The clinical effectiveness and cost effectiveness of antibiotic regimens for pelvic inflammatory disease

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Department of Public Health and Epidemiology
The University of Birmingham

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WEST MIDLANDS HEALTH TECHNOLOGY ASSESSMENT COLLABORATION (WMHTAC)

The West Midlands Health Technology Assessment Collaboration (WMHTAC) produce rapid systematic reviews about the effectiveness of healthcare interventions and technologies, in response to requests from West Midlands Health Authorities or the HTA programme. Reviews usually take 3-6 months and aim to give a timely and accurate analysis of the quality, strength and direction of the available evidence, generating an economic analysis (where possible a cost-utility analysis) of the intervention.

CONTRIBUTIONS OF AUTHORS

Dr Catherine Meads, developed the protocol, conducted the searches, inclusion and exclusions, data extraction and wrote the review. Ms Jayne Wilson did the duplicate inclusions and exclusions, proof read the review and discussed the trend of evidence and conclusions. Dr Trudi Knight did the duplicate data extraction. Dr Chris Hyde helped with the development of the project and protocol and discussed the layout and direction of the review.

CONFLICTS OF INTEREST: NONE

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Grateful thanks go to Dr Jonathon Ross and Mr Janesh Gupta who peer-reviewed this systematic review.

West Midlands Regional Evaluation Panel Recommendation:

The recommendation for the effectiveness of antibiotics for pelvic inflammatory disease was that the results of this review did not fit into any of the available categories so no decision could be made.

Anticipated expiry date: 2007

- This report was completed in July 2004
- The searches were completed in May 2004
- There appear to be no trials currently underway and we are not aware of any trials being planned in this area.

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SUMMARY

- This systematic review investigated the clinical effectiveness and cost-effectiveness of antibiotic treatments for pelvic inflammatory disease, particularly in relation to the seven currently recommended treatment regimens.

- Pelvic inflammatory disease is an infection of the upper reproductive tract that occurs in sexually active women and prevalence estimates vary between 63 and 250 per 10,000 person years at risk. The potential sequelae of pelvic inflammatory disease are chronic pelvic pain, ectopic pregnancy and infertility. Pelvic inflammatory disease is treated on an inpatient or outpatient basis, depending on the severity of symptoms.

- For the assessment of clinical effectiveness 34 randomised controlled trials met the inclusion criteria. Many were small and the reporting quality was generally poor. Most of them had short follow ups of less than two weeks. A very wide variety of antibiotic regimens were compared. All trials except two reported clinical cure rates. Meta-analysis was carried out where two or more trials used the same antibiotics or combinations.

- For several of the standard antibiotic regimens, there was no randomised controlled trial evidence available. For standard treatment regimens with evidence, no significant differences of any of the comparisons were found. Only one non-standard regimen had a significantly worse outcome than the comparator and that was clindamycin used on its own. One large trial compared inpatient and outpatient treatment, using very similar antibiotic combinations. There were no significant differences between the two groups at a mean follow up of 35 months.

- For the assessment of costs and cost-effectiveness, 8 studies were included. All were set in USA, four were cost studies, three were various forms of cost-effectiveness study and one was a quality of life study from one of the randomised trials included in the clinical effectiveness section. The annual cost per case of pelvic inflammatory disease varied between $1,478 and $2,867. The lifetime cost per person with pelvic inflammatory disease varied between $1,060 and $3,180. The lifetime costs rose to $6,350 if women develop chronic pelvic pain and $6,840 with ectopic pregnancy. The quality of life study demonstrated worse quality of life, when measured using using the Short Form – 36, for women who develop chronic pelvic pain compared to those who do not following an episode of pelvic inflammatory disease. The approximate costs of standard antibiotic regimens vary between £10-£62 for outpatient and £38-£739 for inpatient treatment.

- There is no clear evidence to demonstrate the greater efficacy of any of the clinically meaningful interventions reviewed compared to any of the others. It would seem sensible, therefore that, other things being equal, the least expensive drug regimens be used in the first instance. There is a need for large, good quality RCTs, adequately powered to detect small effect sizes, to establish whether any of the recommended antibiotic regimens are relatively more effective than any of the others. There is also a need to improve the diagnosis and management of PID in primary care.

ABBREVIATIONS

Abbreviation	Definition
A&E	Accident and Emergency department
BNF	British National Formulary
CI	Confidence interval
CPP	Chronic pelvic pain
ESR	Erythrocyte sedimentation rate
g	Gram
GP	General practitioner
im	Intramuscular
IP	Inpatient
ITT	Intention to treat
iv	Intravenous
IUD	Intra-uterine device
mg	Milligram
n/a	Not available
n/N	Number with outcome, number of participants
NHS	National Health Service
NR	Not reported
OP	Outpatient
PID	Pelvic inflammatory disease
QALY	Quality adjusted life year
RCT	Randomised controlled trial
RR	Relative risk
SD	Standard deviation
SEM	Standard error of the mean
SF-36	Short form – 36 questionnaire
STD	Sexually transmitted diseases
USA	United States of America

1. AIM OF THE REVIEW

To establish the clinical and cost effectiveness of the different antibiotics and combinations of antibiotics used in the treatment of pelvic inflammatory disease. Also, to investigate the length of antibiotic treatment required, the effectiveness of different routes of administration and whether inpatient treatment is more or less effective than outpatient treatment.

2. BACKGROUND

The female reproductive tract consists of the ovaries, fallopian tubes, uterus, cervix, vagina and vulva. Inflammation of the internal parts of this tract are known as oophoritis, salpingitis, endometritis or parametritis, cervicitis and vaginitis, respectively. Infection of the upper part of the tract is seldom confined to one part so, for example, infection of the fallopian tubes extending into the ovary is called salpingo-oophoritis. Pelvic inflammatory disease (PID) is a sexually transmitted infection of the upper reproductive tract, typically involving the fallopian tubes, ovaries, surrounding tissues and pelvic cavity. The term PID is used synonymously with salpingitis. The infection, often acquired as a result of sexual intercourse, ascends to the upper reproductive tract via the cervix. The most common causes of the infection are *Neisseria gonorrhoeae* (15%) and *Chlamydia trachomatis* (39%).[1] Frequently other bacteria are cultured from the infected fallopian tubes including *Mycoplasma hominis* (38%), and a variety of anaerobes (29%) and aerobes (9%).[1]

The symptoms of PID include low abdominal pain, vaginal or cervical discharge, pyrexia, vomiting, painful sexual intercourse (dyspareunia), irregular menstrual bleeding, urinary symptoms (such as frequency) and symptoms of proctitis. The signs include marked lower abdominal tenderness, cervical motion tenderness, tender palpable mass or masses, raised body temperature and a purulent vaginal discharge which may be bloodstained. Blood tests may show a raised white cell count, erythrocyte sedimentation rate or C reactive protein levels. PID can result in a number of sequelae. In the short term adhesions to surrounding organs can develop. An abscess can form in the fallopian tube (called a pyosalpinx), in an ovary or in the pelvic cavity. If a pelvic abscess forms it can lead to generalised peritonitis. Fitz-Hugh-Curtis syndrome is a perihepatitis which occurs in 10-20% of women with PID.[2] In the longer term PID can lead to chronic pelvic pain, blocked fallopian tubes, infertility and a higher incidence of ectopic pregnancy and hysterectomy.[3]

Diagnosis of PID can be by clinical symptoms and signs or by laparoscopy. Two very similar sets of criteria for diagnosis and grading of PID by Hager (1983) Soper (1991) and Thompson (1980) are shown in Appendix 1. In PID this will show hyperaemia and oedema of the fallopian tubes and a sticky exudate on the tubal surface. The inflammation often bilateral and may be seen to extend into the ovaries and uterus. At laparoscopy, samples are taken for bacterial culture. Laparoscopy is not used routinely for all women with PID symptoms, but for the more severe cases being treated as inpatients and for women entered into trials. If no laparoscopy is performed, culture samples should be taken from the cervix. Chlamydia infection can also be diagnosed from a urine sample.[4] Diagnosis by clinical symptoms and signs only is not reliable, being correct in approximately 65% of cases only.[5] Also PID can be subclinical or ‘silent’ in the acute stage and only diagnosed retrospectively when, for example, the patient is being investigated for infertility. It is estimated that more than 50% of women who have blocked fallopian tubes as a cause of infertility report no previous PID symptoms, despite having serological evidence of past gonorrhoeal or chlamydial infection.[6] In a questionnaire audit of GP management of PID, only 7% (21/297) were able to describe ‘gold standard’ diagnosis and management correctly.[7] Also in another GP audit it was found that more than half of GPs (76/139)do not take an endocervical swab, 37.4% do not include anti-chlamydial antibiotics and 24.5% do not recommend sexual partners to be checked.[8] This suggests that considerable sub-optimal diagnosis and management is occurring.

A very similar syndrome to PID can occur following childbirth, termination of pregnancy (particularly illegal abortion), after pelvic operations and may also be caused by a foreign body in the uterus or carcinoma of the cervix. These causes are usually excluded in studies of PID.

2.1 Description of underlying health problem

2.1.1 Epidemiology of PID

Women with PID are treated by several care providers including hospital emergency departments, gynaecological outpatient clinics, sexually transmitted disease (STD) clinics and by GPs. Therefore epidemiological studies that just include data from one service such as hospital admissions may give very misleading rates. Incidence and prevalence estimates have been derived from patient surveys, outpatient visits, hospital discharge data and extrapolation from STD clinic incidence figures for total gonorrhoeal and chlamydial infections. The incidence of PID is subject to a number of considerations

1. Women can have more than one infection so the incidence rates need to distinguish between first episode incidence and total incidence
2. Because of the low positive predictive value of clinical diagnosis alone, disease rates should ideally be laparoscopically confirmed PID diagnosis
3. Not all cases can ever be diagnosed because of the large proportion with silent or subclinical PID

The rate of PID depends on:

- Age – young, sexually active women are at most risk. The prevalence rates by age group are shown in Table 1.[9]
- Marital status – divorcees are at higher risk than married or single women of the same age
- Method of contraception used – barrier methods are associated with lower risk whereas IUDs are associated with higher risk in the first few weeks after insertion.
- Previous history of PID – recurrence rates can be as high as 30%
- Ethnic group – women of black and Asian ethnic origins are at greater risk than women of white origin. The prevalence in white women is 167 per 10,000 person-years at risk, in black women 264 per 10,000 person-years at risk and in Asian women 193 per 10,000 person-years at risk[4]
- Socioeconomic status – women from more deprived backgrounds are at greater risk
- Diagnostic criteria used[10]

Table 1. Prevalence of PID by age group

Age group	16-19	20-24	25-29	30-34	35-39	40-46
Prevalence per 10,000 person years at risk[9]	223	251	220	188	127	63
Annual rate of hospital discharge per 10,000 women of reproductive age[11]	31.4	44.3	56.9	56.2	54.4	48.9*
* age 40-44						

The rate of PID in the UK appears to be increasing gradually over time.[12] Across the world, PID is a major cause of morbidity. In USA it is the most common gynaecological reason for

admission to hospital, it accounts for 17-40% of gynaecological admissions in sub-Saharan Africa, 15-37% in Southeast Asia and 3-10% in India.[13]

For the population of England, in one year there would be 177,000 cases of PID. This has been calculated from the prevalence figures in Table 1 above and census population estimates and would include all those being treated by their GP. Approximately 46,000 would be discharged from hospital after treatment for PID (USA estimates). Hospital episode statistics for England[14] give considerably fewer admissions (see Table 2) and they would have a mean length of stay of between 3.3 and 5 days. This means that it is likely that trials using US hospital populations may not be completely representative in the UK setting.

Table 2. Hospital episode statistics for PID (2003) [14]

Diagnosis code	Description	Consultant episodes	Admissions	Mean length of stay
N70	Salpingitis/oophoritis	2,271	2,055	5.0
N71	Inflammatory disease of the uterus	1,094	1,069	3.3
N73	Other PID	10,761	10,135	3.4

2.1.2 Consequences of PID

Once a patient has one episode of PID they can get recurrent infections and their risk of developing sequelae increases with the number of episodes experienced. The interval between PID and tubal damage can be as short as one week so it is important to treat the first episode quickly.[7] Approximately 36.9% of patients who have had mild to moderate PID (ie not including those with tubo-ovarian abcesses, surgical emergencies or too ill to tolerate oral treatment) may go on to develop chronic pelvic pain (CPP)[15] although other estimates put the risk to be far less at 18.1%.[16] Other complications include ectopic pregnancy (7%) and infertility (20%).[16] These high rates suggest that initial treatment for PID may not be that successful.

2.2 Current service provision

Treatment of acute PID is by antibiotics, given either orally, parenterally or both. A wide variety of different types and combinations can be given including aminoglycosides, cephalosporins, tetracyclines, broad-spectrum penicillins, clindamycin and metronidazole. High doses are usually given for up to 2 weeks. In the UK, the most usual combination is doxycycline and metronidazole (personal communication, J Ross, 24/6/02), but this combination may not be as effective as other combinations.[13,17] The current version of BNF (issue 47) specifies ofloxacin and metronidazole and treatment for at least 14 days.[18] It also suggests doxycycline plus cefoxitin where patients are severely ill, then switching to oral doxycycline plus metronidazole to complete 14 day's treatment. The Royal College of Obstetricians and Gynaecologists Guideline No 32 (May 2003)[19] gives the evidence base for a number of PID treatment regimens. Another set of guidelines[2] from 1999 suggested very similar regimens with no evidence of superiority of any one over others. Relevant extracts from three of the more recent guidelines are given in Appendix 2. The suggested regimens from these are shown below:

1. oral ofloxacin and oral metronidazole [19-21]
2. im ceftriaxone or im cefoxitin with oral probenecid followed by oral doxycycline and oral metronidazole [19,20]
3. im ceftriaxone or im cefoxitin plus oral probenecid or a third generation cephalosporin and oral doxycycline [21]
4. iv cefoxitin and iv doxycycline followed by oral doxycycline and oral metronidazole [19,20]
5. iv clindamycin and iv gentamicin followed by either oral doxycycline and oral metronidazole or oral clindamycin[19,20]
6. iv ofloxacin and iv metronidazole[19]
7. iv ciprofloxacin and iv (or oral) doxycycline and iv metronidazole[20]

In this systematic review these seven treatment regimens are called standard treatments. Any other treatment regimen used in trials and other studies have been called non-standard treatments.

Treatment can be either as an inpatient or outpatient, depending on the severity of clinical symptoms and signs. It is expected that antibiotics will start to work, showing good clinical improvement within 2-3 days. If this has not occurred then further investigation, parenteral drugs or surgery may be required. If an abscess forms it will require surgical drainage. Sexual partners of women with PID should also be treated.

Treatment success can be defined in two ways:
1. Clinical cure – resolution of symptoms including pain, vaginal discharge pyrexia and lowering of white cell count or C reactive protein levels in the blood. There is no standard definition of clinical cure and the parameters used differ slightly between studies.
2. Microbiological cure – when bacterial cultures that were previously positive become negative.

Repeat microbiological testing is recommended for all cases of gonorrhoea and can be done at 4 weeks. Repeat testing for chlamydia may also be done at 4 weeks when there are persisting symptoms or possibly incomplete treatment of the woman or her sexual partner(s).[2]

2.3 Costs of interventions

The estimated total cost of each standard treatment regimen is shown in Table 3. The costs per day of all the antibiotics included in this systematic review are shown in Appendix 3.

Table 3. Costs of standard treatment regimens

Regimen	Cost per regimen
oral ofloxacin 800mg/day and oral metronidazole 0.8g/day for 14 days[19-21]	£61.18
im ceftriaxone 250mg once or im cefoxitin 2g once with oral probenecid 1g once followed by oral doxycycline 200mg/day and oral metronidazole 800mg/day for 14 days[19,20]	£10.58 or £17.68
im ceftriaxone 250mg or im cefoxitin 2g plus oral probenecid 1g or a third generation cephalosporin and oral doxycycline 200mg for 14 days[21]	£9.46 or £16.56 or £24.62 or £35.37
iv cefoxitin 6g/day and iv (or oral) doxycycline 200mg/day followed by oral doxycycline 200mg/day and oral metronidazole 800mg/day to complete 14 days[19,20]	£37.36
iv clindamycin 2.7g/day and iv gentamicin 2mg/kg loading dose then 4.5mg/kg/day followed by either oral doxycycline 200mg/day and oral metronidazole 200mg/day or oral clindamycin 1.8g/day to complete 14 days[19,20]	£83.79 or £153.09
iv ofloxacin 800mg/day and iv metronidazole 1.5g/day for 14 days[19]	£738.50
iv ciprofloxacin 400mg/day and iv (or oral) doxycycline 200mg/day and iv metronidazole 1.5g/day (unspecified length, presume 14 days)[20]	£533.96
Notes: Assume iv treatment for 3 days and oral treatment for 11 days where patients are treated iv then orally. Clindamycin and gentamicin doses assume 70Kg person. Non-proprietary medicine prices given where possible. Doxycycline iv no longer available in BNF. Probenecid available on named patient basis only so no price available in BNF.	

3. EFFECTIVENESS

3.1 Methods for reviewing effectiveness

A scoping search was undertaken to identify existing reviews and other background material and to estimate the volume and nature of primary studies. The yield from this was used to develop the protocol. Five systematic reviews were identified.[22-26]

3.1.1 Search strategy

The following sources were searched to December 2002:

- Bibliographic databases: Cochrane Library (CDSR, CCTR, DARE), MEDLINE, EMBASE, CINAHL, Web of Science (Science Citation Index)
- Citations of relevant studies
- Relevant internet sources

Cochrane Library (CDSR, CENTRAL, DARE, HTA), MEDLINE, EMBASE and Web of Science (Science Citation Index) were searched again for literature from 2002 to 2004 in May 2004, using the same search terms and citations of new relevant studies were also searched.

There were no date or language restrictions placed on the literature searches. For search strategies, see Appendix 4.

3.1.2 Inclusion and exclusion criteria

The inclusion criteria used in the systematic review to find the most clinically effective classes of antibiotic for acute symptoms and long-term sequelae are shown in Table 4.

Table 4. Clinical effectiveness review inclusion criteria

Patient	Women with PID, diagnosed clinically or laparoscopically
Intervention	Any antibiotic or combination
Control	Placebo or any antibiotic or combination
Outcomes	Clinical cure, microbiological cure, infertility, ectopic pregnancy, chronic pelvic pain, hysterectomy or any other relevant outcomes
Study design	RCTs only

These inclusion criteria enabled the following comparisons to be made: (for definitions of standard treatment regimens see section 2.2)

- Standard antibiotic regimen vs placebo
- Standard antibiotic regimen vs another standard antibiotic or combination
- Standard antibiotic regimen vs any other antibiotic or combination
- Any non- standard antibiotic or combination vs placebo
- Any non-standard antibiotic or combination vs any other non-standard antibiotic or combination
- Any antibiotic or combination vs same antibiotic or combination (to establish other parameters including the most effective dose, duration of treatment, route of administration or location of treatment).

Safety and tolerability of antibiotics used to treat PID are reviewed in the context of RCT evidence only.

Exclusion criteria:
A. RCTs that have not finished recruiting
B. RCTs publishing only baseline characteristics or only follow up results for a small proportions of the trial participants
C. Non randomised and observational comparative studies
D. Studies carried out on animals

Two reviewers, using explicit predetermined criteria, made inclusion and exclusion decisions independently. These were checked for agreement and any differences discussed and resolved, if necessary by a third reviewer. Inclusion and exclusion decisions were made independently of inspection of trial results.

Subsequent to the initial inclusion, exclusion process, it was decided, together with the clinical experts, that it would not be useful to review drugs that were no longer available in the BNF. It was also decided that penicillins and anti-pseudomonal penicillins would not now be used for the treatment of PID so a review of these drugs would not be helpful. Trials which included a variety of pelvic infections, such as endometritis and post surgical infections as well as PID were only included if results were available specifically for the group with PID.

3.1.3 Data extraction and quality assessment strategies

Two reviewers independently extracted the effectiveness and quality assessment data from all included studies into pre-defined data extraction and quality assessment forms. Any discrepancies were resolved by discussion and if necessary by a third reviewer arbitrating. The quality of RCTs was assessed by Jadad score[27].

3.1.4 Methods of analysis and synthesis

The tabulated characteristics and results of the included trials were assessed qualitatively, taking into account any observed clinical heterogeneity. Where there were sufficient good quality trials with results for the same outcome measures, synthesis of results was conducted, using both fixed effects and random effects meta-analytic models.

3.2 Results

3.2.1 Quantity and quality of research available

Database searches found 1126 references of which 122 were duplicates. A total of 187 RCTs and other potentially relevant studies were found from the searches. For a flow diagram of the identification and inclusion of studies see Appendix 5. Thirty-four RCTs were included (32 papers) and 120 studies excluded. A list of excluded studies with reasons for exclusions are shown in Appendix 6. The main reasons for exclusion were that one of the antibiotics used was no longer in the BNF or the study looked at gynaecological infections not including pelvic inflammatory disease.

Of the 34 included trials, one was published as a conference abstract and the others were fully published in one or more peer-reviewed journal articles. However, many were published in the 1980s and the treatment used then may not mirror current practice. One journal article reported two trials, each having three arms. Both had identical treatments in two of the arms and the third had different treatments. Because the results were combined for the two third arms these have been excluded. The remaining two trials have been treated as one trial. The included trials and their drug comparisons and doses used are shown in Appendix 7.

Many of the trials were small (less than 50 patients), conducted in the 1980s in USA or Europe, on in-patients and fewer than half had mandatory laparoscopic diagnosis of PID. Most of the trials reported clinical diagnostic criteria but it is noticeable how much they vary. Drug companies were mentioned in 12 reports, which could be that one of the authors was employed by them,[28-31] the trial was supported by grant[32-38] or the company sponsored the trial.[39] It was noticeable how few mentioned intra-uterine devices for contraception. Where this was mentioned, the rates varied between 2-49%. In 4 trials patients were excluded if they had intra-uterine devices or if these were not removed.

Mostly, ITT analysis was not carried out and the reasons given for exclusion from evaluation of clinical effectiveness are shown in Table 54 on page 80. A number of the trials included pelvic infections rather than just PID and errors in diagnosis and treatment were relatively common. Many of the trals were open label. Given the different recommended daily frequencies of the different drugs, blinding would have been difficult for some comparisons, but was attempted in two of the 34 trials (see Table 55 on page 82). The quality of most of the trials was poor and the median Jadad score was 0. Of the two trials achieving a Jadad score above 1, one was published in 2002[40,41] and the other in 1988.[42]

The trials have been organised in 6 groups: (see definitions of standard regimens in section 2.2).

- Standard regimens vs placebo
- Standard regimens vs other standard regimens
- Standard regimens vs non-standard regimens
- Non-standard regimens vs placebo
- Non-standard regimens vs other non-standard regimens
- Any regimen vs same regimen given in a slightly different way (timing of doses, length of administration, outpatient vs inpatient treatment)

All 34 trials have been assigned to one of these groups only. Within each group each trial may take part in more than one comparison, particularly in the non-standard regimen vs other non-standard regimen group where many treatments included antibiotics from more than one category. The standard regimens vs non-standard regimens group are organised in the order they are given in the current treatment section of this systematic review. The non-standard regimens are ordered by categories of antibiotics as they appear in the BNF.

