National Institute for Health and Care Excellence

Draft for consultation

Termination of Pregnancy

[D] Antibiotic prophylaxis for medical and surgical termination of pregnancy

NICE guideline <TBC>

Evidence reviews

April 2019

Draft for Consultation

These evidence reviews were developed by the National Guideline Alliance hosted by the Royal College of Obstetricians and Gynaecologists

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Antibiotic prophylaxis for medical and surgical termination of pregnancy

This evidence report contains information on 2 review questions relating to antibiotic prophylaxis for medical and surgical termination of pregnancy.

- What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?
- What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Antibiotic prophylaxis for medical termination of pregnancy

Review question

What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Introduction

The aim of this review is to determine the optimal antibiotic prophylaxis regimen (if any) for women who are having a medical termination of pregnancy.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 1: Summary of the protocol (PICO table)

Population	Women who are having medical termination of pregnancy
Intervention	Antibiotic prophylaxis (any dose) using: • Oral azithromycin • Oral doxycycline • Oral or rectal metronidazole
Comparison	• Antibiotic prophylaxis (single agent or combination) versus placebo/ no treatment • Antibiotic prophylaxis A (single agent or combination) versus antibiotic prophylaxis B (single agent or combination)

Outcome	**Critical outcomes:**
	• Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination
	• Post-abortal pelvic inflammatory disease (including endometritis, upper genital tract infection) within 1 month of termination
	• Adherence to antibiotics
	
	Important outcomes:
	• Gastro-intestinal side effects:
	  ○ Nausea
	  ○ Vomiting
	  ○ Diarrhoea
	• Patient satisfaction

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 1991 onwards were considered for this review question, as medical termination with mifepristone was made available in the UK in 1991.

Two cohort studies compared doxycycline to no antibiotic treatment in women undergoing medical termination of pregnancy (Fjerstad 2009; Frye 2015).

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusions are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 2: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Fjerstad 2009 Retrospective cohort study USA	n=227,823 whole study n=115,561 cohort of interest for review Women undergoing medical termination	Period 1: Vaginal misoprostol and standard antiseptic measures up to 63 days of gestation Period 4: Buccal misoprostol and doxycycline 100mg twice a day for 7-days up to 63 days of gestation	• Severe infection within 2 weeks of termination	Different routes of misoprostol administered in the 2 groups of cohorts
Frye 2015 Prospective cohort study USA	n=581 Women presenting for medical termination in the study clinics who could read English or Spanish	Doxycycline 7-day course (dose not specified) No antibiotic prophylaxis	• Nausea • Vomiting • Diarrhoea	Adherence reported in the doxycycline arm only, thus not analysed as no comparison group available

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Comparison 1. Antibiotic prophylaxis with doxycycline versus no antibiotic prophylaxis

Critical outcomes

Severe infection within 1 month

Non-RCT evidence showed a lower clinically important rate of severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or as a cause of death) within 1 month of termination in the doxycycline antibiotic prophylaxis group compared to the no antibiotic prophylaxis group (1 comparative observational study, n=115,561; RR=0.07 [95% CI 0.02, 0.24]; very low quality).

Post-abortal pelvic inflammatory disease within 1 month

No evidence was identified to inform this outcome.

Adherence to antibiotics

No evidence was identified to inform this outcome.

Important outcomes

Gastro-intestinal side effects

Non-RCT evidence did not detect a clinically important difference in the rates of overall nausea (RR=1.17 [95% CI 0.97, 1.40]), nausea lasting more than one day (RR=1.32 [95% CI 0.97, 1.79]), overall diarrhoea (RR=0.80 [0.57, 1.12]), severe diarrhoea (RR=0.65 [0.16-2.71]); or diarrhoea lasting more than 1 day (RR=1.04 [95% CI 0.56, 1.90]) between the doxycycline antibiotic prophylaxis group and the no antibiotic prophylaxis group (1 comparative observational study, n=581; very low quality); however, there was uncertainty around the estimates.

Non-RCT evidence showed higher clinically important rates of severe nausea (RR=2.18 [95% CI 1.14, 4.16]), overall vomiting (RR=1.36 [95% CI 1.00, 1.86])*, severe vomiting (RR=2.72 [95% CI 1.22, 6.09]), and vomiting lasting more than 1 day (RR=3.13 [95% CI 1.43, 6.89]) in the doxycycline antibiotic prophylaxis group compared to the no antibiotic prophylaxis group (1 comparative observational study, n=581; very low quality).

*Lower confidence interval calculated to 3 decimal places and result was >1.

Patient satisfaction

No evidence was identified to inform this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that although severe infection is rare in women undergoing medical termination of pregnancy, that this was considered the most critical outcome for decision making given its seriousness and implications for the woman. Post-termination pelvic inflammatory disease was also considered a critical outcome for decision making, because of potential complications arising if the condition isn't treated with antibiotics quickly. Given that the success of antibiotic prophylaxis is dependent on adherence, adherence was considered a critical outcome.

Gastro-intestinal side-effects and patient satisfaction were considered important outcomes for decision making as antibiotics are commonly associated with gastro-intestinal side-effects that may affect compliance.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using the GRADE methodology. All of the studies in this review were of low quality to begin with because of the comparative observational study design. The quality of evidence was subsequently downgraded to very low quality most often because the analyses were not adjusted for confounders, either in the baseline characteristics of the study or the route of administration of misoprostol between the 2 arms of the study. Additionally, there was uncertainty around the risk estimate for gastro-intestinal adverse-effects ranging from serious to very serious, most often the very serious uncertainty was due to the low adverse event rate.

No evidence was identified on the critical outcomes of post-abortal pelvic inflammatory disease and adherence, or the important outcome of patient satisfaction.

Benefits and harms

The evidence showed that there were lower rates of severe infection with antibiotic prophylaxis compared to no antibiotic prophylaxis. However, because of the very low quality of the evidence, uncertainty regarding risk from non-sexually transmitted infections following medical termination of pregnancy as opposed to surgical termination of pregnancy (such as introduction of new pathogens, increase in cervicovaginal microbiota and new pathogens and/or cervicovaginal microbiota ascending to the upper genital tract), and concerns regarding over-prescribing of antibiotics and the development of antibiotic resistance (antibiotic stewardship) the

committee did not think routine antibiotic prophylaxis was appropriate. The committee raised concerns regarding the different routes of administration of misoprostol used in the study, which could confound the results, particularly regarding risk from non-sexually transmitted infections. Furthermore, the committee discussed the issue of comparing 2 cohorts of women at different time points and that the difference in the rates of severe infection could also be due to a lower incidence of severe infection in that specific time point in addition to the antibiotic prophylaxis. The evidence showed higher rates of severe nausea, severe vomiting, and vomiting lasting more than 1 day with antibiotic prophylaxis compared with no antibiotic prophylaxis, however the committee recognised the risk of bias around this estimate given the unblended study design.

The committee highlighted that evidence included in the review was limited to early medical termination. Women who present later for medical termination of pregnancy may be at higher risk from non-sexually transmitted infections as repeated doses of misoprostol are often required, which increases the opportunity for new pathogens to be introduced and for new pathogens and existing cervicovaginal microbiota to ascend to the upper genital tract. Further, younger, deprived women may be more likely to present later and also be at greater risk for sexually transmitted infections.

Increasingly in the UK, women are choosing early medical termination of pregnancy where sexually transmitted infection test results are unavailable on the day of the termination, thus to err on the side of caution the committee agreed based on their clinical knowledge and experience, that antibiotic prophylaxis should be given for a subgroup of women who are considered high risk for sexually transmitted infections. No evidence was identified on the use of different prophylactic antibiotic regimens in women undergoing medical termination of pregnancy. The committee discussed that the evidence identified in the review only included doxycycline and they were aware that 100mg doxycycline twice a day for 7 days is considered the optimal regimen for treating chlamydia, which is the most common sexually transmitted infection, based on recommendations from the British Association of Sexual Health and HIV (BASHH; 2018) and would be sufficient to treat. However, the committee agreed, based on their knowledge, that the recommendations shouldn't be restricted to doxycycline as azithromycin is also recommended by BASHH and the same spectrum of activity and equivalent efficacy for treating chlamydia as doxycycline. The committee also highlighted that metronidazole is also used in clinical practice as antibiotic prophylaxis but is not widely used as it is poorly tolerated due to gastrointestinal side-effects. Further, it was unclear from the review of antibiotic prophylaxis for surgical termination whether there was any difference in outcomes for women who were given doxycycline and metronidazole compared to doxycycline alone as antibiotic prophylaxis. Therefore, the committee recommended that metronidazole is not routinely given in combination with another broad-spectrum antibiotic. Neither the doxycycline nor azithromycin regimens recommended are effective at treating gonorrhoea or mycoplasma genitalium; however, as these are less prevalent and more susceptible to antibiotic resistance development than chlamydia, the committee agreed that prophylactic treatment for these infections should not be given.

Despite the limited research, the committee decided to prioritise other areas addressed by the guideline for future research and therefore made no research recommendations regarding antibiotic prophylaxis for women who are having medical termination of pregnancy.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations made. Any net effect was likely to be cost saving due to fewer women receiving antibiotic prophylaxis for medical termination of pregnancy.

Other considerations

Risk factors for sexually transmitted infections were not reviewed for this research question. The committee were aware of guidance from BASHH and the British HIV Association (BHIVA) that identified people who may be at elevated risk for sexually transmitted infection (Clutterbuck 2012). They agreed that these were women who may benefit from antibiotic prophylaxis following medical termination of pregnancy and used examples from this in the recommendations. The committee agreed that the use of antibiotic prophylaxis does not replace the need for screening for sexually transmitted infections to facilitate treatment of sexual partners and minimise reinfection and further transmission. However, the committee could not make recommendations about screening for sexually transmitted infections as this was not considered as part of this review question.

Antibiotic prophylaxis for surgical termination of pregnancy

Review question

What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Introduction

The aim of this review is to determine the optimal antibiotic prophylaxis regimen for women who are having a surgical termination of pregnancy.

Summary of the protocol

See Table 1 for a summary of the population, intervention, comparison and outcome (PICO) characteristics of this review.

Table 3: Summary of the protocol (PICO table)

Population	Women who are having surgical termination of pregnancy (using vacuum aspiration or dilatation and evacuation, but NOT sharp curettage)
Intervention	Any oral or rectal antibiotic prophylaxis (any dose)
Comparison	• Antibiotic prophylaxis A (single agent or combination) versus antibiotic prophylaxis B (single agent or combination) • Antibiotic prophylaxis A (oral doxycycline or metronidazole only) – duration A versus antibiotic prophylaxis A –duration B (doxycycline or metronidazole only)

Outcome	**Critical outcomes:**
	• Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination
	• Post-abortal pelvic inflammatory disease (including endometritis, upper genital tract infection) within 1 month of termination
	• Adherence to antibiotics
	
	Important outcomes:
	• Gastro-intestinal side effects:
	  ○ Nausea
	  ○ Vomiting
	  ○ Diarrhoea
	• Patient satisfaction

For further details see the full review protocol in appendix A.

