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Abstract

Gentamicin as an alternative to ceftriaxone in the treatment of gonorrhoea: the G-TOG non-inferiority RCT

Jonathan DC Ross,[1]* Jan Harding,[1] Lelia Duley,[2] Alan A Montgomery,[2] Trish Hepburn,[2] Wei Tan,[2] Clare Brittain,[2] Garry Meakin,[2] Kirsty Sprange,[2] Sukhwinder Thandi,[2] Louise Jackson,[3] Tracy Roberts,[3] Janet Wilson,[4] John White,[5] Claire Dewsnap,[6] Michelle Cole[7] and Tessa Lawrence[1] on behalf of the G-TOG Collaborative Group†

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Background: Gonorrhoea is a common sexually transmitted infection that can cause pain and discomfort, affect fertility in women and lead to epididymo-orchitis in men. Current treatment is with ceftriaxone, but there is increasing evidence of antimicrobial resistance reducing its effectiveness. Gentamicin is a potential alternative treatment requiring further evaluation.

Objectives: To assess the clinical effectiveness and cost-effectiveness of gentamicin as an alternative treatment to ceftriaxone in the treatment of gonorrhoea.

Design: A multicentre, parallel-group, blinded, non-inferiority randomised controlled trial.

Setting: Fourteen sexual health clinics in England.

Participants: Adults aged 16–70 years with a diagnosis of uncomplicated, untreated genital, pharyngeal or rectal gonorrhoea based on a positive Gram-stained smear on microscopy or a positive nucleic acid amplification test (NAAT).

Randomisation and blinding: Participants were randomised using a secure web-based system, stratified by clinic. Participants, investigators and research staff assessing participants were blinded to treatment allocation.

Interventions: Allocation was to either 240 mg of gentamicin (intervention) or 500 mg of ceftriaxone (standard treatment), both administered as a single intramuscular injection. All participants also received 1 g of oral azithromycin.

Main outcome measure: The primary outcome measure was clearance of *Neisseria gonorrhoeae* at all infected sites, confirmed by a negative Aptima Combo 2® (Hologic Inc., Marlborough, MA, USA) NAAT, at 2 weeks post treatment.

Results: We randomised 720 participants, of whom 81% were men. There were 358 participants in the gentamicin group and 362 in the ceftriaxone group; 292 (82%) and 306 (85%) participants, respectively, were included in the primary analysis. Non-inferiority of gentamicin to ceftriaxone could not be demonstrated [adjusted risk difference for microbiological clearance –6.4%, 95% confidence interval (CI) –10.4% to –2.4%]. Clearance of genital infection was similar in the two groups, at 94% in the gentamicin group and 98% in the ceftriaxone group, but clearance of pharyngeal infection and rectal infection was lower in the gentamicin group (80% vs. 96% and 90% vs. 98%, respectively). Reported pain at the injection site was higher for gentamicin than for ceftriaxone. The side-effect profiles were comparable between the groups. Only one serious adverse event was reported and this was deemed not to be related to the trial medication. The economic analysis found that treatment with gentamicin is not cost neutral compared with standard care, with average patient treatment costs higher for those allocated to gentamicin (£13.90, 95% CI £2.47 to £37.34) than to ceftriaxone (£6.72, 95% CI £1.36 to £17.84).

Limitations: Loss to follow-up was 17% but was similar in both treatment arms. Twelve per cent of participants had a negative NAAT for gonorrhoea at their baseline visit but this was balanced between treatment groups and unlikely to have biased the trial results.

Conclusions: The trial was unable to demonstrate non-inferiority of gentamicin compared with ceftriaxone in the clearance of gonorrhoea at all infected sites. Clearance at pharyngeal and rectal sites was lower for participants allocated to gentamicin than for those allocated to ceftriaxone, but was similar for genital sites in both groups. Gentamicin was associated with more severe injection site pain. However, both gentamicin and ceftriaxone appeared to be well tolerated.

Future work: Exploration of the genetic determinants of antibiotic resistance in *N. gonorrhoeae* will help to identify accurate markers of decreased susceptibility. Greater understanding of the immune response to infection can assist gonococcal vaccine development.

Trial registration: Current Controlled Trials ISRCTN51783227.

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List of abbreviations

A&E	accident and emergency
AC2	Aptima Combo 2
AE	adverse event
AMR	antimicrobial resistance
BASHH	British Association for Sexual Health and HIV
BD	Becton, Dickinson and Company
BNF	*British National Formulary*
CEA	cost-effectiveness analysis
CI	confidence interval
DMC	Data Monitoring Committee
eGFR	estimated glomerular filtration rate
G-TOG	Gentamicin in the Treatment Of Gonorrhoea
GEE	generalised estimating equation
GP	general practitioner
HIV	human immunodeficiency virus
i.m.	intramuscular
IQR	interquartile range
IT	information technology
ITT	intention to treat
MedDRA	Medical Dictionary for Regulatory Activities
MIC	minimum inhibitory concentration
MSM	men who have sex with men
NAAT	nucleic acid amplification test
NCTU	Nottingham Clinical Trials Unit
PHE	Public Health England
PI	principal investigator
PIS	patient information sheet
PPI	patient and public involvement
PSA	probabilistic sensitivity analysis
RCT	randomised controlled trial
SAE	serious adverse event
SAP	statistical analysis plan
SmPC	Summary of Product Characteristics
STI	sexually transmitted infection
TMG	Trial Management Group
TSC	Trial Steering Committee
VAS	visual analogue scale

Plain English summary

Gonorrhoea is a common infection, spread by having sex, that causes genital pain and discomfort. In women it can lead to pelvic inflammation and infertility, and in men it can lead to swelling and pain in the testicles. Currently, an antibiotic called ceftriaxone is used to treat gonorrhoea. However, there is evidence that this is becoming less effective over time and it could stop curing patients with gonorrhoea within the next few years.

In this study, we wanted to find out if another antibiotic called gentamicin is as good as ceftriaxone in the treatment of gonorrhoea and whether or not gentamicin could be used to treat gonorrhoea if ceftriaxone stops being effective.

We recruited 720 adults with gonorrhoea and randomly allocated them (by chance) to receive treatment with an injection of either gentamicin (240 mg) or ceftriaxone (500 mg). They all also received a single dose of azithromycin (1 g) taken by mouth.

Overall, 98% of participants given ceftriaxone had their gonorrhoea cured, compared with 91% of participants given gentamicin, a difference of 7%. Therefore, it is likely that doctors will continue to use ceftriaxone (plus azithromycin) as the preferred treatment. Gentamicin did have a cure rate of 94% for genital gonorrhoea and so it might be useful when ceftriaxone is not available or appropriate to use. Cure rates using gentamicin were lower than cure rates using ceftriaxone for gonorrhoea infecting the rectum (90%) and throat (80%), so it may be less useful for patients with infections at these sites.

We also found that gentamicin is likely to cost the NHS more than ceftriaxone.

Gentamicin caused few side effects and seems to be as safe as ceftriaxone, which is reassuring.

Scientific summary

Background

Gonorrhoea is a common sexually transmitted infection (STI) that causes genital pain and discomfort; in women it can lead to pelvic inflammatory disease and infertility, and in men it can lead to epididymo-orchitis. The current treatment is ceftriaxone plus azithromycin, but there is increasing evidence of cephalosporin resistance, which is reducing this regimen's effectiveness against gonorrhoea. A small but increasing number of patients have already been found to have highly resistant strains of gonorrhoea, which have been associated with treatment failure. The Gentamicin in the Treatment Of Gonorrhoea (G-TOG) trial aimed to determine whether or not gentamicin is non-inferior to ceftriaxone in the treatment of gonorrhoea.

Objectives

Primary objective

The primary objective was to determine whether or not gentamicin is an acceptable alternative to ceftriaxone for the treatment of gonorrhoea. This was addressed by determining whether or not the microbiological clearance of *Neisseria gonorrhoeae* in participants allocated to gentamicin was non-inferior to the clearance for participants allocated to ceftriaxone.

Secondary objectives

The secondary objectives were to determine:

- whether or not a single intramuscular (i.m.) dose of gentamicin is safe and well tolerated
- whether or not a single i.m. dose of gentamicin is cost-effective, from the perspective of the NHS, when used to treat gonorrhoea
- the relationship between clinical effectiveness and the laboratory measurement of antibiotic effectiveness [the minimum inhibitory concentration (MIC) required to inhibit growth of *N. gonorrhoeae*].

Methods

Trial design

Blinded, multicentre, non-inferiority, randomised trial comparing the clinical effectiveness, cost-effectiveness and safety of gentamicin with those of ceftriaxone for the treatment of gonorrhoea.

Recruitment

Participants were recruited from outpatient sexual health clinics in England. Some clinics with a large proportion of men who have sex with men attending were specifically selected to maximise the number of participants with pharyngeal and rectal infections.

Eligibility

Adults aged 16–70 years were eligible for recruitment if they had received a positive diagnosis of uncomplicated, untreated (i.e. they not received any antibiotic in the previous 28 days that could have treated gonorrhoea, either partially or completely) genital, pharyngeal and/or rectal gonorrhoea in the previous 4 weeks. The diagnosis was based on a positive Gram-stained smear on microscopy or a positive nucleic acid amplification test (NAAT).

The exclusion criteria were having known concurrent bacterial STI (apart from chlamydia); having known bacterial vaginosis and/or *Trichomonas vaginalis* infection; having known contraindications or an allergy to gentamicin, ceftriaxone, azithromycin or lidocaine; having a current clinical diagnosis of complicated gonorrhoea infection, for example pelvic inflammatory disease or epididymo-orchitis; weighing < 40 kg; and receiving or having received ceftriaxone, gentamicin or azithromycin within the preceding 28 days. Pregnant and/or breastfeeding women were also excluded. Participants were eligible to participate in the trial only once.

Interventions

Both treatments were administered from routine clinic stock as a single i.m. injection.

For the ceftriaxone group, 500 mg of ceftriaxone in powder formulation was dissolved in 1% lidocaine and administered as a single 2-ml i.m. injection.

For the gentamicin group, 240 mg (3 × 80 mg in 2-ml vials) of gentamicin was administered as a single 6-ml i.m. injection.

In addition, all participants received a single oral dose of 1 g of azithromycin, which is currently given in the UK as standard treatment alongside ceftriaxone.

Outcomes

Primary outcome

The primary outcome was clearance of *N. gonorrhoeae*, confirmed by a negative Aptima Combo 2® (Hologic Inc., Marlborough, MA, USA) NAAT, 2 weeks post treatment (as recommended by the British Association for Sexual Health and HIV) at all infected sites.

Secondary outcomes

The secondary outcomes were:

- clinical resolution of symptoms
- frequency of nausea/vomiting, hearing loss, dizziness and rash
- frequency of any other adverse events (AEs) reported by participants
- tolerability of injection as assessed by the participant on a visual analogue scale (VAS)
- comparative cost-effectiveness.

The relationship between clearance of *N. gonorrhoeae* and in vitro measurement of antibiotic MIC to inhibit *N. gonorrhoeae* growth was also assessed.

Effectiveness, tolerability and safety were assessed at a follow-up visit 2 weeks post treatment.

Sample size

Based on 96% clearance for the ceftriaxone regimen, a total sample size of 646 participants (323 in each group) was required for analysis to detect non-inferiority with a lower 95% confidence interval (CI) for the absolute risk difference of 5%, 90% power and a one-sided significance level of 0.025. To allow for a loss to follow-up of 10%, the trial aimed to recruit a total of 720 participants.

Randomisation and blinding

Randomisation was in a 1 : 1 ratio, stratified by recruiting centre. A computer-generated pseudorandom code, using permuted blocks of randomly varying size, was created by the Nottingham Clinical Trials Unit in accordance with their standard operating procedure and held on a secure server. Participants, investigators and research staff assessing the participants were blinded to treatment allocation. The sequence of

treatment allocations remained concealed until the database was locked at the end of the trial, when it was revealed to data analysts.

Statistical methods

Demographic and clinical measures were compared between the randomised arms at baseline using appropriate descriptive statistics for continuous and categorical variables.

The primary approach to between-group comparative analyses was by intention to treat without imputation of missing outcome data. Sensitivity analyses were conducted to investigate the impact of missing primary outcome data using simple and multiple imputation. The primary outcome comparing gentamicin with ceftriaxone was the difference in the proportion of participants clear of infection at 2 weeks' follow-up, along with the 95% CI. Gentamicin was regarded as non-inferior if the lower 95% CI for the risk difference in confirmed clearance was ≥ -5 percentage points (i.e. nearer zero). This was evaluated using a generalised estimating equation for binary outcomes, adjusted by recruiting centre as a random effect, with robust standard errors.

The secondary outcomes were similarly analysed using appropriate regression models dependent on data type, adjusted for clinic site and baseline value of the outcome variable, if collected. To explore treatment efficacy by site of infection, for each of the three infection sites, we separately estimated clearance by treatment arm along with 95% CIs.

The relationship between clinical effectiveness and MIC was examined visually.

Safety and tolerability analyses were descriptive. Frequency counts and percentages of the prespecified main categories of AEs were presented by treatment arm.

Health economics

The economic analysis compared the costs associated with the current standard treatment, ceftriaxone, with those of the proposed alternative treatment, gentamicin, in the treatment of gonorrhoea. Given that the primary objective of the trial was to determine non-inferiority of gentamicin compared with ceftriaxone, the economic analysis focused on establishing whether or not the use of gentamicin rather than ceftriaxone was cost neutral in the treatment of gonorrhoea. This involved the collection and analysis of data on costs and NHS resource use to determine whether or not there were any differences between the two treatments. These data were collected via trial processes and a patient questionnaire at the 2-week follow-up.

Results

The trial randomised 720 participants: 358 to receive gentamicin and 362 to receive ceftriaxone. Eighty-one per cent of participants were male, 69% were white and 13% had an human immunodeficiency virus infection. Fourteen participants did not receive their allocated medication, of whom 10 were in the gentamicin group and four were in the ceftriaxone group. Primary outcome data were available for 306 participants (85%) randomised to receive ceftriaxone and 292 participants (82%) randomised to receive gentamicin. In total, 299 (98%) of the participants allocated to ceftriaxone had clearance at 2 weeks, compared with 276 (91%) of the participants allocated to gentamicin, an adjusted risk difference of –6.4% (95% CI –10.4% to –2.4%). Clearance at genital sites was 98% and 94%, at pharyngeal sites was 96% and 80% and at rectal sites was 98% and 90% in ceftriaxone- and gentamicin-allocated participants, respectively. Nausea was experienced by 12% and 14% of participants, vomiting by 1% and 4%, reduction in hearing by 2% and 1%, dizziness/unsteadiness by 7% and 7% and skin rash by 2% and 4% in the ceftriaxone and gentamicin groups, respectively. The majority of participants reported injection site pain (98% and 99% in the ceftriaxone and gentamicin treatment groups, respectively), with the mean pain score, measured by a VAS, greater in the

gentamicin group (21 vs. 36). The median time to resolution of injection pain was 1 hour for ceftriaxone and 1.5 hours for gentamicin. Fifteen per cent of participants allocated to ceftriaxone and 13% allocated to gentamicin reported at least one AE. The majority of AEs were mild (45/54 in the ceftriaxone group and 35/43 in the gentamicin group). One serious AE (grade 4 dizziness) was reported and it was not considered to be related to the trial treatment.

The economic analysis found that, from a health-care perspective, treatment with gentamicin was not cost neutral compared with standard care. Average patient treatment costs were found to be higher for the gentamicin trial arm (£13.90, 95% CI £2.47 to £37.34) than for the ceftriaxone arm (£6.72, 95% CI £1.36 to £17.84). However, within the economic evaluation, it was not possible to consider the potential issues associated with antimicrobial resistance (AMR) in gonorrhoea.

Conclusions

Implications for health care

The G-TOG trial was unable to demonstrate the non-inferiority of gentamicin compared with ceftriaxone in microbiological clearance of gonorrhoea at 2 weeks' follow-up. Therefore, it is likely that clinicians will want to continue to use ceftriaxone (plus azithromycin) as their preferred first-line therapy. Secondary analyses suggested that gentamicin was potentially non-inferior to ceftriaxone with respect to clearance of genital gonorrhoea (94% vs. 98%), so it is possible that gentamicin could be used for patients who are allergic or intolerant to ceftriaxone or who have a gonorrhoea infection that is resistant to ceftriaxone. However, further work would be needed to confirm non-inferiority. The lower cure rates for rectal (90%) and pharyngeal infection (80%) make gentamicin a less attractive treatment option, but antibiotics are generally less effective at these sites and gentamicin may still be useful as a second- or third-line therapy. A repeat test for gonorrhoea to ensure microbiological cure would be advisable following gentamicin therapy.

Azithromycin is currently used as part of dual therapy for gonorrhoea to 'protect' ceftriaxone by theoretically reducing the risk of resistance developing and by providing microbiological cover in case cephalosporin resistance develops. The observation in the G-TOG trial that a 1-g dose of azithromycin, even in combination with gentamicin, has a significant failure rate raises concerns about the effectiveness of 1 g of azithromycin in the treatment of gonorrhoea and, therefore, whether or not its use as a component of dual therapy will reduce the risk of future AMR developing.

A single dose of 240 mg of gentamicin was found to cause few AEs and had a safety profile comparable to that of ceftriaxone, which provides reassurance regarding its use in clinical practice.

The economic analysis showed that, currently, gentamicin is likely to be more costly than ceftriaxone in the treatment of gonorrhoea. However, it was not possible to take into account the costs associated with AMR for gonorrhoea.

Recommendations for research

Further exploration is needed into why gentamicin treatment is not effective in some patients and whether or not its efficacy can be predicted. Whole-genome sequencing may allow the identification of specific genetic markers of *N. gonorrhoeae* resistance and provide insights into the mechanisms and predictors of resistance.

The development of a preventative or therapeutic gonococcal vaccine is a priority because of increasing resistance and limited future antibiotic options. Greater understanding of the immune response to infection is required to facilitate this.

A 1-g dose of azithromycin combined with gentamicin was associated with a relatively high failure rate, with the lowest clearance rates seen in pharyngeal infection. This suggests that azithromycin may not be the optimal antibiotic to use as part of dual therapy designed to slow the spread of resistance. Further studies are required to evaluate alternative 'second agents'.

Further research is needed to examine the costs associated with AMR in gonorrhoea. In addition, there is a need for the development of appropriate methods for economic evaluations of interventions to address AMR in gonorrhoea and other disease areas.

Trial registration

This trial is registered as ISRCTN51783227.

Funding

Funding for this study was provided by the Health Technology Assessment programme of the National Institute for Health Research.

Chapter 1 Introduction

Background

Gonorrhoea is the second most common bacterial sexually transmitted infection (STI) in the UK, with 36,244 infections reported in 2016.[1] A disproportionate burden of infection is seen in young adults (36% of infections occur in those aged < 25 years) and minority ethnic groups (23% of infections occur in non-white people). The highest rates of infection are in large urban areas and are concentrated in core groups that include men who have sex with men (MSM), black people and minority ethnic groups, and those reporting multiple sexual partners. Over the past few years, there has been a significant rise in rectal gonorrhoea in MSM, thought to reflect an increase in detection using sensitive nucleic acid amplification tests (NAATs)[2] and an increase in unsafe sexual behaviour.[1,3]

Gonorrhoea leads to local inflammation, causing genital pain and discomfort; the localised immune activation associated with infection also facilitates the acquisition and transmission of human immunodeficiency virus (HIV).[4] In women, infection can spread to the fallopian tubes and ovaries, causing pelvic inflammatory disease, with resultant tubal scarring, infertility and chronic pelvic pain and an increased risk of ectopic pregnancy. In men, gonorrhoea can lead to epididymo-orchitis and, in MSM, gonococcal proctitis can lead to abscess and fistula formation. Pharyngeal infection, although usually asymptomatic, is an important reservoir of onward transmission in both women and MSM. It is also harder to treat with antibiotics and can persist even when antimicrobial susceptibility testing suggests that it should be susceptible.[5] It is, therefore, important to know whether or not treatment is effective for infection at all anatomical sites.