Table 5. Standard antibiotic regimens and corresponding trial evidence

Regimen	Trial evidence available?	Sections
oral ofloxacin 800mg/day and oral metronidazole 0.8g/day for 14 days[19-21]	Ofloxacin and metronidazole v clindamycin and gentamicin	3.2.3.1,
im ceftriaxone 250mg once or im cefoxitin 2g once with oral probenecid 1g once followed by oral doxycycline 200mg/day and oral metronidazole 800mg/day for 14 days[19,20]	Cefoxitin and doxycycline vs cefoxitin, probenecid and doxycycline	3.2.3.3,
im ceftriaxone 250mg or im cefoxitin 2g plus oral probenecid 1g or a third generation cephalosporin and oral doxycycline 200mg for 14 days[21]	Ceftriaxone or cefoxitin plus oral probenecid or a third generation cephalosporin and oral doxycycline v non-standard treatments	3.2.4.3
iv cefoxitin 6g/day and iv (or oral) doxycycline 200mg/day followed by oral doxycycline 200mg/day and oral metronidazole 800mg/day to complete 14 days[19,20]	Cefoxitin and doxycycline v clindamycin and gentamicin, Cefoxitin and doxycycline v cefoxitin, probenecid and doxycycline	3.2.3.2, 3.2.3.3,
iv clindamycin 2.7g/day and iv gentamicin 2mg/kg loading dose then 4.5mg/kg/day followed by either oral doxycycline 200mg/day and oral metronidazole 200mg/day or oral clindamycin 1.8g/day to complete 14 days[19,20]	Ofloxacin and metronidazole v clindamycin and gentamicin, Cefoxitin and doxycycline v clindamycin and gentamicin, Intravenous clindamycin and gentamicin followed by either oral doxycycline and oral metronidazole or oral clindamycin v non-standard treatments	3.2.3.1, 3.2.3.2, 3.2.4.5
iv ofloxacin 800mg/day and iv metronidazole 1.5g/day for 14 days[19]	Ofloxacin and metronidazole v clindamycin and gentamicin,	3.2.3.1,
iv ciprofloxacin 400mg/day and iv (or oral) doxycycline 200mg/day and iv metronidazole 1.5g/day (unspecified length, presume 14 days)[20]	No RCT comparisons	

3.2.2 Clinical effectiveness of standard regimens vs placebo

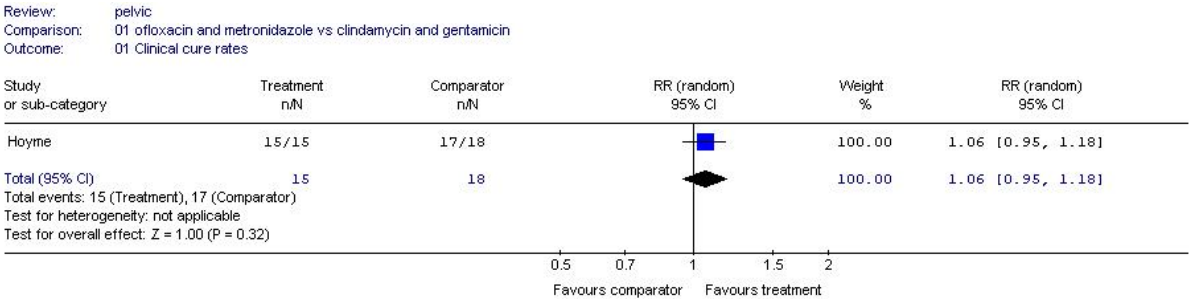
No RCTs found

3.2.3 Clinical effectiveness of standard antibiotic regimens vs any other standard antibiotic regimens

3.2.3.1 Ofloxacin and metronidazole vs clindamycin and gentamicin

One trial (Hoyme 1993)[43] compared iv then oral ofloxacin and metronidazole to clindamycin and gentamicin. This small trial took place in Germany, and the report was brief. The clinical cure rate was 15/15 for ofloxacin and 17/18 for clindamycin and gentamicin. This gives a relative risk of 1.06 (95%CI 0.95-1.18) (see Figure 1). No other results were presented.

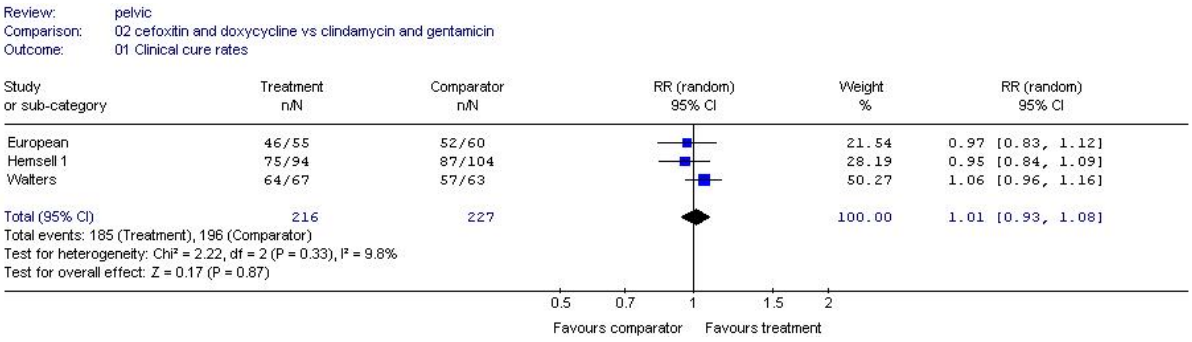
Figure 1. Clinical cure rates of ofloxacin and metronidazole v clindamycin and gentamicin



3.2.3.2 Cefoxitin and doxycycline to clindamycin and gentamicin

Three trials (European 1992,[39] Hemsell 1 1994,[32] Walters 1990[37]) compared cefoxitin and doxycycline (without metronidazole) to clindamycin and gentamicin. Hemsell 1 had a third arm of cefotetan and doxycycline. As cefotetan is no longer in the BNF this arm has been excluded. The drug doses were the same in the included RCTs and duration of treatment was between 10-14 days. Hemsell 1 and Walters trials took place in the US whereas the European trial was located in 10 centres in Europe and Africa. All were inpatient trials that took place in the 1980s and all relatively large. None of the trials had compulsory laparoscopic diagnosis. The results for clinical cure rates are given in Figure 2. Walters also gave microbiological cure rates which were 22/22 and 13/13 for gonorrhoea and 7/8 and 9/10 for chlamydia for the Cefoxitin/doxycycline and clindamycin/gentamicin groups respectively.

Figure 2. Clinical cure rates of cefoxitin and doxycycline v clindamycin and gentamicin



The results show no significant differences between cefoxitin/doxycycline and clindamycin/gentamicin. The only other results reported were mean duration of inpatient treatment in Hemsell 1, for the cefoxitin/doxycycline group 4.4 days (SD 1.1 days) and for the clindamycin group 4.3 days (SD 2.0 days). Side effects results are given in Table 6. None of the results were statistically significant but the general trend was for more side effects in the clindamycin/gentamicin groups.

Table 6. Side effects of cefoxitin and doxycycline v clindamycin and gentamicin

	Cefoxitin/Doxycycline	Clindamycin/Gentamicin
European 1992		
Gastrointestinal	10/82	15/88
Vestibular disturbance	0/82	3/88
Allergic reaction	0/82	3/88
Surgical intervention	1/60	1/60
Withdrew from study because of side effects	0/60	1/60
Hemsell 1 1994		
Pruritis	2/114	11/116
Withdrew from study because of side effects	1/114	0/116
Walters 1990		
Mild rash	1/67	1/63
Diarrhoea	2/67	2/63

3.2.3.3 Cefoxitin and doxycycline vs cefoxitin, probenecid and doxycycline

The PEACH trial[40] was a large multicentre RCT, recently conducted in USA that sought to determine whether PID could be treated equally well by both an outpatient and an inpatient antibiotic regimen. The regimens used are shown in Table 7. Neither arm included oral metronidazole. Because the treatment regimens are slightly different, the RCT is actually a comparison of treatment regimen and location of treatment combined. Also, because iv doxycycline caused phlebitis, after the first 242 patients were treated the iv doxycycline was changed to a single parenteral dose (does not state whether iv or im) followed by oral administration whilst patients remained in hospital.

Table 7. Planned antibiotic comparisons in the PEACH trial

Peach 2002	iv cefoxitin, iv doxycycline followed by oral doxycycline	im cefoxitin with oral probenecid followed by oral doxycycline

The 831 patients were recruited from 13 centres out of 2941 women screened. Seventy five percent of those recruited were of black ethnic origin and 75% educated to high school or less. The baseline characteristics were well balanced except that there were more intrauterine devices and more bacterial vaginosis in the outpatient group. Clinical follow up was at 30 days (23/831 lost to follow up) and also longer term fertility outcomes at a mean follow up of 35 months (number followed up not given). Longer-term follow up was conducted by telephone call or medical note review. The quality of this RCT report was fair as it had a

Jadad score of 3. There was no mention as to whether assessment was performed blind to treatment allocation.

There is no mention of 30-day clinical cure rates. The longer-term follow up results are shown in Table 8. The mean follow up period was 35 months. None showed a statistically significant difference. The numbers followed up for each outcome have been calculated from reported percentages so there may be some rounding errors.

Table 8. PEACH trial longer-term outcomes

	Outpatient	Inpatient
Pregnancy	42.0% (172/410)	41.7% (166/398)
Infertile (for women with at least 1 years' follow up)	18.4% (71/385)	17.9% (67/374)
Recurrent PID (self-reported)	12.4% (51/410)	16.6% (66/398)
Hysterectomy	1.7% (7/410)	1.5% (6/398)
Ectopic pregnancy	1.0% (4/410)	0.3% (1/398)
Tubal obstruction (in women who had hysterosalpingograms)	41.2% (7/17)	33.3% (4/12)
Chronic pelvic pain (in women who had at least two follow ups)	33.7% (128/380)	29.8% (110/369)

The mean time to pregnancy was the same for inpatients and outpatients at 21 months (95%CI 20-23 months). In a Cox proportional hazards model, adjusting for tubal ligation, intrauterine device use and bacterial vaginosis as covariates, the odds ratio for pregnancy for inpatient vs outpatient treatment was 0.90 (95%CI 0.77-1.05).

The adverse events at 30 days are shown in Table 9. The numbers followed up for each outcome have been calculated from reported percentages so there may be some rounding errors. The only significant difference between the two groups was the increased numbers of phlebitis in the inpatient group, caused by iv doxycycline.

Table 9. PEACH trial 30 day adverse events

	Outpatient	Inpatient
Change in treatment	3.3% (14/410)	2.9% (12/389)
Tubo-ovarian abcess	0.9% (4/410)	0.7% (3/398)
Adverse drug reaction	1.7% (7/410)	1.5% (6/398)
Phlebitis	0%	3.4% (14/398)
Tender on examination	20.6% (69/335)	18.4% (63/324)
N gonorrhoea	3.9% (9/231)	2.4% (6/250)
C trachomatis	2.7% (9/333)	3.6% (12/333)
Endometritis on biopsy	45.9% (102/222)	37.6% (85/226)

3.2.3.4 Other standard regimens

No other RCTs of standard regimens compared to other standard regimens were found.

3.2.4 Clinical effectiveness of standard antibiotic regimens vs any other antibiotic or combination

3.2.4.1 Oral ofloxacin and oral metronidazole, iv ofloxacin and iv metronidazole

No RCTs found (But see Clinical effectiveness of standard antibiotic regimens vs any other standard antibiotic regimens)

3.2.4.2 Intramuscular ceftriaxone or cefoxitin with oral probenecid followed by oral doxycycline and oral metronidazole

No RCTs found

3.2.4.3 im ceftriaxone or im cefoxitin plus oral 1g probenecid or a third generation cephalosporin and oral doxycycline

There are six trials included in this section. One trial (Arredondo[28]) compared ceftriaxone and doxycycline to ciprofloxacin and clindamycin. It was a large outpatient trial (n=138) set in South and Central America and diagnosis was confirmed laparoscopically. Two trials (Martens 2[35] and Wendell[38]) compared im cefoxitin, probenecid and doxycycline to oral ofloxacin. However, neither of the cefoxitin/doxycycline groups included metronidazole in the standard treatment package (although a number in Martens 2 also received it). These were outpatient trials and patients just received Cefoxitin once im with one dose of oral probenecid then given oral cefoxitin. Both trials took place in the USA and were relatively large (Martens 2 n=295, Wendel n=96). Three trials (Landers,[44] Soper[42] and Sweet[45])compared cefoxitin and doxycycline (without probenecid) to non-standard treatments. In the Sweet abstract route, dose and duration of treatment were not given. Two were inpatient trials and the third (Sweet) did not specify.

Table 10. Drug comparisons of im ceftriaxone, cefoxitin and doxycycline v non-standard treatments

Arredondo 1997	Ceftriaxone and doxycycline	Ciprofloxacin and clindamycin
Landers 1991	Cefoxitin, doxycycline	Clindamycin, tobramycin
Martens 2 1993	Cefoxitin, Probenecid, doxycycline	Ofloxacin
Soper 1988	Cefoxitin, doxycycline,	Clindamycin, amikacin
Sweet 1985	Cefoxitin, doxycycline	Clindamycin, tobramycin
Wendell 1991	Cefoxitin, Probenecid, doxycycline	Ofloxacin

The clinical cure rates are shown in Figure 3 and other results in Table 11. The results show no significant differences between cefoxitin/probenecid/doxycycline compared to other non-standard treatments. The side effects of treatments are shown in Table 12. They show that there is a general trend towards fewer side effects in the ofloxacin group compared to cefoxitin, probenecid and doxycycline.

Figure 3. Clinical cure rates of ceftriaxone, cefoxitin and doxycycline v non-standard treatments

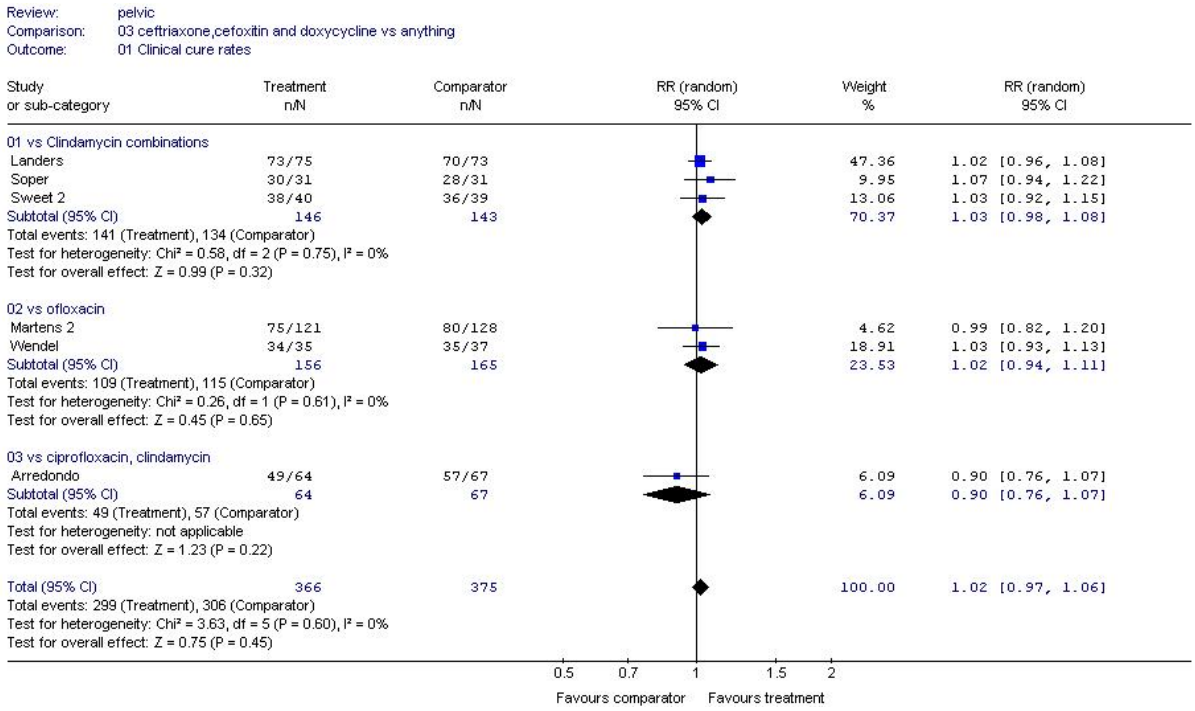


Table 11. Other results of ceftriaxone cefoxitin and doxycycline v non-standard treatments

	Ceftriaxone, cefoxitin and doxycycline	Comparators
Arredondo 1997		
Gonnorroea cure rate	1/1	1/2
Chlamydia cure rate	7/7	8/8
Martens 2 1993		
gonorrhoea or chlamydia or both	18/30	17/26
Soper 1988		
Mean hospital stay duration	6.1 (SD 2.4)	5.8 (SD 3.0)
Wendel 1991		
Gonnorroea cure rate	16/16	21/21
Chlamydia cure rate	10/10	5/6
Landers 1991		
Chlamydia cure rate	19/19	20/20
Soper 1988		
6 week clinical and microbiological relapses	0/31	0/31

Table 12. Side effects of ceftriaxone cefoxitin and doxycycline v non-standard treatments

	Ceftriaxone and doxycycline	Comparator
Arredondo 1997		
Any side effect	52/69	57/69
Withdrawal of treatment due to side effects	1/69	1/69
	Cefoxitin, Probenecid, doxycycline	
Martens 2 1993		Ofloxacin
Nausea/vomiting	19/134*	2/138*
Insomnia	0/134	2/138
Candidal vaginitis	6/134	5/138
Rash	1/134	2/138
No of patients with side effects	20/134*	9/138*
Wendel 1991		Ofloxacin
Nausea/vomiting	3/35	2/37
Headaches	0/35	1/37
Candidal vaginitis	2/35	1/37
Allergy	0/35	1/37
No of patients with side effects	9/35	6/37
	Cefoxitin and doxycycline	
Landers1991		Clindamycin/tobramycin
Rash	2/75	1/73
* $p<0.05$		

3.2.4.4 Intravenous cefoxitin and iv doxycycline followed by oral doxycycline and oral metronidazole

No RCTs found (But see Clinical effectiveness of standard antibiotic regimens vs any other standard antibiotic regimens)

3.2.4.5 Intravenous clindamycin and gentamicin followed by either oral doxycycline and oral metronidazole or oral clindamycin

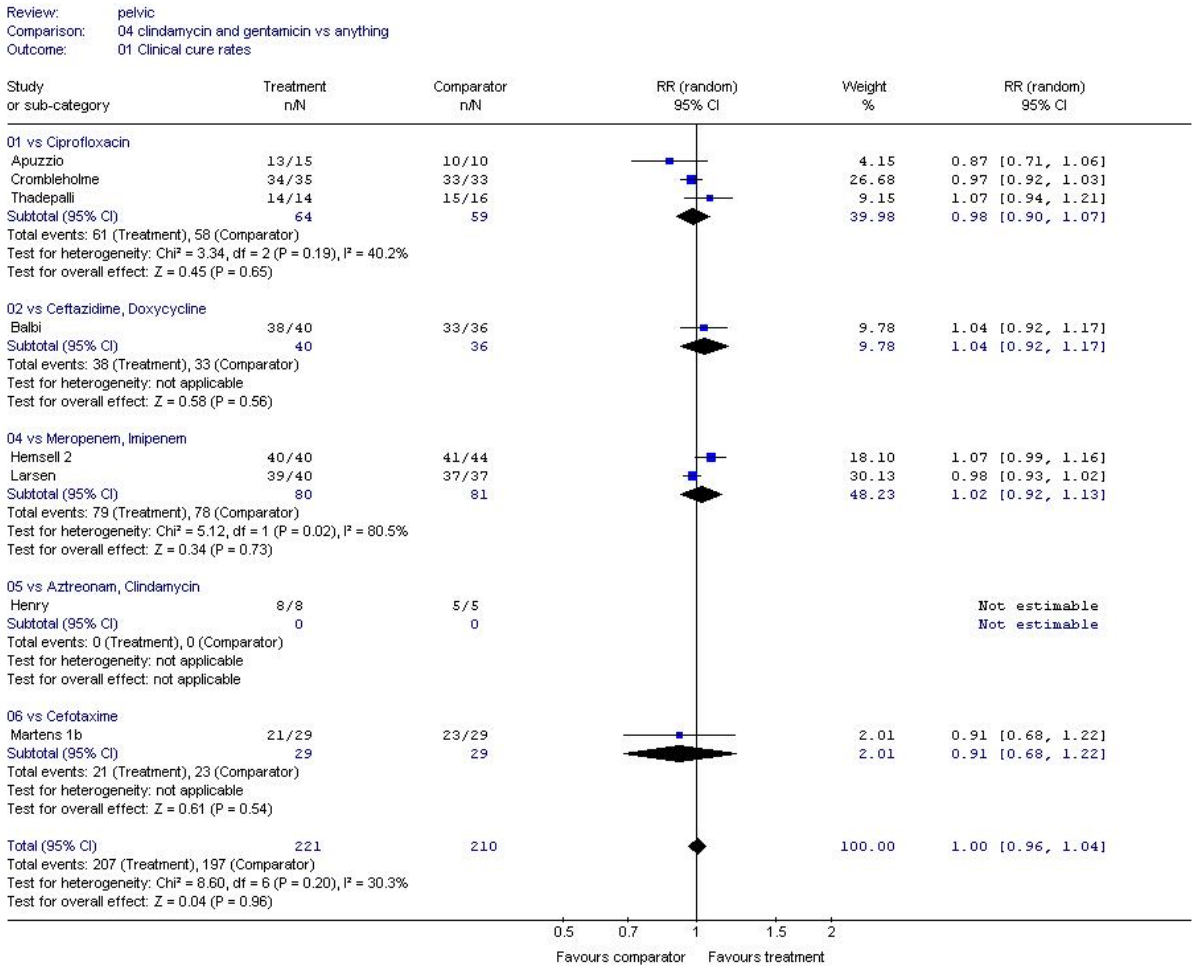
(Also see Clinical effectiveness of standard antibiotic regimens vs any other standard antibiotic regimens)
Eight trials (Apuzzio,[46] Balbi,[47] Crombleholme,[48] Hemsell 2,[33] Henry,[30] Larsen,[31] Martens 1b[49] and Thadepalli[36]) compared clindamycin and gentamicin to non-standard treatments. The trials that specified drug regimens gave similar iv doses and all except Larsen specified continuation with oral clindamycin after the iv phase, mostly for 10 to 14 days, rather than changing to doxycycline or metronidazole. Martens specified a minimum 4 days of treatment but the mean treatment duration was between 5-8 days (see results below). Larsen specified treatment for at least 3 days. All of the comparisons included cephalosporins, beta lactams or the quinolone ciprofloxacin (see Table 13). In Crombleholme, clindamycin could be added to the ciprofloxacin arm but only one patient (out of 33) had this extra treatment. Henry was a direct comparison between gentamicin and aztreonam because clindamycin was given in both arms. Larsen patients were given doxycycline if they were chlamydia positive but the number given this extra treatment was not specified. Where stated, all were inpatient trials, 7/8 were

USA based and 5 were part of larger trials of pelvic infections. None used laparoscopic diagnosis criteria. The clinical cure rates are given in Figure 4.

Table 13. Drug comparisons of iv clindamycin and gentamicin v non-standard treatments

Apuzzio 1989	Clindamycin, gentamicin	Ciprofloxacin
Balbi 1996	Clindamycin, gentamicin	Ceftazidime, doxycycline
Crombleholme 1989	Clindamycin, gentamicin	Ciprofloxacin, (clindamycin)
Hemsell 2 1997	Clindamycin, gentamicin	Meropenem
Henry 1985	Clindamycin, gentamicin	Aztreonam, clindamycin
Larsen 1985	Clindamycin, gentamicin (doxycycline)	Imipenem, cilastin (doxycycline)
Martens 1b 1990	Clindamycin, gentamicin	Cefotaxime
Thadepalli 1991	Clindamycin, gentamicin	Ciprofloxacin

Figure 4. Clinical cure rates of clindamycin and gentamicin v non-standard treatments



The results show no significant differences between clindamycin/gentamicin compared to other non-standard treatments. In Balbi the microbiological cure rates were 12/12 and 16/16 for gonorrhoea and 6/7 and 5/6 for chlamydia. In Crombleholme they were 22/22 and 22/22 for gonorrhoea and 6/6 and 6/7 for chlamydia. In Hemsell 2 satisfactory bacteriologic response was defined as eradication of pre-treatment pathogens, with success or presumed success if no specimen was available for culture after treatment. The follow up results for this

trial were at 2-4 weeks after treatment ended. The numbers with satisfactory bacteriologic responses at end of treatment were 40/40 and 42/44 and at follow up were 12/12 and 14/15. The microbiological cure rates in the Henry trial were 8/8 and 5/5. In Thadepalli they were 12/12 for gonorrhoea and 2/2 for chlamydia in the ciprofloxacin group but equivalent results were not given in the Clindamyin/gentamicin group.

The numbers with a satisfactory clinical result in Hemsell 2 at follow up were 30/30 for clindamycin/gentamicin and 32/33 for Meropenem. Martens trial results for hospital stay duration were not separated out between trials 1a and 1b. The clindamycin/gentamicin group spent 7.5 (SD 3.9, range 5-25) days whereas the combined Cefotaxime group spent 7.1 (SD 3.2, range 4-18) days in hospital. The side effects of treatment in PID were only given in 2 trials (see Table 14) because the others either did not give this information or were trials of mixed pelvic infections where the side effects were not given separately for PID.