Clinical evidence

Included studies

Only studies conducted from 1990 onwards were considered for this review question, as prior to this timeframe surgical techniques used in termination of pregnancy were different, different antibiotics were used, and routine screening for sexually transmitted infections was not carried out.

One RCT compared the combination of metronidazole and doxycycline to doxycycline alone in women presenting for surgical termination of pregnancy with elevated vaginal pH and amines detected in their vaginal discharge (Miller 2004).

One RCT compared a 7-day course of doxycycline to a 3-day course of doxycycline in women presenting for surgical termination of pregnancy (Lichtenberg 2003).

The included studies are summarised in Table 2.

See the literature search strategy in appendix B and study selection flow chart in appendix C.

Excluded studies

Studies not included in this review with reasons for their exclusion are provided in appendix K.

Summary of clinical studies included in the evidence review

A summary of the studies that were included in this review are presented in Table 2.

Table 4: Summary of included studies

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
Lichtenberg 2003 RCT USA	n=800 Women no more than 13^{+0} weeks pregnant presenting for surgical termination of pregnancy	Postoperative doxycycline 100mg twice a day for 3 days Postoperative doxycycline 100mg twice a day for 7 days	• Post-abortal pelvic inflammatory disease at 2-week follow-up • Adherence to antibiotics • Vomiting • Diarrhoea	33.7% loss to follow-up
Miller 2004 RCT USA	n=393 Women presenting for surgical termination of pregnancy with elevated vaginal pH and amines detected in their vaginal discharge	Metronidazole 1g orally prior to procedure, followed by 400mg twice a day for 7-days + postoperative doxycycline 100mg twice a day for 7-days Postoperative doxycycline	• Post-abortal complication score of ≥3 at 7-10 days* • Post-abortal complication score of ≥5 at 7-10 days* *Women returning to clinic for a routine or non-routine visit	35.6% loss to follow-up Post-abortal complication rates reported for all women and women with a positive gram stain for bacterial vaginosis

Study and setting	Population	Intervention/ comparison	Outcomes	Comments
	Women included underwent a first or second trimester procedure n=236 of the 393 women randomised had a positive gram stain for bacterial vaginosis	100mg twice a day for 7-days	because of suspected infection were asked the same standardised questions at 7-10 days follow-up and were reported in the same cohort as women followed-up at 7-10 days	

RCT: randomised controlled trial

See the full evidence tables in appendix D. No meta-analysis was conducted (and so there are no forest plots in appendix E).

Quality assessment of clinical studies included in the evidence review

See the clinical evidence profiles in appendix F.

Economic evidence

Included studies

A systematic review of the economic literature was conducted but no economic studies were identified which were applicable to this review question.

A single economic search was undertaken for all topics included in the scope of this guideline. Please see supplementary material 2 for details.

Excluded studies

No full-text copies of articles were requested for this review and so there is no excluded studies list.

Economic model

No economic modelling was undertaken for this review because the committee agreed that other topics were higher priorities for economic evaluation.

Evidence statements

Comparison 1. Antibiotic prophylaxis with metronidazole and doxycycline versus doxycycline

Critical outcomes

Severe infection within 1 month

No evidence was identified to inform this outcome.

Post-abortal pelvic inflammatory disease within 1 month

RCT evidence did not detect a clinically important difference in the rate of women with elevated vaginal pH and amines in vaginal discharge who had a total post-abortion complication score* ≥3 (RR=1.21 [95% CI 0.72, 2.03]) or ≥5 (RR= 0.8 [95% CI 0.32, 1.97]) between the metronidazole and doxycycline antibiotic prophylaxis group and the doxycycline alone antibiotic prophylaxis group (1 RCT, n=393; very low quality); however, there was uncertainty around the estimates.

RCT evidence did not detect a clinically important difference in the rate of women with a positive gram stain for bacterial vaginosis who had a total post-abortion complication score[1] ≥3 (RR=1.75 [95% CI 0.93, 3.31]; low quality) or ≥5 (RR= 1.29 [95% CI 0.36, 4.7]; very low quality) between the metronidazole and doxycycline antibiotic prophylaxis group and the doxycycline alone antibiotic prophylaxis group (1 RCT, n=236); however, there was uncertainty around the estimates.

Adherence to antibiotics

No evidence was identified to inform this outcome.

Important outcomes

Gastro-intestinal side effects

No evidence was identified to inform this outcome.

Patient satisfaction

No evidence was identified to inform this outcome.

Comparison 2. Antibiotic prophylaxis with doxycycline 3-days versus doxycycline 7-days

Critical outcomes

Severe infection within 1 month

No evidence was identified to inform this outcome.

Post-abortal pelvic inflammatory disease within 1 month

RCT evidence did not detect a clinically important difference in the rate of post-abortal pelvic inflammatory disease within 1 month of termination between the 3 day doxycycline antibiotic prophylaxis group and the 7 day doxycycline antibiotic prophylaxis group (1 RCT, n=800; RR= 0.33 [95% CI 0.01, 8.16]; very low quality); however, there was uncertainty around the estimate.

Adherence to antibiotics

RCT evidence showed there was no clinically important difference between the rate of adherence to antibiotics in the 3 day doxycycline antibiotic prophylaxis group and

[1] The score ranged from 0 to 10 and consisted of the sum of the following, weighted as one point each: 1. vaginal discharge or odour >7 days after abortion; 2. purulent cervical discharge on examination >7 days after abortion; 3. tenderness of the uterus or adnexa on pelvic examination; 4. abnormally heavy bleeding or >3 days or continued bleeding >7 days after abortion; 5. palpable adnexal masses on pelvic examination; 6. self-report of pain, excessive tiredness or feeling unwell 7 days after abortion; and weighted as two points each: 1. temperature greater than 38 degrees Celsius reported for 24 hours or measured on examination; 2. antibiotics given for pelvic infection at a follow up visit

the 7 day doxycycline antibiotic prophylaxis group (1 RCT, n=800; RR= 1.06 [95% CI 0.96, 1.17]; moderate quality).

Important outcomes

Gastro-intestinal side effects

RCT evidence did not detect a clinically important difference in the rates of vomiting (RR= 3 [95% CI 0.12, 73.42]) or diarrhoea (RR= 3 [95% CI 0.12, 73.42 between the 3 day doxycycline antibiotic prophylaxis group and the 7 day doxycycline antibiotic prophylaxis group (1 RCT, n=800; very low quality); however, there was uncertainty around the estimates. No evidence was found for nausea.

Patient satisfaction

No evidence was identified to inform this outcome.

The committee's discussion of the evidence

Interpreting the evidence

The outcomes that matter most

The committee agreed that although severe infection is rare in women undergoing surgical termination of pregnancy that this was considered the most critical outcome for decision making given its seriousness and implications for the woman. Post-termination pelvic inflammatory disease was also considered a critical outcome for decision making, because of potential complications arising if the condition isn't treated with antibiotics quickly. Given that the success of antibiotic prophylaxis is dependent on adherence, adherence was considered a critical outcome.

Gastro-intestinal side-effects and patient satisfaction were considered important outcomes for decision making as antibiotics are commonly associated with gastro-intestinal side-effects that may affect compliance.

The quality of the evidence

The evidence in the pairwise comparisons was assessed using GRADE methodology. The quality of evidence in this review ranged from moderate to very low quality and was most often downgraded because of the uncertainty around the risk estimate due to the low adverse event rate in termination of pregnancy.

The quality of evidence was further downgraded because of a high rate of attrition. The committee discussed that this is a common problem in termination of pregnancy studies as the intervention is acute in a cohort of a generally healthy population requiring minimal follow-up.

No evidence was identified on the critical outcomes severe infection and adherence to antibiotics or the important outcome of patient satisfaction.

Benefits and harms

Routine antibiotic prophylaxis in women undergoing surgical termination of pregnancy is established clinical practice in the UK and is supported by a Cochrane review (Low 2012), which showed perioperative antibiotics for surgical termination of pregnancy reduced post-abortal upper genital tract infection by an average of 41% compared with placebo. Although the authors of this review concluded that

heterogeneity between studies may suggest the effect might not apply to all settings, populations or interventions, the majority of included trials did not apply universal antibiotic prophylaxis and excluded women screening positive for existing infections. In clinical practice, antibiotic prophylaxis would be used universally, as screening results are often unavailable on the day of the termination of pregnancy. Therefore, results from studies that did use universal antibiotic prophylaxis, or where this was unclear, are likely to be of greater relevance than studies that did not use universal prophylaxis, which showed the weakest effect of prophylaxis. Therefore, the committee decided not prioritise the comparison of antibiotic prophylaxis compared to no antibiotic prophylaxis for this evidence review. Nonetheless, the committee agreed that a recommendation to explicitly offer routine antibiotic prophylaxis for women undergoing surgical termination of pregnancy should be made to avoid the misunderstanding that an absence of a strong recommendation for a specific regimen equates to not recommending routine antibiotic prophylaxis in this population of women.

The evidence was unclear whether or not there were clinically important differences in the rates of post-abortal pelvic inflammatory disease, or gastro-intestinal side effects of vomiting and diarrhoea with a 3-day course of doxycycline compared to a 7-day course of doxycycline as antibiotic prophylaxis. However, the evidence was mainly of very low quality and the committee agreed that 7 days of doxycycline should be considered as it would be sufficient to treat sexually transmitted infections, if present, and most pathobionts that are commonly found in the urogenital tract that can cause problems if they ascend to the upper genital tract or the bacterial load increases. Further, there was expert knowledge that there is no evidence of increased antibiotic resistance with 7 days, compared with 3 days, of treatment. This is also consistent with recommendations from the British Association for Sexual Health and HIV (2018) for treating chlamydia. There was no evidence for azithromycin but the committee agreed it should be considered as it has the same spectrum of activity as doxycycline and equivalent efficacy for treating chlamydia. The committee also noted that BNF indications for azithromycin and doxycycline include insertion of intrauterine devices and treatment of pelvic inflammatory disease and severe infection. However, there was no evidence to support a single dose of azithromycin, which has been used routinely in practice as the single dose improves adherence and lessens side effects. The committee agreed that further research on the optimal dose of antibiotic prophylaxis, specifically whether a single dose pre-procedure is as effective as full treatment doses, would be beneficial to inform future practice, so decided to make a research recommendation (see Appendix L). A single dose of doxycycline was also included in the research recommendation for when azithromycin is contraindicated.

