured membranes and experiencing labor, and scheduled cesarean deliveries. Excluded:fever > 38°C, age < 18 years old, diagnosed as chorioamnionitis before delivery, allergy to cefazolin and clindamycin, any exposure to antibiotic within 1 week before delivery. 95 women lost to follow- up: 39 from Group 1; 56 from Group 2 (cord clamp).
Interventions	Prophylactic single-dose antibiotic (2 g ceftriaxone or clindamycin 900 mg if women allergic to penicillin) within 30 to 60 minutes of expected skin incision (n = 410) and placebo after umbilical cord clamping or placebo within 30 to 60 minutes of expected incision and the antibiotic (2 g ceftriaxone or clindamycin 900 mg if women allergic to penicillin) after umbilical cord clamping (n = 391).
Outcomes	Primary outcomes: maternal infectious morbidity including wound infection, UTI, endometritis and pneumonia. Secondary outcomes: neonatal antibiotic administration, admission to the NICU, and hospital readmission rates.
Notes	Single site: St Vincent Hospital in Indianapolis, Indiana, USA, September 2006 to January 2011. Underpowered as noted in article.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	“The randomisation sequence was generated by the hospital statistician.” “The randomisation list was e-mailed to the research pharmacist.” Comments: unclear technique used to generate randomization list, but we suspect that method was appropriate as it was done by a statistician.

Francis 2013 *(Continued)*

Allocation concealment (selection bias)	Low risk	"The randomisation list was e-mailed to the research pharmacist, who was the only person with access to the randomisation information for the duration of the study."
Blinding of participants and personnel (performance bias) All outcomes	Low risk	"Treatment assignment was performed in the pharmacy and all physicians and patients were blinded to which bag contained the antibiotic and which one had saline."
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only pharmacy was aware of timing of antibiotic.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The 95 women lost to follow- up (10.6%), 39 (4.4%) were in the skin incision group and 56 (6.2%) were in the cord clamp group.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Kalaranjini 2013

Methods	Randomized controlled trial.
Participants	874 women undergoing elective cesarean delivery. 437 women in each group. Excluded: history of diabetes mellitus, severe anemia, obese women (BMI >= 25) ruptured membranes, retro positive women, immune-suppressant drugs, history of allergy to ceftriaxone No women lost to follow-up.
Interventions	Single dose of ceftriaxone 1 g intravenously 15-45 minutes before skin incision (n = 437) versus the same medication after cord clamping (n = 437).
Outcomes	Primary outcome: maternal postoperative infectious morbidities such as surgical site wound infection, febrile morbidity, endometritis, UTIs and neonatal sepsis.
Notes	Single site: conducted from October 2010 to July 2012. 1 hospital in Puducherry, India. About 27 women (17 in before skin incision and 10 in cord clamping) continued receiving antibiotics after surgery due to various infections.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	"The patients were randomly categorized into two groups using serially numbered opaque sealed envelope (SNOPE) technique."
Allocation concealment (selection bias)	Low risk	Opaque sealed envelope was used.

Kalaranjini 2013 *(Continued)*

Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not specified, but we suspect that no blinding occurred.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not specified, but we suspect that no blinding occurred.
Incomplete outcome data (attrition bias) All outcomes	Low risk	All women accounted for, no loss to follow-up.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes were stated.
Other bias	Low risk	No other bias evident.

Kandil 2014

Methods	Randomized controlled trial.
Participants	100 primigravid women with singleton pregnancy at term undergoing elective cesarean. Excluded: age < 20 or > 30 years; BMI < 19 or >= 25; exposure to antibiotics within 1 week of delivery; premature rupture of membranes; indication for emergency cesarean; hypersensitivity to cephalosporins; temperature > 37.8 degrees celsius.
Interventions	2 g cefazolin administered 30 minutes preoperatively (n = 50) versus after cord clamp (n = 50).
Outcomes	Endometritis, wound infection, UTI.
Notes	1 hospital in Egypt. June 2011-December 2012.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	50 cards were prepared for each intervention. The cards were placed into opaque envelopes and "shuffled to produce a form of random assignment".
Allocation concealment (selection bias)	Low risk	Sequentially numbered opaque envelopes.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not specified, but we suspect that no blinding occurred.
Blinding of outcome assessment (detection bias) All outcomes	High risk	This was not specified, but we suspect that no blinding occurred.
Incomplete outcome data (attrition bias)	Low risk	None reported.

Kandil 2014 *(Continued)*

All outcomes		
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Macones 2012

Methods	Randomized controlled trial.
Participants	434 women undergoing non-emergency cesarean deliveries >= 36 weeks excluding women with known fetal anomaly, antibiotics within 7 days of admission, overt intrapartum infection, or ruptured membranes > 18 hours.
Interventions	1 g cefazolin administered < 30 minutes preoperatively (n = 217) versus after cord clamp (n = 217). They did not specify intravenous treatment, but we included this trial as it was assumed that cefazolin was administered intravenously.
Outcomes	Primary: postoperative fever, wound infection, endomyometritis, UTI. Secondary: NICU admission, proven or suspected neonatal sepsis (with resistant bacteria), neonatal length of stay (days).
Notes	2 centers in USA. Study period not defined.

Risk of bias

Bias	**Authors' judgement**	**Support for judgement**
Random sequence generation (selection bias)	Low risk	Permuted blocks.
Allocation concealment (selection bias)	Unclear risk	Not mentioned.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Adminstered by anesthesiologist to maintain blinding.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	This was not specified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not specifically mentioned, but it appears that outcomes are available for all enrolled women.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Sullivan 2007

Methods	Randomized controlled trial.
Participants	367 women >= 24 weeks who were undergoing cesarean delivery excluding women with a cephalosporin allergy, age < 18 years, exposure to antibiotics within 7 days, need for emergency surgery.
Interventions	1 g cefazolin administered at 15-60 minutes pre-incision and normal saline after cord clamp (n = 175) versus normal saline at 15-60 minutes pre-incision and 1 g cefazolin after cord clamp (n = 182). They did not specify intravenous treatment, but we included this trial as it was assumed that cefazolin was administered intravenously.
Outcomes	Primary: total infectious morbidity.
Notes	Abstract and paper; study commenced January 2003. 1 hospital in the United States of America.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Simple randomization using random number tables.
Allocation concealment (selection bias)	Low risk	Investigational pharmacy staff delivered both antibiotics and placebo.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Intraoperative labeled bag given by anesthesia.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Double-blind trial but does not describe blinding method.
Incomplete outcome data (attrition bias) All outcomes	Low risk	The preoperative group lost 3 women and the cord clamp group lost 5 women to attrition.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Thigpen 2005

Methods	Randomized controlled trial.
Participants	346 women in active labor excluding women with chorioamnionitis, cephalosporin allergy, antibiotics within 2 weeks of labor.
Interventions	2 g cefazolin administered pre-incision and normal saline after cord clamp (n = 153) versus normal saline pre-incision and 2 g cefazolin after cord clamp (n = 149).
Outcomes	Postoperative infection, neonatal infections and sepsis.