Antibiotic treatment and resistance

Neisseria gonorrhoeae readily develops resistance to antibiotic regimens. Globally, there are now high levels of resistance against penicillins, sulphonamides, tetracyclines and quinolones, all of which are no longer recommended for routine use.[6] A real possibility of multidrug-resistant gonorrhoea and the lack of alternative treatment options has been highlighted.[7] Guidance from the British Association for Sexual Health and HIV (BASHH) recommends treating gonorrhoea with ceftriaxone (given with adjunctive azithromycin) and this currently cures > 95% of patients.[8] Recent surveillance data show a reduction in sensitivity to ceftriaxone with an upwards drift in the minimum inhibitory concentration (MIC); that is, the proportion of cases that remain highly sensitive to ceftriaxone has decreased over time.[3] Sporadic treatment failure of cephalosporins has been reported from a number of countries[9–14] and a patient who failed dual therapy with ceftriaxone plus azithromycin has recently been documented in the UK.[15] The same reduction in antibiotic susceptibility was followed by widespread treatment failure within a few years for other antimicrobials (penicillin, tetracyclines and quinolones) used to treat gonorrhoea. An outbreak of azithromycin-resistant gonorrhoea has been reported in England since November 2014, further highlighting the need to identify other effective treatment regimens.[16] Despite this recent outbreak, azithromycin resistance remains uncommon in England and, overall, levels of azithromycin resistance have probably not increased over the past 3 years since the outbreak was first identified, although a change in laboratory procedures in 2015 makes direct comparisons over time difficult. Current national and international treatment guidelines continue to recommend dual antibiotic therapy, including azithromycin, for the treatment of gonorrhoea.

Alternative treatments

The options for treating gonorrhoea are limited if cephalosporins become ineffective. With the exception of gentamicin, alternative agents have not been fully assessed in vivo [such as ertapenem (Invanz;® Merck, Sharpe & Dohme, Kenilworth, NJ, USA), solithromycin, gepotidicin],[17–20] are reserved for specific infections (e.g. rifampicin for tuberculosis)[21] or have the potential to rapidly develop resistance (e.g. spectinomycin).[22]

Two systematic reviews on gentamicin monotherapy[23,24] reported cure rates for gentamicin of 62–98% in patients with gonorrhoea, but available studies were generally small and of low quality. No adverse events (AEs) were reported in these studies. A more recent non-comparative prospective trial[25] evaluated single-dose gentamicin combined with 2 g of oral azithromycin with a reported cure rate of 100% in mostly genital infections. Limited data are available on the efficacy of gentamicin when treating gonorrhoea in the pharynx or rectum, although antibiotics are sometimes less effective at these sites.

As the susceptibility of *N. gonorrhoeae* to currently recommended antibiotics decreases and multidrug-resistant strains become more common, it is important to demonstrate the efficacy and safety of alternative treatment regimens in patients with gonorrhoea. Gentamicin is a relatively cheap and widely available antibiotic. Despite an apparent dose-related association with renal and vestibulocochlear toxicity, a single one-off dose appears to be well tolerated.[26] In vitro antimicrobial susceptibility data support the use of gentamicin, but there is a need for clinical trial data to assess its efficacy and safety, particularly in pharyngeal and rectal infections.[27]

Research question

Our hypothesis was that gentamicin was not clinically worse than ceftriaxone in the treatment of gonorrhoea. This randomised controlled trial (RCT) tested this hypothesis by comparing the microbiological clearance of *N. gonorrhoeae* following treatment with either gentamicin or ceftriaxone.

Objectives

Primary objective

The primary objective was to determine whether or not gentamicin is an acceptable alternative to ceftriaxone in the treatment of gonorrhoea. This was addressed by determining whether or not the rate of microbiological clearance of *N. gonorrhoeae* in participants treated with gentamicin was non-inferior to the rate of clearance in participants treated with ceftriaxone.

Secondary objectives

The secondary objectives were to determine:

- whether or not a single intramuscular (i.m.) dose of gentamicin is safe and well tolerated
- whether or not a single i.m. dose of gentamicin is cost-effective for the NHS in comparison to ceftriaxone for the treatment of gonorrhoea
- the relationship between clinical effectiveness and the laboratory measurement of antibiotic effectiveness (the MIC required to inhibit growth of *N. gonorrhoeae*).

Chapter 2 Methods

Study design

The Gentamicin in the Treatment Of Gonorrhoea (G-TOG) trial was a blinded, two-arm, multicentre, non-inferiority, randomised trial comparing the clinical effectiveness and safety of gentamicin with that of ceftriaxone in the treatment of gonorrhoea.

Participants were randomised to receive a single i.m. injection of either gentamicin or ceftriaxone. In addition, all participants received 1 g of oral azithromycin as standard treatment. The primary outcome was clearance of *N. gonorrhoeae* at all infected sites, indicated by a negative NAAT, 2 weeks post treatment. The secondary outcomes included clearance of *N. gonorrhoeae* at genital, pharyngeal and rectal sites; clinical resolution of symptoms; frequency of AEs; tolerability of therapy; the relationship between clinical effectiveness and antibiotic MIC for *N. gonorrhoeae*; and cost-effectiveness.

Trial setting and participants

Recruiting centres

The trial was conducted in 14 sexual health clinics in England. Seven sites were originally planned to meet the recruitment target and a further seven sites were added during the trial. Sites were opened between September 2014 and February 2016, with participants being recruited from October 2014 to November 2016.

Identification of participants

Patients with a provisional (microscopy identification of Gram-negative cocci on a Gram stain of genital secretions) or confirmed (indicated by a positive NAAT) diagnosis of gonorrhoea were screened for the trial and approached by a member of the site research team to determine whether or not they were interested in participating. They were provided with a patient information sheet (PIS) and a verbal explanation of the trial and were given the opportunity to ask any questions that they might have. In addition, trial posters were on display in relevant areas of the clinic. These helped to introduce the trial and, if patients were interested, they could ask clinic staff for additional details. All participants gave written informed consent.

To avoid delaying treatment for a transmissible infection with serious sequelae, patients with either a provisional (on microscopy) or confirmed (on NAAT) diagnosis of untreated gonorrhoea were invited to participate and provide written consent at the same clinic visit.

Eligibility criteria

Patients were eligible for inclusion if they were aged 16–70 years and had a positive diagnosis in the previous 4 weeks of uncomplicated, untreated (i.e. they had not received any antibiotic in the previous 28 days that could have treated gonorrhoea, either partially or completely) genital, pharyngeal and/or rectal gonorrhoea. The exclusion criteria were having known concurrent STI(s) (excluding chlamydia); bacterial vaginosis and/or *Trichomonas vaginalis* infection; having contraindications or an allergy to gentamicin, ceftriaxone, azithromycin or lidocaine; being pregnant or breastfeeding; having complicated gonorrhoeal infection, for example pelvic inflammatory disease or epididymo-orchitis; weighing < 40 kg; and having used ceftriaxone, gentamicin or azithromycin in the preceding 28 days.

Assessment of feasibility

At 9 months after the start of recruitment, accrual was reviewed by the Trial Steering Committee (TSC) to determine whether or not the following feasibility criteria had been met for progression:

- Recruitment at 80% of target. If this was not achieved, the Trial Management Group (TMG) would implement effective and realistic strategies to increase recruitment and retention for the study to proceed.
- Percentage of completed follow-ups of > 50%.

If the study did proceed, an additional assessment of recruitment would be carried out.

On 22 June 2015, the trial received approval for progression, having met the feasibility criteria. At 9 months, 88% of target recruitment had been achieved, with follow-up of 74%. Recruitment was assessed regularly at monthly TMG meetings and at further TSC meetings.

Trial procedures

Baseline visit

Demographic information and details of a participant's sexual history and symptoms were collected during the baseline visit. Symptomatic and asymptomatic individuals were eligible for inclusion in the trial. For symptomatic participants, the baseline visit usually took place on the same day as diagnosis, which was based on the microscopy appearances of Gram-stained genital discharge. Asymptomatic participants were recalled to the clinic for treatment after a positive test result for gonorrhoea had been received; once they had given consent to participate in the trial, this second visit (the first following diagnosis) was considered as the baseline visit.

Each participant had swabs taken for NAAT and culture testing to determine the site(s) of infection. A urine sample could be taken in place of a NAAT urethral sample for men. A full sampling profile was required, taking account of a participant's sex and sexual orientation, to reflect potential sites of exposure. This allowed the efficacy of treatment to be assessed at each infected site. When swabs or urine specimens were not part of routine clinical care or had not been taken already during the baseline clinic visit (e.g. symptomatic participants who had only swabs taken for routine care on the same day prior to consent), additional swabs were taken to complete the full sampling profile, as defined in *Table 1*.

TABLE 1 Sampling schedule for trial participants[28]

	Sample		
Sex/reported sexual orientation	**Genital**	**Pharyngeal**	**Rectal**
Females	✓[a]	✓[c]	✓[c]
Heterosexual men	✓[b]	Not required	Not required
MSM	✓[b]	✓[c]	✓[c]

a Culture sample from cervix plus NAAT sample from vagina or cervix.
b Culture sample from urethra plus NAAT sample from urine or urethra.
c Culture sample plus NAAT sample.

All specimens collected were sent to local site laboratories for the identification of *N. gonorrhoeae* and results were reported back to the clinics in the usual manner. The results from the baseline visit informed subsequent testing of previously infected sites at the follow-up visit.

A number of licensed NAATs are available to detect *N. gonorrhoeae*, including the Hologic Aptima Combo 2® (AC2) assay (Hologic, Inc., Marlborough, MA, USA). In centres where the AC2 assay was not used locally for testing, an additional set of swabs (or urine) was taken for the AC2 assay to be performed at Public Health England (PHE). These results were not reported back to the clinic but were reported in batches to the Nottingham Clinical Trials Unit (NCTU). The AC2 assay was, therefore, considered as the reference standard for the trial and the AC2 NAAT result was used as the primary outcome measure. The management of participants was based only on the results of local testing.

Additional blood samples were taken for future measurement of the pre-treatment immune response to gonococcal infection and for measurement of creatinine level.

Follow-up

Participants were asked to return to the clinic 2 weeks post treatment (which was also 2 weeks post randomisation) for a follow-up visit. Participants were reminded of their appointment using the individual clinics' existing recall procedures, such as Short Message Service (SMS) and telephone reminders. During the follow-up visit, swabs (or urine) from previously infected sites were taken for NAAT and culture testing to assess the clearance of *N. gonorrhoeae*. A blood sample was taken to measure the post-treatment immune response and creatinine level. Each participant remained in the trial until this follow-up visit was completed. Participants were considered lost to follow-up if they had not returned for their follow-up appointment within 60 days of the baseline visit; this time point was chosen pragmatically to balance flexibility over when participants could return to the clinic against the potential increased risk of reinfection over a more prolonged time period. The recruitment flow diagram is shown in *Figure 1*.

If follow-up test results at 2 weeks post treatment showed that a participant had gonorrhoea, he or she was offered further investigation and treatment in accordance with local clinic guidelines. This treatment was not considered to be part of the trial.

Randomisation

After providing consent, and after confirmation of eligibility, participants were registered in the trial using a secure web-based registration and randomisation system. Participants were randomised to receive either gentamicin or ceftriaxone by a member of the research team. Staff who performed randomisation had no role in administering trial treatments and remained blinded to the treatment allocation, thereby minimising the risk of selection bias through prediction of the allocation sequence.

Randomisation was based on a computer-generated pseudorandom code using permuted blocks of randomly varying size. The code was created by NCTU in accordance with standard operating procedures and held on a secure server. Randomisation was carried out in a 1 : 1 ratio, stratified by recruiting centre.

The web-based system generated a blinded prescription for G-TOG trial treatment, which required signature by the prescribing doctor. Site staff recorded only 'G-TOG trial drug' in the participants' medical notes. The signed prescription was then passed to an injecting nurse who determined the actual treatment that a participant was randomised to and then administered the injection. The injecting nurse was the only member of the research team who was unblinded to treatment allocation.

Interventions

Participants were randomised to receive either 240 mg of gentamicin (intervention) or 500 mg of ceftriaxone (current standard treatment). Both treatments were administered from routine clinic stock as a single i.m. injection. Any European Union-licensed brands of gentamicin and ceftriaxone were permitted to be used.

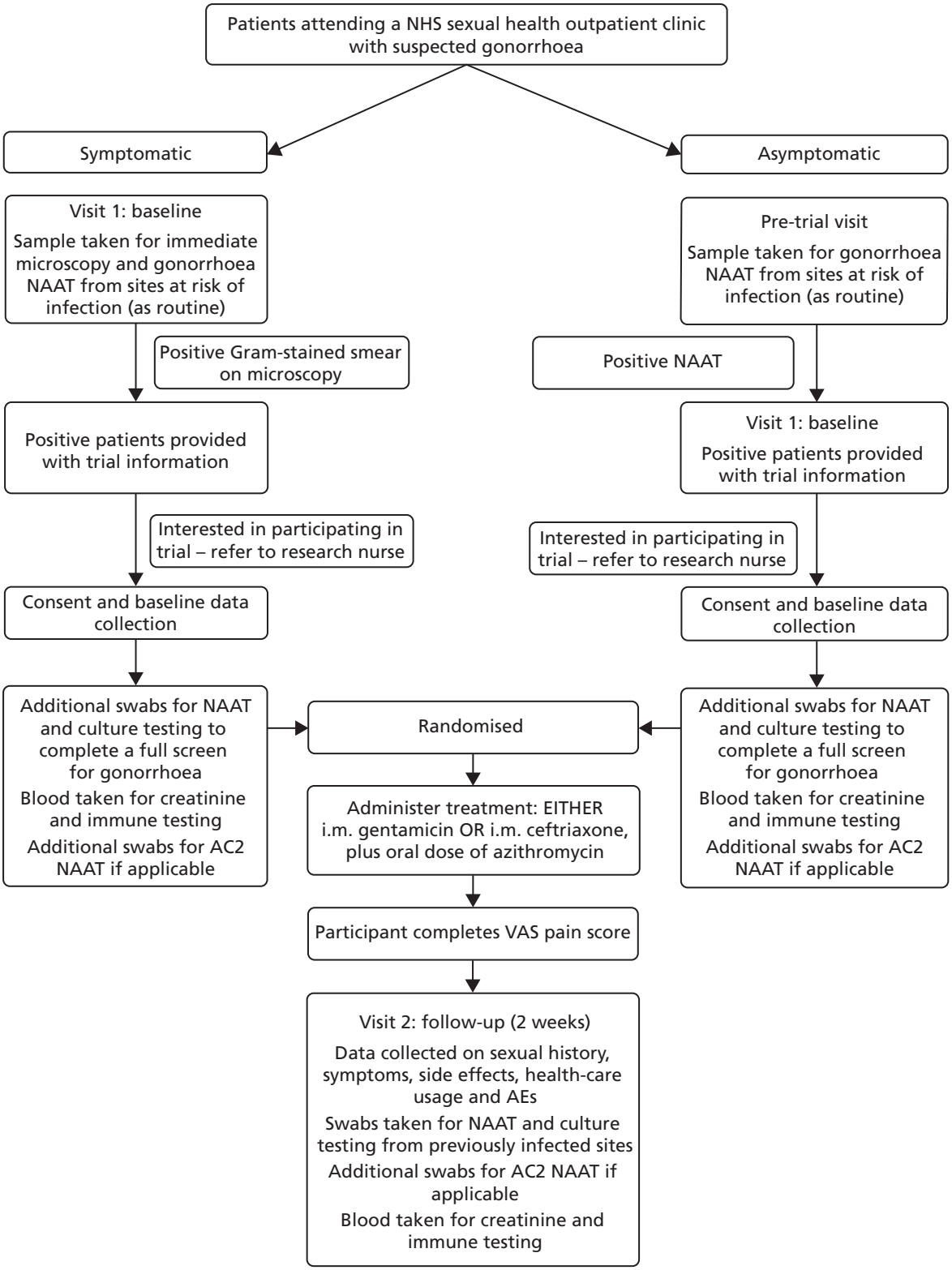

FIGURE 1 The G-TOG trial flow diagram. VAS, visual analogue scale. Reproduced from Brittain *et al.*[28]

The 240 mg of gentamicin was made up from three 2-ml (80-mg) vials, in accordance with the Summary of Product Characteristics (SmPC), and administered as a single 6-ml i.m. injection. For the ceftriaxone arm, 500 mg in a powder formulation was dissolved in 1% lidocaine, in accordance with the SmPC, and administered as a single 2-ml i.m. injection. In addition, all participants received a single oral dose of 1 g of azithromycin, which is currently given as standard treatment alongside ceftriaxone.

In previous trials, a 240-mg dose of gentamicin was most commonly used and the use of different doses has not demonstrated a significant dose–response effect across studies.[23,24] In vitro antimicrobial susceptibility testing also suggests that isolates remain sensitive to gentamicin.[27,29] The dose of ceftriaxone was chosen to be consistent with current UK gonorrhoea treatment guidelines.[30]

Blinding

Nurses administering trial treatments were required to know each participant's allocation as they prepared the drug for injection. Details of the nurses administering treatment at each centre were obtained during the trial set-up stage and access to the online randomisation system and treatment allocation was granted depending on the delegated role. All other staff at the recruiting centres remained blinded to treatment allocation.

Preparation and administration of trial treatments was undertaken in a separate area, away from the blinded research team and participants. In addition, nurses administering treatments were given guidance to provide standardised information to participants at the time of injection, which was the same regardless of treatment allocation, to prevent inadvertent unblinding. This two-step approach maintained blinding for members of the research team who were subsequently involved in the assessment of participants.

To ensure that assessment of outcome was not influenced by knowledge of the allocated treatment, nurses administering trial treatments were not permitted any role in the collection of outcome data.

End of the trial

Participants left the trial when they completed their 2-week follow-up visit.

Failure to receive the allocated treatment and withdrawal from follow-up were reported and reasons for withdrawal (if given) were documented. If a participant did not receive his or her allocated treatment but agreed to remain in the trial, outcome data collection continued in accordance with the protocol.[28] Participants were informed at the start of the trial that data collected up to the point of withdrawal would be retained and used in the final analysis.

Outcome measures

Primary outcome

The primary outcome measure was clearance of *N. gonorrhoeae* at all infected sites, confirmed by a negative NAAT, at 2 weeks post treatment (as recommended by BASHH).

The NAAT is an automated laboratory test and, therefore, not subject to bias through knowledge of treatment allocation. Different licensed NAAT assays for the diagnosis of gonorrhoea are available from different manufacturers [e.g. AC2 NAAT; Becton, Dickinson and Company (BD) NAAT (BD, Franklin Lakes, NJ, USA); Cobas® NAAT (Roche Diagnostics, Basel, Switzerland)]. Sexual health clinics participating in the G-TOG trial used either the AC2 NAAT or the BD NAAT; therefore, in order to ensure consistency and standardisation in diagnostic and follow-up tests, additional samples were taken from participants recruited at centres where the AC2 NAAT method was not used by the local laboratory. Testing of these additional samples by AC2 NAAT was performed by PHE. The results from the AC2 NAAT were used to assess clearance for the primary end point.

Secondary outcomes

The secondary outcomes were:

- clinical resolution of symptoms
- frequency of nausea/vomiting, hearing loss, dizziness and rash
- frequency of any other AEs reported by participants
- tolerability of injection as assessed by participants on a visual analogue scale (VAS)
- cost-effectiveness.

The relationship between clearance of *N. gonorrhoeae* and in vitro measurement of antibiotic MIC to inhibit *N. gonorrhoeae* growth was also assessed.

Effectiveness, tolerability and safety were assessed at the follow-up visit 2 weeks post treatment.

Clinical resolution of symptoms

Resolution of each individual clinical symptom was defined as absence of the symptom at 2 weeks post treatment in those participants with symptoms present at baseline.

Frequency of nausea/vomiting, hearing loss, dizziness and rash

Information recorded for each symptom comprised whether or not the participant had experienced the symptom, the severity of that symptom, the time to the start of the symptom from injection with trial medication, the duration of that symptom and whether or not it had resolved.