Table 14. Side effect of clindamycin and gentamicin v non-standard treatments

	Clindamycin/Gentamicin	Comparison
Balbi 1996		Ceftazidime, Doxycycline
Withdrew from study because of side effects	0/40	0/36
Crombleholme 1989		Ciprofloxacin
Allergies to drug	0/35	2/35

3.2.4.6 Intravenous ciprofloxacin and intravenous (or oral) doxycycline and intravenous metronidazole

No RCTs found

3.2.5 Any non- standard antibiotic or combination vs placebo

No RCTs found

3.2.6 Any non-standard antibiotic or combination compared to any other non-standard antibiotic or combination

3.2.6.1 Broad spectrum penicillins

Six trials compared broad-spectrum penicillin with or without other antibiotics to other non-standard treatments (see Table 15). The doses of amoxicillin/clavulanate varied between 2-4g/day and of ampicillin between 4-12g/day. The Judlin RCT was a direct comparison between ofloxacin and doxycycline because amoxicillin/clavulanate was given to both arms. The Burchell RCT had 3 arms, two of which were a comparison between ampicillin and tetracycline because metronidazole was given in both arms. Only one RCT took place in USA (Spence) with the remainder sited in Europe or South Africa. All were inpatient RCTs, 4 had laparoscopic diagnosis and only one (Judlin) was part of a larger RCT. This last trial had a follow up at six months as opposed to 2-6 weeks for all the other trials.

Table 15. Non-standard broad-spectrum penicillin comparisons

Buisson 1989[50]	Amoxicillin/clavulanate (tetracycline)	Amoxicillin, an aminoglycoside, metronidazole (tetracycline)	
Burchell 1987[51]	Ampicillin, Metronidazole	Doxycycline, oxytetracycline	tetracycline, metronidazole
Ciraru-Vigneron 1986[52]	Amoxicillin/clavulanate (doxycycline)	Ampicillin (or amoxicillin), gentamicin, metronidazole (doxycycline)	
de Beer 1983[53]	Ampicillin	Cefoxitin	
Judlin 1995[54]	Amoxicillin/clavulanate, ofloxacin	Amoxicillin/clavulanate, doxycycline	
Spence 1981[55]	Ampicillin	Doxycycline	

The clinical cure rates are shown in Figure 5. In the third arm of the Burchell RCT the clinical cure rate was also 10/10. The results show no significant differences between broad spectrum penicillins compared to other non-standard treatments. No microbiological cure rates were given. Other results are shown in Table 16 and side effects of treatment in Table 17.

Figure 5. Clinical cure rates of broad-spectrum penicillin comparisons

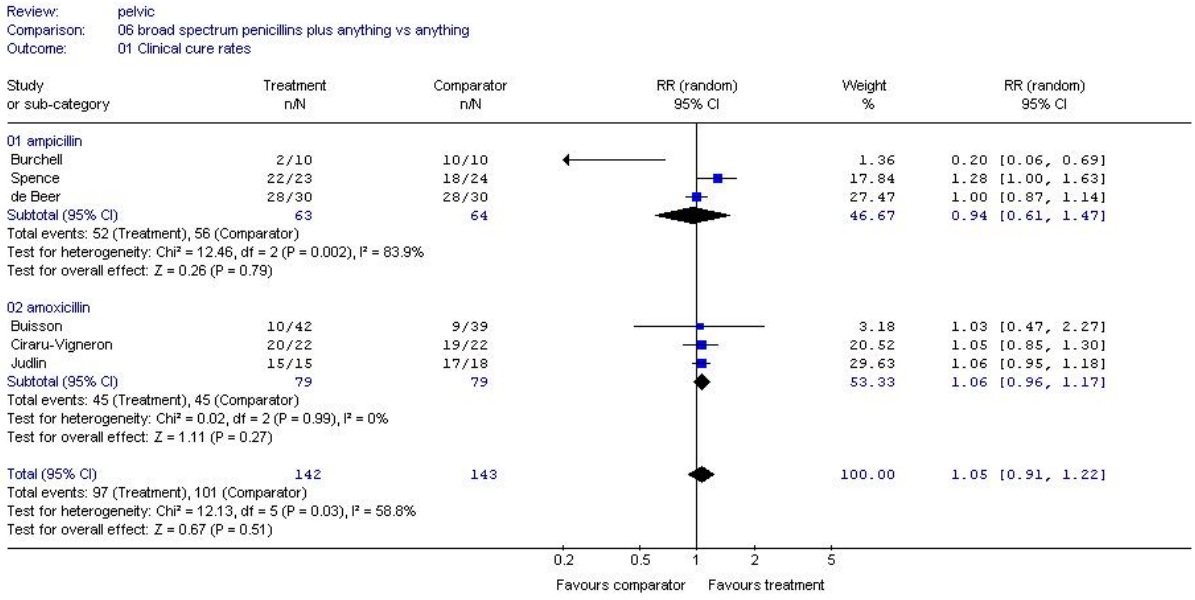


Table 16. Other results for broad-spectrum penicillins

	Broad-spectrum penicillin	Comparator
Buisson 1989		
Clinical cure at 5-6 weeks	18/27	22/29
Ciraru-Vigneron 1986		
Mean duration of hospital treatment	5.3 days	5.7 days
Mean time to normalisation of temperature	2.16 days	1.75 days
Mean time to resolution of spontaneous pain	3.8 days	3.7 days
Mean time to resolution of provoked pain	5.7 days	7.8 days
Mean time to resolution of hyperleucocytosis	5.8 days	6.3 days
de Beer 1983		
Mean ESR at 3 days	40.5 mm/1st h	50.3 mm 1st h
Mean leucocyte count at 3 days	5.7 x 10^9/l	8.5 x 10^9/l
Mean hospital stay duration	3.43 days	3.93 days

Table 17. Side effects of broad-spectrum penicillins

	Broad-spectrum penicillin	Comparator
Buisson 1989		
Angioedema	0/42	1/39
Any side effects	5/42	2/39
Withdrawal of treatment due to side effects	0/42	1/39
Ciraru-Vigneron 1986		
Cutaneous allergy	1/22	0/22
Judlin 1995		
Withdrawal of treatment due to side effects	0/15	0/18

3.2.6.2 Cephalosporins, cephamycins and beta-lactams

Four RCTs compared cephalosporins, cephamycins and beta-lactams with or without other antibiotics to other non-standard combinations. For RCTs and comparisons, see Table 18. Three are comparisons to other antibiotics in this group, one to clindamycin combinations and one to ampicillin (de Beer, reviewed in section 3.2.6.1). They were all inpatient RCTs in USA or Europe. Two were part of larger RCTs of pelvic infections.

Table 18. Non-standard cephalosporins, cephamycins and beta-lactam comparisons

de Beer 1983[53]	Cefoxitin	Ampicillin
Gerstner 1990[56-58]	Ceftriaxone	Cefotaxime
Maggioni 1998[34]	Imipenem with cilastatin	Meropenem
Martens 1a 1990[49]	Cefoxitin	Cefotaxime

The clinical cure rates are shown in Figure 6. The other results are shown in Table 19. The results show no significant differences between cephalosporins, cephamycins and beta-lactams compared to other non-standard treatments.

Figure 6. Clinical cure rates of cephalosporins, cephamycins and beta-lactams comparisons

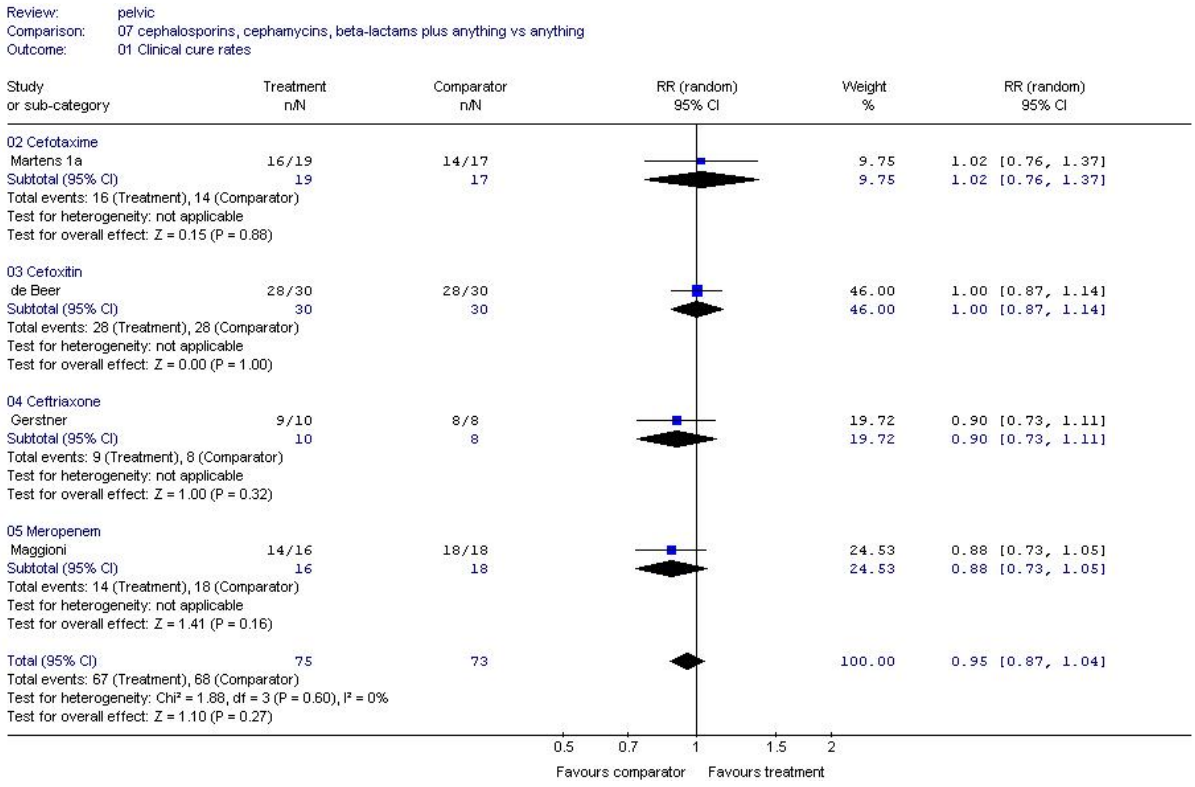


Table 19. Non-standard cephalosporins, cephamycins and beta-lactams other results

	Cephalosporins, cephamycins and beta-lactams	Comparator
de Beer 1983		
Mean ESR at 3 days	50.3 mm 1st h	40.5 mm/1st h
Mean leucocyte count at 3 days	8.5 x 10^9/l	5.7 x 10^9/l
Mean hospital stay duration	3.93 days	3.43 days

3.2.6.3 Tetracyclines

Five trials compared tetracyclines with or without other antibiotics to other non-standard treatments. Four of the five RCTs included doxycycline, the doses of which varied between 100mg-200mg/day for between 1 day and six weeks. The RCTs took place in Europe, Africa, USA and were all small inpatient RCTs. Only one (Judlin) was part of a larger RCT of pelvic infections. The Burchell trial had three arms. The RCTs by Burchell, Judlin and Spence RCTs have already been discussed previously. The Gjonnaess RCT was initially randomised then they closed enrolment to the clindamycin group after 20 patients because of a relatively high number of treatment failures in that group. Results for all patients before and after the randomisation finished are given together. The antibiotic comparisons are shown in Table 20.

Table 20. Non-standard tetracyclines comparisons

Burchell 1987[51]	Doxycycline, oxytetracycline	Ampicillin, Metronidazole	Tetracycline, metronidazole
Gjonnaess 1981[59]	Lymecycline	Clindamycin	
Heinonen 1989[60,61]	Doxycycline, metronidazole	Ciprofloxacin	
Judlin 1995[54]	Doxycycline, amoxicillin/clavulanate	Ofloxacin, amoxicillin/clavulanate	
Spence 1981[55]	Doxycycline	Ampicillin	

The clinical cure rates are shown in Figure 7. The other results are shown in Table 21 and the side effects are shown in Table 22. Heinonen did not give a clinical cure rate but presented their results as a clinical severity score. The results show no significant differences between tetracycline combinations compared to other non-standard treatments apart from the one trial that used clindamycin on its own, where lymecycline was found to be more effective.

Figure 7. Clinical cure rates of tetracycline comparisons

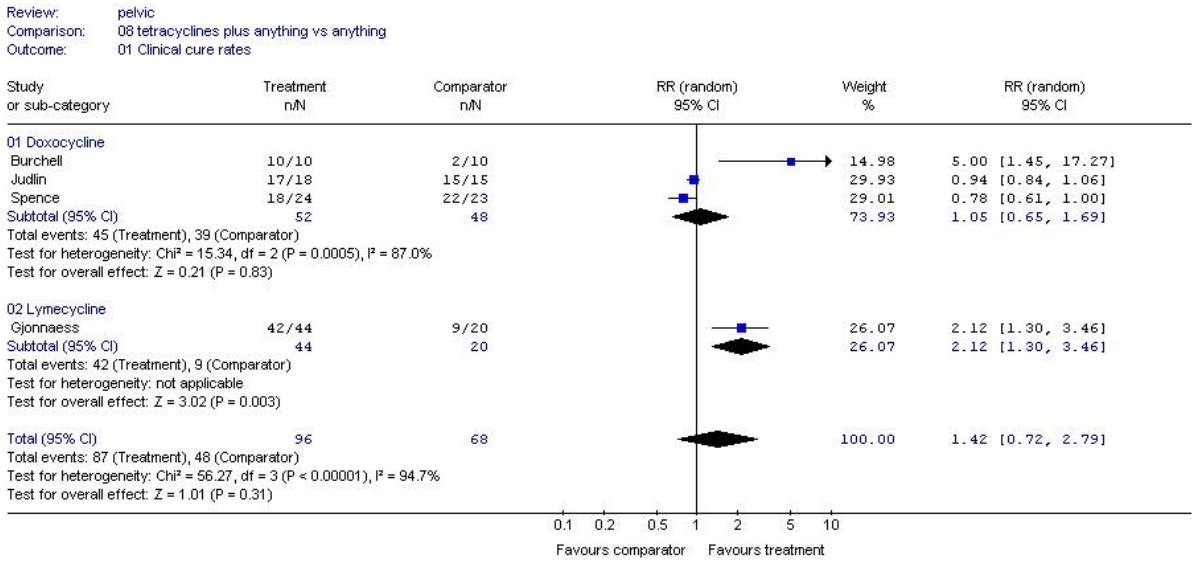


Table 21. Non-standard tetracycline combinations other results

	Tetracycline combinations	Comparator
Gjonnaess 1981		
Mean duration of hospital stay	6.5 days	6.5 days
Heinonen 1989		
Clinical severity score	12 (SD 5, range 6-24)	14 (SD 5, range 7-27)
Gonorrhoea cure rate	1/1	0
Chlamydia cure rate	3/3	6/6
Total microbiological treatment failures	6/20	1/16

Table 22. Non-standard tetracycline combinations side effects

	Tetracycline combinations	Comparator
Heinonen 1989		
Any side effect	11/20	3/16
Withdrawal of treatment due to side effects	0/20	0/16
Judlin 1995		
Withdrawal of treatment due to side effects	0/18	0/15

3.2.6.4 Aminoglycosides

Three trials compared an aminoglycoside with or without other antibiotics to other non-standard combinations. All took place in the 1980's, all were inpatient trials and two of the three used laparoscopic diagnosis. The one that did not (Gall) was part of a larger RCT of pelvic infections. This RCT had tobramycin in both arms so directly compared clindamycin to metronidazole. They also used spectinomycin for some patients but do not say whether it was used in the PID patients. (Spectinomycin is no longer included in the BNF). The antibiotic combinations used are shown in Table 23.

Table 23. Non-standard aminoglycosides comparisons

Buisson 1989[50]	Amoxycillin, an aminoglycoside, metronidazole	Amoxicillin/clavulanate
Ciraru-Vigneron 1986[52]	Ampicillin (or amoxycillin), gentamicin, metronidazole (doxycycline)	Amoxicillin/clavulanate (doxycycline)
Gall 1981[62]	Tobramycin, Metronidazole (spectinomycin)	Tobramycin, Clindamycin (spectinomycin)

The clinical cure rates are shown in Figure 8. The other results are shown in Table 24. The mean fever index in the Gall RCT includes the mean number of hours with an elevated temperature. The results show no significant differences between aminoglycoside combinations compared to other non-standard treatments. The side effects results are shown in Table 25.

Figure 8. Clinical cure rates of aminoglycoside comparisons

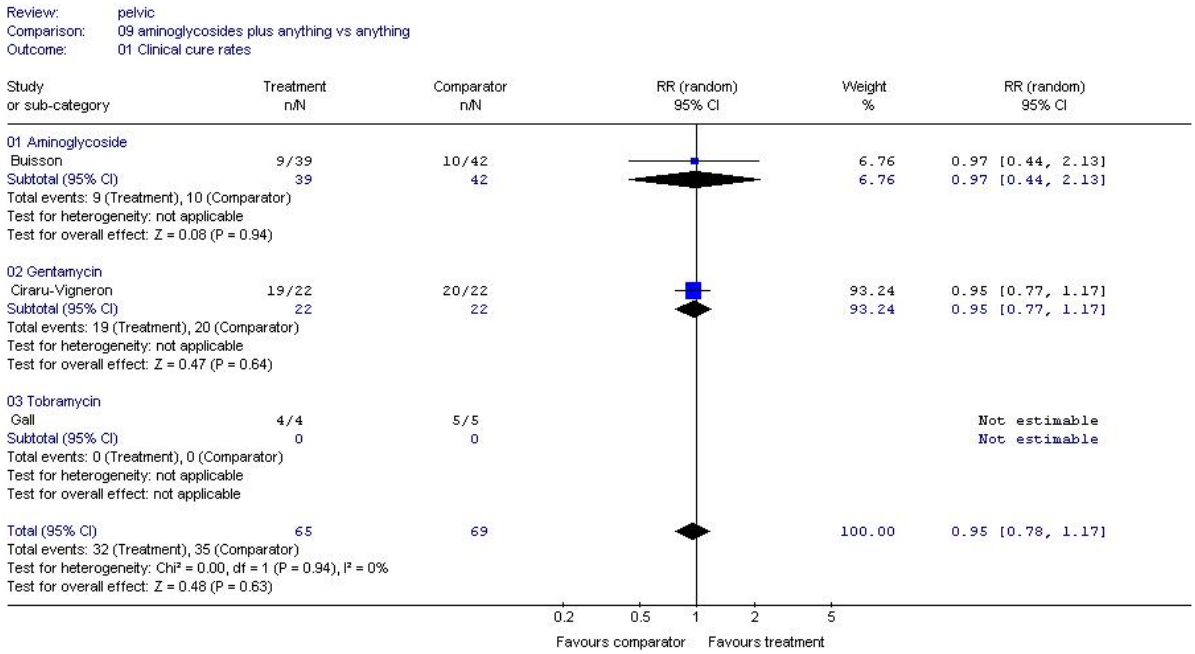


Table 24. Non-standard aminoglycoside combinations other results

	Aminoglycoside combinations	Comparators
Buisson 1989		
Clinical cure rates at 5-6 weeks	9/39	10/42
Ciraru-Vigneron 1986		
Mean duration of hospital treatment	5.7 days	5.3 days
Mean time to normalisation of temperature	1.75 days	2.16 days
Mean time to resulution of spontaneous pain	3.7 days	3.8 days
Mean time to resolution of provoked pain	7.8 days	5.7 days
Mean time to resolution of hyperleucocytosis	6.3 days	5.8 days
Gall 1981		
Mean fever index	20.4F (SEM 7.7)	34.2F (SEM 6.2)

Table 25. Non-standard aminoglycoside combinations side effects

	Aminoglycoside combinations	Comparator
Buisson 1989		
Angioedema	1/39	0/42
Any side effects	2/39	5/42
Withdrawal of treatment due to side effects	1/39	0/42
Ciraru-Vigneron 1986		
Cutaneous allergy	0/22	1/22

3.2.6.5 Macrolides

Two RCTs (Bevan A and Bevan B reported in one journal article[29]) compared Azithromycin to azithromycin plus metronidazole. The doses of metronidazole varied slightly in the two trials. There was a third arm to each trial which was metronidazole plus doxycycline plus cefoxitin plus probenecid for the first trial and doxycycline plus amoxycillin in the second. The results of the two trials have been reported together so it will be treated here as one trial with the combined third arm excluded. This trial was not well reported. It was described as multicentre but was unclear whether it took place in Great Britain or Europe. It may have been sponsored by Pfizer Inc. because one of the three authors was an employee although there is no sponsorship statement. The total number of patients who started the trials in the two arms reviewed here was 213 but only 79 were followed up at 2 weeks. The clinical cure rates were 38/40 for the azithromycin group and 40/40 for the combination group (not statistically significant). The microbiological results at follow up of 35-44 days are shown in Table 26 and the side effects in Table 27. The results show no significant differences between macrolide combinations compared to other non-standard treatments. The severe adverse events in the combination group included gastrointestinal tract problems, headache, dizziness, dyspnoea and hypotension.

Table 26. Non- standard macrolide combinations other results

	Azithromycin	Azithromycin+metronidazole
Chlamydia cure rates	21/22	22/22
M hominis cure rates	9/10	13/16
Gonorrhoea cure rates	5/5	4/5

Table 27. Non- standard macrolide combinations adverse events

	Azithromycin	Azithromycin+metronidazole
Any adverse event	26/106	32/107
Severe adverse event	2/106	8/107
Withdrawn treatment due to adverse event	2/106	4/107
Deaths	0/106	0/107

3.2.6.6 Clindamycin

Two RCTs compared clindamycin with or without other antibiotics to other non-standard combinations and were small inpatient trials in USA and Europe. The dosage of clindamycin varied between 600mg – 2.4g per day. All trials have been reviewed in previous categories. The antibiotic combinations are shown in Table 28.

Table 28. Non-standard clindamycin comparisons

Gall 1981[62]	Tobramycin, clindamycin (spectinomycin)	Tobramycin, metronidazole (spectinomycin)
Gjonnaess 1981[59]	Clindamycin	Lymecycline

The clinical cure rates are shown in Figure 9 and the other results are shown in Table 29. The results show a significant difference between clindamycin used on its own compared to the other non-standard treatment of lymecycline.

Figure 9. Clinical cure rates of clindamycin comparisons

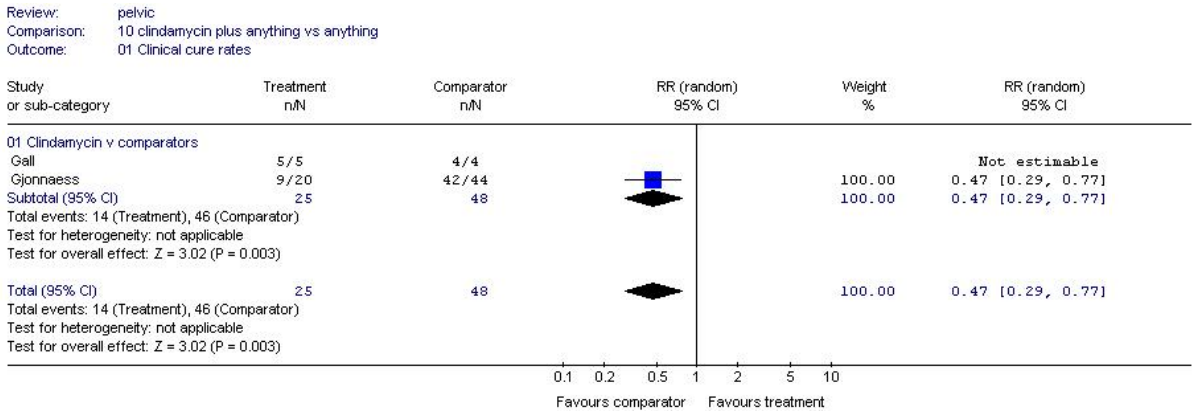


Table 29. Non-standard clindamycin combinations other results

	Clindamycin combinations	Comparators
Gjonnnaess 1981		
Mean duration of hospital stay	6.5 days	6.5 days
Gall 1981		
Mean fever index	34.2F (SEM 6.2)	20.4F (SEM 7.7)

3.2.6.7 Other antibacterials

This category includes chloramphenicol, fucidic acid, vancomycin, teicoplanin, linezolid, quinupristin, dalfopristin, polymixins, sulphonamides and trimethoprim. No RCTs were found using any of these antibacterials alone or in any combination.