Thigpen 2005 *(Continued)*

Notes	1 center in the United States of America from November 2000 until April 2003.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Unclear risk	Study only states that randomization was performed by pharmacy personnel.
Allocation concealment (selection bias)	Low risk	Allocated by pharmacy personnel.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Care providers were unaware of which bag contained antibiotic versus placebo.
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Not specified.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Not specifically mentioned, but it appears that outcomes are available for all enrolled women who were not excluded following randomization.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes stated.
Other bias	Low risk	No other bias evident.

Wax 1997

Methods	Randomized controlled trial.
Participants	90 women undergoing cesarean in labor with a single fetus ≥ 37 weeks' gestation excluding women with an allergy to penicillin or cephalosporin, antibiotic use within 2 weeks of delivery, temperature ≥ 37.8°C in labor, administration of group B streptococcal or subacute bacterial endocarditis prophylaxis during labor, insulin-dependent diabetes mellitus, human immunodeficiency virus infection, chronic glucocorticoid use, or multiple gestation.
Interventions	1 g cefazolin administered over approximately 5 minutes upon decision for cesarean delivery and normal saline after cord clamp, each intervention in identical 50 mL infusions (n = 49) versus normal saline over approximately 5 minutes upon decision for cesarean delivery and 1 g cefazolin after cord clamp (n = 41).
Outcomes	Primary maternal outcomes: endometritis and wound infection. Secondary maternal outcomes: intra-abdominal abscess, septic pelvic thrombophlebitis, or symptomatic UTI. Neonatal outcomes: sepsis screen, sepsis, pneumonia, and meningitis.
Notes	1 center in the United States of America over a 12-month period (exact dates not provided).

Risk of bias

Wax 1997 *(Continued)*

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated randomization.
Allocation concealment (selection bias)	Low risk	Randomization code was produced by, and known only by pharmacy.
Blinding of participants and personnel (performance bias) All outcomes	Low risk	Each participants received 2 bags, effectively blinding to timing of antibiotic.
Blinding of outcome assessment (detection bias) All outcomes	Low risk	Only pharmacy was aware of timing of antibiotic.
Incomplete outcome data (attrition bias) All outcomes	Low risk	7 participants were lost to 2 week follow-up. 14 participants were lost to 6 week follow-up.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes.
Other bias	Low risk	No other bias evident.

Witt 2011

Methods	Randomized controlled trial.
Participants	1112 women with a fetus ≥ 37 weeks' gestation undergoing elective cesarean delivery of a fetus with reassuring fetal heart rate tracing.
Interventions	Group A: 2 g cefazolin in 100 mL saline 20-30 minutes before incision (n = 370). Group B: 2 g cefazolin in 100 mL saline immediately after cord clamp (n = 371). Group C: 100 mL saline 20-30 minutes before incision (n = 371).
Outcomes	Total postoperative infectious morbidity (endometritis, wound infection, UTI).
Notes	1 hospital in Vienna, Austria. 3/1/04 - 1/31/10.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	Computer-generated permuted blocks of 5.
Allocation concealment (selection bias)	Low risk	Only the study nurse was not blinded and handed appropriate infusion bag to anesthesiologist.
Blinding of participants and personnel (performance bias)	Low risk	Women and surgeons masked to administration schedule.

Witt 2011 *(Continued)*

All outcomes		
Blinding of outcome assessment (detection bias) All outcomes	Unclear risk	Infectious morbidity was evaluated by 2 residents who were masked to group assignments.
Incomplete outcome data (attrition bias) All outcomes	Low risk	Protocol violations in Groups 1, 2, and 3 respectively: 12, 7, and 13. 32 women lost to follow- up/protocol violations/withdrawal.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes.
Other bias	Low risk	No other bias evident.

Yildirim 2009

Methods	Randomized controlled trial.
Participants	400 women undergoing elective cesarean delivery prior to labor initially included with 11 excluded due to blood transfusion leaving 389 participants. Additional exclusion criteria included the use of antibiotics in the last 24 hours, pathology that should be treated with antibiotics, pre-existing maternal disease (such as diabetes, collagen vascular disease, immune system problems), chorioamnionitis, fever on admission, need of transfusion before or during cesarean delivery, ruptured membranes, emergency cesarean delivery and preterm cesarean delivery.
Interventions	1 g of cefazolin ≤ 45 minutes pre-incision (n = 194) versus 1 g cefazolin after cord clamp (n = 195). They did not specify intravenous treatment, but we included this trial as it was assumed that cefazolin was administered intravenously.
Outcomes	Rates of postoperative infectious morbidity (endometritis, wound infection, febrile morbidity, UTI), estimated blood loss and operative time. Neonatal outcomes: NICU admission, Apgar score less than 7 at 5 minutes, neonatal sepsis and sepsis workup.
Notes	Conducted June 2007-December 2007 at 1 hospital inTurkey.

Risk of bias

Bias	Authors' judgement	Support for judgement
Random sequence generation (selection bias)	Low risk	2 parts, blocked randomization.
Allocation concealment (selection bias)	Low risk	Sealed, sequentially distributed envelopes indicating group A (pre-incision) or group B (following cord camp) chosen by the participants, opened by the investigator.
Blinding of participants and personnel (performance bias) All outcomes	High risk	This was not specified, but we suspect that no blinding occurred.
Blinding of outcome assessment (detection bias)	High risk	This was not specified, but we suspect that no blinding occurred.

Yildirim 2009 *(Continued)*
All outcomes

Incomplete outcome data (attrition bias) All outcomes	Low risk	None lost to follow- up.
Selective reporting (reporting bias)	Low risk	Prespecified outcomes.
Other bias	Low risk	No other bias evident.