Frequency of any other adverse events

An AE is defined as any untoward medical occurrence in a participant administered a medicinal product that does not necessarily have a causal relationship with the treatment. Participants were asked if they had any AEs in addition to the potential side effects collected. The information collected comprised a verbatim description of the event, the severity of the event and the duration of the event. These AEs were then coded using MedDRA (Medical Dictionary for Regulatory Activities; version 17.1).[31] All AEs were assessed for seriousness. A serious adverse event (SAE) is defined as any untoward medical occurrence that results in death, is life-threatening, requires hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity or is a congenital anomaly/birth defect.

Additional safety information

In addition to the collection of data on side effects and AEs, participants had a blood sample taken to measure their creatinine levels at baseline and at 2 weeks post treatment. These levels were used to calculate the estimated glomerular filtration rate (eGFR).

Tolerability of the intramuscular injection

Tolerability of the injection was measured immediately after the injection and then at the 2-week clinic visit. It was measured using a 100-mm VAS that asked 'How severe was the pain of the injection when at its worst?'. A score of 0 denoted no pain and a score of 100 denoted the worst imaginable pain.

Measurement of antibiotic minimum inhibitory concentrations

Minimum inhibitory concentrations were established at PHE using Etests® (BioMérieux UK Ltd, Basingstoke, UK) for gentamicin (0.016–256 mg/l), ceftriaxone (0.002–32 mg/l) and azithromycin (0.016–256 mg/l) on gonococcal agar with Vitox [gonococcal agar base (BD Difco™; BD, Wokingham, UK) and 1% Vitox (Oxoid Ltd, Basingstoke, UK)]. Before the Etest, the gonococcal isolates were confirmed to be *N. gonorrhoeae* by Gram stain, oxidase test and matrix-assisted laser desorption/ionisation time of flight (MALDI-TOF; Bruker, Billerica, MA, USA).

Research governance

The trial was conducted in accordance with the recommendations adopted by the 18th World Medical Association General Assembly, Helsinki, 1964[32] and later revisions; the *NHS Research Governance Framework for Health and Social Care* (2nd edition);[33] and the principles of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use – Good Clinical Practice guidelines.[34]

The National Research Ethics Service Oxford C – South Central Research Ethics Committee (reference: 14/SC/1030) gave ethics approval for the trial for NHS participants (reference: 155423).

The final protocol, approved on 17 June 2015, was version 2.0. There were a number of administrative and procedural changes made to the protocol during the trial, which are outlined in *Appendix 1*.

Protocol deviations

A protocol deviation was defined as an unanticipated or unintentional divergence or departure from the expected conduct of the trial, inconsistent with the protocol, consent document or other trial procedures. Protocol deviations were recorded by site staff. Protocol violations were defined as deviations that affected eligibility or outcome measures, as assessed by the TMG.

Trial oversight

A number of oversight groups monitored ongoing progress for the duration of the trial and also contributed to interpretation of findings. Roles and responsibilities were defined including the use of charters for the independent TSC and Data Monitoring Committee (DMC).

Trial Management Group

The TMG, which was responsible for the day-to-day running of the trial, comprised the chief investigator, members of NCTU and other core members of the trial team, for example health economists.

Trial Steering Committee

The TSC, which met approximately every 6 months, included an independent chairperson and five independent members and was responsible for overseeing the conduct of the trial. Independent members were professionals in reproductive and sexual health as well as clinical epidemiology. The TSC also had two independent patient and public involvement (PPI) representatives and the chief investigator and trial manager. The TSC monitored trial progress, specifically, advising on recruitment and follow-up strategies and ensuring adherence to the trial protocol. The trial funder and sponsor were invited to attend meetings as observers.

Data Monitoring Committee

The DMC, which met approximately every 6 months, was an independent group with expertise in statistics, primary care and sexual health. They had access, in confidence, to unblinded data by allocated group. The role of the DMC was to safeguard the interests of trial participants, with particular reference to the safety of the intervention; to monitor the overall progress and conduct of the trial; and to assist and advise the TSC and the investigators. The DMC reported to the TSC and, therefore, met shortly before TSC meetings and reported to the TSC on trial safety and recommendations for continuation or stopping of the trial.

Risk assessment and safety monitoring

A risk assessment was conducted as part of protocol development; there was regular monitoring throughout the trial for new risks. The main risks to the trial were loss to follow-up in a young, sometimes transient, population and poor data collection owing to the very short time frame for trial participation of just 2 weeks. However, recruitment sites were well supported by NCTU in obtaining high-quality data and regular central monitoring checks were performed to identify any issues with data collection that could be

followed up at individual site level. Data on AEs and SAEs were collected during the trial. As agreed by the sponsor, the Research Ethics Committee, the DMC and the TSC, the DMC was provided with a list of all AEs and SAEs, including any deaths, for review at each meeting.

Patient and public involvement

Twenty-four patients from three sexual health clinics (Birmingham, London and Manchester) commented on the trial design in June and July 2012. A further 25 patients in Birmingham reviewed a PIS for the trial in April 2013. Input was requested on the trial concept and design, whether or not patients with gonorrhoea would be likely to consent to take part in the proposed trial design and the clarity of the patient information provided. Patients' main concerns following the initial consultation exercise were around the amount of time that participation would involve and whether or not the therapies being offered were safe. In response, the trial procedures were reviewed to optimise patient flow and the draft PIS was revised to expand the information on safety and AEs. Based on the revised patient information, 24 out of 25 patients in the second consultation exercise would have been happy to consider participation in the trial.

Two members of the public joined the TSC and provided input into the design and management of the trial. Specifically, they were invited to comment on all aspects of the trial design and conduct and to contribute to the design and review of documentation given to trial participants to ensure understanding and acceptability. This greatly benefited the research by helping to ensure that our material was acceptable and comprehensible, thus increasing our response rate and reducing the number of missing data. The public members of the TSC commented on the best way of sharing trial findings with the public and contributed as part of the research team to the interpretation of the trial findings. At each stage of the trial, the G-TOG trial team aimed to provide the PPI representatives with clear information in lay terms to allow them to participate in discussing the research, but not to bias their perspective towards that of the researchers/clinicians.

A lay summary of the trial findings, informed by our public members, will also be disseminated to participants who consented to receive the results.

Payments to participants

Participants were not paid to participate in the trial; however, at the end of their follow-up visit they were provided with a £15 voucher to compensate for the additional time associated with taking part in the trial.

Statistical methods

Sample size

Based on a clearance rate of 96% for the ceftriaxone regimen, consistent with previous trials, it was estimated that a total sample size of 646 participants for analysis (323 in each group) would achieve 90% power at the 2.5% one-sided significance level to detect non-inferiority with a lower 95% confidence interval (CI) for the absolute risk difference of 5%. It was planned to randomise a total of 720 participants to allow for a loss to follow-up rate of $\leq 10\%$.

Analysis plan

A statistical analysis plan (SAP) was finalised before database lock and release of treatment codes to the statistician. All summaries and statistical analyses were conducted using Stata® version 13.1 (StataCorp LP, College Station, TX, USA).

Analysis data sets

Intention-to-treat data set

This data set comprised participants as randomised, regardless of adherence to their allocated group and without imputation for missing data [intention-to-treat (ITT) principle].

Safety data set
The safety data set comprised participants as per the treatment that they actually received.

No specific per-protocol analysis data set was required as several sensitivity analyses were planned to investigate the robustness of the primary outcome.

Data derivations

Clearance of *Neisseria gonorrhoeae*
Clearance of *N. gonorrhoeae* at all sites was derived from a post-treatment negative AC2 NAAT at the sites that were positive pre treatment. All sites that were positive pre treatment for an individual participant had to be negative post treatment for gonorrhoea to be considered cleared.

Sensitivity analyses were performed when the AC2 NAAT data were not available and when other data were missing.

Resolution of clinical symptoms
Resolution of each individual clinical symptom was defined as absence of the symptom at 2 weeks post treatment in those participants who had symptoms present at baseline. Each symptom was summarised individually.

Changes in creatinine and estimated glomerular filtration rate
The absolute change in creatinine level from baseline to 2 weeks post treatment for each participant was calculated. In addition, the following variables were derived:

- Whether or not each participant had a clinically important change between baseline and 2 weeks post treatment. A clinically important change was defined by the study team as an increase or decrease of > 30% from baseline.
- Whether or not the creatinine level at 2 weeks post treatment exceeded the upper normal limit value. These upper limits were determined by the local laboratory that analysed the samples.
- eGFR was calculated using the following formula (Chronic Kidney Disease Epidemiology Collaboration).[35] The change in eGFR was then calculated by subtracting the eGFR at 2 weeks post treatment from the eGFR at baseline, where min is minimum, max is maximum, Scr is serum creatinine (mg/dl), $\kappa = 0.7$ (female) or 0.9 (male) and $\alpha = -0.329$ (female) or –0.411 (male):

$$\text{eGFR} = 141 \times \min(\text{Scr}/\kappa, 1)^{\alpha} \times \max(\text{Scr}/\kappa, 1)^{-1.209} \times 0.993^{\text{Age}} \times 1.018\ [\text{if female}] \times 1.159\ [\text{if black}]. \quad (1)$$

Minimum inhibitory concentration data
Data were summarised on a per-participant basis. For overall summaries, when a participant had more than one value for MIC (e.g. when samples had been taken from more than one site), the largest value was used. When data were summarised by clearance, the data derived for the primary end point (i.e. cleared of infection at all sites as determined by the AC2 NAAT) were used.

Missing data
The primary analysis was performed on the ITT data set without imputation of missing data for clearance of *N. gonorrhoeae* at 2 weeks. When the baseline tests did not show any sites positive for *N. gonorrhoeae* or the baseline test results were missing, the results of positive pre-trial tests were used.

Sensitivity analyses of the primary outcome were performed on the ITT data set to check the robustness of the conclusions to missing outcome data. The pattern of missing data was explored overall and in each of the two treatment groups. When clearance at 2 weeks post treatment using the AC2 NAAT was missing, but there were data for the BD NAAT, the result of the BD NAAT was used for a sensitivity analysis.

Three imputation methods were applied when data for the clearance of *N. gonorrhoeae* (both the AC2 and the BD NAAT) at 2 weeks post treatment were missing:

1. multiple imputation using chained equations
2. assume that all missing data show clearance of *N. gonorrhoeae*
3. assume that all missing data show non-clearance of *N. gonorrhoeae*.

Table 2 outlines possible scenarios when a value for the primary outcome could be derived. Scenarios not included in this table resulted in missing primary outcome data.

Analysis of the primary outcome

The analysis of the primary outcome was modified from that specified in the protocol. This amendment was made before the database was locked and the treatment codes revealed.

The initial planned method of analysis was to use a general linear model for binary outcome adjusted by clinic site, with the primary efficacy parameter comparing gentamicin with ceftriaxone being the risk difference in the proportion of participants clear of infection at 2 weeks' follow-up, along with the 95% CI. However, during the trial, additional centres were introduced, some of which could recruit only small numbers of participants. This meant that there was a chance that some centres would have no participants who had 'failed' treatment, making the inclusion of centre as a fixed effect inappropriate. Therefore, the primary approach to the between-group comparative analyses was modified to use generalised estimating equations (GEEs) for binary outcomes adjusted by recruiting centre as a random effect with robust standard errors. The GEE model used an identity link function to enable estimation of adjusted risk difference. The primary efficacy parameter comparing gentamicin with ceftriaxone was the risk difference in the proportion of participants clear of infection at all sites, determined by the AC2 NAAT at the 2-week follow-up, along with the 95% CI. Gentamicin was to be regarded as non-inferior if the lower 95% confidence limit for the risk difference (gentamicin group vs. ceftriaxone group) in confirmed clearance was ≥ -5 percentage points (i.e. closer to zero).

Sensitivity analyses for the primary outcome

In addition to the sensitivity analyses outlined in *Missing data*, we also investigated the treatment efficacy by performing the following sensitivity analyses:

- exclude participants who did not have any positive samples at baseline
- exclude participants who did not receive the allocated treatment
- exclude participants who did not have full baseline samples taken, that is, females and MSM should have had genital, rectal and pharyngeal samples taken and heterosexual men should have had genital samples taken.

TABLE 2 Scenarios of primary outcome availability

Visit				
Baseline		Follow-up		
Tests	Results	Tests	Results	Primary outcome available?
All required samples taken	≥ 1 positive	All positives retested	+ or –	Yes
	No positive[a]	All pre-trial positives retested	+ or –	Yes
Not all required samples taken	≥ 1 positive	All positives (from pre trial and baseline) retested	+ or –	Yes
	No positive	All pre-trial positives retested	+ or –	Yes
Any positive follow-up AC2 NAAT				Yes

a Based on baseline NAAT test and Gram stain test.

It was planned that there would be an additional analysis further adjusting for baseline variables with a marked imbalance between treatment groups identified after the treatment codes were revealed. However, there were no marked imbalances considered likely to influence the results of the trial; therefore, this additional analysis was not appropriate.

Secondary outcomes

Clearance of *Neisseria gonorrhoeae* by infection site

Participants may have had infection at multiple sites on entry to the trial, with up to seven different combinations of one, two and three sites possible. For each of the three infection sites, we separately estimated clearance by treatment arm along with 95% CIs, rather than formally fitting an interaction term for different combinations of infection site in the regression model. Any suggestion of a differential effect according to infected site would require confirmation in future research.

Clinical resolution of symptoms

The evaluation of clinical resolution was performed using GEEs for binary outcomes adjusted by recruiting centre as a random effect. The efficacy parameter comparing gentamicin with ceftriaxone was the risk difference in the proportion of participants clear of clinical symptoms at the 2-week follow up, along with the 95% CI. These symptoms were genital discharge, dysuria, sore throat, anorectal pain, rectal bleeding, rectal discharge, tenesmus, constipation, intermenstrual bleeding and post-coital bleeding. The assessment of all symptoms at baseline was recorded for all participants, irrespective of their site(s) of infection.

Creatinine level at 2 weeks

The creatinine-related binary outcomes [number of participants having a clinically important change and number of participants exceeding the upper limit of normal (using the local laboratory ranges) at 2 weeks post treatment] and change in eGFR were summarised using basic descriptive statistics. Shift plots were presented to identify extreme values.

Minimal inhibitory concentration for trial medications

The MIC distribution data were plotted and summarised overall and, separately, by infection site for each antimicrobial. It was expected that some data values would be below or above quantifiable limits; therefore, plots of the MIC value distribution for each medication (gentamicin, ceftriaxone and azithromycin) were produced. For overall summaries, when a participant had more than one MIC (e.g. when they had samples taken from more than one site), the largest of these MICs was used.

Concomitant medications

Additional antibiotics and other concomitant medications taken during the trial were listed by treatment group.

Side effects/adverse events

Descriptive summaries of side effects and AEs by treatment group were provided:

- Number and percentage of participants who reported each of the following – nausea, vomiting, hearing loss, dizziness and rash. The total numbers of times that these side effects were reported are also summarised.
- Severity and time in hours or days from injection to onset of each of the following – nausea, vomiting, hearing loss, dizziness and rash.
- Visual analogue scale pain score immediately following injection and recollection of injection pain at the 2-week follow-up visit.
- All non-serious AEs and all SAEs were coded using MedDRA.[31] The number and proportion of participants who experienced any AE or SAE were summarised.

Chapter 3 Results

Recruitment

Recruitment commenced in October 2014 and continued until November 2016 when the recruitment target was met (*Figure 2*).

Participant flow is shown in *Figure 3*.

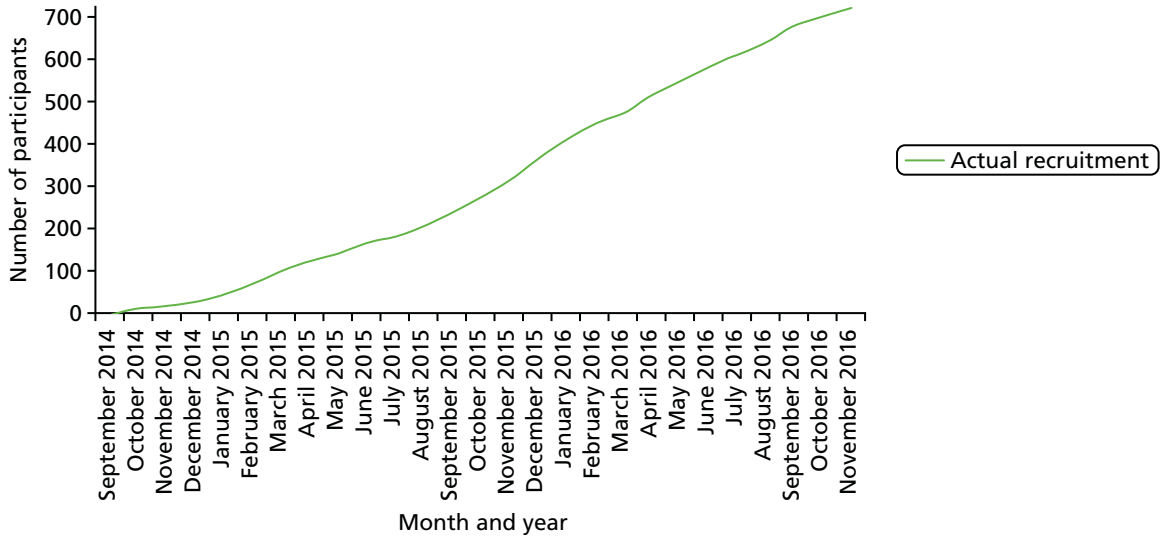

FIGURE 2 Monthly actual recruitment.

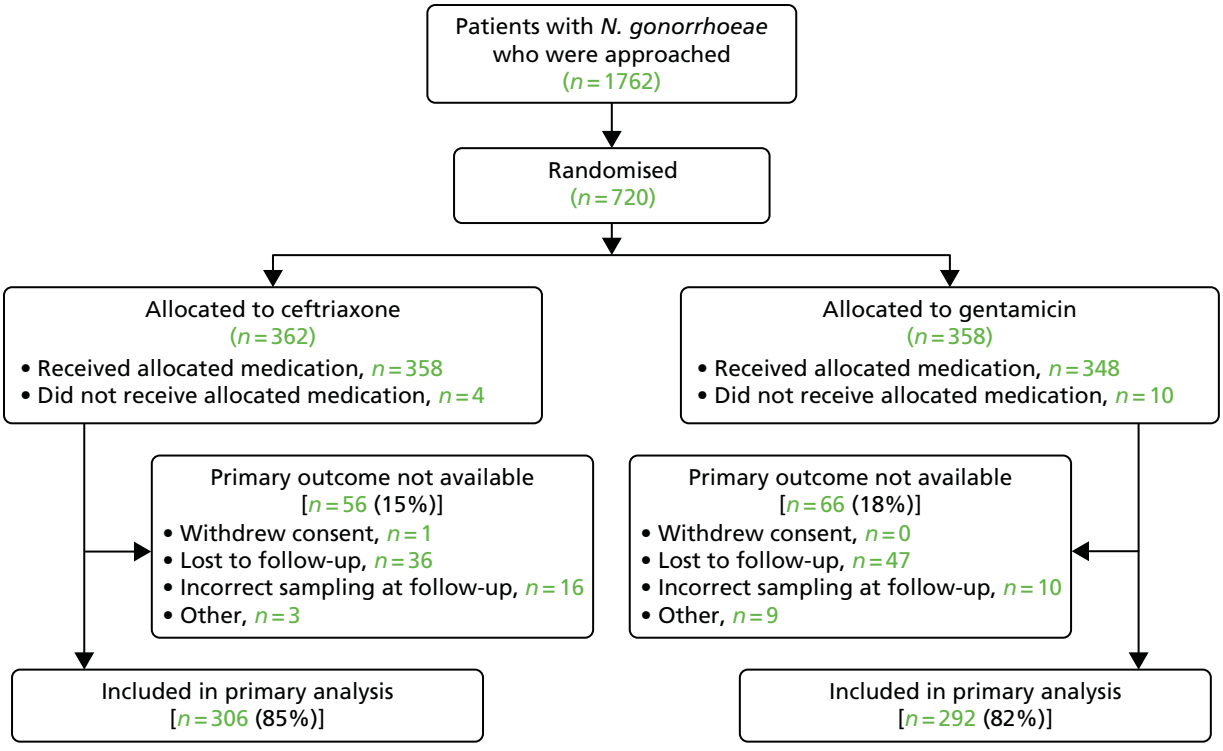

FIGURE 3 The Consolidated Standards of Reporting Trials (CONSORT) flow diagram.