3.2.6.8 Metronidazole

Six trials compared metronidazole with or without other antibiotics v. other combinations and all RCTs have been reviewed above. The two Bevan trials were reported together and have been counted as one large inpatient trial. The other five RCTs were small inpatient trials from Europe, South Africa and USA and one (Gall) was part of a larger RCT of pelvic infections. The antibiotic combinations used are shown in Table 30. The doses of metronidazole ranged from 1.2g – 2g per day. Two RCTs (Bevan, Burchell) had three arms The Bevan trials third arms used different antibiotics and the results were not separated so these arms have been excluded and are not shown in Table 30. The Burchell trial also had three arms and two of these used metronidazole. The ampicillin plus metronidazole arm had a much lower clinical cure rate than the tetracycline plus metronidazole arm. Both comparisons have been used in the Forest plot of clinical cure rates, shown in Figure 10. The other results are shown in Table 31 and side effects in Table 32. The results show no significant differences between metronidazole combinations compared to other non-standard treatments.

Table 30. Non-standard metronidazole comparisons

Bevan 2003[29]	Azithromycin, metronidazole	Azithromycin	
Buisson 1989[50]	Amoxycillin, an aminoglycoside, metronidazole	Amoxicillin/clavulanate	
Burchell 1987[51]	Ampicillin, Metronidazole	Doxycycline, oxytetracycline	Tetracycline, metronidazole
Ciraru-Vigneron 1986[52]	Ampicillin (or amoxycillin), gentamicin, metronidazole (doxycycline)	Amoxicillin/clavulanate (doxycycline)	
Gall 1981[62]	Tobramycin, metronidazole (spectinomycin)	Tobramycin, clindamycin (spectinomycin)	
Heinonen 1989[60,61]	Doxycycline, metronidazole	Ciprofloxacin	

Figure 10. Clinical cure rates of metronidazole comparisons

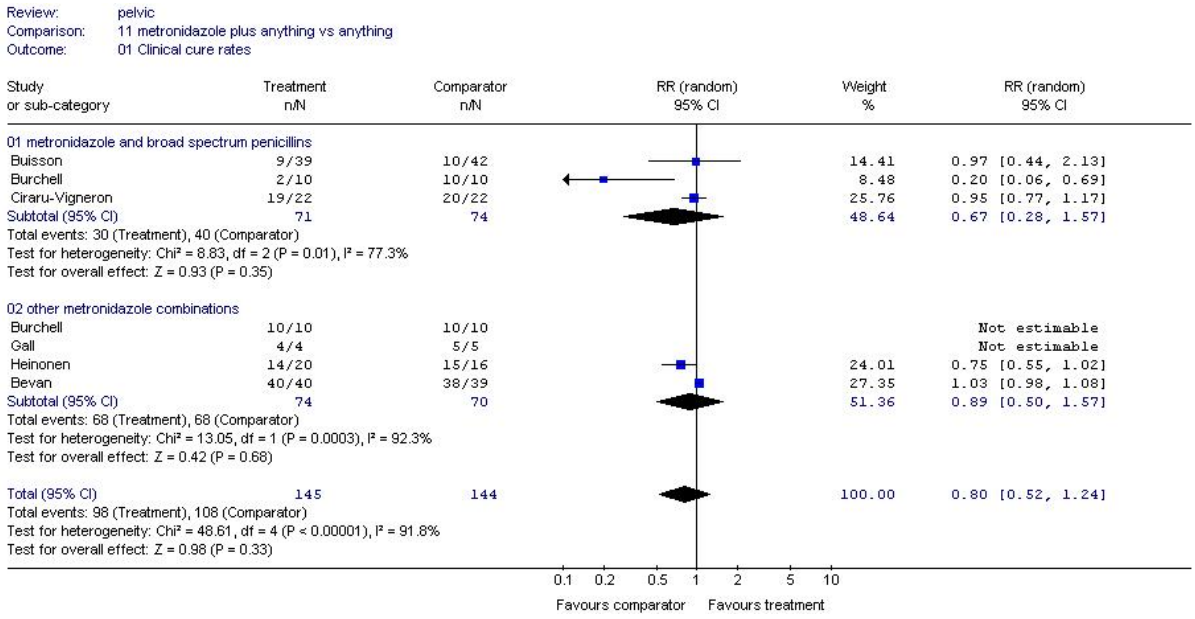


Table 31. Non-standard metronidazole combinations other results

	Metronidazole combinations	Comparator
Bevan 2003		
N gonorrhoeae	4/5	5/5
C trachomatis	22/22	21/22
M hominis	13/16	9/10
Buisson 1989		
Clinical cure at 5-6 weeks	18/27	22/29
Ciraru-Vigneron 1986		
Mean duration of hospital treatment	5.3 days	5.7 days
Mean time to normalisation of temperature	2.16 days	1.75 days
Mean time to resulution of spontaneous pain	3.8 days	3.7 days
Mean time to resolution of provoked pain	5.7 days	7.8 days
Mean time to resolution of hyperleucocytosis	5.8 days	6.3 days
Gall 1981		
Mean fever index	20.4F (SEM 7.7)	34.2F (SEM 6.2)
Heinonen 1989		
Gonorrhoea	1/1	0
Chlamydia	3/3	6/6

Table 32. Non-standard metronidazole combinations side effects

	Metronidazole combinations	Comparator
Bevan 2003		
Any adverse event	32/107	26/106
Severe adverse event	8/107	2/106
Withdrawn treatment due to adverse event	4/107	2/106
Deaths	0/107	0/106
Buisson 1989		
Angioedema	0/42	1/39
Any side effects	5/42	2/39
Withdrawal of treatment due to side effects	0/42	1/39
Ciraru-Vigneron 1986		
Cutaneous allergy	1/22	0/22
Heinonen 1989		
Any side effect	11/20	3/16
Withdrawal of treatment due to side effects	0/20	0/16

3.2.6.9 Quinolones

Two RCTs compared quinolones with or without other antibiotics to other non-standard combinations and were smaller inpatient trials from Europe. Judlin was part of a larger trial of pelvic infections. All trials have been reviewed above. The antibiotic comparisons are shown in Table 33 clinical cure rates in Figure 11, other results in Table 34 and side effects in Table 35. The results show no significant differences between quinolone combinations compared to other non-standard treatments.

Table 33. Non-standard quinolone comparisons

Heinonen 1989[60,61]	Ciprofloxacin	Doxycycline, Metronidazole
Judlin 1995[54]	Ofloxacin, amoxicillin/clavulanate	Doxycycline, amoxicillin/clavulanate

Figure 11. Clinical cure rates of quinolone comparisons

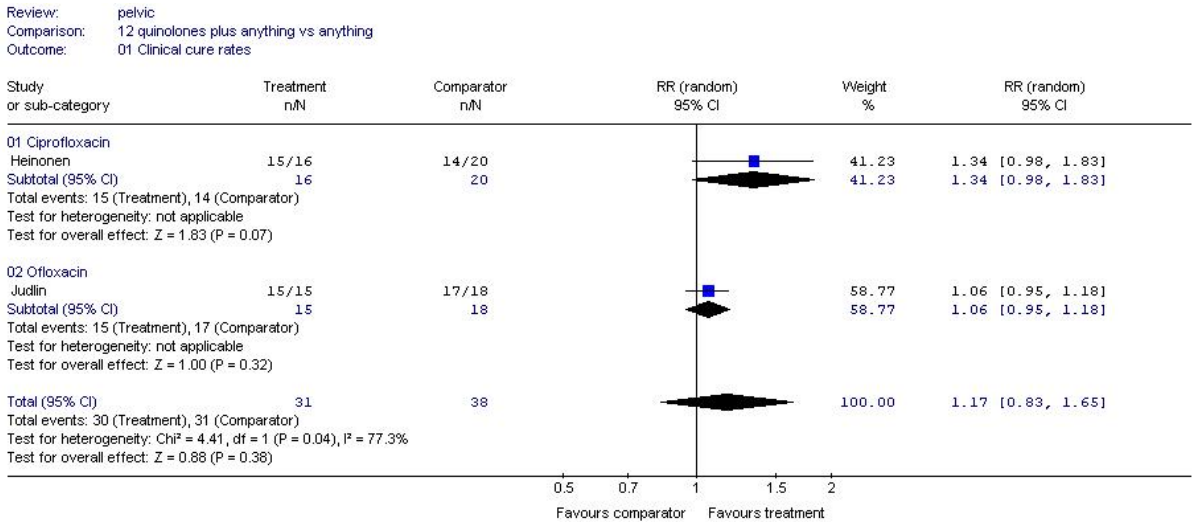


Table 34. Non-standard quinolone combinations other results

	Tetracycline combinations	Comparator
Heinonen 1989		
Gonorrhoea cure rate	0	1/1
Chlamydia cure rate	6/6	3/3

Table 35. Non-standard quinolone combinations side effects

	Tetracycline combinations	Comparator
Heinonen 1989		
Any side effect	3/16	11/20
Withdrawal of treatment due to side effects	0/16	0/20
Judlin 1995		
Withdrawal of treatment due to side effects	0/15	0/18

3.2.7 Any antibiotic or combination vs same antibiotic or combination

3.2.7.1 Amikacin and Netilmicin given once per day vs more than once per day

Two trials compared the pharmacokinetics, efficacy and safety of amikacin and netilmicin given either once daily or the dame dose divided into two for amikacin and three for netilmicin. These two trials were published in the same trial report three times, once where Ibrahim was lead author[63] and twice where Tulkens was lead author.[64,65] The intension of the two RCTs was to establish whether these two drugs were just as effective and safe in single daily doses compared to divided doses. They particularly looked for any signs of hearing loss caused by different dosing regimens.

Table 36. Comparisons of amikacin and netilmicin

Ibrahim a 1990	Amikacin x1 tinidazole, ampicillin	Amikacin x2 tinidazole, ampicillin
Ibrahim b 1990	Netilmicin x1 tinidazole, ampicillin	Netilmicin x3 tinidazole, ampicillin

All patients were clinically cured by the treatments received. One patient had persistence in the offending microbial pathogen in the Netilmicin 3xdaily group. The serum creatinine levels at the seventh day and the numbers of patients with a loss of 15 decibels or more are shown in Table 37. The trial report did not state whether the variations around the point estimates were standard deviations or standard errors.

Table 37. Side effects of amikacin and netilmicin

	Intervention	Control
Amikacin (serum creatinine)	0.86 (0.11)	0.81 (0.12)
Netilmicin (serum creatinine)	0.83 (0.13)	0.83 (0.11)
Amikacin (0.25-8Hz)	1	2
Netilmicin (0.25-8Hz)	0	2
Amikacin (10-18Hz)	3	4
Netilmicin (10-18Hz)	3	9

3.2.7.2 The length of antibiotic therapy needed for each of the antibiotics assessed to achieve clinical cure or microbiological cure

There are no RCTs that specifically address this question

3.2.8 Whether outpatient treatment is more or less effective than inpatient treatment

To some extent the PEACH trial addressed this question and this has been reviewed above (see section 3.2.3.3). There were no other RCTs found.

3.2.9 Assessment of effectiveness

This systematic review has assessed results from 34 different RCTs. The trials were published between 1980 and 2003 and antibiotic practices have changed considerably over this time. It is noticeable from Table 38 that the busiest period of trial investigation was 1990-1994 and that the size of trials has gradually become larger. (Three of the five trials in 1995-1999 were larger trials of pelvic infections which included some PID patients).

Table 38. Size and date of trials

Date of publication	Number of trials	Number of patients randomised	Number of patients per trial
1980-1984	4	180	45
1985-1989	9	465	52
1990-1994	14	1438	103
1995-1999	5	388	78
2000-2004	2	1077	538

It is also noticeable that in a large number of trials patients were excluded from evaluation of effectiveness for a wide variety of different reasons (see Table 54). Eleven used ITT analysis and the remainder gave reasons for not reporting results for all randomised patients. The quality of the trial reports is generally poor, with all but two trials having a Jadad score of 0 or 1. Of the two trials achieving a Jadad score above 1, one was published in 2002[40,41] and the other in 1988.[42]

The vast majority of results demonstrate no clinical superiority of one treatment over another. This may be because of ceiling effects, ie many of the smaller trials had 100% effectiveness in one or both arms. Another possible reason is that all antibiotics are similarly effective, or it could be that most of the trials were underpowered to find a small difference in effectiveness. Lastly, random effects models were used in the meta-analyses, which are known to be less likely to show a significant difference. The reason for using random effects models was because of the clinical heterogeneity of the trials, which was likely to lead to statistical heterogeneity. Some comparisons that were more clinically heterogeneous have subgroups shown on the Forest plots. It could be argued that meta-analysis was inappropriate for some of the more clinically heterogeneous comparisons but in the end surprisingly little statistical heterogeneity was found in some comparisons whereas more was found in others.

The only antibiotic found to be less effective than comparator is clindamycin used on its own. This is from the result of one early RCT where enrolment was discontinued after 20 patients in the clindamycin arm when it was seen that there were a large number of treatment failures (the other arm given lymecycline eventually enrolled 44 patients). The reason for this lack of success could be a statistical ‘blip’ from a small sample size or that clindamycin on its own is not an effective treatment for PID. However, clindamycin is now not used on its own for the treatment of PID so this finding is of academic importance only.

The microbiological results were very mixed. Where reported, a considerable number failed to isolate specific causative agents for PID at the start of the trial so could not ascertain whether the antibiotics had removed the pathogens. There is also the problem of patients having unprotected sex with infected partners after treatment so reinfecting themselves before the follow up swab is taken. The results that were reported were often near 100% cure rates so finding a significant difference between comparators was unlikely. Therefore the microbiological results were inconclusive.

The side effects results varied with the different antibiotics and combinations used. Inevitably, vestibular disturbance and other symptoms of ototoxicity were more common with the aminoglycosides. Nausea and vomiting appeared more common with cefoxitin, probenecid and doxycycline than comparators (Martens 2) and ‘any side effect’ more common in tetracyclines (Heinonen) and azithromycin (Bevan)

3.2.10 Equity issues

A review was made of the number of included RCTs that mentioned the ethnic background of patients included in each trial. The results are shown in Table 39. It is noticeable that only 6 of the 34 trials included mention of ethnic background, many recent ones did not. Also, most of the ones that did report ethnic background have a very high number of participants of black ethnic origin. This may be for a number of reasons:

- The diagnosis rate is higher in black people (the prevalence is higher in black people –see section 2.1.1- but not to this extent)
- Trials are carried out in hospitals where the majority of local residents are of black ethnic origin (this may be true for some single-centre trials but is unlikely for very large multi-centre trials such as PEACH)
- People of black ethnic origin tend to be amongst the poorer in society in USA. This means that often they do not have medical insurance. Therefore, to receive adequate medical treatment enrollment into a clinical trial means that they can obtain free treatment.

Table 39. Ethnic background in trials

Trial	Ethnic group	Percentage of patients	Trial location
Arredondo 1997	Hispanic	96-99%	South and Central America
Crombleholme 1989	Black	71%	USA
Landers 1991	Black	49-50%	USA
Martens 2 1993	Black	57%	USA
Peach 2002	Black	75%	USA
Soper 1988	Black	10-13%	USA

The question is whether antibiotic effectiveness is similar in different ethnic groups. There is a suggestion from one study of consecutive patients treated in the Netherlands that antibiotic resistance for some antibiotics (metronidazole, clarithromycin) may be higher in people originating from Africa and Turkey than in ethnic Dutch participants.[66] This may be due to the different ethnic group forming sub-populations with specific subtypes of bacteria prevalent resulting in different antibiotic resistances or it could be because people of different ethnic backgrounds having different antibiotic resistances.

Subgroup analysis of the PEACH trial with its large number of participants, looking at clinical outcomes by ethnic group and the bacterial strains present may help to resolve this question.

If antibiotic resistance is higher in some ethnic groups compared to others then the results from trials may not be as transferable to another setting as was previously thought. It would also be very important for all trials to publish the ethnic background of participants.

4. ECONOMIC ANALYSIS

4.1 Methods for economic analysis

4.1.1 Costs and cost effectiveness review

A systematic review of the literature on costs, health economic impact and quality of life of PID was carried out. The clinical effectiveness searches were extended to identify relevant economic analyses or any studies reporting costs, cost effectiveness, cost utility or generic quality of life outcomes.

Search Strategy
The following sources were searched to December 2002:

- Bibliographic databases: MEDLINE, EMBASE, NHS EED, HEED
- Internet sites of national economic units

Relevant information found during the clinical effectiveness searches were also used.

A second search of the following sources was carried out to May 2004:

- Bibliographic databases: MEDLINE, EMBASE, NHS EED
- Citations of included studies

Inclusion and exclusion criteria, data extraction and quality assessment
Studies were only included if they met the criteria shown in Table 40:

Table 40. Cost effectiveness review inclusion criteria

Patient	Women with PID, diagnosed clinically or laparoscopically
Intervention	Any antibiotic or combination
Control	Not applicable
Outcomes	Cost, cost consequence, cost effectiveness, cost utility, cost minimization, cost consequences or any generic quality of life
Study design	Any

One reviewer, using explicit predetermined criteria, made the inclusion and exclusion decisions for the economic evaluation review. This was checked by a second researcher. Quality of included studies was assessed using the modified Drummond checklist[67].

Analysis
Analysis of results of included studies was qualitative only. Conclusions were based on clearly tabulated data from included studies.

4.2 Cost effectiveness review results

A total of 22 potentially relevant studies were found from the searches. Eight studies were included and 18 studies excluded. A list of excluded studies with reasons for exclusions are shown in Appendix 6. The main reasons for exclusion were that the studies looked at treating uncomplicated genital infections with the aim to prevent PID and other expensive sequelae. All eight included studies were published in USA between 1980 and 2000 so the treatment used in some may not mirror current practice and the costs may not be relevant to the UK. All were fully published in one or more peer-reviewed journal articles. Five of the eight are cost studies, two are cost-effectiveness studies and one is a quality of life study. All costs are given in US dollars. The included studies details are shown in Table 41, Table 42 and Table 43.

4.2.1 Cost studies

Three of the five cost studies[68-70] show a general trend of increasing direct cost per case of PID between 1980 and 1991. The fourth study[71] is measuring lifetime cost for PID rather than annual cost. However, one would expect that the lifetime cost of PID would be higher than the annual cost per case because of the relative frequency of sequelae so the reason for the lower cost found is unclear.

The Yeh study used much more sophisticated ways to derive an average lifetime cost of PID than the Rein study. It was widely researched for probability and timing of complications from PID. The sensitivity analysis was extensive and the journal article very detailed. The resulting range of lifetime cost of PID per person was similar to that from the Rein study (the only cost study to calculate lifetime cost) ($1,060 - $3,180 vs $1,519). Possibly more useful is the cost where initial treatment has been unsuccessful. Here the discounted average per person lifetime cost was $1,270 - $6,840 depending on the specific complications (CPP - $6,350, ectopic pregnancy - $6,840 and infertility - $1,270) The low cost associated with infertility reflects the fact that many infertile women do not seek infertility treatment. The sensitivity analysis showed that costs were most sensitive to major complications resulting from PID and the cost of surgery for CPP.

For all of the cost studies there are some inherent problems with using hospital discharge data and patient charges for costs. Although they can give an idea of what happens in the real world, as opposed to clinical opinion that gives a more idealised picture of what should happen, they rely on accurate coding and record-keeping. PID could be included in ICD codes in one of three categories (see Table 2 in the epidemiology section) so miscoding is a potential source of error.

Table 41. Review of annual cost studies comparisons table

	Curran 1980[68]	Washington 1986[69]	Washington 1991[70]
Type of economic evaluation	Cost of condition study	Cost of condition study	Cost of condition study
Date of costs	1979	1982-4	1987-8
Location of study	One hospital in San Francisco, USA	Two hospitals in San Francisco, USA	Two hospitals in San Francisco, USA
Perspective	Societal	Societal	Societal
Data collection	Probably retrospective	Probably retrospective	Probably retrospective
Source of cost data	Hospital administration database charges	National and state hospital cost databases	National and state hospital cost databases
Costs included:	Direct – hospitalisation, gynaecologic surgery, outpatient visits. Indirect – costs of loss of housewives' services, lost work output Intangible – not included	Direct – average cost per admission and surgical procedures at one of the hospitals, cost per outpatient visit Indirect – lost wages, lost value of household management, lost value of lifetime earnings from deaths	Direct – physician charges, preadmission visit via A&E or outpatients, hospital charges Indirect – lost wages, lost value of household management, lost value of lifetime earnings from deaths
Quantities and costs reported separately	No	Yes	Yes
Source of effectiveness data	Hospital discharge surveys	National hospital discharge data	California state hospital discharge data
Effectiveness parameters taken into account	Incidence of PID, ectopic pregnancy	Incidence of PID, ectopic pregnancy, infertility	Incidence of PID, ectopic pregnancy, infertility
Discount rate?	4% for economic losses from premature deaths	4% for expected lost lifetime earnings from deaths	4% for expected lost lifetime earnings from deaths
Sensitivity analysis?	Not reported	Not reported	Not reported
Other factors	-	Total cost projected to year 1990 assuming different incidence rates of PID	Total cost projected to year 2000 assuming different incidence rates of PID

	Curran 1980[68]	Washington 1986[69]	Washington 1991[70]
Cost result	Total cost in USA $1,256,322,600 Direct – $698,986,250 Indirect - $557,336,400	Total cost in USA $2,620,000,000 Direct – $1,225,496,000 Indirect - $1,389,600,000	Total cost in USA $4,236,470,000 Direct – $2,728,070,000 Indirect -$1,508,400,000
Total number of cases or treatment visits	850,000	1,272,600	1,477,700
Total cost per case of PID	$1,478	$2,059	$2,867
Direct cost per case of PID	$822	$963	$1,846

Table 42. Review of lifetime cost studies comparisons table

	Rein 2000[71]	Yeh 2003[16]
Type of economic evaluation	Lifetime cost per case of PID	Cost study (Markov model) to determine average lifetime cost of PID
Date of costs	1998	2000
Location of study	-	USA
Perspective	Societal	Societal
Data collection	Probably retrospective	Retrospective from published literature
Source of cost data	MarketScan database	MarketScan database (from [71])
Costs included:	Direct only – Actual patient and insurance payments for outpatient, inpatient and pharmacy costs	Outpatient and inpatient treatment for PID and sequelae of CPP and ectopic pregnancy, infertility and its treatment.
Quantities and costs reported separately	Yes	Yes
Source of effectiveness data	National hospital discharge data	From published literature (extensive referencing)
Effectiveness parameters taken into account	Incidence of PID, ectopic pregnancy, infertility, chronic pelvic pain	PID infection, CPP, ectopic pregnancy, infertility
Discount rate?	5% for expected lifetime costs of treatments	Costs and benefits at 3% per annum
Sensitivity analysis?	Yes on effectiveness estimates	Yes, extensive, on costs, natural history of PID, timing and duration of major clinical complications.
Cost result	Direct cost in USA = $1,880,000,000 Total number of treatment visits = 1,237,309 Lifetime cost of PID per person = $1,519	$1,060 - $3,180 lifetime cost of PID per person.

Table 43. Review of cost-effectiveness studies comparisons table

	McNeely 1998[72]	Adams 2003[73]
Type of economic evaluation	Cost-effectiveness study of 3 antibiotic regimens	Cost effectiveness study of training pharmacy workers in syndromic management of STDs
Date of costs	Not stated (data collected between 1993-7	1997-2000
Location of study	One hospital in Detroit, USA	Lima, Peru
Perspective	Hospital	Societal
Data collection	Prospective costing on same patient sample as used for effectiveness	Prospective
Source of cost data	Accounting offices of the Detroit Medical Centre	Pharmacy costs, study budget reports
Costs included:	Direct - pharmacy costs, physician charges, hospital charges,	Medication, pharmacy personnel costs (not included are referral to physician, transport to physician, consultation, subsequent care)
Quantities and costs reported separately	No	Yes
Source of effectiveness data	Consecutive case series from single hospital n=179	Estimated from census and prevalence studies
Effectiveness parameters taken into account	Efficacy of treatment, incidence of tubo-ovarian abscess, surgical intervention, hospital stay duration	Proportion of patients where adequate management was given
Discount rate?	None undertaken due to short study period	Not reported
Sensitivity analysis?	Not reported	Yes
Other factors	Effectiveness results – Clindamycin/gentamicin – 47% Ampicillin/clindamycin/gentamicin – 87.5%	The proportion of patients with PID or vaginal discharge had greatest impact on cost effectiveness of programme, and medication costs under the societal perspective.
Cost result	Mean hospital costs for PID patients with or without tubo-ovarian abscess – clindamycin/gentamicin - $4,976 Ampicillin/clindamycin/gentamicin - $5,228	Mean societal cost per PID episode - Intervention districts = $1.78 (SD 2.35) Control districts = $2.32 (SD 2.73) (data extracted from part of cost effectiveness results)

4.2.2 Cost-effectiveness studies

The two cost effectiveness studies investigate quite different aspects of care for PID.