The evidence was unclear whether or not there were clinically important differences in the rates of post-abortal pelvic inflammatory disease in women with elevated vaginal pH and amines in vaginal discharge or a positive gram stain for bacterial vaginosis who were given doxycycline and metronidazole compared to doxycycline alone as antibiotic prophylaxis. Although there was no evidence on the gastro-intestinal side effects of the 2 regimens, the committee discussed that in clinical practice metronidazole is poorly tolerated with significant side effects. In light of the evidence and clinical expertise of the committee, the committee agreed that the combination of metronidazole with another broad spectrum antibiotic, such as doxycycline as routine antibiotic prophylaxis should be avoided. However, the committee agreed that metronidazole is effective for a broader range of infections than doxycycline and azithromycin, due to its demonstrated anti-anaerobe properties, so there may be situations where metronidazole is clinically indicated.

Cost effectiveness and resource use

A systematic review of the economic literature was conducted but no relevant studies were identified which were applicable to this review question.

The committee considered that there was unlikely to be a significant resource impact from the recommendations made. The use of antibiotic prophylaxis with doxycycline and azithromycin regimens is established practice in women having a surgical termination of pregnancy. There may be some cost savings from a reduction in the use of combinations of prophylactic antibiotic regimens.

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Appendices

Appendix A – Review protocols

Review protocol for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?
Review question in guideline	What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?
Type of review question	Intervention
Objective of the review	To determine the optimal antibiotic prophylaxis regimen (if any) for women who are having a medical termination of pregnancy.
Eligibility criteria – population	Women who are having medical termination of pregnancy. Exclusions: - Studies with >10% of an indirect population
Eligibility criteria – intervention(s)	Antibiotic prophylaxis (any dose) using: • Oral azithromycin • Oral doxycycline • Oral or rectal metronidazole
Eligibility criteria – comparator(s)	Comparisons: 1. Antibiotic prophylaxis (single agent or combination) versus placebo/ no treatment 2. Antibiotic prophylaxis A (single agent or combination) versus antibiotic prophylaxis B (single agent or combination)
Outcomes and prioritisation	**Critical outcomes:** • Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination • Post-abortal pelvic inflammatory disease (including endometritis, upper genital tract infection) within 1 month of termination • Adherence to antibiotics **Important outcomes:** • Gastro-intestinal side effects during the course of antibiotic treatment: ○ Nausea ○ Vomiting ○ Diarrhoea • Patient satisfaction
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs - If insufficient RCTs: comparative prospective cohort studies n≥100 each arm

Field (based on PRISMA-P	Content
	- If insufficient comparative prospective cohort studies: comparative retrospective cohort studies n≥100 each arm
Other inclusion exclusion criteria	Inclusion: - English-language - Studies conducted from 1991 (see below)
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions: - Complex pre-existing medical conditions - No complex pre-existing medical conditions Gestational age: - < 10 weeks - 10^{+0} to 13^{+6} weeks - >14 weeks
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Dates: from 1991 Studies conducted from 1991 onwards will be considered for this review question, as medical termination with mifepristone was made available in the UK in 1991.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual Appraisal of methodological quality:

Field (based on PRISMA-P	Content
	The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs Newcastle-Ottawa scale for non-randomised studies The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: For severe infection, statistical significance will be used as an MID. For all other outcomes, default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Name of sponsor	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NHS: National Health Service; NICE: National Institute for Health and Care

Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Review protocol for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Field (based on PRISMA-P	Content
Review question in SCOPE	What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?
Review question in guideline	What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?
Type of review question	Intervention
Objective of the review	To determine the optimal antibiotic prophylaxis regimen for women who are having a surgical termination of pregnancy.
Eligibility criteria – population	Women who are having surgical termination of pregnancy (using vacuum aspiration or dilatation and evacuation, but NOT sharp curettage) Exclusions: - Studies with >10% of an indirect population - Surgical termination of pregnancy using sharp curettage
Eligibility criteria – intervention(s)	Any oral or rectal antibiotic prophylaxis (any dose)
Eligibility criteria – comparator(s)	1. Antibiotic prophylaxis A (single agent or combination) versus antibiotic prophylaxis B (single agent or combination) 2. Antibiotic prophylaxis A (oral doxycycline or metronidazole only) – duration A versus antibiotic prophylaxis A –duration B (doxycycline or metronidazole only)
Outcomes and prioritisation	**Critical outcomes:** • Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination • Post-abortal pelvic inflammatory disease (including endometritis, upper genital tract infection) within 1 month of termination • Adherence to antibiotics **Important outcomes:** • Gastro-intestinal side effects: o Nausea o Vomiting o Diarrhoea • Patient acceptability
Eligibility criteria – study design	- Systematic reviews of RCTs - RCTs
Other inclusion exclusion criteria	Inclusion: - English-language - Studies conducted from 1990 (see below)
Proposed sensitivity/sub-group analysis, or meta-regression	Stratified analyses based on the following sub-groups of women, where possible: Medical conditions:

Field (based on PRISMA-P	Content
	- Complex pre-existing medical conditions - No complex pre-existing medical conditions Gestational age: - < 13^{+6} weeks - >14 weeks Antibiotic class: - Nitroimidazole - Tetracycline - Beta-lactam - Macrolide
Selection process – duplicate screening/selection/analysis	Dual weeding will not be performed for this question Sifting, data extraction, appraisal of methodological quality and GRADE assessment will be performed by the systematic reviewer. Quality control will be performed by the senior systematic reviewer. Dual data extraction will not be performed for this question.
Data management (software)	Pairwise meta-analyses will be performed using Cochrane Review Manager (RevMan5). 'GRADEpro' will be used to assess the quality of evidence for each outcome. NGA STAR software will be used for study sifting, data extraction, recording quality assessment using checklists and generating bibliographies/citations,
Information sources – databases and dates	Sources to be searched: Medline, Medline In-Process, CCTR, CDSR, DARE, HTA, Embase Limits (e.g. date, study design): Apply standard animal/non-English language exclusion Limit to RCTs and systematic reviews Dates: from 1990 Studies conducted from 1990 onwards will be considered for this review question, as prior to this timeframe surgical techniques used in termination of pregnancy were different, different antibiotics were used, and routine screening for sexually transmitted infections was not carried out.
Identify if an update	Not an update
Author contacts	For details please see the guideline in development web site.
Highlight if amendment to previous protocol	For details please see section 4.5 of Developing NICE guidelines: the manual
Search strategy – for one database	For details please see appendix B
Data collection process – forms/duplicate	A standardised evidence table format will be used, and published as appendix D (clinical evidence tables) or H (economic evidence tables).
Data items – define all variables to be collected	For details please see evidence tables in appendix D (clinical evidence tables) or H (economic evidence tables).
Methods for assessing bias at outcome/study level	Appraisal of methodological quality: The methodological quality of each study will be assessed using an appropriate checklist: • RoBIS for systematic reviews • Cochrane risk of bias tool for RCTs

Field (based on PRISMA-P	Content
	The quality of the evidence for an outcome (i.e. across studies) will be assessed using GRADE. Standard study checklists will be used to critically appraise individual studies. For details please see section 6.2 of Developing NICE guidelines: the manual The risk of bias across all available evidence will be evaluated for each outcome using an adaptation of the 'Grading of Recommendations Assessment, Development and Evaluation (GRADE) toolbox' developed by the international GRADE working group http://www.gradeworkinggroup.org/
Criteria for quantitative synthesis (where suitable)	For details please see section 6.4 of Developing NICE guidelines: the manual
Methods for analysis – combining studies and exploring (in)consistency	Synthesis of data: Pairwise meta-analysis will be conducted where appropriate for all other outcomes. When meta-analysing continuous data, change scores will be pooled in preference to final scores. For details regarding inconsistency, please see the methods chapter Minimally important differences: For severe infection, statistical significance will be used as an MID. For all other outcomes, default values will be used of: 0.8 and 1.25 for dichotomous outcomes; 0.5 times SD for continuous outcomes.
Meta-bias assessment – publication bias, selective reporting bias	For details please see section 6.2 of Developing NICE guidelines: the manual. If sufficient relevant RCT evidence is available, publication bias will be explored using RevMan software to examine funnel plots.
Assessment of confidence in cumulative evidence	For details please see sections 6.4 and 9.1 of Developing NICE guidelines: the manual
Rationale/context – Current management	For details please see the introduction to the evidence review.
Describe contributions of authors and guarantor	A multidisciplinary committee developed the guideline. The committee was convened by The National Guideline Alliance and chaired by Profession Iain Cameron in line with section 3 of Developing NICE guidelines: the manual. Staff from The National Guideline Alliance will undertake systematic literature searches, appraise the evidence, conduct meta-analysis and cost-effectiveness analysis where appropriate, and draft the guideline in collaboration with the committee. For details please see the methods chapter.
Sources of funding/support	The National Guideline Alliance is funded by NICE and hosted by the Royal College of Obstetricians and Gynaecologists
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Roles of sponsor	NICE funds The National Guideline Alliance to develop guidelines for those working in the NHS, public health, and social care in England
PROSPERO registration number	Not registered

GRADE: Grading of Recommendations Assessment, Development and Evaluation; MID: minimally important difference; NHS: National Health Service; NICE: National Institute for Health and Care Excellence; NGA: National Guideline Alliance; RCT: randomised controlled trial; RoBIS: risk of bias in systematic reviews; SD: standard deviation

Appendix B – Literature search strategies

Literature search strategy for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

The search for this topic was last run on 12th February 2018. It was decided not to undertake a re-run for this topic in November 2018 as this is not a fast moving evidence base and there were unlikely to be any new studies published which would affect the recommendations.