Between 7 October 2014 and 14 November 2016, 1762 patients were approached, of whom, 1042 (59%) were not randomised: 331 were not eligible, 174 declined to participate, 169 felt that participation in the trial would take too much time and 368 were not randomised because of 'other' reasons. The main 'other' reasons included having a needle phobia, having taken antibiotics in the preceding 4 weeks, not being able to attend follow-up and appropriate staff not being available.

In total, 720 patients were randomised from 14 sexual health clinics in England: 362 (50%) were randomised to receive ceftriaxone and 358 (50%) were randomised to receive gentamicin (*Table 3*). All participants were randomised on the day of their clinic visit.

Baseline characteristics

The baseline characteristics of the 720 participants are provided in *Table 4*. The population comprised 585 (81%) men, 134 (19%) women and one participant classified as 'other'. The mean age was 30 years with a range of 16–70 years. Sixty-nine per cent of participants were white and 13% were HIV positive.

Most ($n = 633$, 88%) participants had a positive diagnosis of *N. gonorrhoea*e at their baseline attendance by either NAAT or Gram stain (*Table 5*). There was a slight imbalance between treatment groups in terms of a positive diagnosis using Gram stain (38% in the ceftriaxone group vs. 46% in the gentamicin group), but there was balance between groups in those diagnosed using NAAT and overall. Slightly more participants had infection at the genital site in the gentamicin group than in the ceftriaxone group (61% vs. 52%). Similar percentages of participants in each group had pharyngeal and rectal infections. Fifty-one per cent of participants were infected at only one site, 26% at two sites and 10% at three sites. Overall, baseline characteristics between the two treatment groups were well balanced.

TABLE 3 Trial recruitment by intervention arm and participating site

	Treatment group (*n*)		
Site	Ceftriaxone	Gentamicin	Total (*N*)
Whittall Street Clinic, Birmingham	87	86	173
Barts Sexual Health Centre	35	34	69
Burrell Street Clinic, Guy's and St Thomas Hospital	45	47	92
Leeds Sexual Health	50	50	100
Manchester Centre for Sexual Health	14	16	30
Sheffield	46	44	90
Southampton Department of Sexual Health	14	13	27
Chelsea and Westminster	19	19	38
Brighton	8	8	16
Coventry	18	17	35
Royal Free	3	2	5
Royal Berkshire	7	6	13
St Mary's	12	13	25
John Hunter Clinic	4	3	7
All sites	362	358	720

TABLE 4 Baseline characteristics of participants

Characteristic	Treatment group		
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	Total (*N* = 720)
Age at randomisation (years)			
Mean (SD)	30.2 (10.1)	30.4 (9.9)	30.3 (10)
Median (25th percentile, 75th percentile)	27.5 (22.6, 34.9)	28.2 (22.9, 35.1)	27.9 (22.7, 35.0)
Minimum, maximum	16.1, 70.2	16.5, 68.4	16.1, 70.2
Sex, *n* (%)			
Male	293 (81)	292 (82)	585 (81)
Female	69 (19)	65 (18)	134 (19)
Other	0	1 (< 0.5)	1 (< 0.5)
Ethnicity, *n* (%)			
White	241 (67)	255 (71)	496 (69)
Black	53 (15)	48 (13)	101 (14)
Asian	26 (7)	18 (5)	44 (6)
Mixed	27 (7)	26 (7)	53 (7)
Other	15 (4)	11 (3)	26 (4)
Country of birth, *n* (%)			
UK	258 (71)	253 (71)	511 (71)
Other	104 (29)	105 (29)	209 (29)
If other, region			
Europe (non-UK)	51 (14)	56 (16)	107 (15)
North America	8 (2)	5 (1)	13 (2)
Asia Pacific	18 (5)	14 (4)	32 (4)
Latin America	7 (2)	11 (3)	18 (3)
Middle East	2 (1)	5 (1)	7 (1)
Africa	18 (5)	14 (4)	32 (4)
Creatinine level (μmol/l)			
Mean (SD)	78.6 (15.4)	78.3 (15.8)	78.5 (15.6)
Median (25th percentile, 75th percentile)	78 (69, 88)	77 (67.5, 86.0)	77 (68, 87)
Minimum, maximum	42, 137	26, 154	26, 154
N	343	332	675
Medical history, *n* (%)			
Diabetes mellitus	3 (1)	1 (< 0.5)	4 (1)
Otitis media	9 (2)	7 (2)	16 (2)
Renal disease	3 (1)	4 (1)	7 (1)
Liver disease	8 (2)	5 (1)	13 (2)
Immunodeficiency	34 (9)	24 (7)	58 (8)
Any known drug allergies	17 (5)	25 (7)	42 (6)

continued

TABLE 4 Baseline characteristics of participants (*continued*)

Characteristic	Treatment group		Total (*N* = 720)
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	
HIV infection status,[a] *n* (%)			
Negative	299 (83)	307 (86)	606 (84)
Positive	53 (15)	43 (12)	96 (13)
Unknown	10 (3)	8 (2)	18 (3)

SD, standard deviation.
a Based on previous test or new test at baseline.

TABLE 5 Description of *N. gonorrhoeae* infection and diagnosis at baseline

Baseline diagnosis and infection	Treatment group, *n* (%)		Total (*N* = 720), *n* (%)
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	
Participants with a positive diagnosis at baseline attendance[a]	317 (87)	316 (88)	633 (88)
Participants with infection at each site[a]			
Genital	190 (52)	219 (61)	409 (57)
Pharyngeal	128 (35)	128 (36)	256 (36)
Rectal	159 (44)	147 (41)	306 (43)
Number of sites infected[a]			
1	189 (52)	180 (50)	369 (51)
2	96 (27)	94 (26)	190 (26)
3	32 (9)	42 (12)	74 (10)
Positive diagnosis of *N. gonorrhoeae* using Gram stain[b]	139 (38)	166 (46)	305 (42)
Positive diagnosis of *N. gonorrhoeae* using AC2 NAAT[c]	308 (85)	309 (86)	617 (86)

a Positive tests using either AC2 NAAT or Gram stain.
b Total of 224 and 239 participants had Gram stain test at baseline for ceftriaxone and gentamicin group, respectively.
c Samples from clinics using BD NAAT were also tested using AC2 NAAT at PHE. No results using BD NAAT are presented.

The treatment groups appeared to be balanced with respect to participants' history of STIs [41% of participants had had at least one previous diagnosis of gonorrhoea, 34% of participants had previously had chlamydia, 14% had had syphilis and 3% had had pelvic inflammatory disease (women only)] (*Table 6*). The number and type of sexual partners were similar in the two treatment groups, as were other details of their sexual history (*Tables 7* and *8*).

The results of the clinical examination and symptom assessment at baseline were similar between the treatment groups. Slightly fewer participants in the ceftriaxone group than in the gentamicin group had evidence of genital discharge on clinical examination (45% vs. 54%; *Table 9*). Similarly, at the baseline symptom assessment, 42% of participants in the ceftriaxone group and 50% in the gentamicin group reported the presence of genital discharge (*Table 10*). Few participants had hearing impairment at baseline [8 out of 362 (2%) in the ceftriaxone group and 11 out of 358 (3%) in the gentamicin group]. All impairments were mild with the exception of two participants in the ceftriaxone group who reported severe hearing impairment and one participant in the gentamicin group who reported moderate hearing impairment.

TABLE 6 Participant STI history at baseline

STI history	Treatment group		
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	Total (*N* = 720)
Previously had a positive diagnosis for gonorrhoea, *n* (%)			
No	205 (57)	214 (60)	419 (58)
Yes	152 (42)	142 (40)	294 (41)
Not known	5 (1)	2 (1)	7 (1)
Number of previous episodes experienced			
Median (25th percentile, 75th percentile)	1 (1, 2)	1 (1, 3)	1 (1, 2)
Minimum, maximum	1, 25	1, 6	1, 25
n	152	142	294
Previously had a positive diagnosis for chlamydia, *n* (%)			
No	235 (65)	228 (64)	463 (64)
Yes	121 (33)	127 (35)	248 (34)
Not known	6 (2)	3 (1)	9 (1)
Number of episodes experienced			
Median (25th percentile, 75th percentile)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Minimum, maximum	1, 20	1, 7	1, 20
n	121	127	248
Previously had a positive diagnosis for syphilis, *n* (%)			
No	311 (86)	302 (84)	613 (85)
Yes	48 (13)	53 (15)	101 (14)
Not known	3 (1)	3 (1)	6 (1)
Number of episodes experienced			
Median (25th percentile, 75th percentile)	1 (1, 1)	1 (1, 1)	1 (1, 1)
Minimum, maximum	1, 2	1, 4	1, 4
n	48	53	101
Previously had a positive diagnosis for pelvic inflammatory disease (female only), *n* (%)			
No	67 (97)	64 (97)	131 (97)
Yes	2 (3)	2 (3)	4 (3)
Unknown	0	0	0
Number of episodes experienced			
Median (25th percentile, 75th percentile)	1.5 (1, 12)	2 (1, 3)	1.5 (1, 2.5)
Minimum, maximum	1, 2	1, 3	1, 3
n	2	2	4

continued

TABLE 6 Participant STI history at baseline (*continued*)

STI history	Treatment group		
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	Total (*N* = 720)
Previous HIV test, *n* (%)			
No	69 (19)	66 (18)	135 (19)
Yes	289 (80)	286 (80)	575 (80)
Not known	4 (1)	6 (2)	10 (1)
If yes			
Positive	52 (14)	42 (12)	94 (13)
Negative	237 (65)	244 (68)	481 (67)

TABLE 7 Sexual history at baseline (males)

Baseline sexual history	Treatment group		
	Ceftriaxone (*N* = 293)	Gentamicin (*N* = 292)	Total (*N* = 585)
Number of partners in the previous 3 months			
Median (25th percentile, 75th percentile)	3 (2, 6)	3 (2, 5)	3 (2, 5)
Minimum, maximum	0, 50	0, 99	0, 99
Number of partners in the previous 12 months			
Median (25th percentile, 75th percentile)	7 (3, 20)	6 (3, 18)	6 (3, 20)
Minimum, maximum	1, 192	1, 500	1, 500
Previous history of same-sex partner (ever), *n* (%)			
No	77 (26)	75 (26)	152 (26)
Yes	216 (74)	216 (74)	432 (74)
Not known	0	1 (< 0.5)	1 (< 0.5)
Previous history of receptive anal sexual intercourse (ever), *n* (%)			
No	93 (32)	98 (34)	191 (33)
Yes	200 (68)	193 (66)	393 (67)
Not known	0	1 (< 0.5)	1 (< 0.5)
Previous history of receptive oral sexual intercourse (ever), *n* (%)			
No	55 (19)	47 (16)	102 (17)
Yes	238 (81)	243 (83)	481 (82)
Not known	0	2 (1)	2 (< 0.5)
Previous history of partner born outside the UK (ever), *n* (%)			
No	105 (36)	89 (30)	194 (33)
Yes	181 (62)	196 (67)	377 (64)
Not known	7 (2)	7 (2)	14 (2)
In the previous 3 months, for approximately what proportion of sexual contacts were condoms used?			
Median (25th percentile, 75th percentile)	50 (0, 93)	50 (5, 95)	50 (0, 95)
Minimum, maximum	0, 100	0, 100	0, 100

TABLE 7 Sexual history at baseline (males) (*continued*)

Baseline sexual history	Treatment group		Total (*N* = 585)
	Ceftriaxone (*N* = 293)	Gentamicin (*N* = 292)	
Latest partner			
Sex, *n* (%)			
Male	212 (72)	211 (72)	423 (72)
Female	81 (28)	80 (27)	161 (28)
Missing	0	1 (< 0.5)	1 (< 0.5)
Time (days) since last sexual intercourse			
Median (25th percentile, 75th percentile)	10 (6, 21)	10 (5, 18)	10 (6, 21)
Minimum, maximum	1, 196	1, 210	1, 210
Duration of last relationship, *n* (%)			
One-off	128 (44)	131 (45)	286 (40)
Occasional	56 (19)	60 (21)	134 (19)
Regular	95 (32)	89 (30)	251 (35)
Previous regular	14 (5)	9 (3)	45 (6)
Not known	0	3 (1)	3 (1)
Type of sexual contact[a], *n* (%)			
Genital–genital	152 (52)	144 (49)	296 (51)
Anal–genital	119 (41)	122 (42)	241 (41)
Genital–anal	143 (49)	149 (51)	292 (50)
Oral–genital	214 (73)	211 (72)	425 (73)
Genital–oral	228 (78)	239 (82)	467 (80)
Oral–anal	85 (29)	87 (30)	172 (29)
Anal–oral	87 (30)	74 (25)	161 (28)
Digital–anal	81 (28)	86 (29)	167 (29)
Anal–digital	72 (25)	68 (23)	140 (24)
Use of condoms, *n* (%)			
No	159 (54)	142 (49)	301 (51)
Yes, partially	49 (17)	52 (18)	101 (17)
Yes, consistently, including for oral sex	7 (2)	8 (3)	15 (3)
Yes, consistently, but not for oral sex	78 (27)	89 (30)	167 (29)
Missing	0	1 (< 0.5)	1 (< 0.5)
Partner known to have gonorrhoea, *n* (%)			
No	257 (88)	250 (86)	507 (87)
Yes	36 (12)	41 (14)	77 (13)
Not known	0	1 (< 0.5)	1 (< 0.5)

a Not mutually exclusive.

TABLE 8 Sexual history at baseline (females)

Baseline sexual history	Treatment group: Ceftriaxone (*N* = 69)	Treatment group: Gentamicin (*N* = 65)	Total (*N* = 134)
Number of partners in the previous 3 months			
Median (25th percentile, 75th percentile)	1 (1, 2)	1 (1, 2)	1 (1, 2)
Minimum, maximum	0, 120	0, 100	0, 120
Number of partners in the previous 12 months			
Median (25th percentile, 75th percentile)	3 (1, 4)	2 (1, 4)	2 (1, 4)
Minimum, maximum	1, 120	1, 300	1, 300
Previous history of same-sex partner (ever), *n* (%)			
No	65 (94)	62 (95)	127 (95)
Yes	4 (6)	2 (3)	6 (4)
Not known	0	1 (2)	1 (1)
Previous history of receptive anal sexual intercourse (ever), *n* (%)			
No	48 (70)	45 (69)	93 (69)
Yes	21 (30)	19 (29)	40 (30)
Not known	0	1 (2)	1 (1)
Previous history of receptive oral sexual intercourse (ever), *n* (%)			
No	15 (22)	17 (26)	32 (24)
Yes	54 (78)	47 (72)	101 (75)
Not known	0	1 (2)	1 (1)
Previous history of partner born outside the UK (ever), *n* (%)			
No	42 (61)	46 (71)	88 (66)
Yes	24 (35)	17 (26)	41 (31)
Not known	3 (4)	2 (3)	5 (4)
In the previous 3 months, for approximately what proportion of sexual contacts were condoms used?			
Median (25th percentile, 75th percentile)	0 (0, 50)	0 (0, 50)	0 (0, 50)
Minimum, maximum	0, 100	0, 100	0, 100
Latest partner			
Sex of latest sexual partner, *n* (%)			
Male	69 (100)	63 (97)	132 (98)
Female	0	1 (2)	1 (1)
Missing	0	1 (2)	1 (1)
Time (days) since last sexual intercourse			
Median (25th percentile, 75th percentile)	14 (7, 21)	14 (7, 28)	14 (7, 28)
Minimum, maximum	1, 112	1, 112	1, 112

TABLE 8 Sexual history at baseline (females) (*continued*)

Baseline sexual history	Treatment group		Total (*N* = 134)
	Ceftriaxone (*N* = 69)	Gentamicin (*N* = 65)	
Duration of last relationship, *n* (%)			
One-off	15 (22)	12 (18)	27 (20)
Occasional	8 (12)	10 (15)	18 (13)
Regular	33 (48)	33 (51)	66 (49)
Previous regular	13 (19)	9 (14)	22 (16)
Not known	0	1 (2)	1 (1)
Type of sexual contact,[a] *n* (%)			
Genital–genital	67 (97)	63 (97)	130 (97)
Anal–genital	7 (10)	5 (8)	12 (9)
Genital–anal	0	2 (3)	2 (1)
Oral–genital	48 (70)	37 (57)	85 (63)
Genital–oral	43 (62)	36 (55)	79 (59)
Oral–anal	3 (4)	1 (2)	4 (3)
Anal–oral	4 (6)	2 (3)	6 (4)
Digital–anal	4 (6)	3 (5)	7 (5)
Anal–digital	3 (4)	6 (9)	9 (7)
Use of condoms, *n* (%)			
No	49 (71)	46 (71)	95 (71)
Yes, partially	15 (22)	10 (15)	25 (19)
Yes, consistently, including for oral sex	0	2 (3)	2 (1)
Yes, consistently, but not for oral sex	0	6 (9)	11 (8)
Missing	5 (7)	1 (1)	1 (1)
Partner known to have gonorrhoea, *n* (%)			
No	56 (81)	55 (85)	111 (83)
Yes	13 (19)	9 (14)	22 (16)
Not known	0	1 (2)	1 (1)

a Not mutually exclusive.

TABLE 9 Clinical examination at baseline

Baseline examination	Treatment group		
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	Total (*N* = 720)
Height (cm)			
Mean (SD)	176.1 (9.3)	176.4 (9.2)	176.3 (9.3)
Median (25th percentile, 75th percentile)	177 (170, 183)	178 (171, 183)	177 (170, 183)
Minimum, maximum	147, 198	106, 197	106, 198
Weight (kg)			
Mean (SD)	77 (17.7)	76.2 (13.7)	76.6 (15.8)
Median (25th percentile, 75th percentile)	75 (66, 84.1)	75 (67, 83)	75 (66.6, 83)
Minimum, maximum	41, 193	49.2, 135	41, 193
BMI (kg/m^2)			
Mean (SD)	24.8 (5.2)	24.5 (4.5)	24.7 (4.9)
Median (25th percentile, 75th percentile)	23.7 (21.9, 26.9)	23.7 (21.5, 26.5)	23.7 (21.6, 26.7)
Minimum, maximum	16.7, 59.5	16.6, 46.4	16.6, 59.5
Women			
Cervicitis, *n* (%)			
No	58 (84)	56 (86)	114 (85)
Yes	8 (12)	5 (8)	13 (10)
Not known	3 (4)	4 (7)	7 (5)
Men and women			
Evidence of genital discharge, *n* (%)			
No	195 (54)	164 (46)	359 (50)
Yes	164 (45)	192 (54)	356 (49)
Not known	3 (1)	2 (1)	5 (1)
If yes, colour			
Clear	19 (12)	21 (11)	40 (11)
Mucopurulent	62 (38)	79 (41)	141 (40)
Purulent	83 (51)	92 (48)	175 (49)
If yes, amount			
Scanty	34 (21)	37 (19)	71 (20)
Average	68 (41)	87 (45)	155 (44)
Profuse	59 (36)	68 (35)	127 (36)
Missing	3 (1)	0	3 (1)
Other abnormality, *n* (%)	28 (8)	22 (6)	50 (7)

BMI, body mass index; SD, standard deviation.