McNeely describes itself as a cost-effectiveness study of different antibiotic regimens but there is no attempt to combine costs and effectiveness results into a cost per case cured or a cost per QALY. There were three antibiotic comparisons of cefotetan plus doxycycline (n=103), clindamycin plus gentamicin (n=46) and ampicillin plus clindamycin plus gentamicin (n=30). As cefotetan is no longer in BNF, the results from the other two groups have been reported here only. It is interesting to note that none of the RCTs reviewed in the clinical effectiveness part of this systematic review had the treatment of ampicillin/clindamycin/gentamicin. Also, the effectiveness estimate in the clindamycin/gentamicin case series is not mirrored by any of the RCT results for the same treatment. Although case series are lower in the hierarchy of evidence than RCT evidence, in this instance the case series used may mirror actual clinical practice better. This is because it was a case series of consecutive patients and because the RCTs in the systematic review had such high clinical cure rates whereas the actual incidence of sequelae is relatively high in clinical practice. The resulting mean hospital costs for the two reviewed groups do not differ by much in spite of the fact that the effectiveness estimates were so different.

The Adams study is really investigating the cost effectiveness of a type of training for pharmacists, where the example used was sexually transmitted diseases. The existing and new teaching programmes were assessed using simulated patients, ie healthy people with standardised symptom set descriptions visiting pharmacies. The costing of PID, along with vaginal discharge, urethral discharge and genital ulcer disease was done in order to evaluate the costs and benefits to the wider community of pharmacists' improvements in diagnostic ability. The resulting cost per PID episode was remarkably low.

All seven cost or cost-effectiveness studies were based in the USA and the results may not be that applicable to conditions in the UK for a number of reasons:

- There are different structures of health provision in the USA compared to UK
- The different admissions policies in the USA means that fewer patients are treated as outpatients in the USA than UK and more are treated as inpatients
- Hospital and physician charges are not the same as costs
- The rates of sequelae may be different, depending on the relative success of the different treatments used

4.2.3 Quality of life studies

There was one health related quality of life study found [15] which reported results from the PEACH trial. From 798 women followed up in that trial, 547 had at least two follow up interviews and completed the SF-36 questionnaire. The demographic characteristics of this subgroup were similar to those in the whole trial except that there were more participants of black ethnic origin in this subgroup (79%). Unfortunately the results are not separated by treatment group but are split by presence or absence of CPP and by mild/moderate/severe CPP at follow up of a mean of 35 months. The results are depicted graphically for the six domains of physical functioning, bodily pain, general health, vitality, social functioning and mental health and the two composite scores of physical health and mental health. The results vary widely for all scores and have large standard deviations. Unsurprisingly those with CPP have lower mean scores in all domains and the trend was to have worse scores with worse

CPP but there were no significant differences between CPP and non-CPP groups or mild/moderate/severe groups.

4.2.4 Economic evaluation

As there was no clear benefit in favour of one antibiotic treatment compared to any others, no economic modelling has been undertaken.

5. DISCUSSION AND CONCLUSIONS

5.1 Main results

A wide variety of antibiotics were used in 34 RCTs included in this systematic review. There is not a large amount of evidence available regarding the current recommended treatment regimens for PID and one of the seven regimens had no RCT evidence to reinforce it. There may be cohort or case-control study evidence where RCT evidence is lacking but the protocol for this systematic review excluded these study designs. Although RCTs are generally the best evidence available for clinical effectiveness questions, the quality of RCT evidence in this systematic review is poor. The median Jadad score of the included trials was 0 and only two trials score above 1. A well-conducted, large cohort study may provide better evidence than a small, poor quality RCT and further systematic reviews on treatment for PID may benefit from inclusion of these types of studies.

There were almost no trials carried out in the UK and treatment sensitivities may vary from one country to another. Also where trials stated ethnic origin of participants, a much higher proportion than expected were of black origin. This may have implications on the generalisability of results as antibiotic resistance may vary in different ethnic groups.

In systematic reviews, publication bias is always a potential problem and happens particularly where trials do not find significantly different results. However, in this case most of the trials had no significant differences so publication bias appears to be less of a problem here. It was also useful to note that the general trend over time is for trials to recruit more patients and so increase power to detect small differences in treatment effects.

The evidence that was available suggests that almost every treatment used was about as effective as the other, ie there were no significant differences found between treatments. The notable exception to this was for clindamycin used on its own. As it is not a clinically important treatment option, this finding will not be discussed further. The reasons why there were no significant differences in treatment effectiveness may be because:

- The apparent ceiling effect found in the trial results, or
- The possibility that all antibiotic regimens are effective so differences in effects will be small, or
- Most of the trials were underpowered to find any treatment effects

This finding on clinical effectiveness tallies with the review by Ross in clinical evidence[13]. There, RCT and case series evidence were aggregated to give clinical cure rates for standard inpatient and outpatient treatments. The clinical cure rates varied between 88% to 100% except for doxycycline and metronidazole which had a clinical cure rate of 75%. In this systematic review, there was only one trial that used doxycycline and metronidazole (Heinonen) and compared it to ciprofloxacin. Unfortunately this was the one trial that did not present clinical cure rates but it was noticeable that the microbiological cure rates for the doxycycline/metronidazole group were less than for the comparator. Unfortunately the trial was underpowered to find a significant difference between the two arms, having only 40 patients enrolled and 36 followed up.

What is particularly interesting to note is that the RCT evidence for the most part suggests that the antibiotic regimens used have 90-100% clinical cure rates. However, the incidence of sequelae is somewhere between 18-36%. Obviously these two findings do not tally. The PEACH trial unfortunately does not give the clinical cure rates at the first follow up, so it cannot be used to compare the initial clinical cure rates to rates of subsequent sequelae. None of the other trials give long-term follow-ups, they only give results at between two to six weeks only except for one small trial with follow up at six months. This means that there is a considerable gap in the evidence about effective treatment of PID.

Regarding findings of the costs and cost-effectiveness studies, the annual cost per patient and the lifetime cost per patient were considerable, particularly where the initial treatment was unsuccessful and patients suffered the sequelae of CPP and ectopic pregnancy. The latter is also a life-threatening event. The cost studies suggest that the most efficient treatment is not only beneficial to the patient but potentially also to the NHS. It is interesting to note that the actual costs of the different standard regimens vary from £10.50 to £738.50. At the moment it is difficult to determine whether these cost differences are also mirrored in differences of effectiveness. If there are no differences in clinical effectiveness then tentative conclusions can be made about which of the standard treatment regimens to use, based on their relative costs. For example, cost minimisation suggests that cephalosporins with oral doxycycline and metronidazole would be preferred to oral ofloxacin and metronidazole for outpatient treatment and preferred to clindamycin and gentamicin for inpatient treatment. The most expensive treatment is iv ofloxacin and metronidazole but there is no evidence to suggest that is any more effective than other regimens intended for inpatient treatment.

5.2 Potential methodological strengths and weaknesses this systematic review

We identified the following features as being methodologically robust:

- A clearly defined question
- A comprehensive search strategy incorporating published and partially published material
- Duplicate selection of studies for inclusion and exclusion. Rigorous application of inclusion and exclusion criteria. Details of excluded studies with reasons for exclusions
- Duplicate data extraction and assessment of included study quality
- The inclusion of only clinically meaningful comparisons where antibiotics are available in the UK.
- Use of meta-analysis to amplify the assessment of patterns of results across several trials measuring the same outcome

All of these features are undertaken with the explicit intension of minimising bias, both for and against the interventions reviewed.

5.2.1 Potential weaknesses

Firstly, abstracting data from 34 trials means that there is a large amount of information in this systematic review. Although considerable efforts have been made to prevent errors, it will be inevitable that some have occurred. However, this is likely to generate random error rather than systematic bias.

We did not search for any study designs other than RCTs when carrying out this systematic review. This was the planned policy when developing the protocol for the review and was done because there was RCT evidence available. After appraising this, it is now apparent that

there are considerable gaps in the evidence, not least for assessment of the clinical guidelines for treatment of PID. Therefore a further systematic review incorporating descriptive study evidence may be warranted.

Women who use intra-uterine devices for contraception have an increased risk of PID and may represent a distinct subgroup of the population. It may have been more appropriate to look at the effectiveness of antibiotics for PID separately for this subgroup. Unfortunately 20 of the 34 included trials did not mention intra-uterine devices at all and none looked specifically at PID in this subgroup so there was insufficient information available.

Many trials were published before the Jadad score was widely used and the CONSORT statement was available (1996) so it may not be so appropriate to judge them now on criteria not available when they were written.

Meta-analysis has been used widely to combine results from similar classes of antibiotics where the compartors differed. The reason for this was to determine if there were any general trends in treatment effects. However, it is acknowledged that for some of the comparisons we have not been combining like with like. Partially to offset this we have used subgroups within the Forest plots to distinguish different groups more clearly.

The choice of route of antibiotic administration for a particular patient is especially dependent on the clinical state of the patient when they start treatment. This means that, for example, oral ofloxacin and metronidazole would not be comparable to iv clindamycin and gentamicin. Therefore the patient populations could have been split into mild, moderate or severe PID and a review made of standard regimens for use in each of these categories. However, none of the RCTs reviewed compared a standard regimen for intended for mild PID to one intended for severe PID because it would not be a clinically useful comparison.

5.2.2 Need for further research

Below is a list of potential further research that may be useful to further understanding of the treatment of PID.

- Conducting a systematic review that includes good quality cohort, case-control and case series study designs as well as RCTs to establish evidence base of the current clinical guidelines.
- Conducting large-scale RCTs to determine whether the current clinical guidelines offer the best treatment options. Another possibility is to set up a registry for PID with treatment outcomes. This could be useful also to determine how patients are treated at the moment and whether GP treatment as effective as that in GUM clinics and A&E departments. It would need long-term follow up to establish links between treatment options and subsequent sequelae rates
- The cost effectiveness of best possible treatment regimen compared to current practice

6. CONCLUSIONS

The clinical effectiveness evidence of six of the seven standard antibiotic regimens has been systematically reviewed. There was no evidence to suggest the superiority of any one regimen over another. There was no evidence for one of the standard recommended treatment regimens. All non-standard treatment regimens were similarly effective except one (clindamycin on its own) which would not normally be used now for the treatment of PID. There was no evidence available on the length of antibiotic treatment required. There was limited evidence about a combination of different routes of administration and inpatient versus outpatient treatment for one standard regimen which showed equivalent effectiveness. There were no UK cost or cost-effectiveness studies available. The US cost studies of different treatment regimens used non-standard treatments and case series effectiveness estimates. The cost of inpatient treatment varied between $4,967 and $5,228. The annual cost per PID case varied between $822 and $1,846 and the lifetime cost between $1,060 and $3,180. This increased to $6,350 where patients subsequently developed chronic pelvic pain and $6,840 where they developed ectopic pregnancy.

7. APPENDICES

Appendix 1. Hager and Soper diagnostic criteria

Hager criteria[74]

Table 44. Hager clinical criteria for diagnosis

Criteria	Comments
Abdominal direct tenderness, with or without rebound tenderness	All 3 necessary for diagnosis
Tenderness with motion of cervix and uterus	
Adnexal tenderness	
	Plus
Gram stain of endocervix – positive for gram negative, intracellular diplococci	1 or more necessary for diagnosis
Temperature (greater than 38C)	
Leukocytosis (greater than 10,000)	
Purulent material (white blood cells present) from peritoneal cavity by culdocentesis or laparoscopy	
Pelvic abscess or inflammatory complex on bimanual exam or by sonography	

Table 45. Hager criteria for grading of severity of disease by laparoscopic examination.

Severity	Criteria
Mild	Erythema, oedema, no spontaneous purulent exudates (the tubes may require manipulation to produce purulent exudates), tubes freely moveable
Moderate	Gross purulent material evident, erythema and oedema more marked, tubes may not be freely moveable and fimbria stoma may not be patent
Severe	1. Pyosalpinx or inflammatory complex 2. Abscess (size of any pelvic abscess should be measured)

Table 46. Hager criteria for grading of PID by clinical examination

Grade	Criteria
I.	Uncomplicated (limited to tube[s] and/or ovary[ies]), Without pelvic peritonitis With pelvic peritonitis
II.	Complicated (inflammatory mass involving tube[s] and/or ovary[ies] Without pelvic peritonitis With pelvic peritonitis
III.	Spread to structures beyond pelvis, ie, ruptured tubo-ovarian abscess

Soper criteria[75]

Table 47. Soper clinical criteria for diagnosis

Criteria	Comments
Adnexal tenderness	Both necessary for diagnosis
Signs of a lower genital tract infection	
	Plus
Endometrial biopsy = endometritis	1 or more necessary for diagnosis
Elevated C-reactive protein or erythrocyte sedimentation rate	
Temperature (greater than 38C)	
Leukocytosis	
Positive test for chlamydia or gonorrhoea	

Soper minimum criteria for laparoscopic diagnosis of PID are:

1. Pronounced hyperaemia of the tubal surface
2. Oedema of the tubal wall
3. A sticky exudate on the tubal surface and from the fimbrated ends when patent

Thompson's criteria[51]

Table 48. Thompson's criteria for clinical severity

Sympton	Score
Abdominal tenderness (direct)	0-3
Rebound tenderness	0-3
Decreased bowel sounds	0-3
Pain on cervical movement	0-3
Adnexal enlargement (right)	0-3
Adnexal enlargement (left)	0-3
Adnexal tenderness (right)	0-3
Adnexal tenderness (left)	0-3
0=absent, 1=minimal, 2=moderate, 3=marked. Total severity score range =0 (normal) – 24 (most ill)	

Appendix 2. Clinical guideline extracts

A. Royal College of Obstetricians and Gynaecologists Guideline No 32. Management of acute pelvic inflammatory disease[19]

4.1 Outpatient treatment
Outpatient antibiotic treatment should be commenced as soon as the diagnosis is suspected. In mild or moderate PID (in the absence of a tubo-ovarian abscess), there is no difference in outcome when patients are treated as outpatients or admitted to hospital.[41] It is likely that delaying treatment, especially in chlamydial infections, increases the severity of the condition and the risk of long-term sequelae such as ectopic pregnancy, subfertility and pelvic pain.[76,77] (Evidence level 1b)

Outpatient treatment should be based on one of the following regimens: (Evidence level 1b)

- Oral ofloxacin 400mg twice a day plus oral metronidazole 400mg twice a day for 14 days[25,35,78,79]

OR

- Intramuscular ceftriaxone 250mg immediately or intramuscular cefoxitin 2g immediately with oral probenecid 1g, followed by oral doxycycline 100mg twice a day plus metronidazole 400mg twice a day for 14 days[25,28,32,35,39,80]

Broad spectrum antibiotic therapy is required to cover *N. gonorrhoeae*, *C. trachomatis* and anaerobic infection.[1,80,81] The recommendation to cover *N. gonorrhoeae* in patients presenting with suspected PID in the UK is based on the following facts:

- The most recent British study found gonoccocal infection in 14% of PID patients[1]
- The absence of endocervical gonorrhoea does not exclude gonococcal PID
- At present, there are no large controlled trials from the UK which support the use of regimens that do not cover *N. gonorrhoeae*
- The increasing incidence of gonorrhoea in the UK[82]

Although the combination of oral doxycycline and metronidazole is in common use in the UK, there are no clinical trials assessing its effectiveness.[23] (Evidence level IV)

4.2 Inpatient treatment
Admission to hospital would be appropriate in the following circumstances:[80]

- Surgical emergency cannot be excluded
- Clinically severe disease
- Tubo-ovarian abscess
- PID in pregnancy
- Lack of response to oral therapy
- Intolerance to oral therapy

In more severe cases inpatient antibiotic treatment should be based on intravenous therapy, which should be continued until 24 hours after clinical improvement and followed by oral therapy. (Evidence level 1b)

Recommended regimens are (Evidence level 1b):

- Intravenous cefoxitin 2g three times a day plus intravenous doxycycline 100mg twice a day (oral doxycycline may be used if tolerated), followed by oral doxycycline

100mg twice a day plus oral metronidazole 400mg twice a day for a total of 14 days[25,32,35,39,80]

OR

- Intravenous clindamycin 900mg three times a day plus intravenous gentamicin: 2mg/kg loading dose followed by 1.5mg/kg three times a day (a single daily dose of 7 mg/kg may be substituted), followed by either:
    - Oral clindamycin 450mg four times a day to complete 14 days

    OR
    - Oral doxycycline 100mg twice a day plus oral metronidazole 400mg twice a day to complete 14 days[25,32,39,80]

OR

- Intravenous ofloxacin 400mg twice a day plus intravenous metronidazole 500mg three times a day for 14 days[25,35,83]

Intravenous doxycycline is available from IDIS World Medicines. If parenteral gentamicin is used then serum drug levels and renal function should be monitored.

The choice of an appropriate treatment regimen will be influenced by robust evidence on local antimicrobial sensitivity patterns, robust evidence on the local epidemiology of specific infections in this setting, cost, patient preference and compliance and severity of disease.

Evidence of the efficacy of antibiotic therapy in preventing the long-term complications of PID is currently limited.

B. Clinical Effectiveness Group (Association for Genitourinary Medicine and The Medical Society for the Study of Venerial Diseases). National guideline for the management of pelvic infection and perihepatitis and 2001 guidelines for the management of pelvic infection and perihepatitis.[2,20]

Treatment

The following anti-biotic regimens are evidence based. Intravenous therapy should be continued until 24 hours after clinical improvement and then switch to oral.

Recommended regimens:

- Intravenous cefoxitin 2g three times daily plus intravenous doxycycline 100mg twice daily (oral doxycycline may be used if tolerated) followed by oral doxycycline 100mg twice daily plus oral metronidazole 400mg twice daily for a total of 14 days (III,B).[25,32,35,39,84]
- Intravenous clindamycin 900mg three times daily plus intravenous gentamicin (2mg/kg loading dose followed by 1.5mg/kg three times daily (a single daily dose may be substituted), followed by either oral clindamycin 450mg four times daily to complete 14 days or oral doxycycline 100mg twice daily plus oral metronidazole 400mg twice daily to complete 14 days (III,B)[25,32,39,84]
- Oral ofloxacin 400mg twice daily plus oral metronidazole 400mg twice daily for 14 days (III, B)[25,35,38,83,84]
- Intramuscular ceftriaxone 250mg immediately or intramuscular cefoxitin 2g immediately with oral probenecid 1g followed by oral doxycycline 100mg twice daily plus metronidazole 400mg twice daily for 14 days (III, B)[25,32,35,39,84]

Alternative regimens

- Intravenous ofloxacin 400mg twice daily plus intravenous metronidazole 500mg three times daily (III, B)[25,35,38,83,84]
- Intravenous ciprofloxacin 200mg twice daily plus intravenous (or oral) doxycycline 100mg twice daily plus intravenous metronidazole 500mg three times daily (III, B)[25,61,84]

C. Centers for Disease Control and Prevention (CDC) Recommendations. (Taken from Kane et al 2004 [21])

All outpatients must be treated by regimen A or regimen B.

- Regimen A: Ofloxacin 400mg PO bid for 14 days and metronidazole 500mg PO bid for 14 days
- Regimen B: Ceftriaxone 250mg IM or cefoxitin 2g IM plus probenicid 1 gm PO or a third generation cephalosporin and doxycycline 100mg PO bid for 14 days

Appendix 3. Cost per day of antibiotics used

Antibiotic	iv cost	im cost	Oral cost
Amikacin	40.56	40.56	n/a
Amoxicillin	1.98	1.98	0.26
Amoxicillin/clavulanate	8.91	n/a	1.39
Ampicillin	2.96	2.96	0.48
Azithromycin	n/a	n/a	4.48
Aztreonam	26.85	26.85	n/a
Cefotaxime	9.22	9.22	n/a
Cefoxitin	14.76	14.76	n/a
Ceftazidime	28.35	28.35	n/a
Ceftriaxone	10.94	10.94	n/a
Ciprofloxacin	51.40	n/a	2.40
Clindamycin	12.40	12.40	2.28
Doxycycline	n/a	n/a	0.48
Gentamicin	6.16	6.16	n/a
Imipenem/cilastin	24.00	24.00	n/a
Lymecycline	n/a	n/a	0.51
Meropenem	42.99	42.99	n/a
Metronidazole	10.71	10.71	0.08
Netelmicin	7.84	7.84	n/a
Ofloxacin	42.04	n/a	4.29
Oxytetracycline	n/a	n/a	0.12
Probenecid	n/a	n/a	Named patient basis
Tetracycline	n/a	n/a	0.15
Tinidazole	n/a	n/a	1.15
Tobramycin	11.31	11.31	n/a
Aminoglycoside	n/a	n/a	n/a

Prices are taken from BNF 47. Non-proprietary medicine category is used where possible, if not then least expensive option is used. Standard recommended doses used. N/a = not available in BNF. Amikacin, gentamicin, netilmicin and tobramycin doses assume 70 kg person. Named patient basis means no costs are available in BNF.

Appendix 4. Search strategies

Database: Pre-MEDLINE, MEDLINE January 2003
Search Strategy:

1. pelvic inflammatory disease.mp. [mp=ti, ab, rw, sh] (4274)
2. pelvic inflammatory disease.mp. [mp=ti, ab, rw, sh] (4274)
3. salpingitis.mp. [mp=ti, ab, rw, sh] (1867)
4. oophoritis.mp. [mp=ti, ab, rw, sh] (433)
5. adnexitis.mp. [mp=ti, ab, rw, sh] (303)
6. pid.mp. [mp=ti, ab, rw, sh] (1241)
7. pelvic abscess.mp. [mp=ti, ab, rw, sh] (372)
8. pyosalpinx.mp. [mp=ti, ab, rw, sh] (69)
9. fitz hugh curtis.mp. [mp=ti, ab, rw, sh] (107)
10. adnexitis/ (3514)
11. exp pelvic inflammatory disease/ (7171)
12. exp salpingitis/ (1526)
13. exp oophoritis/ (349)
14. exp adnexitis/ (7171)
15. exp pid/ (510)
16. exp antibiotics/ (359358)
17. antibiotic$.mp. [mp=ti, ab, rw, sh] (189859)
18. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 (9741)
19. 16 or 17 (398004)
20. 18 and 19 (1852)
21. randomized controlled trial.pt. (167185)
22. controlled clinical trial.pt. (61966)
23. randomized controlled trials/ (25457)
24. random allocation/ (46519)
25. double blind method/ (70733)
26. single blind method/ (6814)
27. 21 or 22 or 23 or 24 or 25 or 26 (282821)
28. (animal not human).sh. (2613812)
29. 27 not 28 (269511)
30. clinical trial.pt. (343892)
31. exp clinical trials/ (137764)
32. (clin$ adj25 trial$).ti,ab. (88391)
33. ((singl$ or doubl$ or trebl$ or tripl$) adj25 (blind$ or mask$)).ti,ab. (71201)
34. placebos/ (22015)
35. placebo$.ti,ab. (76435)
36. random$.ti,ab. (255469)
37. research design/ (35215)
38. 30 or 31 or 32 or 33 or 34 or 35 or 36 or 37 (605127)
39. 38 not 28 (563623)
40. 29 or 39 (572695)
41. 20 and 40 (385)
42. from 41 keep 1-385 (385)

Database: EMBASE <1980 to 2002 Week 51>
Search Strategy:

1. pelvic inflammatory disease.mp. or exp Pelvic Inflammatory Disease/ (4536)
2. pid.mp. (1031)
3. salpingitis.mp. or exp SALPINGITIS/ (1236)
4. chlamydia trachomatis.mp. or exp Chlamydia Trachomatis/ (7651)
5. exp adnexitis/ or exp metritis/ or exp pelvioperitonitis/ or exp pelvis abscess/ or exp salpingitis/ (2023)
6. pyosalpinx.mp. (65)

```
   7. metritis.mp. (241)
   8. pelviperitonitis.mp. (13)
   9. pelvioperitonitis.mp. (148)
   10.pelvic abscess.mp. (310)
   11.chronic pelvic pain.mp. or exp Pelvis Pain Syndrome/ (1999)
   12.oophoritis.mp. or exp Ovary Inflammation/ (178)
   13.Fitz Hugh Curtis.mp. (77)
   14.1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13
      (14001)
   15.randomized controlled trial/ (70193)
   16.exp clinical trial/ (256595)
   17.exp controlled study/ (1490482)
   18.double blind procedure/ (45993)
   19.randomization/ (5186)
   20.placebo/ (60806)
   21.single blind procedure/ (3940)
   22.(control$ adj (tril$ or stud$ or evaluation$ or experiment$)).mp.
      (65338)
   23.(control$ adj (trial$ or stud$ or evaluation$ or experiment$)).mp.
      (89170)
   24.((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).mp.
      (65618)
   25.(placebo$ or matched communities or matched schools or matched
      populations).mp. (100313)
   26.(comparison group$ or control group$).mp. (96182)
   27.(clinical trial$ or random$).mp. (431454)
   28.(quasiexperimental or quasi experimental or pseudo experimental).mp.
      (829)
   29.matched pairs.mp. (1368)
   30.15 or 16 or 17 or 18 or 19 or 20 or 21 or 23 or 24 or 25 or 26 or 27
      or 28 or 29 (1806167)
   31.14 and 30 (3407)
   32.antibiotic$.mp. or exp Antibiotic Agent/ (389030)
   33.antimicrobial$.mp. or exp Antiinfective Agent/ (692304)
   34.32 or 33 (715441)
   35.31 and 34 (1066)
   36.limit 35 to (human and female) (559)
   37.from 36 keep 1-559 (559)

Cinahl
Pelvic inflammatory disease (1)
```