Database: Medline & Embase (Multifile)
Last searched on **Embase Classic+Embase** 1947 to 2018 February 09, **Ovid MEDLINE(R) Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)** 1946 to Present
Date of last search: 12th February 2018

#	Searches
1	exp abortion/ use emczd
2	exp pregnancy termination/ use emczd
3	exp Abortion, Induced/ use ppez
4	Abortion Applicants/ use ppez
5	exp Abortion, Spontaneous/ use ppez
6	exp Abortion, Criminal/ use ppez
7	Aborted fetus/ use ppez
8	fetus death/ use emczd
9	abortion.mp.
10	(abort$ or postabort$ or preabort$).tw.
11	((f?etal$ or f?etus$ or gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) and terminat$).tw.
12	((f?etal$ or f?etus$) adj loss$).tw.
13	((gestat$ or midtrimester$ or pregnan$ or prenatal$ or pre natal$ or trimester$) adj3 loss$).tw.
14	(((elective$ or threaten$ or voluntar$) adj3 interrupt$) and pregnan$).tw.
15	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14
16	Azithromycin/ use ppez
17	azithromycin/ use emczd
18	(azithrom$ or Zithromax$ or Z-Max$).mp.
19	Doxycycline/ use ppez
20	doxycycline/ use emczd
21	(doxycyclin$ or Doxychel$ or Doryx$ or Acticlat$ or Monodox$ or Oracea$ or Periostat$ or Vibra-Tab$ or Vibramycin$).mp.
22	Metronidazole/ use ppez
23	metronidazole/ use emczd
24	(metronidazol$ or Flagyl$).mp.
25	16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24
26	exp Anti-Bacterial Agents/ use ppez
27	Antibiotic Prophylaxis/ use ppez
28	exp antibiotic agent/ use emczd
29	antibiotic prophylaxis/ use emczd

#	Searches
30	(antibiotic$ or anti-biotic$ or antibacterial$ or anti-bacterial$ or antimicrobial$ or anti-microbial$).mp.
31	exp Tetracyclines/ use ppez
32	exp tetracycline derivative/ use emczd
33	exp Lactams/ use ppez
34	exp lactam/ use emczd
35	exp Macrolides/ use ppez
36	exp macrolide/ use emczd
37	exp Nitroimidazoles/ use ppez
38	exp nitroimidazole derivative/ use emczd
39	exp Quinolones/ use ppez
40	exp quinolone derivative/ use emczd
41	(tetracyclin$ or lactam$ or macrolid$ or nitroimidazol$ or quinolon$ or fluroquinolon$ or tinidazol$).mp.
42	26 or 27 or 28 or 29 or 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41
43	15 and 42
44	limit 43 to english language [general exclusions filter applied]
45	remove duplicates from 44

Database: Cochrane Library via Wiley Online
Date of last search: 12th February 2018

#	Searches
#1	MeSH descriptor: [Abortion, Induced] explode all trees
#2	MeSH descriptor: [Abortion Applicants] explode all trees
#3	MeSH descriptor: [Abortion, Spontaneous] explode all trees
#4	MeSH descriptor: [Abortion, Criminal] explode all trees
#5	MeSH descriptor: [Aborted Fetus] explode all trees
#6	"abortion":ti,ab,kw (Word variations have been searched)
#7	(abort* or postabort* or preabort*):ti,ab,kw (Word variations have been searched)
#8	((fetal* or fetus* or foetal* or foetus* or gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) and terminat*):ti,ab,kw (Word variations have been searched)
#9	((fetal* or fetus* or foetal* or foetus*) next loss*):ti,ab,kw (Word variations have been searched)
#10	((gestat* or midtrimester* or pregnan* or prenatal* or pre natal* or trimester*) near/3 loss*):ti,ab,kw (Word variations have been searched)
#11	(((elective* or threaten* or voluntar*) near/3 interrupt*) and pregnan*):ti,ab,kw (Word variations have been searched)
#12	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
#13	MeSH descriptor: [Anti-Bacterial Agents] explode all trees
#14	MeSH descriptor: [Antibiotic Prophylaxis] explode all trees
#15	(antibiotic* or anti-biotic* or antibacterial* or anti-bacterial* or antimicrobial* or anti-microbial*):ti,ab,kw (Word variations have been searched)
#16	MeSH descriptor: [Tetracyclines] explode all trees
#17	MeSH descriptor: [Lactams] explode all trees
#18	MeSH descriptor: [Macrolides] explode all trees
#19	MeSH descriptor: [Macrolides] explode all trees

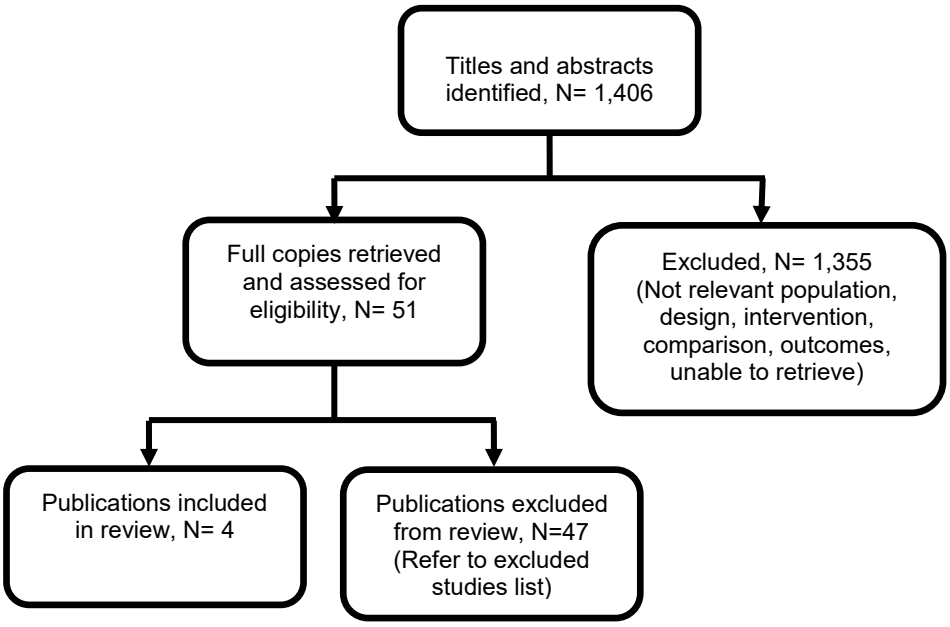
#	Searches
#20	MeSH descriptor: [Nitroimidazoles] explode all trees
#21	MeSH descriptor: [Quinolones] explode all trees
#22	(tetracyclin* or lactam* or macrolid* or nitroimidazol* or quinolon* or fluroquinolon* or tinidazol*):ti,ab,kw (Word variations have been searched)
#23	#13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22
#24	#12 and #23
#25	MeSH descriptor: [Azithromycin] explode all trees
#26	MeSH descriptor: [Doxycycline] explode all trees
#27	MeSH descriptor: [Metronidazole] explode all trees
#28	(azithrom* or Zithromax* or Z-Max* or doxycyclin* or Doxychel* or Doryx* or Acticlat* or Monodox* or Oracea* or Periostat* or Vibra-Tab* or Vibramycin* or metronidazol* or Flagyl*):ti,ab,kw (Word variations have been searched)
#29	#25 or #26 or #27 or #28
#30	#12 and #29
#31	#24 or #30

Appendix C – Clinical evidence study selection

Clinical evidence study selection for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Clinical evidence study selection for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Figure 1: Study selection flow chart



Appendix D – Clinical evidence tables

Clinical evidence tables for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Fjerstad, M., Trussell, J., Sivin, I., Lichtenberg, E. S., Cullins, V., Rates of serious infection after changes in regimens for medical abortion, New England Journal of Medicine, 361, 145-151, 2009 **Ref Id** 773480 **Country/ies where the study was carried out** USA **Study type** Retrospective cohort study (retrospective analysis of data routinely collected for quality control) **Aim of the study**	**Sample size** n=243,692 women underwent medical abortion n= 227,823 women were included in the analysis (n=15,869 excluded as they did not meet the eligibility criteria) **Characteristics** No characteristics of the women included in the study were documented **Inclusion criteria** Women receiving medical termination **Exclusion criteria** Not reported	**Period 1 (January 1, 2005, through March 31, 200 6):** Vaginal misoprostol and standard antiseptic measures were used for the termination of fetuses through 63 days of gestation **Period 2 (April 1, 2006, through June 30, 2007):** Buccal misoprostol (800micrograms; mcg) was used through 56 days of gestation (or, much less commonly, oral misoprostol was used through 49 days of gestation); some Planned Parenthood clinics used the infection-reduction measure of universal	**Outcome: Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination** Period 1: 67/72,195 (rate per 1000 = 0.93 [0.72–1.18]) Period 4: 3/43,366 (rate per 1000 = 0.07 [0.01–0.20])	**Limitations** **Quality of Study:** Risk of bias assessed using Newcastle-Ottawa tool for cohort studies Selection 1) Representativeness of the exposed cohort a) Truly representative of the population of women undergoing medical termination (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star) 3) Ascertainment of exposure a) Secure record (data drawn from Planned Parenthood Health Centres) (one star) 4) Demonstration that outcome of interest was not present at start of study

Study details	Participants	Interventions	Outcomes and Results	Comments
To compare the rates of serious infection before and after changes to an infection control protocol **Study dates** 2005 to mid-2008 **Source of funding** None reported		screening for STI and treatment when screening was positive, whereas others routinely provided antibiotics consisting nearly uniformly of 100mg of oral doxycycline twice a day for 7 days. **Period 3 (July 1, 2007, through December 31, 2007):** Buccal misoprostol (800mcg) was used through 56 days of gestation and all health centres routinely provided the doxycycline regimen. **Period 4 (January 1, 2008, through June 30, 2008):** Buccal misoprostol (800mcg) was used through 63 days of gestation and all health centres routinely provided the doxycycline regimen.		b) Yes, women would not be undergoing medical termination of pregnancy if displaying signs of severe infection (one star) Comparability 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders c) Study not controlled for confounders and baseline characteristics of the cohorts not reported in the paper. Additionally, misoprostol was administered vaginally in period 1 cohort and bucally in period 4 cohort. Outcome 1) Assessment of outcome b) Record linkage (one star) 2) Was follow-up long enough for outcomes to occur a) Yes, follow-up was done at 1-2 weeks, however some cases of late infection 3-4 weeks would not have been picked up. (one star) 3) Adequacy of follow-up cohorts d) No statement - retrospective design Overall quality Poor quality due to 0 stars in comparability domain **Other information**