TABLE 10 Symptom assessment at baseline

Baseline symptoms	Treatment group		
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)	Total (*N* = 720)
Presence of any symptom at baseline, *n* (%)	230 (64)	241 (67)	471 (65)
Presence of symptom at baseline, *n* (%)			
Genital discharge	153 (42)	179 (50)	332 (46)
Dysuria	125 (35)	154 (43)	279 (39)
Anorectal pain	15 (4)	8 (2)	23 (3)
Sore throat	53 (15)	52 (15)	105 (15)
Rectal discharge	12 (3)	10 (3)	22 (3)
Rectal bleeding	9 (2)	8 (2)	17 (2)
Tenesmus	8 (2)	4 (1)	12 (2)
Constipation	11 (3)	4 (1)	15 (2)
Intermenstrual bleeding (women only)	9 (2)	7 (2)	16 (2)
Post-coital bleeding (women only)	5 (1)	7 (2)	12 (2)
Other	26 (7)	26 (7)	52 (7)
Duration (days) of symptom at baseline, median (IQR)			
Genital discharge	4.5 (2.5–8)	4 (2–7)	4 (2–7)
Dysuria	4 (2–7)	4 (2–7)	4 (2–7)
Anorectal pain	7 (5–21)	9.5 (3.5–21)	9 (4–21)
Sore throat	7 (3–14)	5.5 (2–14)	7 (2–14)
Rectal discharge	10.5 (3.5–24.5)	17.5 (10–28)	14 (4–28)
Rectal bleeding	28 (7–77)	17.5 (4.5–80.5)	21 (7–77)
Tenesmus	10.5 (3.5–24.5)	2 (2–11.5)	4 (2.5–21)
Constipation	14 (3–112)	45.5 (4–126)	14 (3–112)
Intermenstrual bleeding (women only)	14 (5–14)	14 (4–28)	14 (5–21)
Post-coital bleeding (women only)	7 (1–14)	14 (2–112)	10.5 (2–70)
Other	7 (2–28)	6.5 (3–28)	7 (2.5–28)
Hearing impairment, *n* (%)			
No	354 (98)	347 (97)	701 (97)
Yes	8 (2)	11 (3)	19 (3)
If yes, severity			
Grade 1 (mild)	6 (75)	10 (91)	16 (84)
Grade 2 (moderate)	0	1 (9)	1 (5)
Grade 3 (severe)	2 (25)	0	2 (11)

IQR, interquartile range.

Compliance with the allocated intervention

Fourteen participants did not receive their allocated treatment: four (1%) in the ceftriaxone arm and 10 (3%) in the gentamicin arm. The reasons for this are given in *Table 11*. These 14 participants also did not receive azithromycin. In addition, three participants were recorded as not receiving azithromycin alongside their allocated treatment: one participant was recorded as not receiving azithromycin as they vomited within 50 minutes of taking it; the other two participants had already been prescribed/provided with azithromycin by another nurse practitioner and so did not receive it as part of trial treatment.

Of the 720 participants randomised, 624 (87%) attended their follow-up visit, 89% in the ceftriaxone group and 84% in the gentamicin group (*Table 12*). The median time from randomisation to follow-up was similar in both treatment groups, at 16 and 15 days in the ceftriaxone and gentamicin groups, respectively, with an interquartile range (IQR) of 14–20 days.

Data sets

The ITT data set was defined as 'participants as randomised', regardless of adherence to the allocated group and without imputation for missing data. There were 720 participants included in the ITT data set: 362 who were randomised to ceftriaxone and 358 who were randomised to gentamicin. All baseline summaries and summaries/analyses of efficacy data are based on this data set. Follow-up data were available for 624 participants: 322 in the ceftriaxone group and 302 in the gentamicin group.

The safety data set was defined as 'all participants according to the treatment that they actually received'. It comprised 706 participants: 358 who received ceftriaxone and 348 who received gentamicin. The 14 participants who had not received ceftriaxone or gentamicin were excluded from this data set but the participants who did not receive azithromycin remained in this data set as they had received either ceftriaxone or gentamicin. This data set was used to summarise safety data at follow-up. Follow-up data were available for 618 participants: 320 who received ceftriaxone and 298 who received gentamicin.

TABLE 11 Compliance with the allocated intervention

	Treatment group, *n* (%)	
Compliance	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)
Full injection of trial medication administered		
No	4 (1)	10 (3)
Yes	358 (99)	348 (97)
Reason for not taking trial medication, *n*		
Allergic to penicillin	1	1
Allergic to azithromycin	0	1
Diagnosis of PID after randomisation	0	2
Diagnosis of BV after randomisation	1	1
Trial drug could not be found/out of stock	0	2
No injecting nurse available	1	1
Found to have hearing impairment after randomisation	1	0
Participant refused injection because of needle phobia	0	1
Unknown	0	1
Azithromycin taken		
No	5 (1)	12 (3)
Yes	357 (99)	346 (97)

BV, bacterial vaginosis; PID, pelvic inflammatory disease.

TABLE 12 Completeness of follow-up

Follow-up attendance	Treatment group	
	Ceftriaxone ($N = 362$)	Gentamicin ($N = 358$)
Attended follow-up visit, *n* (%)	322 (89)	302 (84)
Time from randomisation to follow-up visit, *n* (%)		
< 14 days	4 (1)	3 (1)
14 days	101 (31)	124 (41)
15–21 days	162 (50)	121 (40)
22–28 days	27 (8)	34 (11)
5–6 weeks	24 (7)	12 (4)
> 6 weeks	4 (1)	8 (3)
Time (days) from randomisation to follow-up		
Mean (SD)	18.5 (6.9)	18.4 (8.4)
Median (25th percentile, 75th percentile)	16 (14, 20)	15 (14, 20)
Primary outcome data available, *n* (%)	306 (85)	292 (82)

SD, standard deviation.

Primary outcome

The primary outcome – clearance of *N. gonorrhoeae* at all infected sites confirmed by a negative NAAT 2 weeks post treatment – was available for 598 (83%) participants overall: 306 (85%) and 292 (82%) in the ceftriaxone and gentamicin groups, respectively.

The main reasons for not having evaluable data were participants not returning for their follow-up visit and incorrect sampling at the follow-up visit (*Table 13*). At the start of the trial, a small number of participants were not asked by the recruiting site to return for follow-up, in error. This occurred after they

TABLE 13 Completeness of follow-up for primary outcome

Primary outcome	Treatment group	
	Ceftriaxone group ($N = 362$)	Gentamicin group ($N = 358$)
Primary outcome available, *n* (%)	306 (85)	292 (82)
Primary outcome not available, *n* (%)	56 (15)	66 (18)
Reason primary outcome not available, *n*		
Participant withdrew consent	1	0
Loss to follow-up	36	47
Incorrect sampling at follow-up	16	10
Other	3	9
Other reasons, *n*		
Penicillin allergy	1	1
Ineligible post randomisation	1	2
Baseline test for gonorrhoea negative	1	1
No trial medication given	0	2
Did not attend appointments	0	3

reported exclusion criteria post randomisation (e.g. penicillin allergy), tested negative for gonorrhoea at baseline or did not receive trial medication. This was corrected by site training. Slightly more participants in the gentamicin group failed to come back for their follow-up visit.

In total, of those with evaluable data for the primary outcome, 299 out of 306 (98%) participants in the ceftriaxone group and 267 out of 292 (91%) participants in the gentamicin group had clearance of gonorrhoea from all sites (*Table 14*).

The baseline characteristics for participants who had evaluable primary outcome data were similar between the two treatment groups, with the exception of site of infection: 50% of participants in the ceftriaxone group had a genital infection compared with 60% in the gentamicin group. For those randomised to ceftriaxone, there were more men (89% vs. 79%) and more genital infections (64% vs. 50%) in the group without clearance data than in the group with clearance data. For those randomised to gentamicin, there were fewer men (71% vs. 84%) in the group without clearance data than in the group with clearance data (see *Appendix 3*, *Table 34*).

The adjusted risk difference was –6.4% (gentamicin vs. ceftriaxone), with a 95% CI of –10.4% to –2.4% (*Table 15* and *Figure 4*). The lower 95% confidence limit (–10.4%) was < –5%, the predefined threshold for determining non-inferiority. Therefore, non-inferiority was not demonstrated.

TABLE 14 Clearance of *N. gonorrhoeae*

	Treatment group, *n* (%)	
Clearance	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)
Participants with clearance data	306 (85)	292 (82)
Results of clearance data		
Clearance of *N. gonorrhoeae*	299 (98)	267 (91)
Not cleared of *N. gonorrhoeae*	7 (2)	25 (9)

TABLE 15 Clearance rate of *N. gonorrhoeae* at 2 weeks post randomisation

Treatment group	Clearance rate of *N. gonorrhoeae* (%)	Adjusted risk difference of gentamicin vs. ceftriaxone[a] (%)	95% CI (%)
Ceftriaxone	98	–6.4	–10.4 to –2.4
Gentamicin	91		

a Adjusted by site, using general linear model for binary outcome.

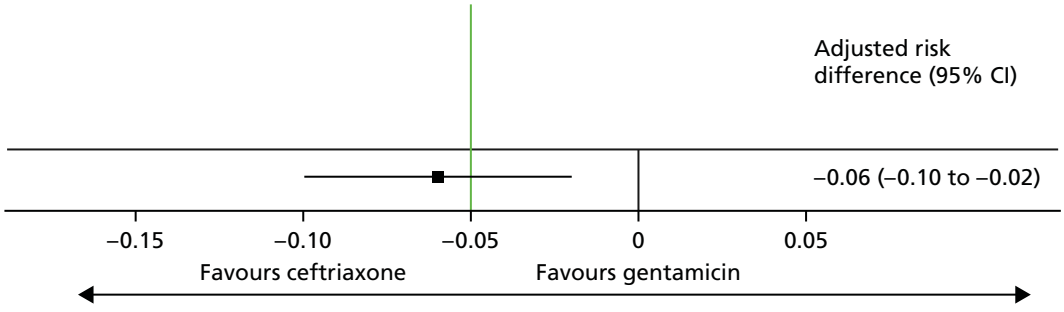

FIGURE 4 Clearance of *N. gonorrhoeae* at 2 weeks post randomisation. The non-inferiority margin is –0.05.

Sensitivity analyses for the primary outcome

Sensitivity analyses for the primary outcome are presented in *Table 16* and *Figure 5*. Although the adjusted risk differences varied between the different sensitivity analyses, all analyses performed were supportive of the primary analysis, with the lower 95% confidence limits of the 95% CIs all being < –5%.

Secondary outcomes

Clearance of N. gonorrhoeae *by infection site*

Of the participants who had a genital infection, 98% in the ceftriaxone group and 94% in the gentamicin group were cleared at their follow-up visit (*Table 17* and *Figure 6*). The adjusted risk difference was –4.4% (95% CI –8.7% to 0%). A greater proportion of participants with pharyngeal infection receiving ceftriaxone had clearance at their follow-up visit (96%) than participants receiving gentamicin (80%). The adjusted risk difference was –15.3% (95% CI –24.0% to –6.5%). Similarly, a greater proportion of participants with rectal infection in the ceftriaxone group showed clearance (98%) than patients in the gentamicin group (90%) (adjusted risk difference –7.8%, 95% CI –13.6% to –2.0%). Clearance at genital site by sex is also provided in *Appendix 3*, *Table 34*.

Clinical resolution of symptoms

There was no evidence of any difference between the treatment groups in terms of resolution of symptoms (*Table 18*). The 95% CIs for the adjusted risk differences are wide for those cases when the number of participants experiencing some symptoms at baseline was small. For all 12 participants who had post-coital bleeding, this symptom had resolved at 2 weeks post randomisation. These data are therefore not included in *Table 18*. The complete summary data of symptoms at baseline and follow-up are included in *Appendix 3*, *Table 35*.

TABLE 16 Sensitivity analyses for clearance of *N. gonorrhoeae* at 2 weeks post randomisation

Scenario	Treatment group	Number of participants included in analysis	Clearance rate of *N. gonorrhoeae* (%)	Adjusted risk difference[a] (%)	95% CI (%)
Exclude those without any positive samples at baseline	Ceftriaxone	268	98	–7.1	–11.4 to –2.8
	Gentamicin	261	91		
Exclude those who did not receive allocated treatment	Ceftriaxone	304	98	–6.5	–10.5 to –2.4
	Gentamicin	289	91		
Exclude those who did not have full required samples taken at baseline	Ceftriaxone	269	98	–5.9	–10.0 to –1.8
	Gentamicin	260	92		
Assume missing clearance data as not cleared	Ceftriaxone	362	83	–8.1	–14.1 to –2.1
	Gentamicin	358	75		
Assume missing clearance data as cleared	Ceftriaxone	362	98	–5.3	–8.6 to –1.9
	Gentamicin	358	93		
Multiple imputation of missing clearance data	Ceftriaxone	362	97	–5.1	–8.7 to –1.5
	Gentamicin	358	92		
Use local BD NAAT if AC2 NAAT not available	Ceftriaxone	317	97	–6.2	–10.2 to –2.2
	Gentamicin	295	91		

a Adjusted by site, using general linear model for binary outcome.

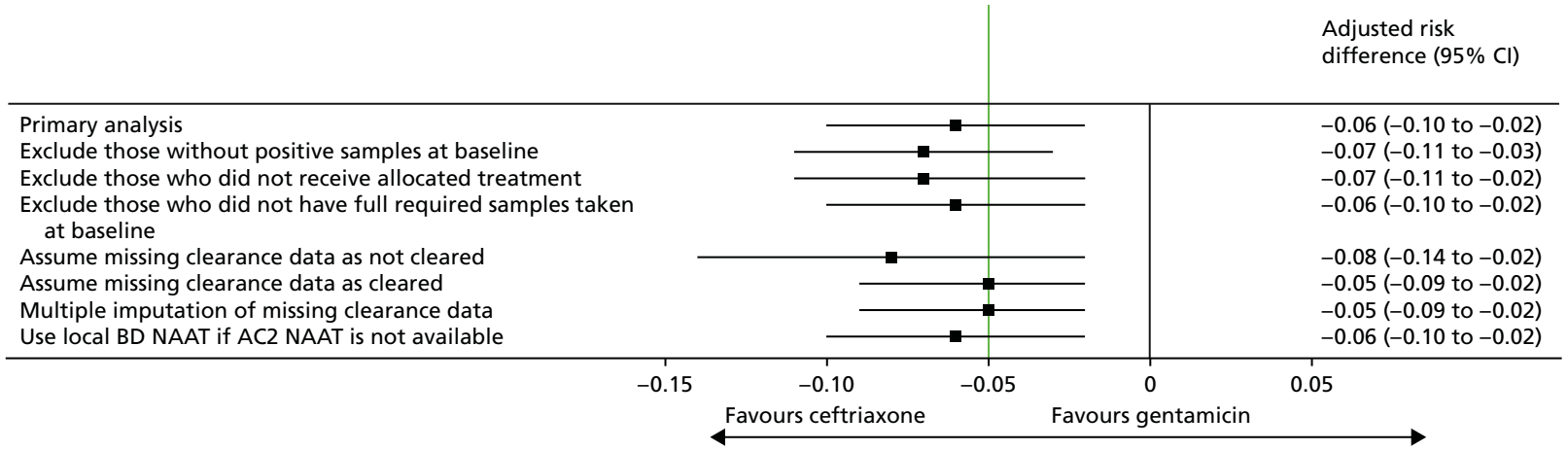

FIGURE 5 Sensitivity analyses for clearance of *N. gonorrhoeae* at 2 weeks post randomisation. The non-inferiority margin is –0.05.

TABLE 17 Clearance of *N. gonorrhoeae* by infection site

Clearance at infection site	Treatment group	
	Ceftriaxone	Gentamicin
Genital infection	**N = *154***	**N = *174***
Cleared of *N. gonorrhoeae*, *n* (%)	151 (98)	163 (94)
95% CI (%)	96 to 100	90 to 97
Not cleared of *N. gonorrhoeae*, *n* (%)	3 (2)	11 (6)
Risk difference (95% CI) for clearance (%)	–4.4 (–8.7 to 0)	
Pharyngeal infection	**N = *113***	**N = *102***
Cleared of *N. gonorrhoeae*, *n* (%)	108 (96)	82 (80)
95% CI (%)	92 to 99	72 to 88
Not cleared of *N. gonorrhoeae*, *n* (%)	5 (4)	20 (20)
Risk difference (95% CI) for clearance (%)	–15.3 (–24.0 to –6.5)	
Rectal infection	**N = *137***	**N = *119***
Cleared of *N. gonorrhoeae*, *n* (%)	134 (98)	107 (90)
95% CI	95 to 100	84 to 95
Not cleared of *N. gonorrhoeae*, *n* (%)	3 (2)	12 (10)
Risk difference (95% CI) for clearance (%)	–7.8 (–13.6 to –2.0)	

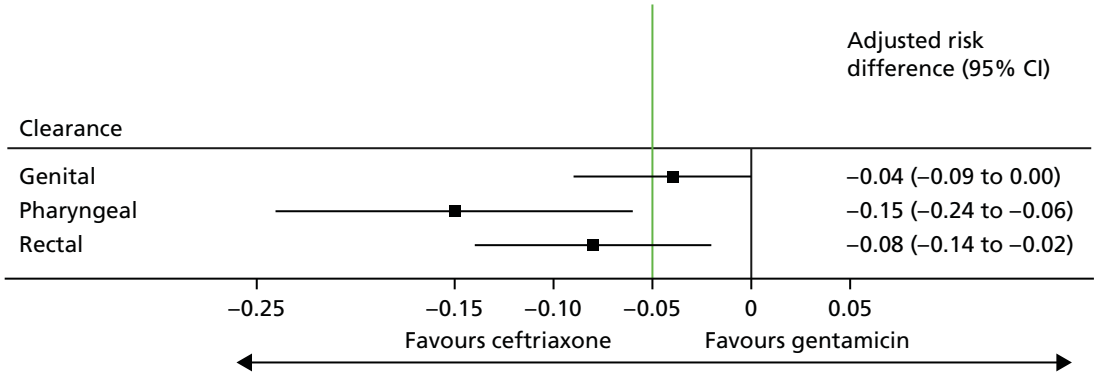

FIGURE 6 Clearance of *N. gonorrhoeae* by infection site. The non-inferiority margin is –0.05.

TABLE 18 Clinical resolution of symptoms in participants who had the symptom present at baseline

Symptom	Number of participants included in analysis	Adjusted risk difference (gentamicin vs. ceftriaxone)[a] (%)	95% CI (%)
Genital discharge	276	–0.1	–5.5 to 5.2
Dysuria	234	–7.7	–13.6 to 1.9
Sore throat	92	4.0	–7.4 to 15.4
Anorectal pain	20	–24.4	–62.5 to 13.7
Rectal bleeding	15	12.5	–10.4 to 35.4
Rectal discharge	20	–9.9	–43.7 to 23.9
Tenesmus	10	12.5	–10.4 to 35.4
Constipation	15	–12.6	–57.8 to 32.6
Intermenstrual bleeding (female only)	14	11.1	–9.0 to 31.6

a Adjusted by site.

Frequency of nausea, vomiting, reduction in hearing, dizziness and rash

The frequencies of the expected side effects of gentamicin and ceftriaxone were summarised based on the safety data set. This data set excluded the 14 participants who did not receive either ceftriaxone or gentamicin. There were 358 participants who received ceftriaxone and 348 participants who received gentamicin included in the safety data set. Of these participants, follow-up data were available for 618 participants: 320 who had received ceftriaxone and 298 who had received gentamicin.

Nausea

The percentages of participants experiencing nausea were similar in the ceftriaxone group [12% (38/320)] and the gentamicin group [14% (41/298)]. In total, 2% of participants in each group had grade 2 nausea (oral intake significantly decreased). All other reports of nausea were grade 1 (able to eat normally). The time to onset of nausea from the time of injection was similar in both treatment groups, as was the duration of nausea and the percentage of participants fully recovered by follow-up (95% in both treatment groups).

Vomiting

The incidence of vomiting was low, with three participants (1%) in the ceftriaxone group and 12 (4%) in the gentamicin group experiencing at least one episode. All participants in the ceftriaxone group experienced grade 1 vomiting (one episode in 24 hours), whereas, in the gentamicin group, eight participants (3% of the total number of participants) experienced grade 1 and four (1%) experienced grade 2 vomiting (2–5 episodes in 24 hours).

Reduction in hearing

Five participants in the ceftriaxone group (2%) and three (1%) in the gentamicin group reported a mild reduction in their hearing. Of these participants, one in each group had not fully recovered by their follow-up visit.