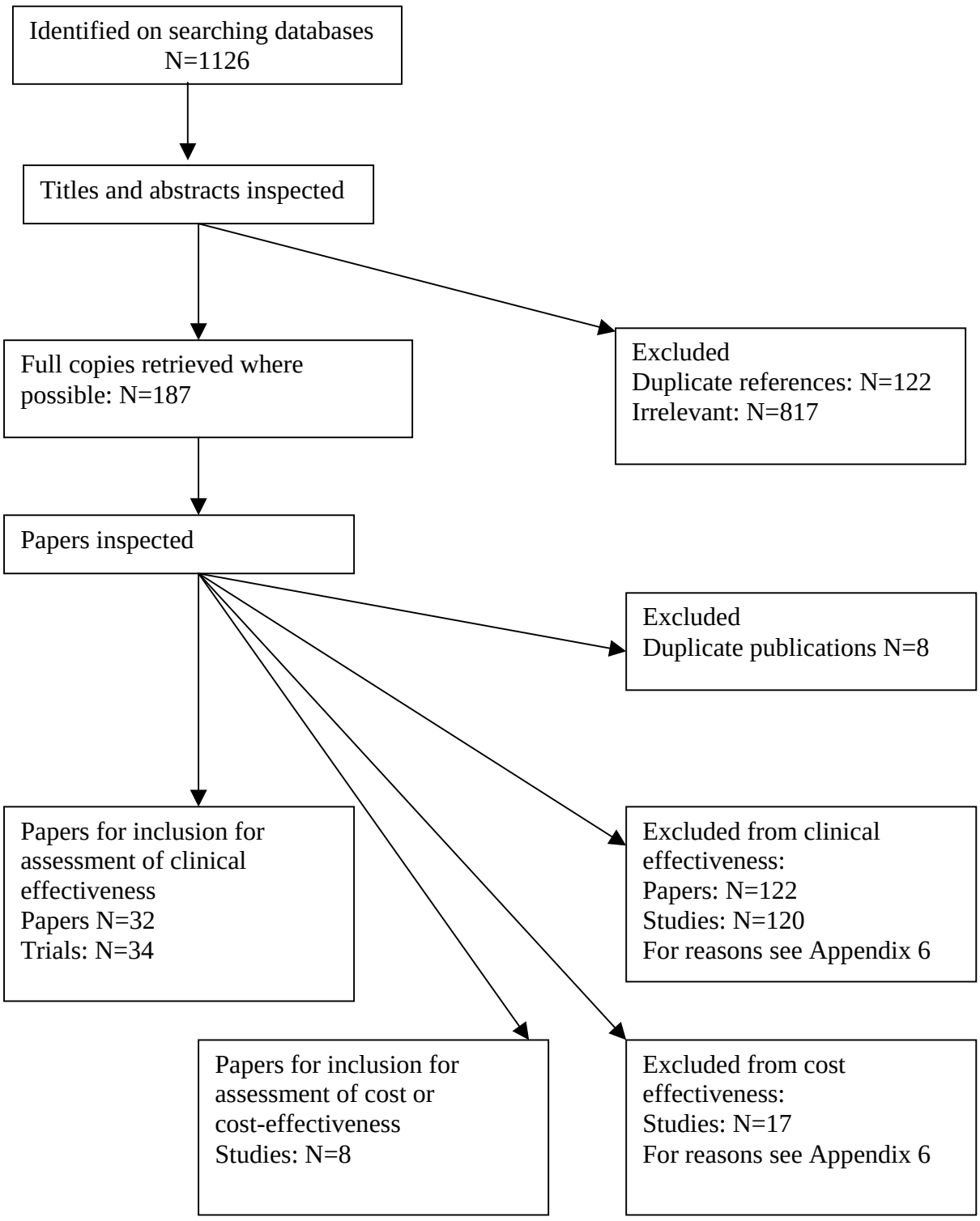
Cochrane Library

1. adnexal diseasesx1.me (1213)
2. (Fitz and (Hugh and Curtis)) (2)
3. (Pelvic and abscess) (57)
4. (Pelvic and (inflammatory and disease)) (262)
5. anti-infective-agentsx.me (10892)
6. 1 or 2 or 3 or 4 (1421)
7. 5 and 6 (83)

(SR – 1, DARE – 3, CCTR – 73, NHSEED – 6)

Web of Science
(adnexitis or salpingitis or pelvic inflammatory disease) and antibiotic* and random* (31)

Appendix 5. Flow diagram of identification and inclusion of effectiveness studies



Appendix 6. Excluded studies

Table 49. Excluded clinical effectiveness studies and reasons for exclusion

Reference	Reason for exclusion
Acar B, Zissis NP. Piperacillin alone vs triple antibiotic combination in gynecological infections. *Journal of Chemotherapy* 1989; **1**(6):403-406.	Penicillin
Andersson,P.O.; Hackl,H.; Jensen,P.; Larsen,K.R. A comparison of two different dosages of pivampicillin and doxycycline in patients with gynaecological infections. Current Medical Research and Opinion 1980;6(8):513-7	Antibiotic not in BNF (pivampicillin)
Bajares,De Lilue M; Mazzali,De,I; Santiago,A.; Ferrini,A.; Adames,Z. Comparative study between roxithromycin and doxicycline in Mycoplasma and Chlamydia infections. Revista de Obstetricia y Ginecologia de Venezuela, Vol 53(4) (pp 211-216), 1993	Antibiotic not in BNF (roxitromicina)
Bassil,S.; Le Bouedec,G.; Mage,G.; Pouly,J.L.; Canis,M.; Wattiez,A.; Chapron,C.; Bruhat,M.A. [The role of anti-inflammatory agents in the treatment of acute salpingitis. A gynaecological study of 40 patients with celioscopic control]. [French]. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction 1991;20:1063-7	RCT of anti-inflammatory agent in PID (piroxicam)
Batteiger,B.E.; Jones,R.B.; White,A. Efficacy and safety of ofloxacin in the treatment of nongonococcal sexually transmitted disease. American Journal of Medicine 1989;87(6C):75S-77S	Not PID
Berkeley,A.S.; Freedman,K.S.; Hirsch,J.C.; Ledger,W.J. Randomized, comparative trial of imipenem/cilastatin and moxalactam in the treatment of serious obstetric and gynaecologic infections. Surgery, Gynecology & Obstetrics 1986;162:204-8	Antibiotic not in BNF (moxalactam)
Bevan CD, Ridgeway GL, Rothermel CD. Efficacy and safety of azithromycin as monotherapy or combined with metronidazole compared with two tstandard multidrug regimens for the treatment of acute pelvic inflammatory disease. Journal of International Medical Research 2003;31:45-54 *Third arms of trials A and B	Results not given separately for the two sets of antibiotics used
Black,J.R.; Long,J.M.; Zwickl,B.E.; Ray,B.S.; Verdon,M.S.; Wetherby,S.; Hook III,E.W.; Handsfield,H.H. Multicenter gynaecological study of single-dose ofloxacin versus amoxicillin-probenecid for treatment of uncomplicated gonococcal infection. Antimicrobial Agents & Chemotherapy 1989;33(2):167-70	Not PID
Blanco,J.D.; Gibbs,R.S.; Duff,P.; Castaneda,Y.S.; St Clair,P.J. Randomized comparison of ceftazidime versus clindamycin-tobramycin in the treatment of obstetrical and gynaecological infections. Antimicrobial Agents & Chemotherapy 1983;24(4):500-4	No PID in one arm of RCT
Bowden,F.J.; Jacups,S.; Huffam,S.; Savage,J.; O'Brien,M. Azithromycin and pelvic inflammatory disease in the Northern Territory. Medical Journal of Australia 2001;174:366-7	Trial abandoned mid recruitment
Bowie,W.R.; Willetts,V.; Megran,D.W. Dose-ranging study of fleroxacin for treatment of uncomplicated Chlamydia trachomatis genital infections. Antimicrobial Agents & Chemotherapy 1989;33(10):1774-7	Antibiotic not in BNF (Fleroxacin)
Brihmer,C.; Mardh,P.A.; Kallings,I.; Osser,S.; Robech,M.; Sikstrom,B.; Wanger,L. Efficacy and safety of azithromycin versus lymecyline in the treatment of genital chlamydial infections in women. Scandinavian Journal of Infectious Diseases 1996;28:451-4	Not PID
Brihmer C, Brundin J. Second look laparoscopy after treatment of acute salpingitis with doxycycline/benzylpenicillin procaine or trimethoprim-sulfamethoxazole. *Scandinavian Journal of Infectious Diseases – Supplementum* 1988; **53**:65-69. Brihmer C, Kallings I, Nord CE, Brundin J. Second look laparoscopy; evaluation of two different antibiotic regimens after treatment of acute salpingitis. *European Journal of Obstetrics, Gynecology, & Reproductive Biology* 1989; **30**(3):263-274.	Penicillin

Reference	Reason for exclusion
Brobson Lutz Jr F. Single-dose efficacy of ofloxacin in uncomplicated gonorrhea. American Journal of Medicine 1989;87(Supp 6C):69S-74S	Not PID
Brunham RC, Kuo C, Stevens CE, Holmes KK. Treatment of concomitant Neisseria gonorrhoeae and Chlamydia trachomatis infections in women: comparison of trimethoprim-sulphamethoxazole with ampicillin-probenecid. Reviews of Infectious Diseases 1982;4(2):491-9	Not PID
Brunham RC, Bins B, Guijon F, Danforth D, Kosseim ML, Rand F, McDowell J, Rayner E. Etiology and outcome of acute pelvic inflammatory disease. Journal of Infectious Diseases 1988:158(3):510-7	Not PID
Chatwani,A.; Dandalou,V.; Harmanli,O.; Nyirjesy,P. Trospectomycin in acute pelvic inflammatory disease: A preliminary report. Infectious Diseases in Obstetrics & Gynecology 1997;5:215-8	Antibiotic not in BNF (Trospectomycin)
Cirau-Vigneron,N.; Barrier,J.; Becue,J.; Chartier,M.; Giraud,J.R.; Landes,P.; Leng,J.; Raudrant,D.; Reme,J.M. Amoxycillin/clavulanic acid ('Augmentin') compared with a combination of aminopenicillin, aminoglycoside and metronidazole in the treatment of pelvic inflammatory disease. Pharmatherapeutica 1989;5:312-9	Antibiotic not in BNF (aminopenicillin)
Confino,E.; Friberg,J.; Vermesh,M.; Madanes,A.; Suarez,M.; Gleicher,N. Mezlocillin versus doxycycline in the treatment of acute salpingitis. Mount Sinai Journal of Medicine 1988;55(2):154-8	Antibiotic not in BNF (Mezlocillin)
Cramers,M.; Kaspersen,P.; From,E.; Moller,B.R. Pivampicillin compared with erythromycin for treating women with genital Chlamydia trachomatis infection. Genitourinary Medicine 1988;64:247-8	Not PID
Crombleholme,W.R.; Ohm-Smith,M.; Robbie,M.O.; DeKay,V.; Sweet,R.L. Ampicillin/sulbactam versus metronidazole-gentamicin in the treatment of soft tissue pelvic infections. American Journal of Obstetrics & Gynecology 1987;156:507-12	Antibiotic not in BNF (Sulbactam)
Crombleholme,W.; Landers,D.; Ohm-Smith,M.; Robbie,M.O.; Hadley,W.K.; DeKay,V.; Dahrouge,D.; Sweet,R.L. Sulbactam/ampicillin versus metronidazole/gentamicin in the treatment of severe pelvic infections. Drugs 1986;31(Supp 2):11-13	Antibiotic not in BNF (Sulbactam)
Cunningham FG, Hauth JC, Strong JD, Herbert WN, Gilstrap L.C., Wilson RH, *et al*. Evaluation of tetracycline or penicillin and ampicillin for treatment of acute pelvic inflammatory disease. *New England Journal of Medicine* 1977; **296**:1380-1383.	Penicillin
Dittmar,F.-W.; Weissenbacher,E.R. Therapy of adnexitis – enhancement of the basic antibiotic therapy with hydrolytic enzymes. International Journal of Experimental & Clinical Chemotherapy 1992;5(2):73-81	Not RCT of antibiotics
Dodson MG, Faro S, Gentry L. Treatment of acute pelvic inflammatory disease with aztreonam, a new monocyclic βlactam antibiotic and clindamycin. Obstetrics and Gynaecology 1986;67:657-62	Not RCT
Duarte,G.; Quintana,S.M.; Gir,E.; Marana,H.R.; Pereira,Da Cunha. [Evaluation of doxycycline for the complementary treatment of acute inflammatory pelvic disease. A double-blind study.] Revista Brasileira de Medicina. 1995;52(6):651-6	Not RCT
Eykyn S, Jenkins C, King A, Phillips I. Antibacterial activity of cefuroxime, a new cephalosporin antibiotic, compared with that of cephaloridine, cephalothin and cephamandole. Antimicrobial Agents and Chemotherapy 1976;9(4):690-5	In vitro study
Falk,V. Treatment of acute non-tuberculous salpingitis with antibiotics alone and in combination with glucocorticoids. A prospective double blind controlled study of the clinical course and prognosis. Acta Obstetricia et Gynecologica Scandinavica 1965;44(6):5-118	Not RCT
Faro S. Ticarcillin/clavulanate. An alternative to combination antibiotic therapy for treating soft tissue pelvic infections in women. Journal of Reproductive Medicine 1990;35(3(supp):353-8	Not RCT

Reference	Reason for exclusion
Faro,S.; Martens,M.G.; Phillips,L.E.; LaPread,E.; Riddle,G.D.; Turner,R.M. Ceftizoxime versus cefotaxime in the treatment of gynaecologic patients with pelvic inflammatory disease. Current Therapeutic Research, Clinical & Experimental 1988;43(3):349-54	Antibiotic not in BNF (Ceftizoxime)
Fischbach,F.; Deckardt,R.; Graeff,H. [Ciprofloxacin/metronidazole vs. cefoxitin/doxycycline: comparison of two therapy schedules for treatment of acute pelvic infection]. Geburtshilfe und Frauenheilkunde 1994;54:337-340 and Deckardt,R.; Fischbach,F.; Graeff,H.[Ciprofloxacin/metronidazole versus cefoxitin/doxycycline: Comparison of two antibiotic regimes in the treatment of acute adnexitis]. Archives of Gynecology & Obstetrics 1991;250(1-4):427-9	Results not separate for PID
Frongillo,R.F.; Custo,G.M.; Gilardi,G.; Martella,L.; Palumbo,M. Imipenem versus netilmicin plus chloramphenicol in gynaecological upper tract infections: A comparative study. International Journal of Experimental & Clinical Chemotherapy 1992;5(1):41-4	Results not separate for PID
Garey KW, Amsden GW. Intravenous Azithromycin. Annals of Pharmacotherapy 1999;33:218-28	Both trials not RCTs
Gaudin,G. [Comparative clinical study between Rocephin (Roche) and doxycycline, amoxycillin, erythromycin and amoxycillin + metronidazole combination in gynecology]. Gynakologische Rundschau 1985;25:86-95	Results not separate for PID
Gerber,B.; Wilken,H.; Zacharias,K.; Barten,G.; Splitt,G. Treatment of acute salpingitis with tetracycline/metronidazole with or without additional balneotherapy, augmentan or ciprofloxacin/metronidazole: A second-look-laparoscopy study. Geburtshilfe und Frauenheilkunde, Vol 52(3) (pp 165-170), 1992	Not RCT of antibiotics
Gibbs RS. A trial of spectinomycin hydrochloride compared with aqueous penicillin G plus kanamycin for treatment of severe pelvic inflammatory disease. Sexually Transmitted Diseases 1980;7(1)21-3	Antibiotic not in BNF (spectinomycin, kanamycin)
Gilstrap L.C., Maier RC, Gibbs RS, Connor KD, St Clair PJ. Piperacillin versus clindamycin plus gentamicin for pelvic infections. *Obstetrics and Gynecology* 1984; **64**:762-766.	Anti-pseudomonal penicillin
Giraud,J.R.; Chartier,M.; Ciraru-Vigneron,N.; Becue,J.; Landes,P.; Leng,J.-J.; Raudrant,D.; Reme,J.M. [A comparison of the efficacy of and tolerance to Augmentin used alone and as one of three drugs used to treat acute upper genital tract infections. Results of a multicentre trial 152 cases.] Contraception, Fertilite, Sexualite 1989;17(10):941-8	Results not separate for PID
Goffi PS, Aguiar LF, Vara AS, Moraes FC. [Fentiac in pelvic inflammatory disease. A double blind, randomised, placebo-controlled study in ambulatory patients] Farmacologia Clinica 1989;98(4):241-6	Antibiotic not in BNF (fentiazac)
Gribble,M.J. Cefotetan: a second-generation cephalosporin active against anaerobic bacteria. Committee on Antimicrobial Agents, Canadian Infectious Disease Society. Canadian Medical Association Journal 1994;151(5):537-42	Antibiotic not in BNF (cefotetan)
Gruber,F.; Tomic,D.; Brajac,I. [Comparative trial with azithromycin and doxycycline in gonococcal and chlamydial infections in females]. Giornale Italiano di Dermatologia e Venereologia, Vol 131(6) (pp 403-406), 1996	Not PID
Gunning,J. A comparison of parenteral sulbactam/ampicillin versus clindamycin/gentamicin in the treatment of pelvic inflammatory disease. Drugs 1986; 31 Suppl 2:14-7	Antibiotic not in BNF (Sulbactam)
Gunning JE. A comparison of piperacillin and clindamycin plus gentamicin in women with pelvic infections. *Surgery, Gynecology & Obstetrics* 1986; **163**(2):156-162.	Anti-pseudomonal penicillin
Hager,W.D.; Pascuzzi,M.; Vernon,M. Efficacy of oral antibiotics following parenteral antibiotics for serious infections in obstetrics and gynecology. Obstetrics & Gynecology 1989;73(3 part 1):326-9	Not PID
Handsfield,H.H.; McCormack,W.M.; Hook III,E.W.; Douglas Jr,J.M.; Covino,J.M.; Verdon,M.S. et al. A comparison of single-dose cefixime with ceftriaxone as treatment for uncomplicated gonorrhea. New England Journal of Medicine 1991;325(19):1337-41	Not PID

Reference	Reason for exclusion
Handsfield,H.H.; Dalu,Z.A.; Martin,D.H.; Douglas Jr,J.M.; McCarty,J.M.; Schlossberg,D. et al. Multicenter trial of single-dose azithromycin vs. ceftriaxone in the treatment of uncomplicated gonorrhea. Sexually Transmitted Diseases 1994;21(2):107-11	Not PID
Hanssen PW, Paavonen J, Kiviat N, Landers D, Sweet RL, Eschenbach DA, Holmes KK. Ambulatory treatment of suspected pelvic inflammatory disease with Augmentin, with or without doxycycline. American Journal of Obstetrics and Gynaecology 1988;158(3 part 1):577-9	Not RCT
Harding G, Vincelette J, Rachlis A, Fong I, Mandell L, Feld R, Bailey D. A preliminary report on the use of ceftizoxime vs clindamycin/tobramycin for the therapy of intra-abdominal and pelvic infections. Journal of Antimicrobial Chemotherapy 1982;10(supp C):191-2	Antibiotic not in BNF (ceftizoxime)
Harding,G.K.; Nicolle,L.E.; Haase,D.A.; Aoki,F.Y.; Stiver,H.G.; Blanchard,R.J.; Kirkpatrick,J.R. Prospective, gynaecolog, comparative trials in the therapy for intraabdominal and female genital tract infections. Reviews of Infectious Diseases 1984;6(supp 1):S283-92	Antibiotic not in BNF (ceftizoxime)
Harding GK, Buckwold FJ, Ronald AR, Marrie TJ, Brunton S, Koss JC et al. Prospective randomised comparative study of clindamycin, chloramphenicol and ticarcillin, each in combination with gentamicin in therapy for intra-abdominal and female genital tract sepsis. Journal of Infectious Diseases 1980;142(3):384-93	Not PID
Heinonen PK, Teisala K, Punnonen R, Aine R, Lehtinen M, Miettinen A, Paavonen J. Treating pelvic inflammatory disease with doxycycline and metronidazole or penicillin and metronidazole. Genitourinary Medicine 1986;62:235-9	Not RCT
Hemsell,D.L.; Cunningham,F.G.; Nolan,C.M.; Miller,T.T. Clinical experience with cefotaxime in obstetric and gynaecologic infections. Reviews of Infectious Diseases 1962;4(Supp):S432-8	A, not RCT B, not PID
Hemsell,D.L.; Bawdon,R.E.; Hemsell,P.G.; Nobles,B.J.; Heard,M.C. Single-agent therapy for acute pelvic inflammatory disease: Sulbactam/ampicillin versus cefoxitin. Journal of International Medical Research 1980;18(Supp4):85D-89D	Antibiotic not in BNF (sulbactam)
Hemsell DL, Hemsell PG, Heard MC, Nobles BJ. Piperacillin and a combination of clindamycin and gentamicin for the treatment of hospital and community acquired acute pelvic infections including pelvic abscess. *Surgery, Gynecology & Obstetrics* 1987; **165**(3):223-229.	Anti-pseudomonal penicillin
Hemsell,D.L.; Nobles,B.J.; Heard,M.C.; Hemsell,P.G. Upper and lower reproductive tract bacteria in 126 women with acute pelvic inflammatory disease. Microbial susceptibility and clinical response to four therapeutic regimens. Journal of Reproductive Medicine 1988;35(10):799-805	Antibiotic not in BNF (ceftizoxime)
Hemsell,D.L.; Heard,M.C.; Nobles,B.J. Comparative bacteriology of parenteral single-agent vs. combination therapy in salpingitis. Advances in Therapy 1991;8(1):27-35	Antibiotic not in BNF (ceftizoxime)
Hemsell,D.L.; Wendel,G.D.; Gall,S.A.; Newton,E.R.; Gibbs,R.S.; Knuppel,R.A.; Lane,T.W. Multicenter comparison of cefotetan and cefoxitin in the treatment of acute obstetric and gynaecologic infections. American Journal of Obstetrics & Gynecology 1988;158:722-7	Antibiotic not in BNF (cefotetan)
Hillis,S.D.; Joesoef,R.; Marchbanks,P.A.; Wasserheit,J.N.; Cates,Jr W.; Westrom,L. Delayed care of pelvic inflammatory disease as a risk factor for impaired fertility. American Journal of Obstetrics & Gynecology 1993;168:1503-9	Not RCT
Holloway,W.J. Infection in women: Clinical experience with beta-lactamase inhibitors. Journal of Reproductive Medicine for the Obstetrician and Gynecologist 1988;33(SUPP):595-7	Results not separate for PID
Hook III,E.W.; Jones,R.B.; Martin,D.H.; Bolan,G.A.; Mroczkowski,T.F.; Neumann,T.M.; Haag,J.J.; Echols,R. Comparison of ciprofloxacin and ceftriaxone as single-dose therapy for uncomplicated gonorrhea in women. Antimicrobial Agents & Chemotherapy 1993;37(8):1670-3	Not PID