BMI: body mass index
NICU: neonatal intensive care unit
UTI: urinary tract infection

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

Study	Reason for exclusion
Cunningham 1983	Not a randomized controlled trial.
De Palma 1980	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Women continued to receive antibiotics postoperatively.
Gordon 1979	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Women continued to receive antibiotics postoperatively.
Gul 1999	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Women continued to receive antibiotics postoperatively.
Nokiani 2009	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Women continued to receive antibiotics postoperatively.
Rodriguez 1990	There is insufficient information provided in the abstract. There was no information on randomization (sequence generation and allocation concealment were not described). There was no blinding. The group sizes were very different 55 versus 84. It was not clear whether this was due to chance. There was no information on attrition. There were no usable data (most results were not reported according to randomization group but according to risk), the results that were reported by randomization group did not present the data (P values only)).
Seton 1996	There is insufficient information provided in the abstract. This was described as a small pilot study. There was no information on sequence generation or allocation concealment although it was described as a double blind-trial. It was not clear whether the placebo was identical. There was no information on attrition or missing data (it was not stated how many were randomized to each group although percentages in the results suggest 20 women were randomized to each arm). There were no SDs reported for continuous data. The intervention was not clear. The women were randomized to receive antibiotics before or after cord clamping; but the interval was not described (it was not clear whether the antibiotic was administered immediately before cord clamping, after skin incision or immediately after or a long period after).
Tassi 1987	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Women continued to receive antibiotics postoperatively.
van Beekhuizen 2008	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Comparison was made between single dose and multiple day regimens.

Study	Reason for exclusion
Van Velzen 2009	Antibiotic regimens were not limited to preoperative versus post-cord clamp. Comparison was made between single dose and multiple day regimens.
Xu 1997	Antibiotic regimens were limited to preoperative versus postoperative but were not given at cord clamp.

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

Pevzner 2009

Methods	Randomized controlled trial.
Participants	50 women undergoing scheduled cesarean delivery.
Interventions	2 g cefazolin preoperatively versus after cord clamp (number randomized to each group not specified).
Outcomes	Primary: endometritis and wound infection. Secondary: neonatal sepsis work-up, sepsis, pneumonia, and meningitis. Followed 6 weeks postoperatively for late complications.
Notes	Abstract pilot study, in USA. Does not currently provide enough information to make an assessment of methodologic quality.

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

Zhang 2012

Trial name or title	Timing of perioperative antibiotics for cesarean: a multicenter randomized controlled study.
Methods	Randomized control trial.
Participants	Women were eligible for the trial if they were > 37 weeks' gestation and undergoing cesarean delivery. Exclusion criteria: allergy to cefathiamidine, exposure to any antibiotic agent within 1 week of delivery, > 37.5°C before cesarean or age < 18 years or > 40 years.
Interventions	Cefethiamidine administered 30 minutes prior to skin incision but no more than 120 minutes before versus after cord clamping.
Outcomes	Endomyometritis, wound infection, urinary tract infection, neonatal sepsis, neonatal sepsis workup, neonatal admission, neonatal dysbacteriosis, temperature after cesarean, number of white blood count and neutrophile granulocyte after cesarean, ratio of neonatal stool coccus and bacillus.
Starting date	December 2011-June 2012.
Contact information	Zhang Chuan, Department of Pharmacy West China Second University Hospital, Sichuan University (email: zhang_chuan@yahoo.cn)

Zhang 2012 *(Continued)*

Notes	Settings - 3 facilities (West China Second University Hospital Sichuan University, Sichuan Women and Children's Health, Nanchong Central Hospital).

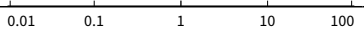
DATA AND ANALYSES

Comparison 1. Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Composite morbidity (as defined by trials)	10	5041	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.45, 0.72]
1.1 Cephalosporin 1 g	5	2144	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.35, 0.86]
1.2 Cephalosporin 2 g	5	2897	Risk Ratio (M-H, Fixed, 95% CI)	0.57 [0.43, 0.76]
2 Endomyometritis	10	5041	Risk Ratio (M-H, Fixed, 95% CI)	0.54 [0.36, 0.79]
2.1 Cephalosporin 1 g	5	2144	Risk Ratio (M-H, Fixed, 95% CI)	0.58 [0.30, 1.12]
2.2 Cephalosporin 2 g	5	2897	Risk Ratio (M-H, Fixed, 95% CI)	0.51 [0.32, 0.83]
3 Wound infection	10	5041	Risk Ratio (M-H, Fixed, 95% CI)	0.59 [0.44, 0.81]
3.1 Cephalosporin 1 g	5	2144	Risk Ratio (M-H, Fixed, 95% CI)	0.55 [0.30, 1.01]
3.2 Cephalosporin 2 g	5	2897	Risk Ratio (M-H, Fixed, 95% CI)	0.61 [0.43, 0.88]
4 UTI/cystitis/pyelonephritis	8	4001	Risk Ratio (M-H, Fixed, 95% CI)	1.02 [0.65, 1.59]
5 Pelvic abscess	1	741	Risk Ratio (M-H, Fixed, 95% CI)	1.00 [0.06, 15.97]
6 Respiratory infection (pneumonia)	4	1849	Risk Ratio (M-H, Fixed, 95% CI)	2.30 [0.34, 15.45]
7 Hospital length of stay (days)	2	1342	Mean Difference (IV, Fixed, 95% CI)	-0.17 [-0.30, -0.04]
8 Febrile Illness	4	2650	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.63, 1.35]

Analysis 1.1. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 1 Composite morbidity (as defined by trials).

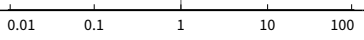
Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.1.1 Cephalosporin 1 g					
Kalaranjini 2013	3/437	6/437		3.45%	0.5[0.13,1.99]
Macones 2012	7/217	9/217		5.18%	0.78[0.29,2.05]
Sullivan 2007	7/175	20/182		11.28%	0.36[0.16,0.84]
Wax 1997	1/49	3/41		1.88%	0.28[0.03,2.58]
Yildirim 2009	11/194	15/195		8.61%	0.74[0.35,1.56]
Subtotal (95% CI)	**1072**	**1072**		**30.39%**	**0.55[0.35,0.86]**
Total events: 29 (Preoperative), 53 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=2.39, df=4(P=0.67); I^2=0%					
Test for overall effect: Z=2.65(P=0.01)					
1.1.2 Cephalosporin 2 g					
Bhattacharjee 2013	19/476	47/477		27.01%	0.41[0.24,0.68]
Francis 2013	20/410	29/391		17.08%	0.66[0.38,1.14]
Kandil 2014	3/50	4/50		2.3%	0.75[0.18,3.18]
Thigpen 2005	18/153	30/149		17.48%	0.58[0.34,1]
Witt 2011	10/370	10/371		5.74%	1[0.42,2.38]
Subtotal (95% CI)	**1459**	**1438**		**69.61%**	**0.57[0.43,0.76]**
Total events: 70 (Preoperative), 120 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=3.71, df=4(P=0.45); I^2=0%					
Test for overall effect: Z=3.86(P=0)					
Total (95% CI)	**2531**	**2510**		**100%**	**0.57[0.45,0.72]**
Total events: 99 (Preoperative), 173 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=6.11, df=9(P=0.73); I^2=0%					
Test for overall effect: Z=4.68(P<0.0001)					
Test for subgroup differences: Chi^2=0.02, df=1 (P=0.88), I^2=0%					