Dizziness/unsteadiness

A total of 24 participants in the ceftriaxone group (7%) and 21 in the gentamicin group (7%) reported dizziness or unsteadiness. In the ceftriaxone group, 20 reported grade 1 severity (not interfering with function), three reported grade 2 severity (interfering with function but not interfering with daily activity) and one reported grade 4 severity (bedridden or disabled) events. The grade 4 severity event was reported as a SAE and was not considered to be related to the trial medication. In the gentamicin group, 19 participants reported grade 1 severity and two participants reported grade 2 severity events.

Skin rashes

Five participants in the ceftriaxone group (2%) and 12 participants in the gentamicin group (4%) reported skin rashes; all five participants in the ceftriaxone group and 11 out of the 12 participants in the gentamicin group reported a grade 1 skin rash (localised skin eruption). One participant in the gentamicin group reported a grade 2 skin rash (diffuse skin eruption covering $\leq$ 50% of the body surface area). All participants in the ceftriaxone group had fully recovered by their follow-up visit, whereas 6 out of the 12 participants in the gentamicin group had not fully recovered.

Injection pain

In total, 315 out of the 320 participants in the ceftriaxone group (98%) and 294 of the 298 participants in the gentamicin group (99%) recorded injection pain. The median time for the pain to completely resolve was slightly longer in the gentamicin group than in the ceftriaxone group (1.5 hours vs. 1 hour; IQR: 0–24 hours for the gentamicin group and 0–12 hours for the ceftriaxone group).

The results for all expected side effects of ceftriaxone and gentamicin are summarised in *Table 19*.

TABLE 19 Summary of side effects following treatment

Side effect	Treatment group	
	Ceftriaxone ($N = 320$)	Gentamicin ($N = 298$)
Any nausea*, n *(%)	***38 (12)***	***41 (14)***
Severity, *n* (%)		
Grade 1 (able to eat normally)	30 (9)	36 (12)
Grade 2 (oral intake significantly decreased)	8 (2)	5 (2)
Grade 3 (no significant intake or requiring i.v. fluids)	0 (0)	0 (0)
Time from injection to onset, *n* (%)		
< 2 hours	22 (58)	24 (59)
2–6 hours	8 (21)	10 (24)
6–24 hours	4 (11)	3 (7)
1–3 days	2 (5)	2 (5)
> 3 days	2 (5)	2 (5)
Duration (hours)		
Median (25th percentile, 75th percentile)	3 (1–9)	3 (1–24)
Minimum, maximum	1, 240	1, 240
Fully recovered, *n* (%)		
No	2 (5)	2 (5)
Yes	36 (95)	39 (95)
Any vomiting*, n *(%)	***3 (1)***	***12 (4)***
Severity, *n* (%)		
Grade 1 (1 episode in 24 hours)	3 (1)	8 (3)
Grade 2 (2–5 episodes in 24 hours)	0 (0)	4 (1)
Grade 3 (≥ 6 episodes in 24 hours or need for i.v. fluids)	0 (0)	0 (0)
Time from injection to onset, *n* (%)		
< 2 hours	1 (33)	5 (42)
2–6 hours	0 (0)	1 (8)
6–24 hours	0 (0)	1 (8)
1–3 days	1 (33)	3 (25)
> 3 days	1 (33)	2 (17)
Duration (hours)		
Median (25th percentile, 75th percentile)	1 (1–3)	1.5 (1–36)
Minimum, maximum	1, 3	1, 72
Fully recovered, *n* (%)		
No	0	0
Yes	3 (100)	12 (100)

continued

TABLE 19 Summary of side effects following treatment (*continued*)

Side effect	Treatment group	
	Ceftriaxone (*N* = 320)	Gentamicin (*N* = 298)
Any reported reduction in hearing,* n *(%)	***5 (2)***	***3 (1)***
Severity, *n* (%)		
Mild	5 (2)	3 (1)
Moderate	0 (0)	0 (0)
Severe	0 (0)	0 (0)
Duration (hours)		
Median (25th percentile, 75th percentile)	144 (72–264)	96 (2–336)
Minimum, maximum	12, 504	2, 336
Time from injection to onset, *n* (%)		
< 2 hours	1 (20)	0 (0)
2–6 hours	0 (0)	0 (0)
6–24 hours	0 (0)	1 (33)
1–3 days	2 (40)	1 (33)
> 3 days	2 (40)	1 (33)
Fully recovered, *n* (%)		
No	1 (20)	1 (33)
Yes	4 (80)	2 (67)
Any reported dizziness or unsteadiness,* n *(%)	***24 (7)***	***21 (7)***
Severity, *n* (%)		
Grade 1 (not interfering with function)	20 (6)	19 (6)
Grade 2 (interfering with function but not interfering with daily activities)	3 (1)	2 (1)
Grade 3 (interfering with daily activities)	0 (0)	0 (0)
Grade 4 (bedridden or disabled)	1 (0)	0 (0)
Duration (hours)		
Median (25th percentile, 75th percentile)	2 (1–15)	4 (1–24)
Minimum, maximum	1, 72	0, 168
Time from injection to onset, *n* (%)		
< 2 hours	13 (54)	10 (48)
2–6 hours	5 (21)	5 (24)
6–24 hours	2 (8)	4 (19)
1–3 days	0 (0)	1 (5)
> 3 days	4 (17)	1 (5)
Fully recovered, *n* (%)		
No	1 (4)	2 (10)
Yes	23 (96)	19 (90)

TABLE 19 Summary of side effects following treatment (*continued*)

Side effect	Treatment group	
	Ceftriaxone (*N* = 320)	Gentamicin (*N* = 298)
***Any new skin rash*, n (%)**	***5 (2)***	***12 (4)***
Severity, *n* (%)		
Grade 1 (localised skin eruption)	5 (2)	11 (4)
Grade 2 (diffuse skin eruption covering ≤ 50% of body surface area)	0 (0)	1 (0)
Grade 3 (generalised skin eruption covering > 50% of body surface area)	0 (0)	0 (0)
Duration (hours)		
Median (25th percentile, 75th percentile)	24 (24–24)	72 (36–324)
Minimum, maximum	6, 72	4, 744
Fully recovered, *n* (%)		
No	0 (0)	6 (50)
Yes	5 (100)	6 (50)
***Injection pain*, n (%)**	***315 (98)***	***294 (99)***
How long (hours) did it take to completely resolve the pain associated with injection?		
Median (25th percentile, 75th percentile)	1 (0–12)	2 (0–24)
Minimum, maximum	0, 240	0, 432

i.v., intravenous.

Other adverse events

Table 20 shows that the percentage of participants reporting other AEs at their follow-up visit was similar in both treatment groups: 15% (48/320) in the ceftriaxone group and 13% (38/298) in the gentamicin group, with the majority of AEs being mild. The most frequent class of AEs reported was gastrointestinal disorders: 14 participants reported these in the ceftriaxone group (4%) and 22 participants reported these in the gentamicin group (7%). The majority of these gastrointestinal disorders consisted of diarrhoea. Nervous system disorders were reported by 10 participants in the ceftriaxone group and three participants in the gentamicin group. The events that coded to nervous system disorders were headaches (six in the ceftriaxone group and one in the gentamicin group), dizziness (one in the ceftriaxone group and one in the gentamicin group), migraine (one in the ceftriaxone group), lethargy (one in the ceftriaxone group and one in the gentamicin group) and Bell's palsy (one in the ceftriaxone group).

Five per cent of AEs in the ceftriaxone group and 6% in the gentamicin group were reported to be related to the trial medication. Three AEs (only one of which was related to the trial medication) were reported to be severe: one in the ceftriaxone group and two in the gentamicin group. These were 'diarrhoea', 'grade 4 dizziness' and 'sickness'. Of these, the grade 4 dizziness was also classified as a SAE. All were resolved by the follow-up visit.

The SAE was grade 4 dizziness in a participant in the ceftriaxone group, which had occurred 4 days after randomisation. It was considered to be unrelated to the trial medication and was resolved before the follow-up visit.

A full list of AEs is provided in *Appendix 3*.

TABLE 20 Summary of AEs

AEs	Treatment group	
	Ceftriaxone ($N = 320$)	Gentamicin ($N = 298$)
Total number of AEs	54	43
Total number of AEs thought to be related to trial medication	48	38
Participants with any AE, *n* (%)	48 (15)	38 (13)
Participants with AE related to trial medication, *n* (%)	15 (5)	17 (6)
Participants with any SAE, *n* (%)	1 (<0.5)	0 (0)
Severity of AE, *n* (%)		
Mild	45 (83)	35 (81)
Moderate	8 (15)	6 (14)
Severe	1 (2)	2 (5)
MedDRA[31] SOC codes,[a] *n* (%)		
Ear and labyrinth disorders	3 (3)	0 (0)
Gastrointestinal disorders	14 (14)	22 (22)
General disorders and administration site conditions	6 (6)	3 (3)
Infections and infestations	7 (7)	5 (5)
Investigations	5 (5)	2 (2)
Metabolism and nutrition disorders	0 (0)	2 (2)
Musculoskeletal and connective tissue disorders	2 (1)	4 (4)
Neoplasms benign, malignant and unspecified (including cysts and polyps)	1 (1)	0 (0)
Nervous system disorders	10 (10)	3 (3)
Pregnancy, puerperium and perinatal conditions	1 (1)	0 (0)
Psychiatric disorders	1 (1)	0 (0)
Respiratory, thoracic and mediastinal disorders	3 (3)	1 (1)
Skin and subcutaneous tissue disorders	1 (1)	1 (1)

SOC, system organ classes.
a Number of participants are in parentheses.

Creatinine level and estimated glomerular filtration rate

The percentage of participants who had an increase in creatinine level of > 30% was similar in both treatment groups: 3% (10/358) in the ceftriaxone group and 3% (9/348) in the gentamicin group (*Table 21*). The follow-up creatinine value for 9% (28/304) of participants in the ceftriaxone group and 13% (38/289) of participants in the gentamicin group exceeded the upper limit of normal, as defined by their local laboratory. Changes in eGFR between baseline and follow-up were similar in both arms (see *Table 21*).

The shift plots in *Figures 7* and *8* demonstrate the shifts in creatinine level from baseline to visit 2. AEs relating to creatinine were reported for seven participants: five who had received ceftriaxone and two who had received gentamicin. All were mild and five out of the seven AEs were not thought to be related to trial medication. The grid lines represent the lowest of the lower bounds and highest of the upper bounds of normality between all of the local laboratories. The diagonal line represents the line of unity (no change).

TABLE 21 Summary of creatinine levels and eGFR pre and post treatment

Creatinine levels and eGFR	Treatment group	
	Ceftriaxone (*N* = 358)	Gentamicin (*N* = 348)
Creatinine level		
At baseline (µmol/l)		
Mean (SD)	78.7 (15.4)	78.3 (15.8)
N	341	329
At 2 weeks post treatment (µmol/l)		
Mean (SD)	79.7 (14.4)	80.2 (15.6)
N	304	289
Change in creatinine level, *n* (%)		
Number of participants who met clinically important change from baseline to 2 weeks post treatment[a]	10 (3)	9 (3)
Number of participants who exceeded upper limit of normal value at 2 weeks post treatment[b]	27 (7)	38 (11)
eGFR (ml/minute/1.73m²)		
At baseline, mean (SD)	110.6 (18.2)	111.5 (17.7)
At 2 weeks post treatment, mean (SD)	109.2 (17.4)	108.7 (17.9)
Change in eGFR at 2 weeks post treatment, median (IQR)	–1.3 (–6.7 to 4.3)	–1.4 (–6.9 to 3.7)

SD, standard deviation.
a Defined as a change of > 30% from baseline.
b There are specific lower and upper limits of normal values for each individual local site.

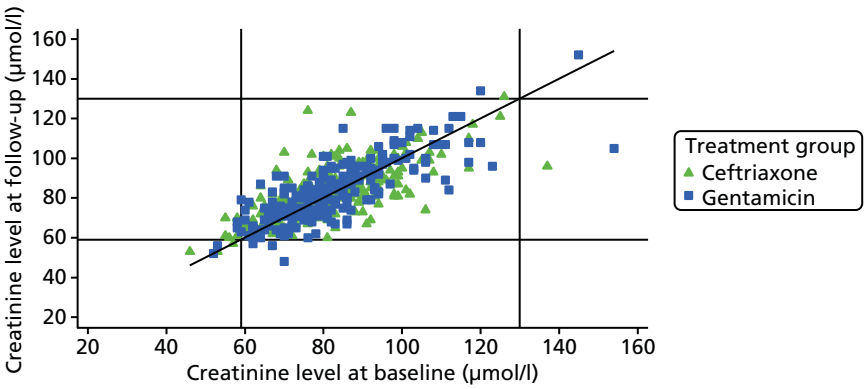

FIGURE 7 Shift plot of pre- and post-treatment creatinine levels in males.

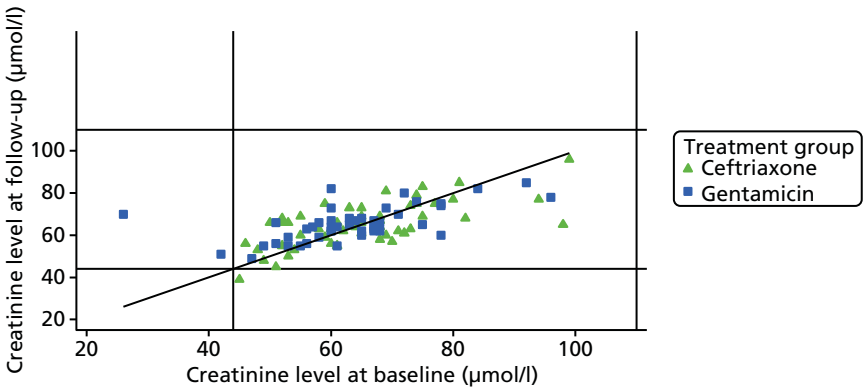

FIGURE 8 Shift plot of pre- and post-treatment creatinine levels in females.

Tolerability of injection

Injection site pain

The VAS score (1–100) completed immediately after injection with the trial treatment showed higher mean and median values (i.e. more pain) for the gentamicin group (*Table 22*). The pain scores recalled at the 2-week follow-up visit were also higher in the gentamicin group.

Minimum inhibitory concentrations

Gentamicin

Figure 9 shows the MIC distribution for gentamicin for the 367 participants for whom isolate data were available.

Figure 10 shows the gentamicin MICs of isolates from participants who received gentamicin and achieved microbiological clearance (as defined by a negative AC2 NAAT at all previously infected sites, 2 weeks after treatment). Data were available for 149 participants. The proportion who had clearance of *N. gonorrhoeae* at all sites was 90%. All isolates from non-responders had a MIC of 4 mg/l.

TABLE 22 Summary of VAS score by treatment arm

VAS score	Treatment group	
	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)
VAS score for injection site pain immediately after injection		
Mean (SD)	21.2 (19.4)	36 (23.2)
Median (25th percentile, 75th percentile)	15 (6, 30)	31.5 (18, 53.5)
Minimum, maximum	0, 86	0, 100
N	353	348
Recalled VAS score for pain at baseline injection after 2 weeks		
Mean (SD)	20.4 (20.5)	34.3 (25)
Median (25th percentile, 75th percentile)	15 (4, 30)	31 (13, 55)
Minimum, maximum	0, 100	0, 100
N	313	295

SD, standard deviation.

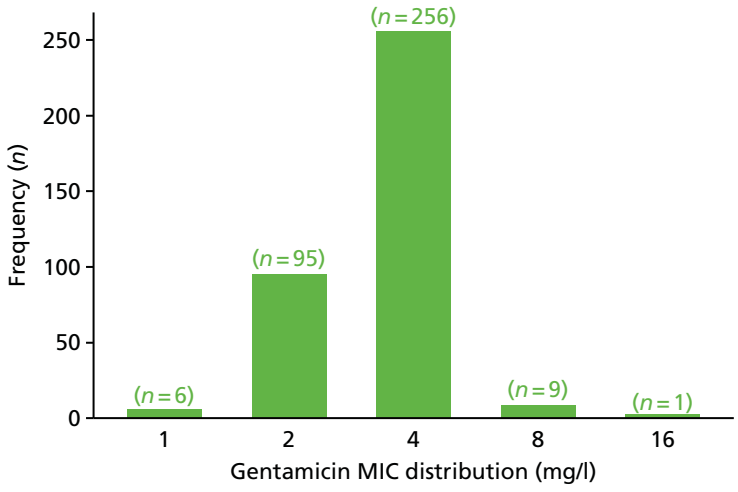

FIGURE 9 Gentamicin overall MIC distribution (mg/l) at baseline (all participants with sample data).

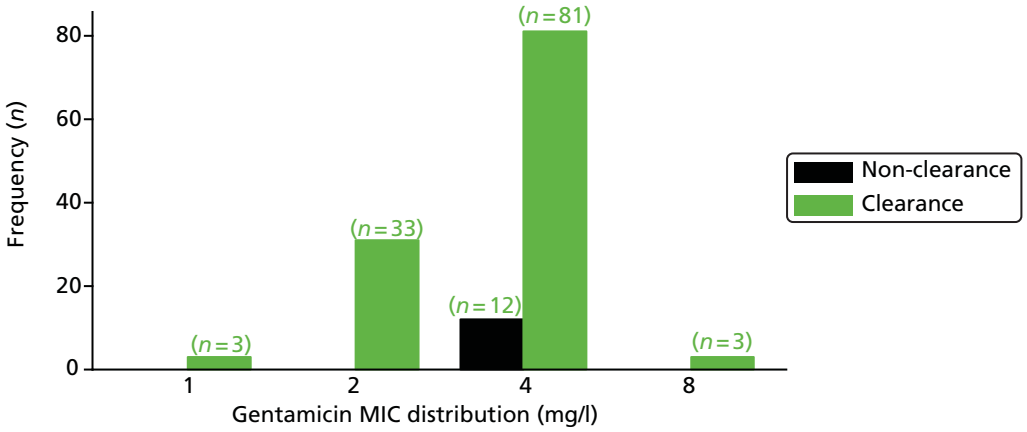

FIGURE 10 Distribution of gentamicin MIC (mg/l) for participants who received gentamicin, by clearance at 2 weeks post treatment.

Ceftriaxone

Figure 11 shows the MIC distribution for ceftriaxone for the 364 participants for whom isolate data were available. Fifty-nine participants (16%) harboured isolates with MIC values of ≤ 0.002 mg/l.

Figure 12 shows the ceftriaxone MICs of isolates from participants who received ceftriaxone and achieved microbiological clearance (as defined by a negative AC2 NAAT at all previously infected sites, 2 weeks after treatment). Data were available for 170 participants. The proportion of these participants who had clearance of *N. gonorrhoeae* at all sites was 96%. The six non-responders had MICs ranging from ≤ 0.002 to 0.008 mg/l.

Azithromycin

Figure 13 shows the MIC distribution for azithromycin for the 357 participants for whom isolate data were available. The distribution of MICs ranged from 0.032 to 4 mg/l.

Figure 14 shows the azithromycin MICs of isolates from participants who received azithromycin and achieved microbiological clearance (as defined by a negative AC2 NAAT at all previously infected sites, 2 weeks after treatment). Data were available for 305 participants. The proportion of these participants who had clearance of *N. gonorrhoeae* at all sites was 93%. The two non-respondents had MICs ranging from 0.064 to 1 mg/l.

Further plots showing the MIC distribution by infection site are available in *Appendix 3*.

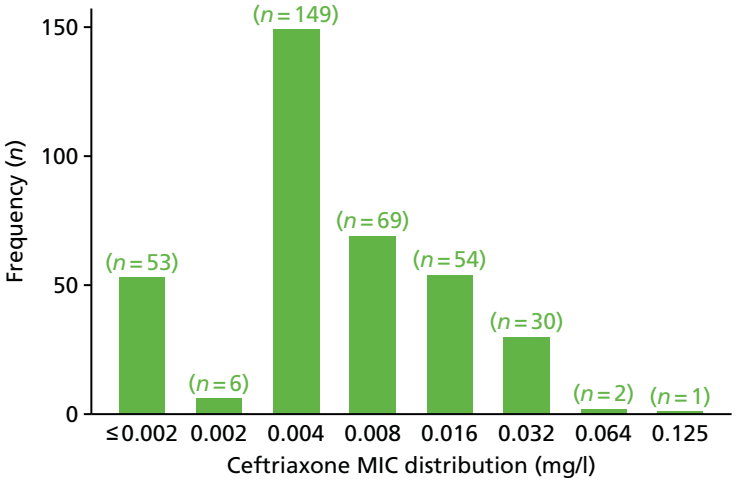

FIGURE 11 Ceftriaxone overall MIC distribution (mg/l) at baseline (all participants with sample data).