Study details	Participants	Interventions	Outcomes and Results	Comments
		Follow-up: Visits routinely scheduled 1 to 2 weeks after ingestion of mifepristone. The importance of the follow-up visit was emphasized to women, and staff members made three attempts to reach women who had not returned for follow-up by the end of 2 weeks.		None
Full citation Frye, L. J., Chong, E., Winikoff, B., N. C. T. Trial Investigators, What happens when we routinely give doxycycline to medical abortion patients?, Contraception, 91, 19-24, 2015 **Ref Id** 773555 **Country/ies where the study was carried out** USA	**Sample size** n= 910 informed of study (n=451 doxycycline; n=459 no treatment) n= 581 analysed (n=278 doxycycline [165 did not enrol, 8 disqualified, 2 did not consent, 6 took unrelated antibiotics]; n=303 no treatment [138 did not enrol, 18 disqualified, 4 did not consent, 14 took unrelated antibiotics) **Characteristics**	**Doxycycline arm:** 7-day course (dose not specified but most likely to be 100mg twice daily in line with clinical practice) **No-doxycycline arm:** No details reported Women completed a survey in clinic 7-14 days after mifepristone to assess occurrence of side effects.	**Outcome: patient adherence (Only for doxycycline arm, therefore not analysed)** Any pills taken: 271/278 Missed any doses: 123/271 (missed >1: 81/123; missed 27/123) More than 1 pill remaining at follow-up: 98/265 Extension of regimen (>8 days): 22/236	**Limitations** **Quality of Study:** Risk of bias assessed using Newcastle-Ottawa tool for cohort studies Selection 1) Representativeness of the exposed cohort a) Truly representative of the population of women undergoing medical termination (one star) 2) Selection of the non-exposed cohort a) Drawn from the same community as the exposed cohort (one star)

Study details	Participants	Interventions	Outcomes and Results	Comments
Study type Prospective cohort study **Aim of the study** To compare the side effects experienced by women who were prescribed doxycycline following medical termination to those who were not and assesses the adherence to one prescribed regimen. **Study dates** October 2012 to December 2013 **Source of funding** Funding for this project was supplied by an anonymous donor without financial interests in the outcome of this study.	Age in years (SD in parentheses): doxycycline= 27.1 (6.3); no doxycycline= 27.1 (6.1) Gestational age in days (SD in parentheses): doxycycline= 47.9 (7.9); no doxycycline= 45.3 (9.6) p-value <0.001 Parity (SD in parentheses): doxycycline= 2.6 (2.1); no doxycycline= 2.6 (1.8) Had previous medical termination: doxycycline= 34.1%; no doxycycline= 29.6% Difficulty paying for termination: p-value <0.001 not hard at all: doxycycline= 37.3%; no doxycycline= 61.6% somewhat hard: doxycycline= 42.1%; no doxycycline= 25.1% very hard: doxycycline= 20.5%; no doxycycline= 13.3% Race: p-value <0.001		<u>Early termination of regimen (<7 days):</u> 81/236 <u>Perfect adherence (defined as self-report indicating no missed doses, 0 or 1 pill left at follow-up, and pills taken for 7 or 8 days):</u> 67/236 **Outcome: nausea** <u>Overall</u> doxycycline: 133/278; no doxycycline: 124/303 <u>Severe (no definition provided)</u> doxycycline: 26/278; no doxycycline: 13/303 <u>>1 day</u> doxycycline: 70/278; no doxycycline: 58/303 **Outcome: vomiting** <u>Overall</u> doxycycline: 70/278; no doxycycline: 56/303 <u>Severe (no definition provided)</u>	3) Ascertainment of exposure c) Written self-report 4) Demonstration that outcome of interest was not present at start of study a) Yes Comparability 1) Comparability of cohorts on the basis of the design or analysis controlled for confounders c) Baseline characteristics of the 2 cohorts were not matched, with statistical significant differences in mean gestational age, race, education, and difficulty paying for the termination. Additionally, no confounders were accounted for in the analyses. Outcome 1) Assessment of outcome b) Self-report 2) Was follow-up long enough for outcomes to occur a) Yes, gastro-intestinal side-effects are usually short-lived and captured during treatment, the 7-14 days window adequately captures this (one star) 3) Adequacy of follow-up cohorts

Study details	Participants	Interventions	Outcomes and Results	Comments
	White or Caucasian: doxycycline= 45.5%; no doxycycline= 29.4% Hispanic or Latina: doxycycline= 17.5%; no doxycycline= 31.4% Black or African American: doxycycline= 26.2%; no doxycycline= 18.1% Multiracial: 5.8%; no doxycycline= 8.7% Other: doxycycline= 5.1%; no doxycycline= 12.4% Education: p-value <0.001 Less than high school: doxycycline= 2.9%; no doxycycline= 13.5% High school graduate: doxycycline= 54.2%; no doxycycline= 47.6% College graduate: doxycycline= 38.8%; no doxycycline= 32.8% Advanced degree: doxycycline= 4%; no doxycycline= 6.1% **Inclusion criteria**		doxycycline: 20/278; no doxycycline: 8/303 <u>>1 day</u> doxycycline: 23/278; no doxycycline: 8/303 **Outcome: diarrhoea** <u>Overall</u> doxycycline: 47/278; no doxycycline: 64/303 <u>Severe (no definition provided)</u> doxycycline: 3/278; no doxycycline: 5/303 <u>>1 day</u> doxycycline: 19/278; no doxycycline: 20/303	b) subjects lost to follow up unlikely to introduce bias - small number lost 2.9% due to disqualification and a description for the reasons for disqualification provided Overall quality Poor quality due to 0 stars in comparability domain **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	Women presenting for a medical termination in the study clinics who could read English or Spanish **Exclusion criteria** Any woman who was currently taking antibiotics for reasons unrelated to her medical termination were excluded			

Mcg: micrograms; SPSS: Statistical Package for Social Scientists; STI: sexually transmitted infection

Clinical evidence tables for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Study details	Participants	Interventions	Outcomes and Results	Comments
Full citation Lichtenberg, E. S., Shott, S., A randomized clinical trial of prophylaxis for vacuum abortion: 3 versus 7 days of doxycycline, Obstetrics & GynecologyObstet Gynecol, 101, 726-31, 2003 **Ref Id** 773004	**Sample size** n= 800 randomised (n= 400 7-days doxycycline; n=400 3-days doxycycline) n= 530 analysed (n= 257 7-days doxycycline; n=273 3-days doxycycline) **Characteristics**	**Intervention, arm 1:** doxycycline 100mg twice daily, oral (postoperative, 7 days) **Control, arm 2:** doxycycline 100mg twice daily, oral (postoperative, 3 days)	**Outcome: post-abortal pelvic inflammatory disease** 7-days doxycycline= 1/400; 3-days doxycycline= 0/400 **Outcome: adherence to antibiotics** 7-doxycycline= 97.7% (n=251 returnees); 3-	**Limitations** **Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk (Randomised into 2 groups using a table of random numbers) Allocation concealment: Low risk (A study coordinator kept the randomisation code: she also formulated the masked antibiotic packets but did not perform the

Study details	Participants	Interventions	Outcomes and Results	Comments
Country/ies where the study was carried out USA **Study type** Randomised controlled trial **Aim of the study** To test whether reducing the duration of doxycycline oral prophylaxis from 7 days to 3 days would increase the incidence of post termination infection. **Study dates** November 1995 - May 1996 **Source of funding** Not reported	Age in years (SD in parentheses): 7-day course= 26.2 (6.4); 3-day course: 27.1 (6.7) Race: -White: 7-day course= 47.8%; 3-day course: 48.7% -Hispanic: 7-day course= 26.5%; 3-day course: 23% -Black: 7-day course= 18.7%; 3-day course: 21.6% -Other: 7-day course= 7%; 3-day course: 6.7% Gravidity (SD in parentheses): 7-day course= 3.1 (2); 3-day course: 3.2 (2.2) Parity (SD in parentheses): 7-day course= 0.9 (1); 3-day course: 0.1 (1.1) No of previous elective terminations (SD in parentheses): 7-day course= 26.2 (6.4); 3-day course: 27.1 (6.7) No of previous spontaneous abortions (SD in parentheses): 7-		days doxycycline= 97.4% (n=266 returnees) **Outcome: vomiting** 7-days doxycycline= 0/400; 3-days doxycycline= 1/400 **Outcome: diarrhoea** 7-days doxycycline= 0/400; 3-days doxycycline= 1/400	clinical service, data analysis, or interpretation of outcomes) Blinding of participants and personnel: Low risk (Postoperatively, the recovery room charge nurse dispensed antibiotic packets in identical opaque brown envelopes by individual allocation. Generic doxycycline and similar-appearing placebo tablets. Identical appearing packets contained either 14 doxycycline tablets or 6 doxycycline tablets and 8 placebos. Women receiving placebos were carefully instructed to begin these after finishing all doxycycline tablets and were not aware that some tablets were chemically inactive.) Blinding of outcome assessors: Low risk (Postoperatively, the recovery room charge nurse dispensed antibiotic packets in identical opaque brown envelopes by individual allocation. Generic doxycycline and similar-appearing placebo tablets. Identical appearing packets contained either 14 doxycycline tablets or 6 doxycycline tablets and 8 placebos. Women receiving placebos were carefully instructed to begin these after finishing all doxycycline tablets and were not aware that some tablets were chemically inactive.)

Study details	Participants	Interventions	Outcomes and Results	Comments
	day course= 26.2 (6.4); 3-day course: 27.1 (6.7) **Inclusion criteria** Women no more than 13^{+0} weeks pregnant Speak English Live within 50 mile radius **Exclusion criteria** Allergic to tetracyclines Breast-feeding On current antibiotic therapy Febrile (higher than 37.5 degrees Celsius orally), symptomatic for pelvic infection Unable to swallow pills Women whose care was being funded by a health maintenance organisation because these women were often instructed by the referring site to seek follow-up care with their primary physician.			Incomplete outcome data (attrition bias): high risk (33.7% of women randomised did not return for follow-up) Selective reporting: low risk Other bias: low risk (The baseline characteristics of the 2 treatment groups were similar) **Other information** None
Full citation Miller, L., Thomas, K., Hughes, J. P., Holmes, K. K., Stout, S.,	**Sample size** n= 393 randomised (n=196 metronidazole and	**Arm 1:** Metronidazole 1g orally prior to the procedure,	**Outcome: post-abortal pelvic**	**Limitations**