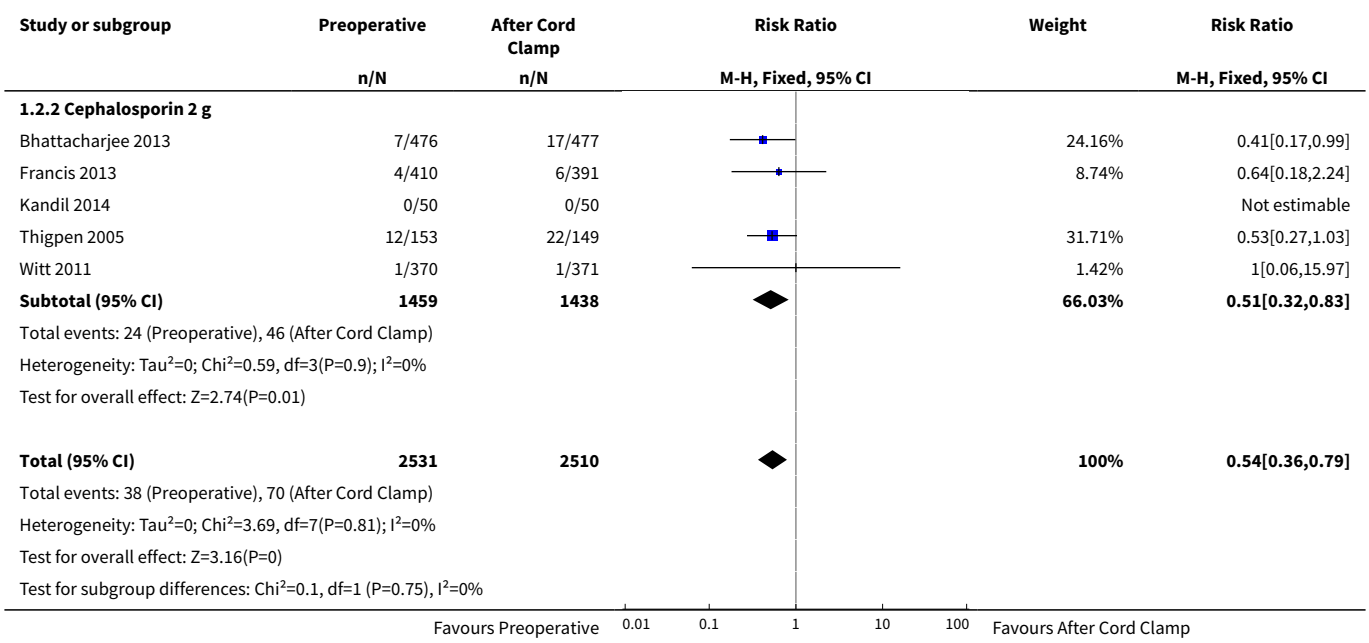
Favours Preoperative — Favours After Cord Clamp

Analysis 1.2. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 2 Endomyometritis.

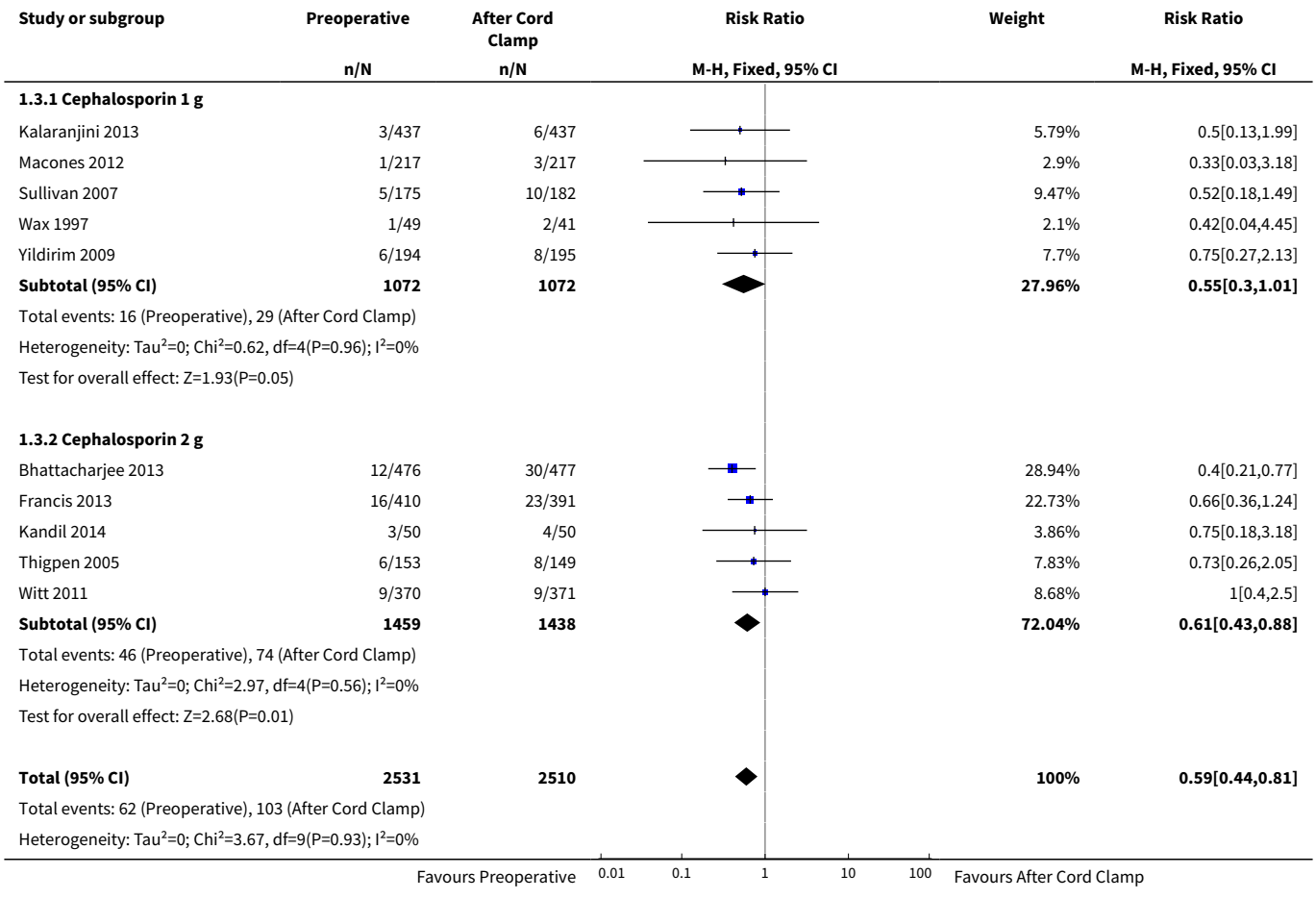
Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
1.2.1 Cephalosporin 1 g					
Kalaranjini 2013	0/437	0/437			Not estimable
Macones 2012	6/217	6/217		8.54%	1[0.33,3.05]
Sullivan 2007	2/175	10/182		13.95%	0.21[0.05,0.94]
Wax 1997	1/49	1/41		1.55%	0.84[0.05,12.97]
Yildirim 2009	5/194	7/195		9.93%	0.72[0.23,2.22]
Subtotal (95% CI)	**1072**	**1072**		**33.97%**	**0.58[0.3,1.12]**
Total events: 14 (Preoperative), 24 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=2.89, df=3(P=0.41); I^2=0%					
Test for overall effect: Z=1.61(P=0.11)					