Reference	Reason for exclusion
Horner,M.; Heller-Vitouch,C.; Ziegler,C.; Soltz-Szots,J. Azithromycin in the treatment of chlamydial cervicitis and urethritis. Acta Dermatovenerologica Alpina, Panonica et Adriatica, Vol 4(3) (pp 121-125), 1995	Not PID
Jaworska-Karwowska,J. [Evaluation of the results of treatment of acute adnexitis with sulfonamides and antibiotics in the course of balneotherapy]. Ginekologia Polska 1980;51(6):539-43	Not RCT
Jemsek,J.G.; Harrison,F. Ampicillin/sulbactam vs. cefoxitin for the treatment of pelvic inflammatory disease. Infectious Diseases in Obstetrics & Gynecology 1997;5:319-25	Antibiotic not in BNF (sulbactam)
Jeskanen,L.; Karppinen,L.; Ingervo,L.; Reitamo,S.; Happonen,H.-P.; Lassus,A. Ciprofloxacin versus doxycycline in the treatment of uncomplicated urogenital Chlamydia trachomatis infections. A double-blind comparative study. Scandinavian Journal of Infectious Diseases – Supplement 1989;60:62-5	Not PID
Johnson,R.B. The role of azalide antibiotics in the treatment of chlamydia. American Journal of Obstetrics & Gynecology 1991;164:1794-6	Not PID
Katz,B.P.; Caine,V.A.; Batteiger,B.E.; Jones,R.B. A gynaecological trial to compare 7- and 21-day tetracycline regimens in the prevention of recurrence of infection with Chlamydia trachomatis. Sexually Transmitted Diseases 1991;18(1)36-40	Results not separate for PID
Knuppel,R.A.; O'Bryan,D.; Lake,M. Cefotetan: comparative and noncomparative studies in obstetric and ynaecologic infections. Southern Medical Association Journal 1988;81(2):185-8	Antibiotic not in BNF (cefotetan)
Kosseim,M.; Ronald,A.; Plummer,F.A.; D'Costa,L.; Brunham,R.C. Treatment of acute pelvic inflammatory disease in the ambulatory setting: Trial of cefoxitin and doxycycline versus ampicillin-sulbactam. Antimicrobial Agents & Chemotherapy 1991;35(8):1651-6	Antibiotic not in BNF (sulbactam)
Kotoulas,I.-G.; Cardamakis,E.; Michopoulos,J.; Chronis,G.; Antoniou,S. Comparison of ceftriaxone plus ornidazole, ceftazidime plus ornidazole, and ornidazole in the treatment of pelvic inflammatory disease (PID). International Journal of Experimental & Clinical Chemotherapy 1992;5(3):159-64	Antibiotic not in BNF (ornidazole)
Kovacs,G.T.; Westcott,M.; Rusden,J.; Asche,V.; King,H.; Haynes,S.E.; Moore,E.K.; Hall,B.E. A prospective single-blind trial of minocycline and doxycycline in the treatment of genital Chlamydia trachomatis infection in women. Medical Journal of Australia 1989;150:483-5	Not PID
Kumamoto,Y.; Sakai,S.; Hirose,T.; Tsunekawa,T.; Machida,T.; Kiyota,H.; Okazaki,T.; Kishi,H.; Higashihara,E.; Aso,Y.; Niijima,T.; Saitoh,I.; Yoshida,M.; Kataniwa,Y.; Taguchi,S.; Yamazaki,M.; Kojima,H.; Noguchi,Y.; Hashimoto,S. Efficacy of ofloxacin in sexually transmitted male urethritis and cervicitis. Japanese Journal of Antibiotics 1988;41(10):1445-79	Not RCT
Larsen,J.W.,Jr.; Voise,C.T.; Grossman,J.H.,III. Comparison of cefoxitin and clindamycin-gentamicin for pelvic infections. Clinical Therapeutics 1986;9(1):77-83	Results not separate for PID
Lebceuf,D.; Rousset,D.; Cacault,J.A.; Engelman,P. [Prospective gynaecological study comparing the efficacy and tolerance of clindamycin-gentamicin versus metronidazole-gentamicin in acute utero-adnexal infections in gynaecologic patients]. Revue Francaise de Gynecologie et d Obstetrique 1987;82(1):9-15	No PID in intervention group
Le Bouedec G, Pouly JL, Mage G, Canis M, Wattiez A, Abbas Muhktar B, Bruhat MA. Salpingites aigues bacteriennes. Importance de l'inflammation residuelle. Journal de Gynecologie, Obstetrique et Biologie de la Reproduction 1990;19:765-722	Antibiotic not in BNF (sulbactam)
LeFrock,J.L.; Molavi,A.; Carr,B.; Schell,R.; Smith,B.; Rolston,K.; Lentnek,A. Comparative clinical evaluation of mezlocillin and cefoxitin. Journal of Antimicrobial Chemotherapy 1982;9(suppA):199-203	Antibiotic not in BNF (mezlocillin)

Reference	Reason for exclusion
Linneman CC, Heaton CL, Ritchey M. Treatment of chlamydia Trachomatis infections: comparison of 1g and 2g doses of erythromycin daily for seven days. Sexually Transmitted Diseases 1987;14(2):102-6	Not PID
Livengood III CH, Hill GB, Addison WA. Pelvic inflammatory disease: Findings during inpatient treatment of clinically severe, laparoscopy-documented disease. *American Journal of Obstetrics & Gynecology* 1992; **166**(2):519-524.	Antibiotic not in BNF (cefamandole)
Longhi,S. [Prevalence of Chlamydia trachomatis in chronic inflammatory disease of the urogenital tract and comparison among the clinical effectiveness of minocyclin, miocamycin and norfloxacin]. Giornale Italiano di Ricerche Cliniche e Terapeutiche, Vol 12(6) (pp 167-170), 1991	Not PID
Martin DH, Mroczkowski TF, Dalu ZA, McCarty J, Johnes RB, Hopkins SJ, Johnson RB. [Randomised multicentre study of the use of azithromycin vs doxycycline against Chlamydia Trachomatis]. Zeitschr. Antimikr. Antincoplast. Chemother. 1991;9(1/2):16-7	Not PID
Matsuda,S.; Shimizu,T.; Maki,M.; Chimura,T.; Yajima,A.; Takahashi,K.; Cho,N.; Terashima,Y.; Ohya,A.; Kohara,T.; Hogaki Yagami,M.Y.; Tateno,M.; Noda,K.; Ninomiya,K.; Okada,H.; Ichijo,M.; Hirabayashi,K.; Fujiwara,A. Comparative double-blind clinical trial of ceftibuten (7432-S) and bacampicillin (BAPC) against gynaecological infections. Chemotherapy 1989;37(S-1):667-700	Antibiotic not in BNF (ceftibuten)
Matsuda,S.; Shimizu,T.; Chimura,T.; Yajima,A.; Takahashi,K.; Cho,N.; Terashima,Y.; Hogaki,M.; Kohara,T.; Hayashi,S.; Tateno,M.; Kuwabara,S.; Noda,K.; Ninomiya,K.; Yagami,Y.; Okada,H.; Sugimoto,O.; Noda,K.; Ichijo,M. Comparative double-blind study of lomefloxacin (NY-198) and bacampicillin (BAPC) on the infections in obstetrics and gynecology. Chemotherapy 1989;37(7):969:1005	Antibiotic not in BNF (bacampicillin)
Matsuda,S.; Ando,S.; Oh,K.; Kawamata,C.; Takahashi,K.; Endo,H.; Goto,J.; Asano,K.; Akagi,K.; Yamamoto,H.; Takeda,Y.; Iguchi,T.; Harada,M.; Hashiguchi,K.; Cho,N.; Notake,Y.; Miyakawa,Z.; Shimizu,A.; Kunii,K. Basic and clinical studies on azithromycin in obstetrics and gynecology. Japanese Journal of Chemotherapy 1995;43(S-6):299-312	Not RCT
McCormack WM, Nowroozi K, Alpert S, Sackel SG, Lee Y-H, Lowe EW, Rankin JS. Acute Pelvic Inflammatory Diseasr, characteristics of patients with gonococcal and nongonococcal infection and evaluation of their response to treatment with aqueous procaine penicillin G and spectinomycin hydrochloride. Sexually Transmitted Diseases 1977;4(4):125-31	Antibiotic not in BNF (spectinomycin)
McCormack,W.M.; Martin,D.H.; Hook III,E.W.; Jones,R.B. Daily oral grepafloxacin vs. twice daily oral doxycycline in the treatment of Chlamydia trachomatis endocervical infection. Infectious Diseases in Obstetrics & Gynecology 1998;6:109-15	Antibiotic not in BNF (grepafloxacin)
McGregor,J.A.; Crombleholme,W.R.; Newton,E.; Sweet,R.L.; Tuomala,R.; Gibbs,R.S. Randomized comparison of ampicillin-sulbactam to cefoxitin and doxycycline or clindamycin and gentamicin in the treatment of pelvic inflammatory disease or endometritis. Obstetrics & Gynecology 1994;83(6):998-1004	Antibiotic not in BNF (sulbactam)
Okada,H.; Yamamoto,T.; Yasuda,J.; Kanao,M.; Shimizu,T.; Yorozu,Y.; Torii,Y.; Haga,H.; Mizoguchi,H.; Mure,K.; Hasegawa,T.; Saito,S.; Nishino,T.; Saito,T.; Kimura,H.; Hayakawa,K.; Takaoka,Y.; Fujimoto,S.; Makinoda,S. Comparative clinical study on ciprofloxacin and cefroxadine in the treatment of infections in obstetrics and gynecology. Chemotherapy 1988;36(11):821-57	Antibiotic not in BNF (cefroxadine)
Paavonen J, Vesterinen E, Aantaa K, Rasanen J. Factors predicting abnormal hysterosalpingography findings in patients treated for acute pelvic inflammatory disease. International Journal of Gynaecology and Obstetrics 1985;23:171-5	Penicillin

Reference	Reason for exclusion
Pastorek,J.G.,Jr.; Aldridge,K.E.; Cunningham,G.L.; Faro,S.; Graffeo,S.; McNeeley,G.S.; Tan,J.S. Comparison of ticarcillin plus clavulanic acid with cefoxitin in the treatment of female pelvic infection. American Journal of Medicine 1985;79(Supp5B):161-3	Results not separate for PID
Poindexter AN. Comparative studies of mezlocillin, carbenicillin and ampicillin in the treatment of acute pelvic infection. Journal of antimicrobial chemotherapy 1982;9(suppA):159-61	Antibiotic not in BNF (mezlocillin, carbenicillin)
Reed,S.D.; Landers,D.V.; Sweet,R.L. Antibiotic treatment of tuboovarian abscess: Comparison of broad-spectrum beta-lactam agents versus clindamycin-containing regimens. American Journal of Obstetrics & Gynecology 1991;164:1556-62	Not RCT
Reedy,M.B.; Sulak,P.J.; Miller,S.L.; Ortiz,M.; Kasberg-Preece,C.; Kuehl,T.J. Evaluation of 3-day course of doxycycline for the treatment of uncomplicated chlamydia trachomatis cervicitis. Infectious Diseases in Obstetrics & Gynecology 1997;5:18-22	Not PID
Roy S, Wilkins J. Cefotaxime in the treatment of female pelvic soft tissue infections. *Infection* 1985; **13 Suppl 1**:S56-S61.	Penicillin
Roy,S.; Koltun,W.; Chatwani,A.; Martens,M.G.; Dittrich,R.; Luke,D.R. Treatment of acute gynaecologic infections with trovafloxacin. Trovafloxacin Surgical Group. American Journal of Surgery 1998;176(Supp 6A):67S-73S	Antibiotic not in BNF (trovafloxacin)
Ruiz Conde,M.A.; Lanzon,R.; Catalan,T.; Horno,M.; Perez,Medina T.; Bajo Arenas,J.M. et al. A multi-centre comparative study between meropenem and clindamycin-gentamicin combination in the treatment of obstetric and/or gynaecological infections in gynaecologic patients. Clinica e Investigacion en Ginecologia y Obstetricia, Vol 26(5) (pp 202-207), 1999	Results not separate for PID
Rustomjee,R.; Kharsany,A.B.M.; Connolly,C.A.; Abdool Karim,S.S. A gynaecological controlled trial of azithromycin versus doxycycline/ciprofloxacin for the syndromic management of sexually transmitted infections in a resource-poor setting. Journal of Antimicrobial Chemotherapy 2002;49:875-8	Not PID
Sanders,H.J. Therapy of chlamydia infections with tetracyclines. International Journal of Experimental & Clinical Chemotherapy 1990;3(2):101-6	Not PID
Sanfilippo,J.S.; Schikler,K.N. Mezlocillin versus penicillin and tobramycin in adolescent pelvic inflammatory disease: A prospective study. International Pediatrics 1989;4(1):53-6	Antibiotic not in BNF (mezlocillin)
Schnider G, Birken RA, Poindexter AN. A comparison of netilmicin and gentamicin in the treatment of pelvic infections. *Obstetrics & Gynecology* 1979; **54**(5):554-557.	Penicillin
Sendag,F.; Terek,C.; Tuncay,G.; Ozkinay,E.; Guven,M. Single dose oral azithromycin versus seven day doxycycline in the treatment of non-gonococcal mucopurulent endocervicitis. Australian and New Zealand Journal of Obstetrics and Gynaecology, Vol 40(1) (pp 44-47), 2000	Not PID
Senft,H.H.; Stiglmayer,R.; Eibach,H.W.; Koerner,H. Sulbactam/ampicillin versus cefoxitin in the treatment of obstetric and gynaecological infections. Drugs 1986;31(supp2):18-21	Antibiotic not in BNF (sulbactam)
Stamm,W.E.; Guinan,M.E.; Johnson,C. Effect of treatment regimens for Neisseria gonorrhoeae on simultaneous infection with Chlamydia trachomatis. New England Journal of Medicine, Vol 310(9) (pp 545-549), 1984	Not PID
Steingrimsson,O.; Olafsson,J.H.; Thorarinsson,H.; Ryan,R.W.; Johnson,R.B.; Tilton,R.C. Azithromycin in the treatment of sexually transmitted disease. Journal of Antimicrobial Chemotherapy 1990;25(suppA):109-14	Not PID
Stiglmayer,R.; Senft,H.H.; Eibach,H.W.; Korner,J. Sulbactam ampicillin versus cefoxitin in the treatment of gynaecological infections: An antibiotic therapeutic study (Reprinted from ZAC, vol 4, pg 123, 1986). INT J ANTIMICROBIAL AGENTS 1996;6:S61-S65	Antibiotic not in BNF (sulbactam)

Reference	Reason for exclusion
Stoykov S, Popov J. [Application of the antibiotic cefoxitin (mefoxin) in gynaecologic practice]. Akusherstvo Ginekologiia 1997;36(3):57-9	Not PID
Sweet,R.L.; Roy,S.; Faro,S.; O'Brien,W.F.; Sanilippo,J.S.; Seidlin,M. Piperacillin and tazobactam versus clindamycin and gentamicin in the treatment of gynaecologic women with pelvic infection. Obstetrics & Gynecology 1994;83:280-6	Results not separate for PID
Sweet RL, Landers DV, Schachter J, Crombleholme WR. Sulbactam/ampicillin in the treatment of acute pelvic inflammatory disease. International Journal of Gynaecology and Obstetrics 1989;supp2:13-9	Antibiotic not in BNF (sulbactam)
Sweet,R.L.; Schachter,J.; Landers,D.V.; Ohm-Smith,M.; Robbie,M.O. Treatment of hopitalized patients with acute pelvic inflammatory disease: Comparison of cefotetan plus doxycycline and cefoxitin plus doxycycline. American Journal of Obstetrics & Gynecology 1988;158:736-43	Antibiotic not in BNF (cefotetan)
Sweet,R.L.; Ohm-Smith,M.; Landers,D.V.; Robbie,M.O. Moxalactam versus clindamycin plus tobramycin in the treatment of obstetric and gynaecologic infections. American Journal of Obstetrics & Gynecology 1985;152:808-17	Antibiotic not in BNF (moxalactam)
Sweet RL, Robbie MO, Ohm-Smith M, Hadley WK. Comparative study of piperacillin versus cefoxitin in the treatment of obstetric and gynecologic infections. *American Journal of Obstetrics & Gynecology* 1983; **145**(3):342-349.	Anti-pseudomonal penicillin
Swenson RM, Lorber B. Clindamycin and carbenicillin in treatment of patients with intraabdominal and female genital tract infections. Journal of Infectious Diseases 1977;135(supp):S40-4	Antibiotic not in BNF (carbenicillin)
Thompson SE, III, Hager WD, Wong KH, Lopez B, Ramsey C, Allen SD, *et al*. The microbiology and therapy of acute pelvic inflammatory disease in hospitalized patients. *American Journal of Obstetrics & Gynecology* 1980; **136**(2):179-186.	Penicillin
Thompson SE, Brooks C, Eschenbach DA, Spence MR, Cheng S, Sweet R, *et al*. High failure rates in outpatient treatment of salpingitis with either tetracycline alone or penicillin/ampicillin combination. *American Journal of Obstetrics & Gynecology* 1985; **152**(6 Pt 1):635-641.	Penicillin
Thorpe Jr,E.M.; Stamm,W.E.; Hook III,E.W.; Gall,S.A.; Jones,R.B.; Henry,K.; Whitworth,G.; Johnson,R.B. Chlamydial cervicitis and urethritis: Single dose treatment compared with doxycycline for seven days in community based practises. Genitourinary Medicine 1996;72:93-7	Not PID
Tison E, Marpeau L, Pigne A, Tessier F, Barrat J. [Treatment of acute non-chlamydial salpingitis. Study of the efficacy and tolerance of a single-therapy antibiotic: Augmentin]. [French]. *Journal de Gynecologie, Obstetrique et Biologie de la Reproduction* 1988; **17**(4):513-519.	Penicillin
Van Gelderen CJ. A comparative trial of ceftriaxone and a penicillin/chloramphenicol combination in gynaecological infections complicated by peritonitis. *South African Medical Journal* 1987; **Suppl 2**:13-15.	Penicillin
Walker,C.K.; Landers,D.V.; Ohm-Smith,M.J.; Robbie,M.O.; Luft,J.; Schachter,J.; Sweet,R.L. Comparison of cefotetan plus doxycycline with cefoxitin plus doxycycline in the inpatient treatment of acute salpingitis. Sexually Transmitted Diseases 1991;18(2):119-23	Antibiotic not in BNF (cefotetan)
Wasserheit JN, Bell TA, Kiviat NB, Wolner-Hanssen P, Zabriskie V, Kirby BD et al. Microbial causes of proven pelvic inflammatory diseas and efficacy of clindamycin and tobramycin. Annals of Internal Medicine 1986;104:187-93	Not RCT
Witte EH, Peters AA, Smit IB, Linden MC, Mouton RP, Meer JW, Erp EJ. A comparison of perfloxacin/metronidazole and doxycycline/metronidazole in the treatment of laparoscopically confirmed acute pelvic inflammatory disease. Earopean Journal of Obstetrics and Gynaecology and Reproductive Biology 1993;50:153-8	Antibiotic not in BNF (perfloxacin)
Yamamoto,T.; Yasuda,J.; Tomioka,M.; Kanao,M.; Okada,H. [Fundamental and clinical studies on aztreonam in the field of obstetrics and gynecology.] Japanese Journal of Antibiotics 1985;38(12):3634-44	Not RCT

Reference	Reason for exclusion
Ziegler,C.; Stary,A.; Mailer,H.; Kopp,W.; Gebhart,W.; Soltz-Szots,J. Quinolones as an alternative treatment of chlamydial, mycoplasma and gonococcal urogenital infections. Dermatology 1992;185:128-31	Not PID

Table 50. Excluded cost, cost effectiveness and quality of life studies and reasons for exclusion

Reference	Reason for exclusion
Foran RM, Brett JL, Wulf PH. Evaluating the cost impact of intravenous antibiotic dosing frequencies. Pharmacoeconomics 1991;25:546-52	No mention of PID
Friedland LR, Kulick RM, Biro FM, Patterson AL. Cost-effectiveness decision analysis of intramuscular ceftriaxone versus oral cefixime in adolescents with gonococcal cervicitis. Annals of Emergency Medicine 1996;27(3):299-304	About prevention of PID not treatment
Genc M, Mardh PA. Cost effective treatment of uncompliated gonorrhoea including co-infection with chlamydia trachomatis. Pharmacoeconomics 1997;12(3):374-83	About prevention of PID not treatment
Haddix AC, Hillis SD, Kassler WJ. The cost-effectiveness of azithromycin for chlamydia trachomatis infections in women. Sexually transmitted diseases 1995;22(5):274-80	About prevention of PID not treatment
Handsfield HH, Stamm WE. Treating chlamydial infection: compliance versus cost. Sexually transmitted diseases 1997;25(1):12-3	No mention of PID
Henry-Suchet J, Tannous W. Prise en charge medicale des salpingites chroniques a chlamydia trachomatis resistant aux antibiotiques habituels interets de ofloxacine seule ou associee a d'autres antichlamydiens. Contraception, fertilite et sex 199321(9):627-9	Not a cost study
Howell MR, Gaydos JC, McKee KT, Quinn TC, Gaydos CA. Control of chlamydia trachomatis infections in female army recruits: cost effective screening to prevent pelvic inflammatory disease. Sexually transmitted diseases 1999;26(9):519-26	About prevention of PID not treatment
Howell MR, Kassler WJ, Haddix A. Partner notification to prevent pelvic inflammatory disease in women: cost effectiveness of two strategies. Sexually transmitted diseases 1997;24(5):287-92	About prevention not treatment
Jones GL, Kennedy SH, Jenkinson C. Health-related quality of life measurement in women with common benign gynaecologic conditions: a systematic review. American journal of obstetrics and gynaecology 2002;187(2):501-11	No mention of PID
Kerr JR, Barr JG, Smyth ET, O'Hare J. Technique for calculation of the true costs of antibiotic therapy. European Journal of clinical microbiology and infectious diseases 1992;11(9):823-7	No mention of PID
Kuhn GJ, Campbell A, Merline J, O'Neil BJ. Diagnosis and follow-up of chlamydia trachomatis infections in the ED. American Journal of Emergency Medicine 1998;16(2):157-9	Costs for PID patients not separate
Lea AP, Lamb HM. Azithromycin A pharmacoeconomic review of its use as a single dose regimen in the treatment of uncomplicated urogenital chlamydia trachomatis infections in women. Pharmacoeconomics 1997;12(5):596-611	About prevention of PID not treatment
Majid D, Douglas JM, Schwartz JS. Doxycycline compared with azithromycin for treating women with genital chlamydia trachomatis infections: an incremental cost-effectiveness analysis. Annals of internal medicine 1996;124:389-99	About prevention of PID not treatment
McGregor JA, Christensen FB, French JI. Intramuscular imipenem/cilastatin treatment of upper reproductive tract infection in women: efficacy and use characteristics. Chemotherapy 1991;37(supp 2):31-6	Only 4/29 patients had salpingitis, results not separate.
Petitta A, Hart SM, Bailey EM. Economic evaluation of three methods of treating urogenital chlamydial infections in the emergency department. Pharmacotherapy 1999;19(5):648-54	About prevention of PID not treatment
Stones R, Selfe SA, Fransman S, Horn SA. Psychosocial and economic impact of chronic pelvic pain. Bailliere's clinical obstetrics and gynaecology 2000;14(3):415-31	Not PID
Wynd MA, Hemsell BL, Paladino JA. Cost-effectiveness of ampicillin/sulbactam versus cefoxitin in the treatment of pelvic inflammatory disease. Journal of infectious disease pharmacotherapy 1999;4(1):35-48	Antibiotic not in BNF (sulbactam)