Study details	Participants	Interventions	Outcomes and Results	Comments
Eschenbach, D. A., Randomised treatment trial of bacterial vaginosis to prevent post-abortion complication, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 111, 982-8, 2004 **Ref Id** 773019 **Country/ies where the study was carried out** USA **Study type** Randomised controlled trial **Aim of the study** To determine whether seven days of oral metronidazole, started on the day of the procedure, in addition to standard doxycycline prophylaxis, would reduce signs and symptoms of post-termination infectious complications. **Study dates** May 1999 to June 2000	doxycycline; n=197 placebo and doxycycline) n= 236 randomised with positive gram stain for bacterial vaginosis (n=116 metronidazole and doxycycline; n=120 placebo and doxycycline) n= 253 analysed (n=131 metronidazole and doxycycline; n=122 placebo and doxycycline) n= 154 analysed with positive gram stain for bacterial vaginosis (n=79 metronidazole and doxycycline; n=75 placebo and doxycycline) **Characteristics** Age in years (SD in parentheses): metronidazole and doxycycline= 24 (6); placebo and doxycycline= 23 (6) White ethnicity (SD in parentheses): metronidazole and doxycycline= 64 (50);	followed by 400mg twice a day for the following week + Doxycycline 100mg twice a day for 7 days **Arm 2:** Doxycycline 100mg twice a day for 7 days All women were asked to telephone the clinic after the procedure if they experienced symptoms including fever, excessive bleeding, or pain. A telephone appointment was made for 7-10 days post-procedure and a standardised follow up questionnaire was administered. Information on compliance, side effects and symptoms of infection (including days of bleeding, abnormal vaginal discharge, fever, feeling unwell or ill [malaise], abdominal or	**inflammatory disease** Total post-abortion complication score of >3 (all women) Metronidazole + doxycycline: 28/196; placebo + doxycycline: 23/197 Total post-abortion complication score of >5 (all women) Metronidazole + doxycycline: 8/196; placebo + doxycycline: 10/197 Total post-abortion complication score of >3 (women with bacterial vaginosis confirmed by gram stain) Metronidazole + doxycycline: 22/116; placebo + doxycycline: 13/120 Total post-abortion complication score of >5 (women with bacterial vaginosis	**Quality of study:** Risk of bias assessed using Cochrane risk of bias tool Random sequence generation: Low risk (A computerised random number generator program was used to generate a single, balanced block of 310 subjects. Subsequently, with additional funding, 90 more subjects were randomised in blocks of 10.) Allocation concealment: Low risk (An off-site institutional pharmacy (Harborview Medical Center, Seattle, Washington, USA) supplied the randomisation schedule and allocation verification. The resulting assignment schedule of 400 subjects was concealed throughout the duration of the study period and it was not broken until data analysis was complete.) Blinding of participants and personnel: Low risk (Blinded. An off-site institutional pharmacy (Harborview Medical Center, Seattle, Washington, USA) supplied study medications. Placebo tablets identical in appearance to metronidazole were not available, so gelatine capsules were used to dispense pulverised study medication.) Blinding of outcome assessors: Low risk (Blinded. An off-site institutional

Study details	Participants	Interventions	Outcomes and Results	Comments
Source of funding New investigator award funded by the University of Washington NIH STD Cooperative Research Centre (NIA AI 31448).	placebo and doxycycline= 69 (58) Douched in last year (SD in parentheses): metronidazole and doxycycline= 347 (37)*; placebo and doxycycline= 34 (29) Parity = 0 (SD in parentheses): metronidazole and doxycycline= 52 (40); placebo and doxycycline= 55 (45) Previous terminations >1 (SD in parentheses): metronidazole and doxycycline= 72 (56); placebo and doxycycline= 61 (50) Sex partners last 6 months >2 (SD in parentheses): metronidazole and doxycycline= 34 (26); placebo and doxycycline= 33 (28) Past bacterial vaginosis (SD in parentheses): metronidazole and doxycycline= 121 (16);	pelvic pain) and interim clinic visits(s) were collected. Women returning to the clinic for a routine or non-routine post-termination visit because of suspected infection within 12 weeks following the procedure were asked standardised questions identical to those administered by phone. The woman's temperature was recorded and a pelvic exam was performed to assess cervical mucopurulence and tenderness, uterine examination finding (tender, boggy, enlarged or normal), adnexal masses or tenderness and whether and why antibiotics were prescribed. If hospitalisation or a post-termination visit occurred elsewhere, records or information about the visit were	confirmed by gram stain) Metronidazole + doxycycline: 5/116; placebo + doxycycline: 4/120	pharmacy (Harborview Medical Center, Seattle, Washington, USA) supplied study medications. Placebo tablets identical in appearance to metronidazole were not available, so gelatine capsules were used to dispense pulverised study medication.) Incomplete outcome data (attrition bias): high risk (35.6% of women randomised did not return for follow-up) Selective reporting: low risk Other bias: low risk (The baseline characteristics of the 2 treatment groups were similar) **Other information** None

Study details	Participants	Interventions	Outcomes and Results	Comments
	placebo and doxycycline= 23 (19) Weeks of gestational age (SD in parentheses): metronidazole and doxycycline= 13 (5); placebo and doxycycline= 13 (6) First trimester procedure (SD in parentheses): metronidazole and doxycycline= 67 (51); placebo and doxycycline= 67 (55) Laminaria used 1 day (SD in parentheses): metronidazole and doxycycline= 24 (6); placebo and doxycycline= 23 (6) Laminaria used 2 days (SD in parentheses): metronidazole and doxycycline= 5 (4); placebo and doxycycline= 6 (5) Complicated procedure (SD in parentheses): metronidazole and doxycycline= 2 (2);	sought and abstracted using the standardised visit form.		

Study details	Participants	Interventions	Outcomes and Results	Comments
	placebo and doxycycline= 0 (0) Reaspiration during procedure (SD in parentheses): metronidazole and doxycycline= 2 (2); placebo and doxycycline= 1 (1) Doxycycline given before surgery (SD in parentheses): metronidazole and doxycycline= 3 (2); placebo and doxycycline= 9 (8) History of pelvic inflammatory disease (SD in parentheses): metronidazole and doxycycline= 3 (2); placebo and doxycycline= 5 (4) GC or CT in past year (SD in parentheses): metronidazole and doxycycline= 1 (1); placebo and doxycycline= 4 (3) Gram positive (SD in parentheses):			

Study details	Participants	Interventions	Outcomes and Results	Comments
	metronidazole and doxycycline= 79 (60); placebo and doxycycline= 75 (61) *Result extracted from paper, appears to be typing error **Inclusion criteria** All women presenting for surgical termination at a single facility between May 1999 and June 2000 with elevated vaginal pH and amines detected in their vaginal discharge **Exclusion criteria** Women planning a medical termination, under general anaesthesia or with current vaginal bleeding (since cervical mucus, macroscopic blood and urine can cause false card positive). Non-English speaking Metronidazole allergy Alcohol dependence			

Study details	Participants	Interventions	Outcomes and Results	Comments
	Current antibiotic use within 5 days of enrolment Refusal of the verbal consent for bacterial vaginosis screening Unwilling to be contacted by phone in 7-10 days to be asked questions about symptoms History of heart murmur Doxycycline allergy Inability to swallow gelatine capsules			

CT: chlamydia trachomatis; GC: gonorrhoea; NIG: National Institutes of Health; SD: standard deviation; STD: sexually transmitted diseases

Appendix E – Forest plots

Forest plots for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

There are no forest plots as no meta-analyses was performed.

Forest plots for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

There are no forest plots as no meta-analyses was performed.

Appendix F – GRADE tables

GRADE tables for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Table 5: Clinical evidence profile: Comparison 1. Antibiotic prophylaxis with doxycycline versus no antibiotic prophylaxis

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	No prophylactic antibiotic coverage	Relative (95% CI)	Absolute	Quality	Importance
Severe infection within 1 month of termination												
1 (Fjerstad 2009)	observational studies	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	3/43366 (0.007%)	67/72195 (0.09%)	RR 0.07 (0.02 to 0.24)	1 fewer per 1000 (from 1 fewer to 1 fewer)	VERY LOW	CRITICAL
Nausea - Overall												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	133/278 (47.8%)	124/303 (40.9%)	RR 1.17 (0.97 to 1.4)	70 more per 1000 (from 12 fewer to 164 more)	VERY LOW	IMPORTANT
Nausea - Severe												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	26/278 (9.4%)	13/303 (4.3%)	RR 2.18 (1.14 to 4.16)	51 more per 1000 (from 6 more to 136 more)	VERY LOW	IMPORTANT
Nausea - >1 day duration												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	70/278 (25.2%)	58/303 (19.1%)	RR 1.32 (0.97 to 1.79)	61 more per 1000 (from 6	VERY LOW	IMPORTANT

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	No prophylactic antibiotic coverage	Relative (95% CI)	Absolute	Quality	Importance
										fewer to 151 more)		
Vomiting - Overall												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	70/278 (25.2%)	56/303 (18.5%)	RR 1.36 (1 to 1.86)*	67 more per 1000 (from 0 more to 159 more)	VERY LOW	IMPORTANT
Vomiting - Severe												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	20/278 (7.2%)	8/303 (2.6%)	RR 2.72 (1.22 to 6.09)	45 more per 1000 (from 6 more to 134 more)	VERY LOW	IMPORTANT
Vomiting - >1 day duration												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	23/278 (8.3%)	8/303 (2.6%)	RR 3.13 (1.43 to 6.89)	56 more per 1000 (from 11 more to 156 more)	VERY LOW	IMPORTANT
Diarrhoea - Overall												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	Serious[3]	none	47/278 (16.9%)	64/303 (21.1%)	RR 0.8 (0.57 to 1.12)	42 fewer per 1000 (from 91 fewer to 25 more)	VERY LOW	IMPORTANT
Diarrhoea - Severe												
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	3/278 (1.1%)	5/303 (1.7%)	RR 0.65 (0.16 to 2.71)	6 fewer per 1000 (from 14 fewer to 28 more)	VERY LOW	IMPORTANT
Diarrhoea - >1 day duration												

Quality assessment							No of patients		Effect		Quality	Importance
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Doxycycline	No prophylactic antibiotic coverage	Relative (95% CI)	Absolute		
1 (Frye 2015)	observational studies	Serious[2]	no serious inconsistency	no serious indirectness	very serious[4]	none	19/278 (6.8%)	20/303 (6.6%)	RR 1.04 (0.56 to 1.9)	3 more per 1000 (from 29 fewer to 59 more)	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: relative risk
**Lower confidence interval calculated to 3 decimal places and result was >1*
[1] The quality of evidence was downgraded by 1 because different methods of mifepristone administration were applied in the 2 arms. Additionally, baseline characteristics of the cohorts were not reported in the paper to assess if the populations were otherwise similar.
[2] The quality of evidence was downgraded by 1 because the study was not adjusted for confounders and there were statistically significant differences in mean gestational age, race, education, and difficulty paying for the termination at baseline between the 2 arms.
[3] The quality of evidence was downgraded by 1 as the 95% CI crosses 1 MID
[4] The quality of the evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

GRADE tables for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Table 6: Clinical evidence profile: Comparison 1. Antibiotic prophylaxis with metronidazole and doxycycline versus doxycycline