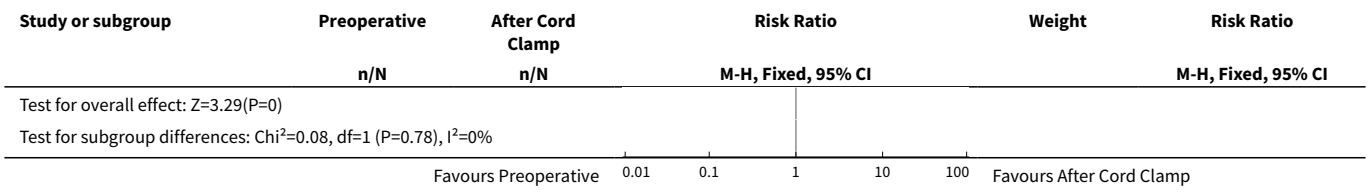


Favours Preoperative — Favours After Cord Clamp

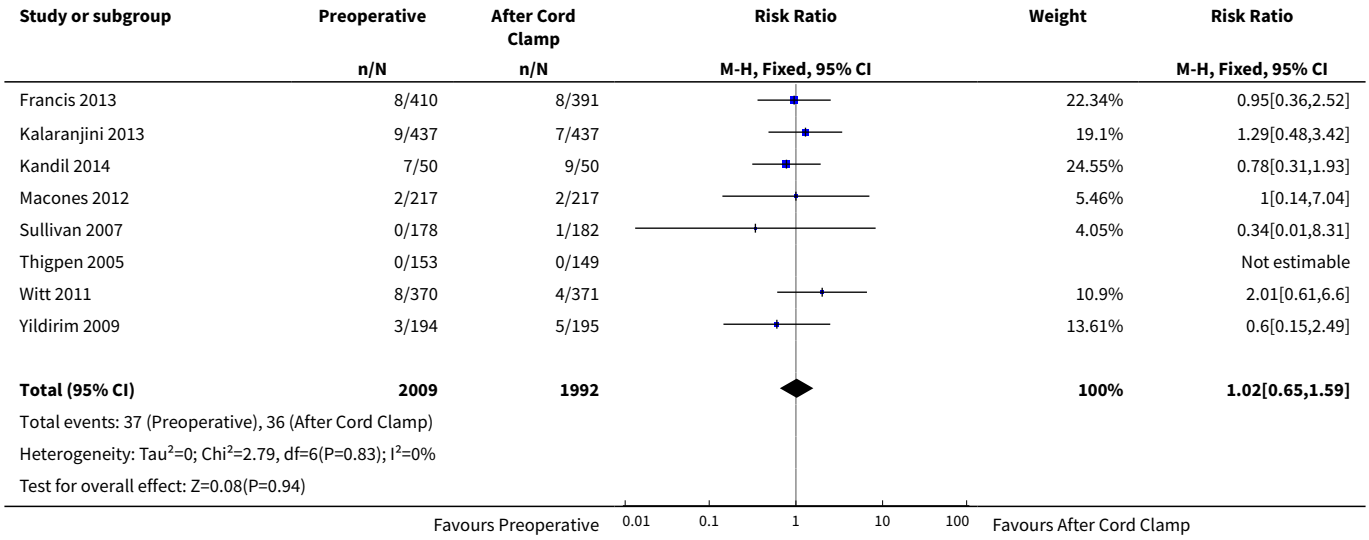


Analysis 1.3. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 3 Wound infection.

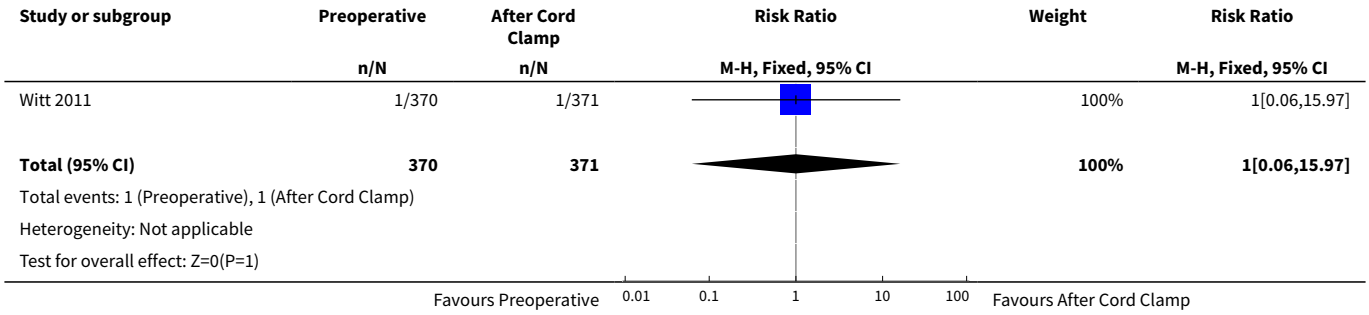




Analysis 1.4. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 4 UTI/cystitis/pyelonephritis.