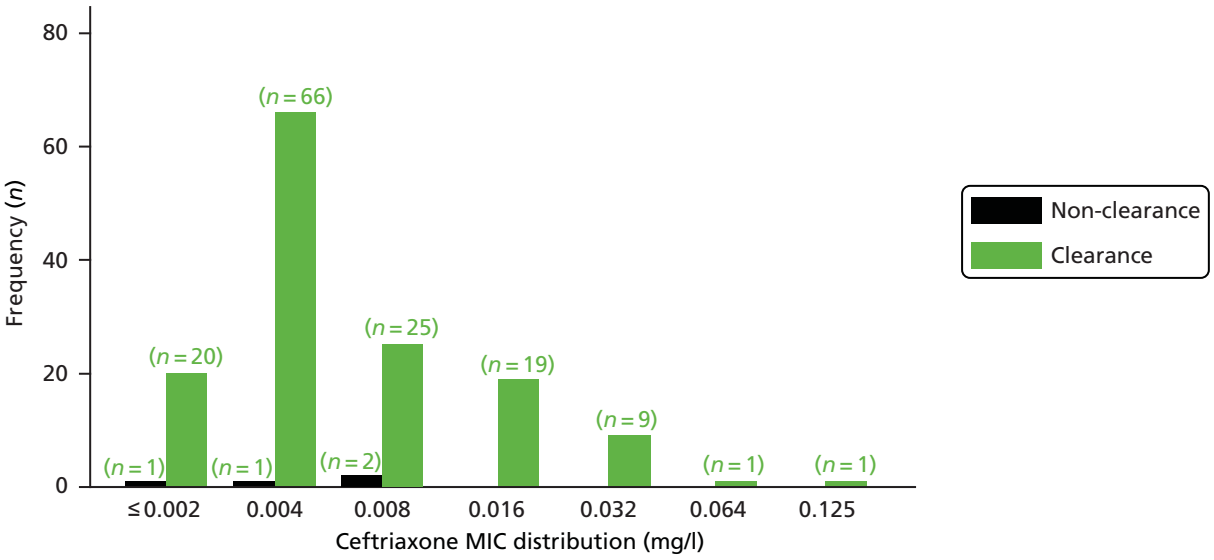

FIGURE 12 Distribution of ceftriaxone MIC (mg/l) for participants who received ceftriaxone, by clearance at 2 weeks post treatment.

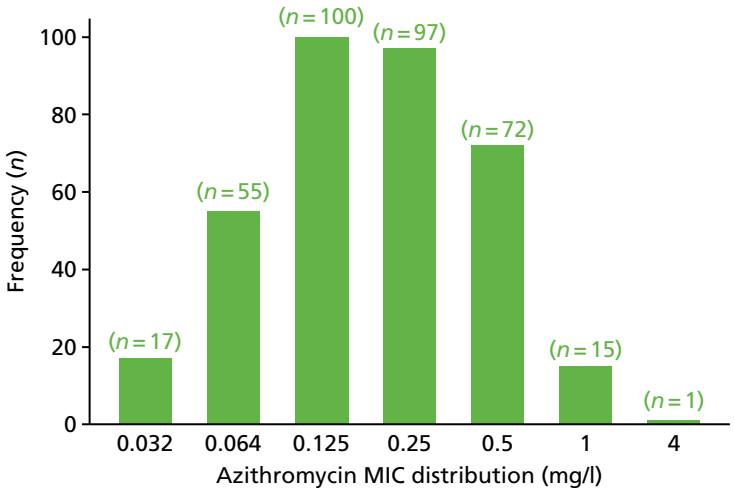

FIGURE 13 Azithromycin overall MIC distribution (mg/l) at baseline (all participants with sample data).

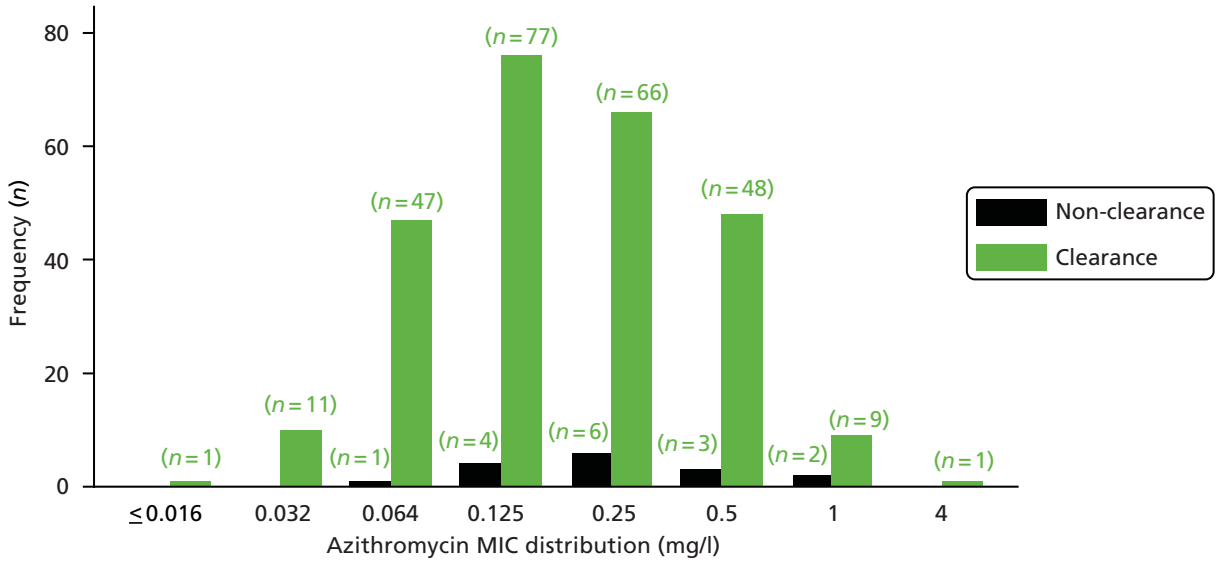

FIGURE 14 Distribution of azithromycin MIC (mg/l) for all participants, by clearance at 2 weeks post treatment.

Medications taken during the trial

A similar proportion of participants in both treatment arms took additional antibiotics in the period from randomisation to follow-up (*Table 23*).

Other antibiotics taken during the trial

A listing of other antibiotics that participants took during the trial is provided in *Appendix 3*.

Sexual behaviour and condom use during the trial

Tables 24 and *25* show the sexual behaviour of males and females, respectively, after receiving their trial medication. Out of 257 males in the ceftriaxone group and 251 males in the gentamicin group, 98 (38%) and 88 (35%), respectively, reported having had sex between receiving their randomised treatment and the 2-week follow-up. Of these, 40 males out of 98 (41%) and 37 males out of 88 (42%), respectively, never used a condom. Out of 65 females in the ceftriaxone group and 50 females in the gentamicin group, 20 (31%) and 16 (32%), respectively, reported having had sex between receiving trial treatment and the 2-week follow-up visit. Of these, 7 females out of 20 (35%) and 10 females out of 16 (63%) reported never using a condom. The risk of reinfection as a result of having sex in the follow-up period and the failure to use condoms in this period was therefore deemed similar in the two treatment groups.

Protocol deviations

Protocol deviations were reported in 121 out of 362 (33%) participants receiving ceftriaxone and 124 out of 358 (35%) participants receiving gentamicin; the majority of deviations were considered minor. There were only two major deviation categories: not receiving treatment according to randomisation and not fulfilling the eligibility criteria. Fourteen participants did not receive treatment according to randomisation and 20 deviations from the eligibility criteria were reported for 18 participants. These included participants being found to have contraindications to trial medication and having a disallowed concomitant disease. A list of the protocol deviations recorded on the deviation log can be found in *Appendix 3*.

TABLE 23 Additional antibiotic use during trial

	Treatment group, (*n*)	
Antibiotic	Ceftriaxone (*N* = 362)	Gentamicin (*N* = 358)
Taken at least one non-trial antibiotic	13	16
Azithromycin	2	1
Doxycycline	9	9
Ceftriaxone	0	3
Metronidazole	1	1
Trimethoprim	0	1
Ofloxacin	0	1
Clarithromycin	1	0

TABLE 24 Sexual history between randomisation and 2-week follow-up visit (males)

Sexual history	Treatment group	
	Ceftriaxone (*N* = 257)	Gentamicin (*N* = 251)
Sexual contact since receiving treatment for gonorrhoea		
No, *n* (%)	157 (61)	163 (65)
Yes, *n* (%)	98 (38)	88 (35)
Not known, *n* (%)	2 (1)	0
If yes, number of partners		
Median (25th percentile, 75th percentile)	1 (1, 2)	1 (1, 2)
Minimum, maximum	1, 6	1, 13
Previous partners		
Median (25th percentile, 75th percentile)	1 (0, 1)	1 (0, 1)
Minimum, maximum	0, 3	0, 5
New partners		
Median (25th percentile, 75th percentile)	1 (0, 1)	0 (0, 1)
Minimum, maximum	0, 6	0, 12
Number of episodes of sexual contact since receiving treatment for gonorrhoea		
Median (25th percentile, 75th percentile)	2 (1, 3)	2 (1, 4)
Minimum, maximum	1, 15	1, 20
Type of sexual contact,[a] *n* (%)		
Genital–genital	48 (19)	43 (17)
Genital–oral	73 (28)	67 (27)
Oral–genital	67 (26)	61 (24)
Genital–anal	51 (20)	47 (19)
Anal–genital	36 (14)	42 (17)
Oral–anal	24 (9)	29 (12)
Anal–oral	22 (9)	25 (10)
Digital–anal	26 (10)	26 (10)
Anal–digital	21 (8)	21 (8)
Use of condoms since receiving treatment for gonorrhoea, *n* (%)		
No	40 (15)	37 (15)
Yes, partially	6 (2)	11 (4)
Yes, consistently, including for oral sex	15 (6)	7 (3)
Yes, consistently, but not for oral sex	37 (14)	33 (13)
Unknown	2 (1)	0
N/A	157 (61)	163 (65)

N/A, not applicable.
a Not mutually exclusive.

TABLE 25 Sexual history between randomisation and 2-week follow-up visit (females)

Sexual history	Treatment group	
	Ceftriaxone (*N* = 65)	Gentamicin (*N* = 50)
Sexual contact since receiving treatment for gonorrhoea		
No, *n* (%)	45 (69)	34 (68)
Yes, *n* (%)	20 (31)	16 (32)
If yes, number of partners		
Median (25th percentile, 75th percentile)	1 (1, 1)	1 (1, 1)
Minimum, maximum	1, 5	1, 2
Previous partners		
Median (25th percentile, 75th percentile)	1 (0.5, 1)	1 (1, 1)
Minimum, maximum	0, 1	0, 1
New partners		
Median (25th percentile, 75th percentile)	0 (0, 1)	0 (0, 0.5)
Minimum, maximum	0, 5	0, 1
Number of episodes of sexual contact since receiving treatment for gonorrhoea		
Median (25th percentile, 75th percentile)	1 (1, 2.5)	1 (1, 2.5)
Minimum, maximum	1, 14	1, 4
Type of sexual contact,[a] *n* (%)		
Genital–genital	19 (29)	13 (26)
Genital–oral	5 (8)	3 (6)
Oral genital	8 (12)	3 (6)
Genital–anal	0	0
Anal–genital	1 (2)	1 (2)
Oral–anal	0	0
Anal–oral	0	0
Digital–anal	0	0
Anal–digital	0	0
Use of condoms since receiving treatment for gonorrhoea, *n* (%)		
No	7 (11)	10 (20)
Yes, partially	5 (8)	2 (4)
Yes, consistently, including for oral sex	3 (5)	2 (4)
Yes, consistently, but not for oral sex	5 (8)	2 (4)
Unknown	0	0
N/A	45 (69)	34 (68)

N/A, not applicable.
a Not mutually exclusive.

Chapter 4 Economic evaluation of gentamicin compared with ceftriaxone in the treatment of gonorrhoea

Introduction and aims

The aim of the economic evaluation was to compare the costs and outcomes associated with the current standard treatment, ceftriaxone, in the treatment of gonorrhoea with those of the proposed alternative treatment, gentamicin. The primary aim of the G-TOG trial was to determine whether or not gentamicin is an acceptable alternative to ceftriaxone in the treatment of gonorrhoea. There are several scenarios in which a decision might be taken to use an alternative treatment. For example, the use of an alternative antibiotic might be recommended to preserve the effectiveness of the current standard treatment, as antibiotic resistance is linked to consumption.[36] In addition, an alternative treatment might be needed in the context of developing antimicrobial resistance (AMR) to the current standard treatment, as has happened repeatedly with gonorrhoea over the last 70–80 years.[37]

The G-TOG trial was designed as a non-inferiority trial to assess whether or not the rate of microbiological clearance of *N. gonorrhoeae* in participants treated with gentamicin is non-inferior to the rate of microbiological clearance in participants treated with ceftriaxone. The economic analysis, therefore, focused on establishing whether or not the use of gentamicin rather than ceftriaxone is cost neutral in the treatment of gonorrhoea, in which case gentamicin could be used as a substitute for ceftriaxone without additional resource implications. This involved the examination of costs and resource use to determine whether or not there were any differences between the two treatments.

Methods

Overview

A cost-effectiveness analysis (CEA) was undertaken from the perspective of the NHS. The main outcome considered was the clearance of gonorrhoea, as this was the primary outcome of the trial. A health-care perspective was deemed to be the most relevant as the RCT is concerned with the non-inferiority of gentamicin in the treatment of gonorrhoea; hence, the costs to the NHS associated with the two treatments need to be assessed. A within-trial economic evaluation was undertaken that reflected the objectives of the trial and the short follow-up period.

A simple decision tree was deemed to be the most suitable way of presenting the alternative patient pathways and synthesising the available data. The model was necessary in order to analyse alternative patient pathways, particularly in the sensitivity analyses, and collate available data. A decision-analytic model involves using mathematical relationships to set out the consequences that are associated with the different policy options under consideration.[38] This allows the costs and outcomes for each option to be evaluated, taking into account the probability of the consequences. Data on resource use and costs were collected prospectively via trial reporting mechanisms and additional data were sourced from the literature.

Model structure

A decision tree model was developed using TreeAge Pro 2016 (TreeAge Software, Inc., Williamstown, MA, USA). The structure was informed by the trial objectives and patient pathways were indicated by the clinical data. As shown in *Figure 15*, participants entered the model at the point of randomisation to receive the alternative treatment (gentamicin) or the standard treatment (ceftriaxone). Following the initial

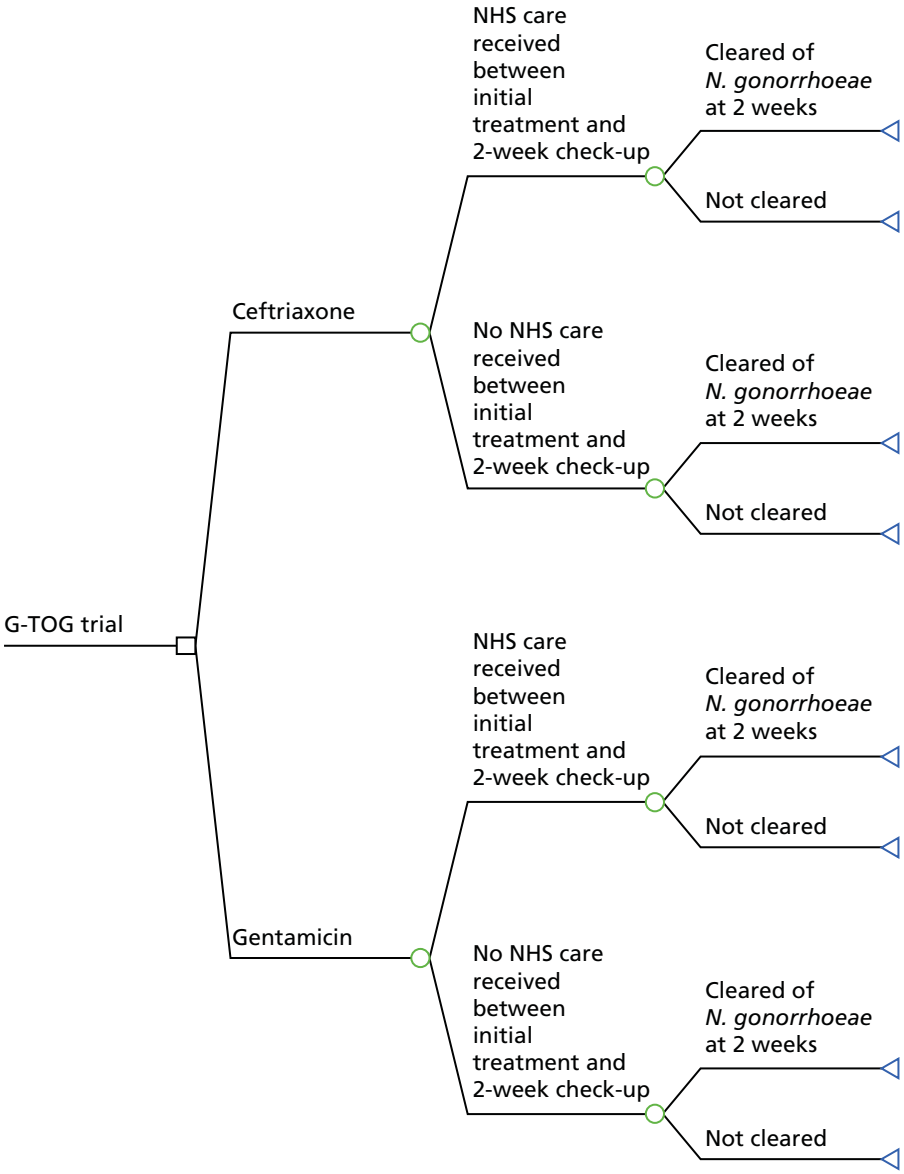

FIGURE 15 Model structure.

course of antibiotic treatment, participants either received additional NHS care [e.g. general practitioner (GP) visit] or did not access care. At 2 weeks post treatment, participants either were cleared of *N. gonorrhoeae* at all sites, confirmed by a negative NAAT, or were not cleared and required further treatment.

If clearance of *N. gonorrhoeae* at all sites was not confirmed (at 2 weeks post treatment), participants were treated with a further course of antibiotics. For the purposes of the economic evaluation, the base-case analysis followed current guidelines and it was assumed that all participants who were not cleared of infection would be treated with a course of ceftriaxone. However, in the sensitivity analyses, alternative scenarios were also explored, including the use of alternative antibiotic treatments when participants were not cleared of the infection at all sites.

Clinical data

The primary outcome of the economic evaluation reflected the primary outcome of the trial – the clearance of *N. gonorrhoeae* at all infected sites (confirmed by a negative NAAT) at 2 weeks post treatment (*Table 26*). The primary approach to analysis was ITT without imputation of missing outcome data, as specified in the SAP. Data were also collected on whether or not participants required further NHS care following the initial treatment.