Quality assessment							No of patients		Effect			
No of studies	Design	Risk of bias	Inconsistency	Indirectness	Imprecision	Other considerations	Metronidazole + doxycycline	Doxycycline	Relative (95% CI)	Absolute	Quality	Importance
Post-abortal pelvic inflammatory disease within 1 month of termination - Total post-abortion complication score equal to or more than 3 in women with elevated vaginal pH + amines in vaginal discharge												
1 (Miller 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	28/197 (14.2%)	23/196 (11.7%)	RR 1.21 (0.72 to 2.03)	25 more per 1000 (from 33 fewer to 121 more)	VERY LOW	CRITICAL
Post-abortal pelvic inflammatory disease within 1 month of termination - Total post-abortion complication score equal to or more than 5 in women with elevated vaginal pH + amines in vaginal discharge												
1 (Miller 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/197 (4.1%)	10/196 (5.1%)	RR 0.8 (0.32 to 1.97)	10 fewer per 1000 (from 35 fewer to 49 more)	VERY LOW	CRITICAL
Post-abortal pelvic inflammatory disease within 1 month of termination - Total post-abortion complication score equal to or more than 3 in women with bacterial vaginosis confirmed by gram stain												
1 (Miller 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	22/116 (19%)	13/120 (10.8%)	RR 1.75 (0.93 to 3.31)	81 more per 1000 (from 8 fewer to 250 more)	LOW	CRITICAL
Post-abortal pelvic inflammatory disease within 1 month of termination - Total post-abortion complication score equal to or more than 5 in women with bacterial vaginosis confirmed by gram stain												
1 (Miller 2004)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	5/116 (4.3%)	4/120 (3.3%)	RR 1.29 (0.36 to 4.7)	10 more per 1000 (from 21 fewer to 123 more)	VERY LOW	CRITICAL

CI: confidence interval; MID: minimally important difference; RR: relative risk

[1] The quality of evidence was downgraded by 1 as there was a high rate of attrition (>20%) which was unexplained other than lost to follow-up.
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs
[3] The quality of evidence was downgraded by 1 as the 95% CI crossed 1 MID

Table 4: Clinical evidence profile: Comparison 2. Antibiotic prophylaxis with doxycycline 3-days versus doxycycline 7-days

Quality assessment							No of patients		Effect			
No of studies	**Design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Doxycycline 3-days**	**Doxycycline 7-days**	**Relative (95% CI)**	**Absolute**	**Quality**	**Importance**
Post-abortal pelvic inflammatory disease within 1 month of termination												
1 (Litchenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/400 (0%)	1/400 (0.25%)	RR 0.33 (0.01 to 8.16)	2 fewer per 1000 (from 2 fewer to 18 more)	VERY LOW	CRITICAL
Adherence to antibiotics												
1 (Litchenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	266/400 (66.5%)	251/400 (62.8%)	RR 1.06 (0.96 to 1.17)	38 more per 1000 (from 25 fewer to 107 more)	MODERATE	CRITICAL
Gastro-intestinal side-effects: vomiting												
1 (Litchenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/400 (0.25%)	0/400 (0%)	RR 3 (0.12 to 73.42)	-	VERY LOW	IMPORTANT
Gastro-intestinal side-effects: diarrhoea												
1 (Litchenberg 2003)	randomised trials	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	1/400 (0.25%)	0/400 (0%)	RR 3 (0.12 to 73.42)	-	VERY LOW	IMPORTANT

CI: confidence interval; MID: minimally important difference; RR: relative risk
[1] The quality of evidence was downgraded by 1 as there was a high rate of attrition (>20%) which was unexplained other than lost to follow-up.
[2] The quality of evidence was downgraded by 2 as the 95% CI crosses 2 MIDs

Appendix G – Economic evidence study selection

Economic evidence for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Economic evidence for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix H – Economic evidence tables

Economic evidence tables for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Economic evidence tables for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix I – Economic evidence profiles

Economic evidence profiles for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Economic evidence profiles for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

No economic evidence was identified which was applicable to this review question.

Appendix J – Economic analysis

Economic analysis for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

No economic analysis was conducted for this review question.

Economic analysis for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

No economic analysis was conducted for this review question.

Appendix K – Excluded studies

Excluded studies for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

Excluded studies for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Clinical studies

Study	Reason for Exclusion
Achilles, S. L., Reeves, M. F., Society of Family, Planning, Prevention of infection after induced abortion: release date October 2010: SFP guideline 20102, Contraception, 83, 295-309, 2011	Study design not of interest for review: narrative review
Acog Committee on Practice Bulletins, ACOG Practice Bulletin No. 74. Antibiotic prophylaxis for gynecologic procedures, Obstetrics & GynecologyObstet Gynecol, 108, 225-34, 2006	Study design not of interest for review: narrative review
Anonymous,, ACOG educational bulletin. Antibiotics and gynecologic infections. American College of Obstetricians and Gynaecologists. Number 237, June 1997 (Replaces No. 153, March 1991), International Journal of Gynaecology & Obstetrics Int J Gynaecol Obstet, 58, 333-40, 1997	Study design not of interest for review: narrative review
Baird, A. S., Porter, C. C., Termination of pregnancy, Obstetrics, Gynaecology and Reproductive Medicine, 20, 212-218, 2010	Study design not of interest for review: narrative review
Beal,M.W., Update on Medication Abortion, Journal of Midwifery and Women's Health, 52, 23-30, 2007	Study design not of interest for review: narrative review
Bettahar, K., Pinton, A., Boisrame, T., Cavillon, V., Wylomanski, S., Nisand, I., Hassoun, D., Medical induced abortion, Journal de Gynecologie Obstetrique et Biologie de la Reproduction, 45, 1490-1514, 2016	Non-English language publication: article in French
Blackwell, A. L., Thomas, P. D., Wareham, K., Emery, S. J., Health gains from screening for infection of the lower genital tract in women attending for termination of pregnancy, Lancet, 342, 206-10, 1993	Intervention not of interest for review: prevalence and sequelae of genital tract infections in women undergoing ToP
Caruso, S, Mari, L, Cacciatore, A, Mammana, G, Agnello, C, Cianci, A, Antibiotic prophylaxis with prulifloxacin in women undergoing induced abortion: a randomized controlled trial, Minerva ginecologica, 60, 1-5, 2008	Comparison not of interest for review: comparison of various prulifloxacin prophylactic regimens (duration)
Chen, S, Li, J, Hoek, A, Universal screening or prophylactic treatment for Chlamydia trachomatis infection among women seeking	Comparison not of interest for review: prophylactic antibiotics versus screen and treat

Study	Reason for Exclusion
induced abortions: which strategy is more cost-effective? (Provisional abstract), Sexually Transmitted Diseases, 34, 230-236, 2007	
Colombo, Uf, Bregozzo, T, Bizioli, B, Viezzoli, T, Randomized study for the antibiotic prophilaxis of the postabortive endometritis, Patologia e clinica ostetrica e ginecologica, 18, 209-211, 1990	Non-English language publication: article in Italian
Costescu, D., Guilbert, E., Bernardin, J., Black, A., Dunn, S., Fitzsimmons, B., Norman, W. V., Pymar, H., Soon, J., Trouton, K., Wagner, M. S., Wiebe, E., Gold, K., Murray, M. E., Winikoff, B., Reeves, M., Medical Abortion, Journal of Obstetrics and Gynaecology Canada, 38, 366-389, 2016	Study design not of interest for review: narrative review
Creinin, M., Blumenthal, P., Shulman, L., Mifepristone-misoprostol medical abortion mortality, MedGenMed Medscape General Medicine, 8 (2) (no pagination), 2006	Study design not of interest for review: narrative review
Crowley, T., Low, N., Turner, A., Harvey, I., Bidgood, K., Horner, P., Antibiotic prophylaxis to prevent post-abortal upper genital tract infection in women with bacterial vaginosis: randomised controlled trial, BJOG: An International Journal of Obstetrics & GynaecologyBjog, 108, 396-402, 2001	Population not of interest for review: surgical termination of pregnancy
Davis, V. J., Induced Abortion Guidelines, Journal of obstetrics and gynaecology canada, 28, 1014-1027, 2006	Study design not of interest for review: narrative review
Fjerstad, M., Trussell, J., Sivin, I., Lichtenberg, S., Cullins, V., Reducing serious infection following medical abortion, European Journal of Contraception and Reproductive Health Care, 15, 48-49, 2010	Study published in abstract form and not enough data provided to analyse in the review
Fjerstad, M., Trussell, J., Lichtenberg, E. S., Sivin, I., Cullins, V., Severity of infection following the introduction of new infection control measures for medical abortion, Contraception, 83, 330-5, 2011	No outcome of interest for review: sub-group analysis of different types of severe infection from Fjerstad 2009
Guiahi, M., Davis, A., Society of Family, Planning, First-trimester abortion in women with medical conditions: release date October 2012 SFP guideline #20122, Contraception, 86, 622-30, 2012	Study design not of interest for review: narrative review
Gupta, J. K., Williams, C., Evidence for preventing infection in abortion care, European Journal of Contraception and Reproductive Health Care, 12, 191-193, 2007	Study design not of interest for review: narrative review
Henriques, C. U., Wilken-Jensen, C., Thorsen, P., Moller, B. R., A randomised controlled trial of prophylaxis of post-abortal infection: ceftriaxone versus placebo, British Journal of Obstetrics &	Population not of interest for review: surgical termination of pregnancy

Study	Reason for Exclusion
GynaecologyBr J Obstet Gynaecol, 101, 610-4, 1994	
Houang, E. T., Antibiotic prophylaxis in hysterectomy and induced abortion. A review of the evidence, Drugs, 41, 19-37, 1991	Study design not of interest for review: narrative review
Larsson, P. G., Platz-Christensen, J. J., Thejls, H., Forsum, U., Pahlson, C., Incidence of pelvic inflammatory disease after first-trimester legal abortion in women with bacterial vaginosis after treatment with metronidazole: a double-blind, randomized study, American Journal of Obstetrics & GynecologyAm J Obstet Gynecol, 166, 100-3, 1992	Population not of interest for review: surgical termination of pregnancy
Linet, T., Surgical methods of abortion, Journal de gynecologie obstetrique ET biologie de la reproduction, 45, 1515-1535, 2016	Non-English language publication: Article in French
Low, N, Forbes, Lj, Sterne, Ja, How are the results of systematic reviews used in clinical guidelines? A case study of recommendations for the use of prophylactic antibiotics for women undergoing induced abortion, Second Symposium on Systematic Reviews: Beyond the Basics; 1999 Jan 5-7; Oxford, UK, 1999	Study design not of interest for review: narrative review
Low, Nicola, Mueller, Monika, Van, Vliet Huib Aam, Kapp, Nathalie, Perioperative antibiotics to prevent infection after first-trimester abortion, Cochrane Database of Systematic Reviews, 2012	No relevant studies for current reviews
May, Win, Gülmezoglu, A Metin, Ba-Thike, Katherine, Antibiotics for incomplete abortion, Cochrane Database of Systematic Reviews, 2007	Population not of interest for review: women undergoing surgical evacuation due to incomplete abortion
Morrill, M. Y., Schimpf, M. O., Abed, H., Carberry, C., Margulies, R. U., White, A. B., Lowenstein, L., Ward, R. M., Balk, E. M., Uhlig, K., Sung, V. W., Antibiotic prophylaxis for selected gynecologic surgeries, International Journal of Gynecology and Obstetrics, 120, 10-15, 2013	No relevant studies for current reviews
Nalbanski, B, Tsekova, K, Ivanov, S, Antibiotic prophylaxis in limited gynecological surgeries for pregnancy termination, Akusherstvo i ginekologiia, 42, 7-9, 2003	Non-English language publication: article in Bulgarian
Nanda, Kavita, Lopez, Laureen M, Grimes, David A, Peloggia, Alessandra, Nanda, Geeta, Expectant care versus surgical treatment for miscarriage, Cochrane Database of Systematic Reviews, 2012	Intervention nor population of interest for review: expectant care versus surgical treatment in miscarriage
Nielsen, I. K., Engdahl, E., Larsen, T., No effect of single dose ofloxacin on postoperative infection rate after first-trimester abortion. A	Population not of interest for review: surgical termination of pregnancy