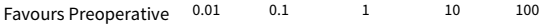


Analysis 1.5. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 5 Pelvic abscess.



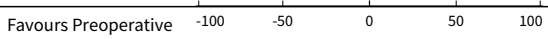
Analysis 1.6. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 6 Respiratory infection (pneumonia).

Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Francis 2013	2/410	1/391		67.62%	1.91[0.17,20.95]
Sullivan 2007	1/175	0/182		32.38%	3.12[0.13,76.06]
Thigpen 2005	0/153	0/149			Not estimable
Yildirim 2009	0/194	0/195			Not estimable
Total (95% CI)	**932**	**917**		**100%**	**2.3[0.34,15.45]**
Total events: 3 (Preoperative), 1 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=0.06, df=1(P=0.81); I^2=0%					
Test for overall effect: Z=0.86(P=0.39)					



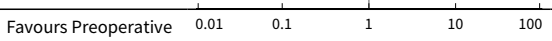
Analysis 1.7. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 7 Hospital length of stay (days).

Study or subgroup	Preoperative N	Preoperative Mean(SD)	After Cord Clamp N	After Cord Clamp Mean(SD)	Mean Difference Fixed, 95% CI	Weight	Mean Difference Fixed, 95% CI
Bhattacharjee 2013	476	4.4 (1.2)	477	4.6 (1.3)		67.16%	-0.21[-0.37,-0.05]
Yildirim 2009	194	2.3 (1.1)	195	2.4 (1.2)		32.84%	-0.09[-0.32,0.14]
Total ***	**670**		**672**			**100%**	**-0.17[-0.3,-0.04]**
Heterogeneity: Tau^2=0; Chi^2=0.73, df=1(P=0.39); I^2=0%							
Test for overall effect: Z=2.58(P=0.01)							



Analysis 1.8. Comparison 1 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (maternal outcomes), Outcome 8 Febrile Illness.

Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhattacharjee 2013	26/476	33/477		62.26%	0.79[0.48,1.3]
Kalaranjini 2013	9/437	5/437		9.44%	1.8[0.61,5.33]
Macones 2012	5/217	8/217		15.11%	0.63[0.21,1.88]
Yildirim 2009	9/194	7/195		13.19%	1.29[0.49,3.4]
Total (95% CI)	**1324**	**1326**		**100%**	**0.93[0.63,1.35]**
Total events: 49 (Preoperative), 53 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=2.78, df=3(P=0.43); I^2=0%					
Test for overall effect: Z=0.4(P=0.69)					

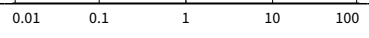


Comparison 2. Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes)

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Sepsis	5	2907	Risk Ratio (M-H, Fixed, 95% CI)	0.76 [0.51, 1.13]
2 Neonatal sepsis work up	4	1170	Risk Ratio (M-H, Fixed, 95% CI)	0.92 [0.69, 1.23]
3 Infection with a resistant organism	1	379	Risk Ratio (M-H, Fixed, 95% CI)	0.70 [0.12, 4.14]
4 Infection (other)	1	302	Risk Ratio (M-H, Fixed, 95% CI)	0.93 [0.52, 1.64]
5 ICU admission	6	3708	Risk Ratio (M-H, Fixed, 95% CI)	0.91 [0.74, 1.13]
6 ICU length of stay (days)	3	1731	Mean Difference (IV, Random, 95% CI)	-0.07 [-2.60, 2.46]
7 Neonatal antibiotic treatment	1	90	Risk Ratio (M-H, Fixed, 95% CI)	0.84 [0.12, 5.68]
8 Fever	1	953	Risk Ratio (M-H, Fixed, 95% CI)	0.67 [0.28, 1.62]

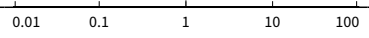
Analysis 2.1. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 1 Sepsis.

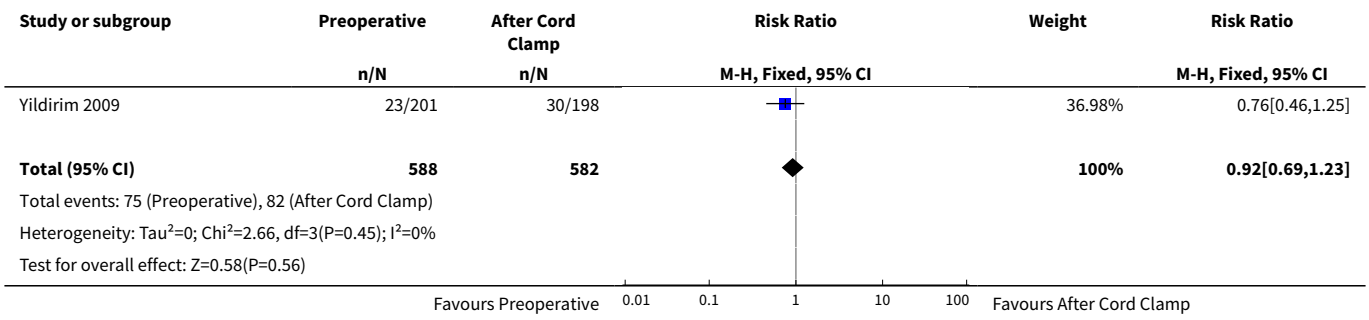
Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Bhattacharjee 2013	15/476	19/477		35.15%	0.79[0.41,1.54]
Kalaranjini 2013	4/437	8/437		14.81%	0.5[0.15,1.65]
Sullivan 2007	6/185	7/194		12.65%	0.9[0.31,2.62]
Thigpen 2005	7/153	7/149		13.13%	0.97[0.35,2.71]
Yildirim 2009	9/201	13/198		24.25%	0.68[0.3,1.56]
Total (95% CI)	**1452**	**1455**		**100%**	**0.76[0.51,1.13]**
Total events: 41 (Preoperative), 54 (After Cord Clamp)					
Heterogeneity: Tau^2=0; Chi^2=0.87, df=4(P=0.93); I^2=0%					
Test for overall effect: Z=1.36(P=0.18)					