Appendix 7. Included trial details

Table 51. Antibiotic comparisons

Trial	Intervention	Control	
Apuzzio 1989[46]	Ciprofloxacin iv 600mg/day for 3-5 days then oral 1.5g/day to complete 10-14 days treatment (some changed to clindamycin and gentamicin, ampicillin and gentamicin or metronidazole)	Clindamycin iv 2.7g/day for 3-5 days then oral 1.8g/day to complete 10-14 days treatment Gentamicin iv initially 4.5mg/kg/day then peak and trough levels obtained for further dosing for 3-5 days (some also given ampicillin)	
Arredondo 1997[28]	Ciprofloxacin 500g/day for 14 days Clindamycin oral 1.8g/day for 14 days Plus one placebo im injection	Ceftriaxone im 250mg one dose Doxycycline oral 200mg/day for 14 days Plus oral placebo for 14 days	
Balbi 1996[47]	Gentamicin iv 2mg/kg one dose then 4.5mg/kg/day for 4 days Clindamycin iv 2.7mg/day for 4 days then oral 1.8g/day for 10 days (Two also given ampicillin)	Ceftazidime iv 3g/day for 4 days Doxycycline oral 200mg/day for 14 days (Three also given gentamicin)	
Bevan 2003[29]	Azithromycin iv 500mg once then oral 250mg for 7 days	Azithromycin iv 500mg once then oral 250mg for 7 days Metronidazole iv 1.5g/day for one day then oral 1.2g/day for 12 days (trial A) or oral 1.5g/day for 12 days (trial B)	
Buisson 1989[50]	Amoxycillin/clavulanate iv 3g/day for at least 2 days (mean 4.12 days) then oral 3-4g to complete 19 days treatment. Tetracycline 200mg/day if chlamydia found. (One crossover to amoxycillin, aminoglycoside and metronidazole)	Amoxycillin iv 3-4g/day for 4 days then oral 1.5-2g/day to complete 17 days treatment An Aminoglycoside im 3-5mg/kg/day for 7 days Metronidazole iv or suppository 1.5g/day then continued at same dose on discharge Tetracycline 200mg/day if chlamydia found.	
Burchell 1987[51]	Doxycycline iv 200mg then 100mg/day for 1 day then Oxytetracycline oral 1g/day for 14 days	Ampicillin iv 4g/day for 1 day then Metronidazole oral 2g/day for 14 days	Tetracycline suppository 3g/day for 1 day then Metronidazole oral 1.2g/day for 14 days
Ciraru-Vigneron 1986[52]	Amoxicillin/clavulanate iv then oral 4g/day (If Chlamydia positive doxycycline for 3 weeks)	Ampicillin iv 6g/day then amoxycillin oral 3g/day Gentamicin im 160mg/day for 7 days Metronidazole iv then oral 1.5g/day (If Chlamydia positive doxycycline for 3 weeks)	
Crombleholme 1989[48]	Ciprofloxacin iv 600mg/day for 2-5 days then oral 1.5g/day to complete 14 days treatment (clindamycin could be added if significant anaerobic infection) (One crossover to clindamycin and gentamicin)	Clindamycin iv 2.4g/day for 4 days then oral 1.2g/day to complete 14 days treatment Gentamicin iv 3mg/kg/day for 4 days	
de Beer 1983[53]	Ampicillin iv 2g then 6g/day for 2 days then oral 6g/day ?duration (1 also given gentamicin, 1 given gentamicin and metronidazole)	Cefoxitin iv 2g then 3g/day for 3 days (Two also given gentamicin)	
European 1992[39]	Clindamycin iv 2.7g/day for at least 4 days then oral 1.8g/day to complete 14 days treatment	Cefoxitin iv 8g/day for at least 4 days Doxycycline iv 200mg/day for at least 4 days then oral 200mg/day to complete 14	

Trial	Intervention	Control
	Gentamicin iv 2mg/kg then 4.5mg/kg/day for at least 4 days, adjusted by serum levels (One also given cephalexin)	days treatment (Two also given ofloxacin)
Gall 1981[62]	Metronidazole iv 15mg/kg then iv 30mg/kg/day for 5 days then oral 1g/day for 5 or more days Tobramycin iv 3mg/kg/day for 5 days (if gonorrhoea spectinomycin im 4g/day for 5 days) (One also given doxycycline)	Clindamycin iv 1.2-2.4mg/day for 5 days then oral 1.2g/day for 5 or more days Tobramycin iv 3mg/kg/day for 5 days (if gonorrhoea spectinomycin im 4g/day for 5 days)
Gerstner 1990[56-58]	Ceftriaxone iv 1g/day for 4-5 days (some also given doxycycline, erythromycin, metronidazole)	Cefotaxime iv 3g (?9g)/day for 4-5 days (some also given doxycycline, erythromycin, metronidazole)
Gjonnaess 1981[59]	Clindamycin (?route) 600mg/day for 14 days (Nine crossover to lymecycline)	Lymecycline (?route) 600mg/day for 14 days
Heinonen 1989[60,61]	Ciprofloxacin iv 400mg/day for 2 days then oral 1.5g for 12 days	Doxycycline iv 200mg/day for 2 days then oral 150mg for 12 days Metronidazole iv 1.5g/day for 2 days then oral 1.2g for 12 days (One also given spectinomycin)
Hemsell 1 1994[32]	Cefoxitin iv 8g/day for ?2 days Doxycycline iv 200mg/day for ?2days then oral 200mg/day to complete 10-14 days treatment	Clindamycin iv 2.7g/day for ?2 days then oral 1.8g/day to complete 10-14 days treatment Gentamicin 2mg/kg then 4.5mg/kg/day for ?2 days
Hemsell 2 1997[33]	Meropenem iv 1.5g/day for 2 days (some also given other antibiotics)	Clindamycin iv 2.7g/day for 2 days Gentamicin 2mg/kg then 4.5mg/kg/day for at least 2 days (some also given other antibiotics)
Henry 1985[30]	Aztreonam iv or im 2-6g ?duration Clindamycin iv or oral 1.8g/day ?duration	Clindamycin iv or oral 1.8g/day ?duration Gentamicin iv 3-5mg/kg/day ?duration
Hoyme 1993[43]	Ofloxacin ?IV then oral 400mg/day for ?10 days Metronidazole iv then oral 1g for 10 days	Clindamycin iv 1.2 g then 24g for ?10 days Gentamicin iv 240mg/day for 10 days
Ibrahim a 1990[63 64,65]	Netilmicin 6.6mg/kg/day for 7 days Ampicillin 4g/day ?duration Tinidazole 0.8g/day ?duration	Netilmicin 6.6mg/kg/day for 7 days Ampicillin 4g/day ?duration Tinidazole 0.8g/day ?duration
Ibrahim b 1990[63]	Amikacin 14mg/kg/day for 7 days Ampicillin 4g/day ?duration Tinidazole 0.8g/day ?duration	Amikacin 14mg/kg/day for 7 days Ampicillin 4g/day ?duration Tinidazole 0.8g/day ?duration
Judlin 1995[54]	Ofloxacin ?route 400mg/day for 3 weeks Amoxicillin/clavulanate ?route 2g/day for 3 weeks	Doxycycline ?route 200mg/day for 6 weeks Amoxicillin/clavulanate ?route 2g/day for 6 weeks
Landers 1991[44]	Cefoxitin iv 8g/day for 4 days Doxycycline iv 200mg/day for 4 days then oral 200mg/day to complete 14 days treatment.	Clindamycin iv 2.4g/day for 4 days then oral 1.8g/day to complete 14 days treatment Tobramycin iv 2mg/kg then 4.5mg/kg/day for 4 days
Larsen 1992[31]	Imipenem/cilastin iv 1.5-2g/day for 3 days minimum (Doxycycline 200 mg/day if chlamydia)	Clindamycin iv 2.7g/day for 3 days min. Gentamicin iv or im 1.5mg/kg then 3mg/kg/day for 3 days min. (Doxycycline 200 mg/day if chlamydia) (One also given ampicillin)

Trial	Intervention	Control
Maggioni 1998[34]	Meropenem iv 1.5g/day for 5 days	Imipenem/Cilastatin iv 1.5g/day for 5 days
Martens 1a 1990[49]	Cefotaxime ?route 6g/day for 4 days	Cefoxitin?route 6g/day
Martens 1b 1990[49]	Cefotaxime ?route 6g/day for 4 days	Clindamycin ?route 2.7g/day for 4 days Gentamicin ?route 120mg then 240mg/day for 4 days
Martens 2 1993[35]	Ofloxacin oral 800mg/day for 10 days (some also given oral metronidazole)	Cefoxitin im 2g once Probenecid oral 1g once Doxycycline oral 200mg/day for 10 days (some also given oral metronidazole)
PEACH 2002[40,41]	Cefoxitin im 2g once Probenecid oral 1g once Doxycycline oral 200mg/day for 14 days (3.3% changed drug treatment)	Cefoxitin iv 8g/day Doxycycline iv or im 200mg then oral 200mg/day for 14 days (2.9% changed drug treatment)
Soper 1988[42]	Cefoxitin iv 8g/day Doxycycline iv 200mg/day then oral 200mg/day to complete 10 day course (One changed to clindamycin, gentamicin and ampicillin, one also given metronidazole at follow up)	Clindamycin iv 2.4g/day then oral 1.2g to complete 10 day course Amikacin iv 15mg/kg/day (Two also given ampicillin)
Spence 1981[55]	Ampicillin iv 12g/day for 4 days then oral 2g to complete 10 day course (One given other antibiotics)	Doxycycline iv 200mg then 200mg/day for 4 days then oral 200mg /day to complete 10 day course (Six given other antibiotics)
Sweet 1985[45]	Cefoxitin (no dose/duration given) Doxycycline (no dose/duration given)	Clindamycin (no dose/duration given) Tobramycin (no dose/duration given)
Thadepalli 1991[36]	Ciprofloxacin iv 600mg/day for 3 days then oral 1g/day for 1 week	Clindamycin iv 2.4g/day for 3 days then oral ?2.4g/day for 1 week Gentamicin iv 240g/day, adjusted on serum levels ?duration
Walters 1990[37]	Clindamycin iv 2.7g/day for 4 days then oral 1.8g/day to complete 14 day course Gentamicin 2mg/kg then 4.5mg/kg/day for 4 days (Three also given iv penicillin or ampicillin)	Cefoxitin iv 8g/day for 4 days Doxycycline iv 200mg/day for 4 days then oral 200mg/day to complete 14 day course (Two given iv ampicillin, gentamicin and clindamycin)
Wendel 1991[38]	Cefoxitin im 2g once Probenecid oral 1g once Doxycycline oral 200mg/day for 10 days	Ofloxacin oral 800mg/ day for 10 days

Table 52. Trial details

Trial	Multi-centre/ country	Date of enrollment	Inpatient/ outpatient	Laparoscopic diagnosis	IUD use
Apuzzio 1989[46]	USA	1987-8	IP	No	NR
Arredondo 1997[28]	Chile, Mexico, Peru, Colombia,	-	OP	Yes	41% (All removed before treatment)
Balbi 1996[47]	Italy	1989-92	NG	No	Excluded
Bevan 2003[29]	European	-	IP	Yes	NR
Buisson 1989[50]	France	1986-7	IP	Yes	34%
Burchell 1987[51]	South Africa	-	IP	Yes	NR
Ciraru-Vigneron 1986[52]	France	-	IP	Yes	NR
Crombleholme 1989[48]	USA	-	IP	No	NR
de Beer 1983[53]	South Africa	-	IP	No	NR
European 1992[39]	10 centres in Europe, Africa	1987-9	IP	Optional	NR
Gall 1981[62]	USA	-	IP	No	NR
Gerstner 1990[56-58]	Austria	-	IP	No	NR
Gjonnaess 1981[59]	Norway	-	IP	Yes	49%
Heinonen 1989[60,61]	Finland	1987-8	IP	Yes	39%
Hemsell 1 1994[32]	USA	1988-91	IP	Optional	Included only if removed wihin 48 hours
Hemsell 2 1997[33]	USA	-	IP	No	NR
Henry 1985[30]	USA	-	IP	No	NR
Hoyme 1993[43]	Germany	-	IP	Yes	NR
Ibrahim a and b 1990[63-65]	Belgium	1986-8	IP	Yes	NR
Judlin 1995[54]	France	1988	IP	Yes	NR
Landers 1991[44]	USA	-	IP	Optional	4%
Larsen 1992[31]	USA	1988-9	IP	No	NR
Maggioni 1998[34]	Italy	-	IP	Optional	NR
Martens 1a 1990[49] and Martens 1b 1990[49]	USA	-	IP	No	NR
Martens 2 1993[35]	USA	1986-8	OP	No	Excluded

Trial	Multi-centre/ country	Date of enrollment	Inpatient/ outpatient	Laparoscopic diagnosis	IUD use
PEACH 2002[40,41]	USA	1996-9	Both	Optional	2%
Soper 1988[42]	USA	-	IP	No	3%
Spence 1981[55]	USA	-	IP	Optional	NR
Sweet 1985[45]	USA	-	?	?	NR
Thadepalli 1991[36]	USA	-	IP	No	~5%
Walters 1990[37]	USA	1986-8	IP	No	7%
Wendel 1991[38]	USA	1987	OP	No	NR

Table 53. Trial diagnostic criteria

Trial	Diagnostic criteria
Apuzzio 1989[46]	Hager criteria used for diagnosis
Arredondo 1997[28]	Clinicaldiagnosis confirmed by laparoscopy. Grading of mild/moderate only using Hager's and Soper's criteria
Balbi 1996[47]	All 3 present at the same time: 1. Spontaneous pain and pain when the lower abdominal area was pressed 2. Pain caused by movements exerted on the cervix 3. Adnexal ache
Bevan 2003[29]	Hager's criteria for diagnosis
Buisson 1989[50]	Diagnosis of PID confirmed by laparoscopy
Burchell 1987[51]	Diagnosis "according to established criteria" Severity by Thompson's criteria
Ciraru-Vigneron 1986[52]	Fever, pain, local signs (guarding, lateral uterine mass), isolation of pathological bacteria, leucocytosis, high ethrocyte sedimentation rate, echography and eventually laparoscopy
Crombleholme 1989[48]	History of lower abdominal pain and direct lower abdominal tenderness with or without rebound, tenderness with motion of the cervix and uterus and adnexal tenderness. Also must have at least one of Gram stain of the endocervix positive for gram negative intracellular bacteria, direct fluorescent antibody test revealing chlamydia, elevated erythrocyte sedimentation rate, temperature greater than 38C, leucocytosis greater than 10,500 white blood cell/mm^3 purulent material (white blood cells and bacteria) from the peritoneal cavity by culdocentesis or a pelvic abscess or inflammatory ciomplex on bimanual examination or by sonography
de Beer 1983[53]	Temperature above 38C and abdominal or pelvic pain with clinical signs consistent with pelvic infection. These were guarding, lower abdominal rebound tenderness, adnexal tenderness and tenderness with displacement of the uterine cervix.
European 1992[39]	Abdominal, parametrial and cervical motion tenderness plus either fever, leukocytosis, pelvic mass or purulent material in the peritoneal cavity. Grading of severity by Hager criteria
Gall 1981[62]	NR
Gerstner 1990[56-58]	NR
Gjonnaess 1981[59]	Laparoscopic diagnosis of PID
Heinonen 1989[60,61]	History of lower abdominal pain of less than 3 weeks duration and the presence of cervical motion tenderness, uterine and adnexal tenderness in bimanual examination, raised erythrocyte sedimentation rate, C-reactive protein, white cell count and/or body temperature. Pelvic sonography used to strengthen diagnosis where necessary

Trial	Diagnostic criteria
Hemsell 1 1994[32]	Women with lower abdominal and pelvic pain who had lower abdominal and cervical motion and adnexal tenderness plus at least one of temperature at least 38C, leucocytosis at least 10,500, raise erythrocyte sedimentation rate, endocervical specimen positive for gram-negative intracellular diplococci, an endocervical or endometrial culture positive for gonorrhoea or culture positive for chlamydia, ultrasound findings consistent with an adnexal inflammatory mass or purulence in or a positive culture of intraperitoneal material obtained by culdocentesis or laparoscopy
Hemsell 2 1997[33]	NR
Henry 1985[30]	Presence of at least three of lower abdominal, pelvic and uterine tenderness or pain, fever greater than 38C, objective evidence of an abscess documented by sonography, radiography, nuclear scanning or computerised tomography
Hoyme 1993[43]	Clinical diagnosis confirmed by laparoscopy
Ibrahim a and b 1990[63-65]	Diagnosis confirmed by laparoscopy. Graded moderate or severe only by Hager's criteria
Judlin 1995[54]	Pelvic pain, lymphocytosis, uterine haemorrhage, digestive problems, temperature at least 37.8C, rebound tenderness, guarding, cervical motional tenderness. Diagnosis confirmed by laparoscope
Landers 1991[44]	Laparoscopically confirmed diagnosis or clinical criteria of direct abdominal tenderness, cervical motion tenderness, adnexal tenderness, plus one or more of temperature at least 38C, leucocytosis at least 10,500/mm^3 purulent material on culdocentesis, evidence of pelvic abscess on ultrasonography or pelvic examination, evidence of gonococcal or chlamydial cervicitis (by positive monoclonal antibody test or by Gram stain showing gram negative intracellular diplococci) or by mucopurulent cervicitis
Larsen 1992[31]	NR
Maggioni 1998[34]	NR
Martens 1a 1990[49] and Martens 1b 1990[49]	Temperature at least 38C, lower abdominal tenderness, cervical or uterine tenderness on palpation and motion, adnexal tenderness on palpation. Also may be present were purulent endocervical discharge, white blood cells at least 14,00/mm^3 adnexal mass or abscess, nausea and vomiting
Martens 2 1993[35]	All three of direct lower abdominal tenderness with or without rebound tenderness, cervical motion tenderness, adnexal tenderness, plus one or more of recent positive endocervical culture for gonorrhoea or chlamydia, temperature more than 38C, white cell count greater than 10,000 /mm^3 leucocytic cervical discharge. Graded into mild moderate and severe based on amount of abdominal or pelvic discomfort
PEACH 2002[40,41]	History of pelvic discomfort for 30 days or less, uterine or adnexal tenderness on bimanual examination, leucorrhoea and/or mucopurulent cervicitis and/or untreated known positive gonococcal or chlamydial cervicitis

Trial	Diagnostic criteria
Soper 1988[42]	Lower abdominal pain and bilateral adnexal tenderness on bimanual pelvic examination, leucocytes predominant in vaginal smear plus at least two of temperature over 38C, leukocytosis more than 11,000//mm^3 purulent material from the peritoneal cavity by culdocentesis, inflammatory compley on bimanual examination or sonography and/or erythrocyte sedimentation rate over 20mm/hour. Graded using Soper criteria and only Ib, IIa and IIb included
Spence 1981[55]	Lower abdominal pain and tenderness, abdominal rebound tenderness, tenderness on manipulation of the uterus, adnexal tenderness with or without adnexal masses, white cell count over 10,000//mm^3 plus for inclusion – nausea and vomiting or unable to tolerate oral medication
Sweet 1985[45]	NR
Thadepalli 1991[36]	Lower abdominal pain associated with fever and chills, cervical motion tenderness with or without signs of adnexal masses. (CDC criteria)
Walters 1990[37]	Hager criteria for diagnosis
Wendel 1991[38]	All three of direct lower abdominal tenderness with or without rebound tenderness, cervical motion tenderness, adnexal tenderness, plus one or more of recent positive endocervical culture for gonorrhoea or chlamydia, temperature more than 38C, white cell count greater than 10,000 /mm^3

Table 54. Randomisation numbers and departures from ITT analysis

Trial	No patients randomised	No patients followed up	Reasons for not reporting results from all those randomised (ie not ITT analysis)	Subgroup of larger trial?
Apuzzio 1989[46]	?	25	One patient was not evaluated because she was given additional antibiotic.	Yes (pelvic infections)
Arredondo 1997[28]	138	131	Less than 48 hours treatment for reasons other than side effects or less than 4 days therapy, required additional antibiotics for non-protocol related infections or was infected with pathogens resistant to all of the study drugs.	No
Balbi 1996[47]	78	76	Two excluded because of previous intolerance to penicillin (not study drug)	No
Bevan 2003[29]	213	79	ITT given for patients assessed at day 2. Follow up results given for patients' nearest assessment to day 15 (between days 9 and 26 inclusive) Microbiological follow up at day 35-44.	No
Buisson 1989[50]	82	81	One not evaluated because developed angioedema (on amoxicillin, aminoside, metronidazole)	No
Burchell 1987[51]	40	30	Ten excluded because laparoscopic examination and cultures did not confirm PID diagnosis	No
Ciraru-Vigneron 1986[52]	44	? (results given as percentages)	-	No
Crombleholme 1989[48]	80	70	Incorrect diagnosis, left hospital after one dose of antibiotics, already had antibiotics, entered into trial twice, no cultures taken before discharge	No
de Beer 1983[53]	60	60	-	No
European 1992[39]	170	115	Failure to follow randomisation scheme, protocol deviation, incorrect diagnosis	No
Gall 1981[62]	9	9	-	Yes (pelvic infections)
Gerstner 1990[56-58]	18	18	-	Yes (pelvic infections)
Gjonnaess 1981[59]	64	64	-	No
Heinonen 1989[60,61]	40	36	Incorrect diagnosis (diagnosis changed after laparoscopy and cultures)	No
Hemsell 1 1994[32]	230	198	Violation of inclusion/exclusion criteria, incorrect dose of study drugs, left hospital against medical advice, treated for less than 48 hours, withdrew from study, reactions from study drugs, given penicillin for syphilis	Yes (3rd trial arm excluded – antibiotic not in BNF)
Hemsell 2 1997[33]	105	84	Failure to isolate a pre-treatment pathogen, resistance of pathogen to study drugs, given another antibiotic, treatment for less than 48 hours, unacceptable clinical diagnosis	Yes (pelvic infections)
Henry 1985[30]	13	13	-	Yes (pelvic infections)
Hoyme 1993[43]	33	33	-	No
Ibrahim a and b	78	78	-	No

Trial	No patients randomised	No patients followed up	Reasons for not reporting results from all those randomised (ie not ITT analysis)	Subgroup of larger trial?
1990[63 64,65]				
Judlin 1995[54]	33	33	-	Yes (pelvic infections)
Landers 1991[44]	162	148	Incorrect diagnosis or refusal of the patient to remain in hospital long enough to complete treatment	No
Larsen 1992[31]	?77	77	Results for evaluable patients presented only	Yes (pelvic infections)
Maggioni 1998[34]	?	34	Treatment for less than 48 hours, misdiagnosis, pathogens resistant to study drug, concomitany antibiotics, incorrect dose of study drug	Yes (pelvic infections)
Martens 1a 1990[49] and Martens 1b 1990[49]	99	94	Protocol violations such as incorrect antibiotic administration	No
Martens 2 1993[35]	295	249	Noncompliance, no attendance at any of the three follow ups, protocol violations at admission	No
PEACH 2002[40,41]	864	798	Ineligible, refused after initial consent, no follow up	No
Soper 1988[42]	62	62	-	No
Spence 1981[55]	47	47	-	No
Sweet 1985[45]	79	79	-	No
Thadepalli 1991[36]	33	30	Protocol violations, incorrect diagnosis	Yes (pelvic infections)
Walters 1990[37]	147	130	Less than 48hrs treatment, wrong diagnosis, needing emergency surgery, left hospital against medical advice	No
Wendel 1991[38]	96	72	Noncompliance with regimen, no follow ups attended	No
* considered eligible for randomisation				

Table 55. Trial quality

Trial	Randomisation method	Allocation concealment	Blinding methods	Jadad score
Apuzzio 1989[46]	-	-	-	0
Arredondo 1997[28]	-	-	Encapsulated tablets	1
Balbi 1996[47]	-	-	-	1
Bevan 2003[29]	-	-	Open label	1
Buisson 1989[50]	-	-	-	1
Burchell 1987[51]	-	-	-	0
Ciraru-Vigneron 1986[52]	-	-	-	1
Crombleholme 1989[48]	-	-	Non-blind	1
de Beer 1983[53]	-	-	-	0
European 1992[39]	-	-	Open label	1
Gall 1981[62]	First 6 patients assigned to intervention (? No PID in this group), remaining 41 randomly allocated	-	-	0
Gerstner 1990[56-58]	-	-	Open	0
Gjonnaess 1981[59]	Initially randomised, then closed one group when 20 patients allocated (other group has 44 in)	-	-	0
Heinonen 1989[60,61]	-	-	-	0
Hemsell 1 1994[32]	Randomisation codes used	-	Open label	0
Hemsell 2 1997[33]	Pre-determined randomisation schedule for each centre	-	Open label	1
Henry 1985[30]	-	-	-	0
Hoyme 1993[43]	-	-	-	0
Ibrahim a and b 1990[63-65]	-	-	-	0
Judlin 1995[54]	-	-	Open label	0
Landers 1991[44]	-	-	Unblinded	0
Larsen 1992[31]	-	Done by hospital pharmacy	Open label	0
Maggioni 1998[34]	-	Sequential opening of codebreak envelopes	Open	0
Martens 1a 1990[49] and	Randomisation codes, stratified by	-	-	0

Trial	Randomisation method	Allocation concealment	Blinding methods	Jadad score
Martens 1b 1990[49]	uncomplicated/ complicated PID			
Martens 2 1993[35]	Computer generated code	-	-	0
PEACH 2002[40,41]	Computer generated, random block lengths stratified by site	Opaque envelopes sequentially opened	Blinding of patients not possible (IP vs OP) No statement on whether follow up assessment was blind to treatment group	3
Soper 1988[42]	Random number table	Sealed envelope	-	2
Spence 1981[55]	-	By pharmacy	Not blinded	0
Sweet 1985[45]	-	-	-	0
Thadepalli 1991[36]	Computer generated randomisation scheme	-	-	1
Walters 1990[37]	Computer generated	-	Open label	0
Wendel 1991[38]	Random code numbers	None	Open label	0

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