Study	Reason for Exclusion
clinical, controlled trial, Acta Obstetricia et Gynecologica Scandinavica, 72, 556-559, 1993	
Paul, A. C., Choy, C. C., A randomised comparison of strategies for reducing infective complications of induced abortion, British Journal of Obstetrics and Gynaecology, 106, 288-289, 1999	Study design not of interest for review: author reply
Penney, G. C., Preventing infective sequelae of abortion, Journal of the British Fertility Society, 2, 107-112, 1997	Comparison not of interest for review: prophylactic antibiotics versus screen and treat
Penney, G. C., Thomson, M., Norman, J., McKenzie, H., Vale, L., Smith, R., Imrie, M., A randomised comparison of strategies for reducing infective complications of induced abortion, British Journal of Obstetrics & Gynaecology, 105, 599-604, 1998	Comparison not of interest for review: prophylactic antibiotics versus screen and treat
Prieto,J.A., Eriksen,N.L., Blanco,J.D., A randomized trial of prophylactic doxycycline for curettage in incomplete abortion, Obstetrics and Gynecology, 85, 692-696, 1995	Population not of interest for review: women undergoing suction curettage for incomplete abortion
Ramin,K.D., Ramin,S.M., Hemsell,P.G., Nobles,B.J., Heard,M.C., Johnson,V.B., Hemsell,D.L., Prophylactic antibiotics for suction curettage in incomplete abortion, Infectious Diseases in Obstetrics and Gynecology, 2, 213-217, 1995	Population not of interest for review: women undergoing suction curettage for incomplete abortion
Reeves, M. F., Lohr, P. A., Hayes, J. L., Harwood, B. J., Creinin, M. D., Doxycycline serum levels at the time of dilation and evacuation with two dosing regimens, Contraception, 79, 129-33, 2009	Comparison not of interest for review: timing of pre-operative doxycycline prophylaxis
Reeves, M. F., Loi, T. T., Hoang, T. T. D., Thang, H. V., Hien, L. V., Creinin, M. D., A randomized double-blinded comparison of singledose pre-operative doxycycline to 5-day post-operative doxycycline for the prevention of infection following first-trimester uterine evacuation, International Journal of Gynecology and Obstetrics, 3), S461, 2012	Study only published as abstract, not enough information to extract for review
Rizvi,J.H., Zuberi,N.F., Women's health in developing countries, Best Practice and Research in Clinical Obstetrics and Gynaecology, #20, 907-922, 2006	Study design not of interest for review: narrative review
Russo, J. A., Achilles, S., DePineres, T., Gil, L., Controversies in family planning: postabortal pelvic inflammatory disease, Contraception, 87, 497-503, 2013	Study design not of interest for review: narrative review
Sawaya, G. F., Grady, D., Kerlikowske, K., Grimes, D. A., Antibiotics at the time of induced abortion: the case for universal prophylaxis based on a meta-analysis, Obstetrics & GynecologyObstet Gynecol, 87, 884-90, 1996	Systematic review: no additional relevant studies identified to add to review

Study	Reason for Exclusion
Shannon, C., Brothers, L. P., Philip, N. M., Winikoff, B., Infection after medical abortion: A review of the literature, Contraception, 70, 183-190, 2004	Study design not of interest for review: narrative review
Sorensen, J. L., Thranov, I., Hoff, G., Dirach, J., Early- and late-onset pelvic inflammatory disease among women with cervical Chlamydia trachomatis infection at the time of induced abortion - A follow-up study, Infection, 22, 242-246, 1994	Population not of interest for review: surgical termination of pregnancy
Sorensen, J. L., Thranov, I., Hoff, G., Dirach, J., Damsgaard, M. T., A double-blind randomized study of the effect of erythromycin in preventing pelvic inflammatory disease after first trimester abortion, British Journal of Obstetrics & GynaecologyBr J Obstet Gynaecol, 99, 434-8, 1992	Population not of interest for review: surgical termination of pregnancy
Stevenson, M. M., Radcliffe, K. W., Preventing pelvic infection after abortion, International Journal of STD and AIDS, 6, 305-312, 1995	Study design not of interest for review: narrative review
Titapant,V., Cherdchoogieat,P., Effectiveness of cefoxitin on preventing endometritis after uterine curettage for spontaneous incomplete abortion: a randomized controlled trial study, Journal of the Medical Association of Thailand, 95, 1372-1377, 2012	Population not of interest for review: women undergoing uterine curettage for spontaneous incomplete abortion
Trussell, J., Nucatola, D., Fjerstad, M., Lichtenberg, E. S., Reduction in infection-related mortality since modifications in the regimen of medical abortion, Contraception, 89, 193-6, 2014	Comparisons not in the PICO: vaginal misoprostol + no antibiotics versus buccal misoprostol + screen-and-treat or universal antibiotics (no stratification in the analyses for screen-and-treat and universal antibiotics, therefore unable to tell which regimen was exerting effect)
Wilkinson, C., Hamilton-Fairley, D., Moller, B., A randomised controlled trial of prophylaxis of post-abortal infection: Ceftriaxone versus placebo [13], British Journal of Obstetrics and Gynaecology, 102, 591-592, 1995	Study design not of interest for review: letter to editor
Yonke, N., Leeman, L. M., First-Trimester Surgical Abortion Technique, Obstetrics and Gynecology Clinics of North America, 40, 647-+, 2013	Study design not of interest for review: narrative review

PICO: population, intervention, comparison and outcome; ToP: termination of pregnancy

Economic studies

No economic evidence was identified for this review. See supplementary material 2 for further information.

Appendix L – Research recommendations

Research recommendations for review question: What is the optimal antibiotic prophylaxis regimen (including no antibiotic prophylaxis as an option) for women who are having medical termination of pregnancy?

No research recommendations were made for this review question.

Research recommendations for review question: What is the optimal antibiotic prophylaxis regimen for women who are having surgical termination of pregnancy?

Is a single dose of azithromycin or doxycycline before the procedure as effective as a full course of treatment at preventing infection after surgical termination of pregnancy?

Why this is important?

Upper genital tract infection after a termination has been associated with serious reproductive sequelae including secondary infertility, dyspareunia, pelvic pain, and future miscarriages. The use of prophylactic antibiotics is 1 of the key advances in perioperative infection control. Administration of antibiotic prophylaxis before surgical termination of pregnancy is established clinical practice in the UK. However, the evidence to inform which antibiotics to use and when they should be administered is very limited meaning recommendations made are largely based on expert opinion.

Table 7: Research recommendation rationale

Research question	Is a single dose of azithromycin or doxycycline before the procedure as effective as a full course of treatment at preventing infection after surgical termination of pregnancy?
Importance to 'patients' or the population	Prevention of post-termination of pregnancy infection has the potential to reduce long-term sequelae however, the best antibiotic regimen to be administered after surgical termination of pregnancy is not clear from the studies available. In addition, treatment courses of oral antibiotics can have adverse effects, reducing acceptability and adherence limiting their acceptability and potentially increasing the risk of resistance.
Relevance to NICE guidance	Ability to more clearly define the optimal antibiotic regimen for prophylaxis before surgical termination of pregnancy
Relevance to the NHS	Antibiotic usage should be appropriately prescribed to ensure adherence and prevent overuse and potential resistance
National priorities	There is a national drive to rationalise antibiotic usage but also awareness about the importance of preventing peri-procedure infections to reduce future risk.
Current evidence base	Although there is good evidence that antibiotics administered at the time of surgical termination of pregnancy reduces the risk of post- termination infection, there is little to recommend 1 antibiotic regimen over another. In addition, many of the studies employed antibiotics that are no longer considered optimal for Chlamydia, thought to be an important risk factor for post- termination infection.
Equality	Applies to all women undergoing surgical termination of pregnancy

NHS: National Health Service; NICE: National Institute for Health and Care Excellence

Table 8: Research recommendation modified PICO table

Criterion	Explanation
Population	Women having a surgical termination of pregnancy
Intervention	Azithromycin 500 mg orally 1 hour pre-procedure or 200 mg doxycycline 1 hour pre-procedure if unable to take azithromycin
Comparator	Azithromycin 1 g orally 1 hour pre-procedure followed by 500mg azithromycin once daily for 2 days or doxycycline 100 mg orally twice a day for 7 days if unable to take azithromycin (Note. first dose of doxycycline to be taken 1 hour pre-procedure)
Outcome	**Primary outcome:** • Post-abortal pelvic inflammatory disease (including endometritis, and upper genital tract infection) within 1 month of termination **Secondary outcomes:** • Severe infection (defined as sepsis, requiring hospitalisation, requiring intravenous antibiotics, or infection as cause of death) within 1 month of termination • Adherence to antibiotics • Gastro-intestinal side effects during the course of antibiotic treatment: • Nausea • Vomiting • Diarrhoea • Patient acceptability
Study design	Randomised controlled trial
Timeframe	1 month follow-up
Additional information	In the event that a larger, ideally multicentre, trial could be conducted, it would be useful to add additional arms in order to test other antibiotics commonly used in prophylaxis in gynaecological and obstetric procedures such as metronidazole, co-amoxiclav and oflaxacin as single-dose sole agents. Neither metronidazole nor co-amoxiclav have significant action against Chlamydia. Therefore in such an extension an additional comparator could be to investigate the role of an STI screen and recall for targeted treatment should Chlamydia be detected.

STI: sexually transmitted infection