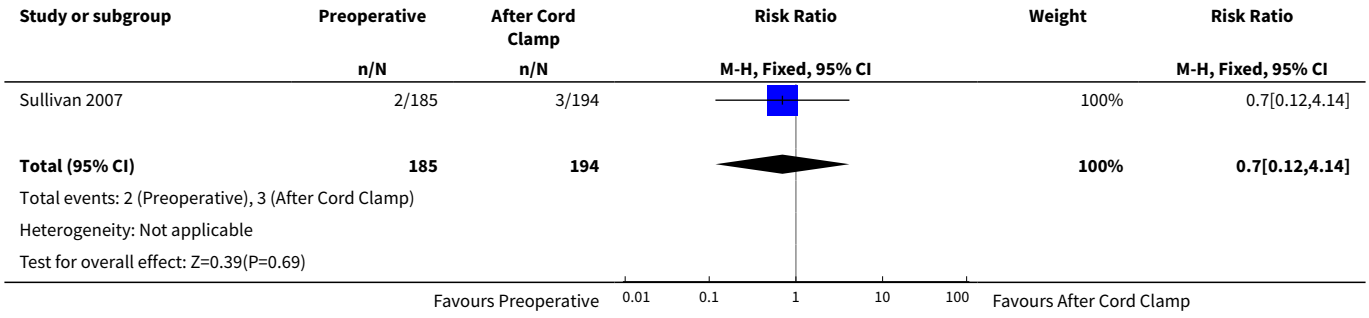
Analysis 2.2. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 2 Neonatal sepsis work up.

Study or subgroup	Preoperative n/N	After Cord Clamp n/N	Risk Ratio M-H, Fixed, 95% CI	Weight	Risk Ratio M-H, Fixed, 95% CI
Sullivan 2007	35/185	36/194		43%	1.02[0.67,1.55]
Thigpen 2005	11/153	14/149		17.36%	0.77[0.36,1.63]
Wax 1997	6/49	2/41		2.66%	2.51[0.54,11.77]

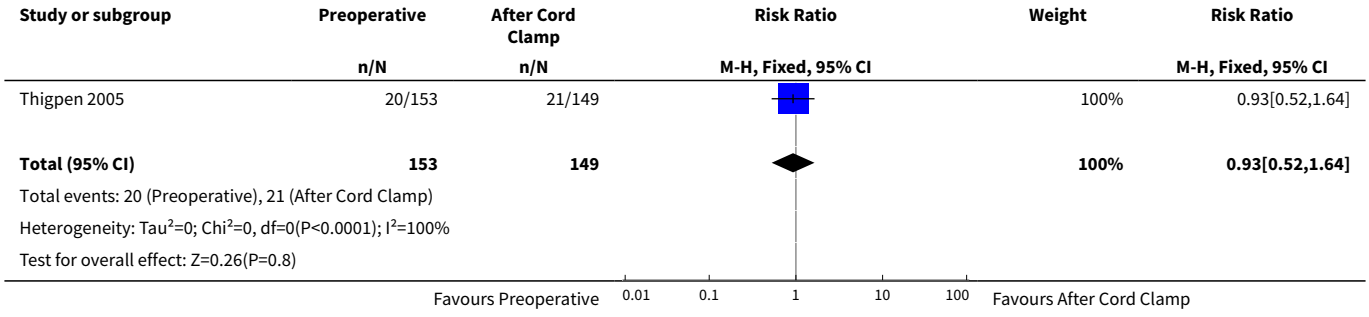




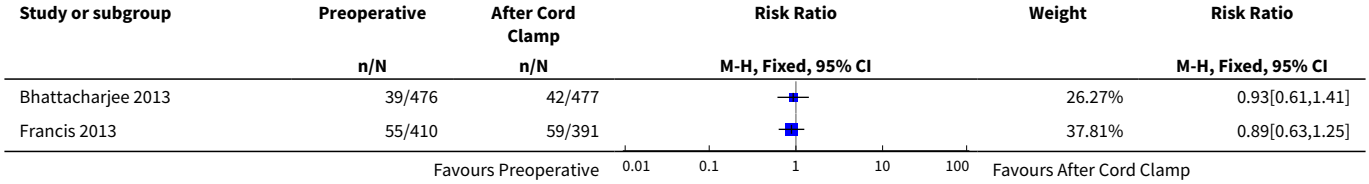
Analysis 2.3. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 3 Infection with a resistant organism.

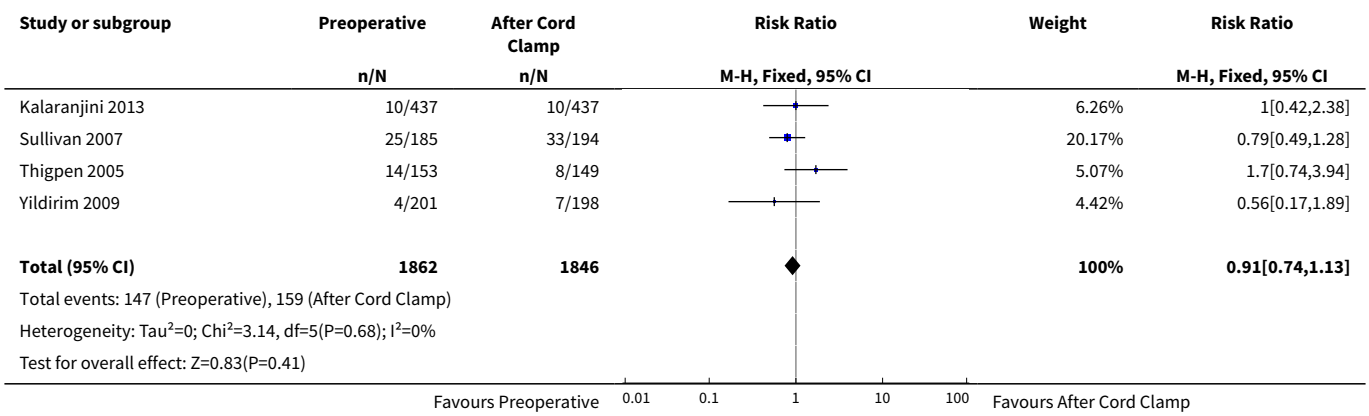


Analysis 2.4. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 4 Infection (other).

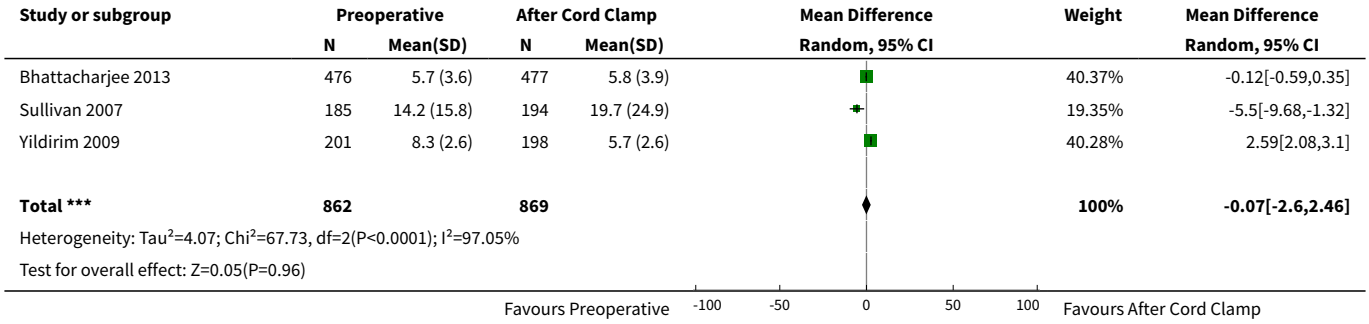


Analysis 2.5. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 5 ICU admission.

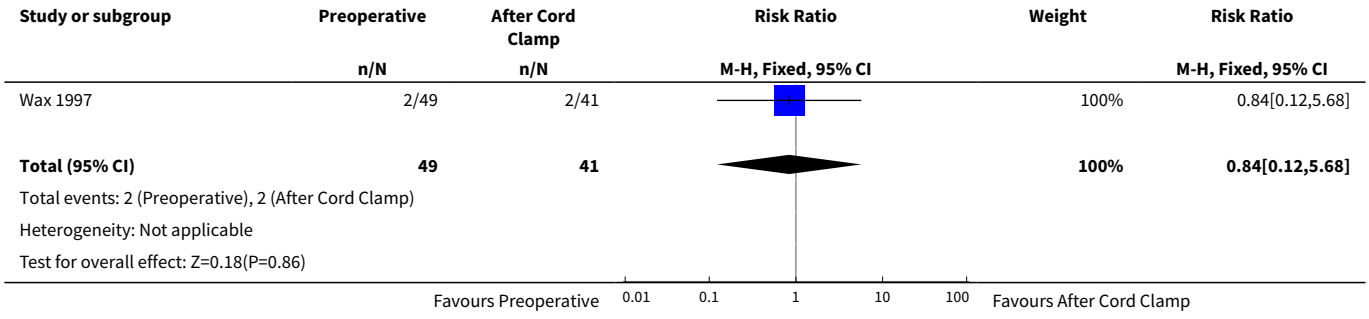




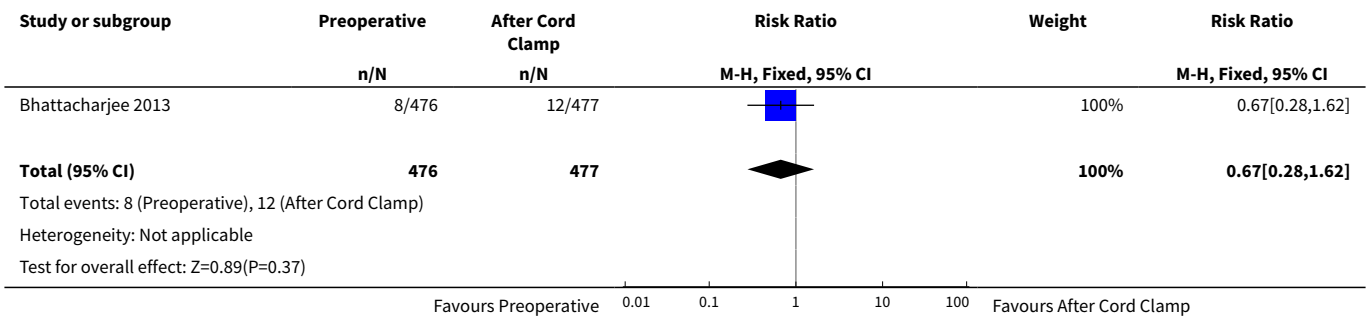
Analysis 2.6. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 6 ICU length of stay (days).



Analysis 2.7. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 7 Neonatal antibiotic treatment.



Analysis 2.8. Comparison 2 Prophylactic intravenous antibiotics administered before cesarean incision versus after neonatal umbilical cord clamping (neonatal outcomes), Outcome 8 Fever.



CONTRIBUTIONS OF AUTHORS

A. Dhanya Mackeen, Roger Packard and Erika Ota abstracted data from the studies and entered data into RevMan. A. Dhanya Mackeen, Roger Packard, Vincenzo Berghella, and Erika Ota prepared the first draft. Erika Ota prepared the 'Summary of findings' tables. All authors approved the final version of the update for publication. A. Dhanya Mackeen is guarantor for the review.

DECLARATIONS OF INTEREST

None known.

SOURCES OF SUPPORT

Internal sources

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External sources

- No sources of support supplied

DIFFERENCES BETWEEN PROTOCOL AND REVIEW

We have assessed the quality of the body of evidence using the GRADE approach (Schunemann 2009) - this was not pre-specified in our published protocol (Baxter 2011).

We added a subgroup analysis based on dose of cephalosporin (1 g versus 2 g).

We changed the definition of our primary outcome of composite morbidity to include sepsis (including septic shock), endomyometritis, wound infection, or death attributed to infection. We removed necrotizing fasciitis and bacteremia as these would have been included in infection and sepsis.

In addition, some sections of the methods have been updated in accordance with the Cochrane Pregnancy and Childbirth Group's standard methods text:

- assessment of reporting biases;
- subgroup analysis and investigation of heterogeneity.

We have also made minor edits to the list of planned outcomes:

Secondary maternal outcomes

- 'Urinary tract infection' has been edited to 'Urinary tract infection, cystitis and pyelonephritis'
- 'Upper respiratory infection (pneumonia) has been edited to 'Respiratory infection (e.g. pneumonia)'

- 'Fever' has been changed to 'Febrile illness'
- 'Sepsis' has been changed to 'Sepsis, including septic shock'
- Clarified that the unit for hospital length of stay is in days

Secondary infant outcomes

- 'Neonatal workup for infection' has been edited to 'Neonatal sepsis workup'
- Length of ICU stay has been clarified as 'Length of ICU stay (days)'
- 'Antibiotic treatment' has been edited to 'Neonatal antibiotic treatment'
- Febrile illness has been added as a new secondary outcome

INDEX TERMS

Medical Subject Headings (MeSH)

Anti-Bacterial Agents [*administration & dosage]; Antibiotic Prophylaxis [*standards]; Cesarean Section [*adverse effects]; Drug Administration Schedule; Endometritis [prevention & control]; Injections, Intravenous; Randomized Controlled Trials as Topic; Surgical Wound Infection [*prevention & control]; Urinary Tract Infections [prevention & control]

MeSH check words

Female; Humans; Pregnancy