TABLE 26 Probabilities used in the decision-tree model

Treatment group description	Trial data, *n*/*N*	Probability	Distribution
Ceftriaxone			
Requiring NHS treatment after the initial visit	10/322	0.03	Beta
Not requiring NHS treatment after the initial visit	312/322	0.97	Beta
Clearance of *N. gonorrhoeae*	299/306	0.98	Beta
Not cleared of *N. gonorrhoeae*	7/306	0.02	Beta
Gentamicin			
Requiring NHS treatment after the initial visit	8/302	0.03	Beta
Not requiring NHS treatment after the initial visit	294/302	0.96	Beta
Clearance of *N. gonorrhoeae*	267/292	0.91	Beta
Not cleared of *N. gonorrhoeae*	25/292	0.09	Beta

Treatment costs

Trial participants allocated to the gentamicin arm received 240 mg of gentamicin as a single i.m. injection. This was obtained from three 80-mg ampoules, with an estimated cost of £1 per ampoule [£3 overall, estimated using the *British National Formulary* (BNF)],[39] as shown in *Table 27*. Participants allocated to the ceftriaxone arm received a 500-mg dose. Ceftriaxone was purchased in units of 1 g and mixed with 4 ml (1%) of lidocaine solution. Only half of the preparation was administered to the participant (half was discarded); we therefore included costs for one vial of 1 g of ceftriaxone powder (£1.10) per participant and two 2-ml lidocaine ampoules (£0.22 per ampoule).[39] Hence, the initial costs associated with gentamicin treatment were higher than those associated with the current standard treatment, ceftriaxone. Other equipment (such as syringes) would be required by both arms of the trial and so these costs were not included. In both trial arms, participants received a single oral dose of azithromycin, an initial consultation with a health-care professional and a follow-up visit. These costs were excluded from the analysis as they were incurred equally across the trial arms.

To check that there was no difference in the length of time required for delivery of the treatment therapy, a survey was undertaken with research nurses involved in the delivery of the two treatments. The survey aimed to check whether or not the delivery of the treatment and the length of the consultation were affected by the drug that was being administered. The survey received responses from 21 nurses who were administering injections. The majority of nurses (17 respondents, 81%) stated that there was no difference in the time taken to administer the two treatments. Just four nurses (19%) responded that there was a difference, all of whom stated that appointments to administer gentamicin were longer than those to administer ceftriaxone. The main reason given for the longer time needed to administer gentamicin was the increased pain associated with gentamicin injections (given as a reason by three of the nurses who felt that gentamicin took longer to administer). Two nurses stated that appointments to administer gentamicin took 0–5 minutes longer and two stated that an additional time of up to 10 minutes was needed. Given the survey results, for the base-case analysis additional time was not included to administer the gentamicin treatment; however, increased time was explored as part of the sensitivity analysis.

TABLE 27 Trial treatments

Resource use	Cost item	Base-case value (£)	Distribution	Source
Gentamicin treatment	Per participant	3.00	Gamma	BNF[39]
Ceftriaxone treatment	Per participant	1.54	Gamma	BNF[39]

NHS resource use and costs incurred after initial treatment

NHS resource use by participants was collected during the trial at all participating sites using a form completed by a nurse/assessor. Data were collected on whether or not participants had visited their GP/nurse at their general practice, a GP out-of-hours service, health professionals at a sexual health clinic or an accident and emergency (A&E) department and on the use of other services. Data were also collected on whether or not participants were prescribed other medication (other than the trial treatment). In addition, details of any AEs and associated resource use were recorded. Unit cost estimates were applied to resource use data to generate individual-level cost estimates. The sources of unit costs included routine and published literature (e.g. *Unit Costs of Health and Social Care 2016*[40]).

Resource use was similar across trial arms, with the main resources that were used relating to GP visits and sexual health centre visits (*Table 28*). No participants reported that they had been hospitalised during the trial or attended A&E.

Further treatment costs owing to non-clearance of infection

Within the trial, when infection was not cleared at all sites (as indicated by a NAAT), further treatment was given. Participants in the gentamicin arm were assumed to be treated with ceftriaxone (unless there was a contraindication for this treatment). Participants in the ceftriaxone arm were assumed to have been given a second course of ceftriaxone unless the culture demonstrated resistance to this treatment. For the purposes of the economic evaluation, it was assumed that in both trial arms, when infection was not cleared at 2 weeks post treatment, a sexual health clinic appointment would be needed and that a course of the standard treatment (ceftriaxone) would be given (*Table 29*). This was to reflect current guidelines;[8] other scenarios were explored in the sensitivity analysis.

Analysis

The within-trial analysis took the form of a CEA, with results reported in terms of the cost per participant successfully treated (measured in terms of microbial clearance of *N. gonorrhoeae* at all infected sites, 2 weeks post treatment). As the trial was concerned with the immediate post-treatment period of 2 weeks, discounting was not undertaken. All costs are given in Great British pounds for 2015/16.

TABLE 28 NHS resource use after initial treatment and before the 2-week follow-up

Resource use	Cost item	Unit cost (£)	Treatment group (*n*)		Total cost (£)	
			Ceftriaxone	Gentamicin	Ceftriaxone	Gentamicin
GP consultation	Per visit	36.00	6	3	216.00	108.00
Sexual health clinic: health advisor consultation	Per visit	93.00[a]	1	2	93.00	186.00
Sexual health clinic: doctor consultation	Per visit	130.00[b]	5	4	650.00	520.00
NHS 111 call	Per call	6.10[c]	1	1	6.10	6.10
Total costs					965.00	820.10
Total number of patients accessing additional treatment			10	8		
Total cost per patient accessing additional treatment					95.60	102.51

a Assumed to be equivalent to non-consultant-led family planning clinic – first appointment (*NHS Reference Costs 2015 to 2016*[41]).
b Assumed to be equivalent to consultant-led genitourinary consultation – first-appointment (*NHS Reference Costs 2015 to 2016*[41]).
c Assumed to be equivalent to nurse-led telephone consultation.[40]

TABLE 29 Costs of further treatment for participants when infection was not cleared

Resource use	Cost item	Unit cost (£)	Source
Sexual health clinic: nurse/health advisor consultation	Per visit	93.00[a]	*NHS Reference Costs 2015 to 2016*[41]
Second course of antibiotic treatment	Per participant	1.54[b]	*NHS Reference Costs 2015 to 2016*[41]
Total costs		94.54	

a Assumed to be equivalent to non-consultant-led family planning clinic – first appointment.
b Assumes one injection of ceftriaxone.

Sensitivity analysis

Both deterministic and probabilistic sensitivity analyses were undertaken to explore the uncertainty in the parameter estimates on the results produced by the model.[42] In the deterministic sensitivity analysis, one or more parameters were varied while keeping the others at their baseline value. Deterministic analysis can help to identify which values are important in leading to a particular decision and can help to identify threshold values.[43,44]

A range of deterministic sensitivity analyses was carried out. First, the cost of the interventions was varied to reflect the purchase of different solutions/equipment based on prices reported in the BNF.[39] Second, the costs of additional treatment for those without clearance of *N. gonorrhoeae* was varied to take into account different scenarios for the development of AMR in gonorrhoea. The cost was increased to reflect a scenario in which two further treatments of ceftriaxone were given and two follow-up visits to a clinic. Third, the rates of clearance for gonorrhoea were varied to reflect different rates at different sites, using the lowest and highest 95% CIs reported in *Table 17* for different sites. Fourth, the time taken to administer the gentamicin treatment was varied to reflect the responses of a minority of nurses in the survey who indicated that gentamicin injections took longer to administer. The cost of treatment was increased to take into account a scenario in which an additional 10 minutes would be needed to administer gentamicin than to administer ceftriaxone, assuming that the cost of the time of the nurse administering the treatment would be equivalent to that of a GP nurse.[40]

A probabilistic sensitivity analysis (PSA) was also undertaken to allow uncertainty to be explored more comprehensively. A PSA involves varying all parameters simultaneously and sampling multiple sets of parameter values from defined probability distributions. A Monte Carlo simulation was used to sample from the distributions; this involved 1000 repeated random draws to analyse how variation in the parameters used in the model would affect the results. Beta distributions were used for binomial data and gamma distributions were used for costs, in line with recommendations for specifying distributions for parameters.[42]

Results

The results of the analysis are shown in *Table 30*. A higher proportion of participants treated with ceftriaxone were cleared of infection with *N. gonorrhoeae* (98%) than participants treated with gentamicin

TABLE 30 Summary of the results of the base-case analysis

Treatment group	Average cost (£) per participant (95% CI)	% cleared of infection at 2 weeks post treatment	ICER
Ceftriaxone	6.72 (1.36 to 17.84)	98	Dominates
Gentamicin	13.90 (2.47 to 37.34)	91	

ICER, incremental cost-effectiveness ratio.

(91%). The average participant costs associated with gentamicin were higher than those associated with ceftriaxone. The main difference in costs related to the need for additional consultations and treatment for participants who were not successfully cleared of infection at all sites (at 2 weeks post treatment). Hence, the analysis found that treatment with gentamicin is not non-inferior to ceftriaxone and that it is not cost neutral. The average cost per participant treated was £13.90 for gentamicin, compared with £6.72 for ceftriaxone.

The results of the one-way deterministic sensitivity analyses are shown in *Table 31*. First, the results arising from varying the costs associated with the antibiotic treatments are presented. The costs associated with antibiotics might increase if penalties were introduced to discourage their use to slow down the development of AMR. As expected, increasing the costs of the treatments increased the overall costs per participant treated in both arms. Second, results from increasing the costs of additional treatment for those without clearance of *N. gonorrhoeae* 2 weeks after treatment are shown. It is evident that this increased overall costs for both trial arms, but particularly for the gentamicin arm as a result of the higher proportion of participants in this arm who were not cleared of infection. The results for the third scenario show that varying the rates of clearance to reflect the results at different sites (see *Table 31*) affects the relative cost-effectiveness of the treatments. If the rates for clearance of genital infection are used, ceftriaxone still dominates, but the difference in cost per participant between the groups is smaller. Clearance rates for gentamicin would need to be higher than those for ceftriaxone for gentamicin to be cost neutral, owing to the higher costs associated with gentamicin treatment. In the final scenario, increasing the costs associated with administering the gentamicin treatment led to increased costs for the gentamicin arm.

The scatterplot in *Figure 16* shows the results of the PSA involving 1000 simulations. It is evident that the majority of the simulations generated did not show that gentamicin was non-inferior to ceftriaxone and that the costs of gentamicin were shown to be higher. A large proportion of the points are in the north-west quadrant, indicating that treatment with ceftriaxone dominates treatment with gentamicin (gentamicin is not shown to be non-inferior and is unlikely to be cost neutral).

TABLE 31 Deterministic sensitivity analysis: selected results

Deterministic sensitivity analysis scenarios	Value		Treatment group, average cost per participant (£)	
	Original	Revised	Ceftriaxone	Gentamicin
Base case	–	–	6.72	13.90
(1) Varying the cost (£) of antibiotics				
Gentamicin	3.00	1.54–12.00		12.44–22.90
Ceftriaxone	1.54	1.00–9.58	6.15–14.92	
(2) Increasing the cost (£) of additional treatment for those without clearance of *N. gonorrhoeae*	94.54	247.62	10.20	26.92
(3) Varying the rates of clearance of *N. gonorrhoeae*				
Gentamicin arm (%)	91	72–97		32.55–8.66
Ceftriaxone arm (%)	98	92–100	10.16–4.54	
(4) Increasing the cost (£) of gentamicin treatment (longer consultation time)	3.00	9.00		19.90

Note
Costs are in Great British pounds (2015/16).

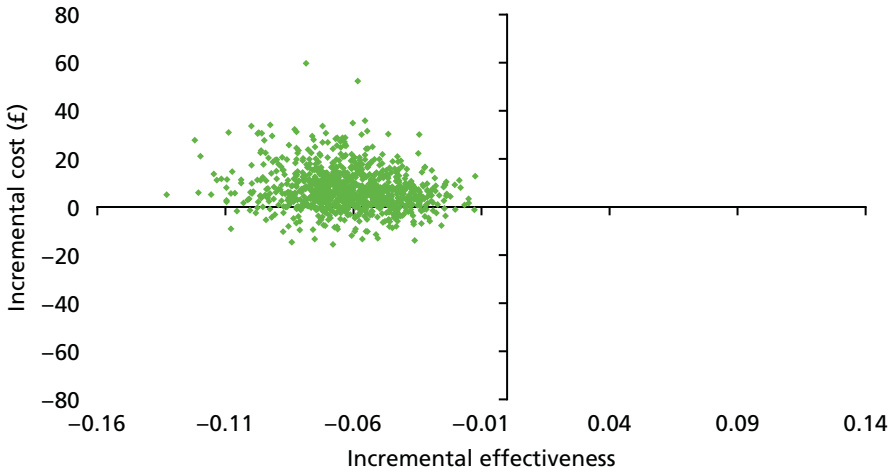

FIGURE 16 Incremental cost-effectiveness scatterplot for clearance of infection: gentamicin vs. ceftriaxone.

Discussion

The results show that gentamicin is likely to be more costly than ceftriaxone in the treatment of gonorrhoea. Currently, it is not shown that gentamicin is non-inferior to ceftriaxone in the treatment of gonorrhoea, nor is there evidence that it is cost neutral.

A major limitation of the economic analysis is that it was necessarily restricted because it was not possible to fully take into account the potential costs associated with AMR in gonorrhoea, nor the potential value associated with preserving the effectiveness of ceftriaxone. These issues were outside the scope of the current trial but may warrant further investigation. A strength of the economic evaluation is that it draws on prospective data collected during the RCT. Although assumptions were made about treatment strategies when infection was not cleared, these were based on published clinical guidelines.

There is currently a lack of evidence about how economic evaluations should be undertaken for interventions addressing AMR.[45] Very few economic evaluations have been undertaken that assess different antibiotic strategies in the context of developing AMR.[46,47] The costs associated with AMR in gonorrhoea require further analysis and there is an urgent need to develop appropriate methods for economic evaluations of interventions to address AMR in gonorrhoea and other disease areas.[48]

Chapter 5 Discussion

The main trial finding is that single-dose gentamicin (240 mg) is not shown to be non-inferior to single-dose ceftriaxone (500 mg) for the treatment of gonorrhoea, when both drugs are combined with a single dose of oral azithromycin (1 g). The trial was not designed to assess superiority, but the magnitude of the risk difference (–6.4%, 95% CI –10.4% to –2.4%) and the consistency of the findings on sensitivity analyses suggest that gentamicin may be less effective than ceftriaxone for the microbiological cure of gonorrhoea. The difference in efficacy was most marked for pharyngeal gonorrhoea (risk difference –15.3%, 95% CI –24.0% to –6.5%) and rectal gonorrhoea (risk difference –7.8%, 95% CI –13.6% to –2.0%). For genital gonorrhoea, gentamicin achieved microbiological cure in 94% of infections compared with a 98% clearance rate for ceftriaxone (risk difference –4.4%, 95% CI –8.7% to 0.0%).

Both ceftriaxone and gentamicin were generally well tolerated. Nausea was the most commonly reported side effect of treatment, occurring in 12% of participants receiving ceftriaxone and 14% receiving gentamicin. Few participants reported vestibulocochlear symptoms; these symptoms, when reported, occurred similarly between treatment arms: reduction in hearing in 2% of participants receiving ceftriaxone and 1% receiving gentamicin and dizziness or unsteadiness in 7% (ceftriaxone) and 7% (gentamicin). The proportion of participants with either clinically important changes in creatinine level from baseline or a creatinine level exceeding the upper limit of normal was similar in both groups; a high/increased or abnormal creatinine level was recorded as an AE for only seven participants. All AEs were mild and in three out of the seven cases they were thought by the local principal investigator (PI) to be related to treatment. The mean change in eGFR [median (25th percentile, 75th percentile)] was similar in the two treatment groups and not considered of clinical importance, being –1.3 ml/minute/1.73 m^2 [median (–6.7 ml/minute/1.73 m^2, 4.3 ml/minute/1.73 m^2)] for the ceftriaxone group and –1.4 ml/minute/1.73 m^2 [median (–6.9 ml/minute/1.73 m^2, 3.8 ml/minute/1.73 m^2)] for the gentamicin group. Almost all participants receiving either ceftriaxone or gentamicin reported injection site pain (98% and 99%, respectively) but the severity of the pain was less for ceftriaxone (median VAS score immediately after injection 15.0) than for gentamicin (median VAS score 31.5). Injection site pain resolved within a median of 1 hour (IQR 0–12 days) for ceftriaxone and 1.5 hours (IQR 0–24 days) for gentamicin.

A single SAE occurred in a participant who developed severe dizziness 4 days after receiving ceftriaxone. On subsequent review, he gave a history of eating biscuits containing cannabis shortly before developing these symptoms.

Efficacy of gentamicin for the treatment of gonorrhoea

The trial was designed to assess the efficacy of gentamicin compared with ceftriaxone and the primary end point was microbiological cure 14 days after treatment. There are a number of factors that could affect the response to gentamicin treatment.

Antimicrobial resistance

The mechanisms leading to gentamicin resistance have not been fully elucidated but include reduced uptake into infected cells as a result of decreased cell membrane permeability to the antibiotic[49] or modification of the drug by cellular enzymes, which reduce its activity.[50] For spectinomycin, which is in the same drug class of aminoglycosides and has a similar mechanism of action, mutations within 16S ribosomal ribonucleic acid that inhibit binding of the drug to the ribosome have been associated with high-level resistance.[51] In vitro measurement of the MIC for gentamicin in cultured isolates of *N. gonorrhoeae* provides a phenotypic assessment of antimicrobial susceptibility, but the 'breakpoint' MIC value, below which clinical cure occurs and above which treatment is ineffective, has not been established. It has been tentatively suggested that an isolate with a MIC of < 8 mg/l is susceptible, with a MIC of 8–16 mg/l is intermediate and with a MIC of > 16 mg/l is resistant.[29,52] The European Network for STI Surveillance found that 95% of isolates had gentamicin MICs in the range of 4–8 mg/l,[27] using the agar dilution technique. Isolates of *N. gonorrhoeae*

from participants in the G-TOG trial had a similar susceptibility profile, with 70% having a MIC of 4–8 mg/l using the Etest technique.

Previously proposed MIC 'cut-offs' points associated with AMR in *N. gonorrhoeae* for gentamicin, ceftriaxone and azithromycin are shown in *Table 32*.

The measurement of MICs requires a positive *N. gonorrhoeae* culture sample. Participants in the G-TOG trial had samples taken for culture at their baseline attendance and 2-week follow-up but culture is less sensitive than NAAT, particularly for extragenital sites, and, therefore, the data on in vitro susceptibility (using MICs) are limited to the subset of individuals who had a positive culture sample available. For genital infections, culture isolates were available for 356 out of 402 (88%) NAAT-positive samples at baseline; for rectal infections, this number was 146 out of 301 (47%) and for pharyngeal infections it was 88 out of 256 (34%).

Caution is, therefore, required in the interpretation of the antibiotic susceptibility profiles, which represent only a subgroup of the overall trial population, especially for those with pharyngeal and rectal infections. Overall, the culture-positive and culture-negative groups were similar with respect to age, sex and ethnicity, although there was a greater proportion of males among those with no culture result available (94% compared with 79% in the culture-positive group and 78% in the culture-negative group) and there were fewer white participants (59% compared with 66% and 74% in the culture-positive and culture-negative groups, respectively).

The extent of tissue penetration of different antimicrobials at the genital, rectal and pharyngeal sites is not known, nor is the extent of interindividual variation in tissue drug levels. This makes it difficult to interpret how the MIC values measured in vitro relate to the relative antibiotic susceptibility of gonococcal isolates in individual trial participants.

There did not appear to be any association between the in vitro gentamicin MIC and response to treatment.

The structurally similar antibiotic spectinomycin has been reported to be less effective for the treatment of pharyngeal gonorrhoea,[55] probably because it fails to achieve bactericidal concentrations within the infected tissues for a sufficiently long time period to clear infection.[5] It is possible that this mechanism is also relevant for gentamicin.

Participants in both treatment groups received oral azithromycin and treatment failure was associated with a reduction in in vitro susceptibility (shift of the azithromycin MIC distribution to the right). Overall, treatment failure occurred in 14 out of 262 (5%) participants who had isolates with an azithromycin MIC of ≤ 0.5 mg/l compared with 2 out of 12 (17%) participants who had isolates with an azithromycin MIC of ≥ 1 mg/l.

TABLE 32 Minimum inhibitory concentrations associated with AMR in *N. gonorrhoeae* for gentamicin, ceftriaxone and azithromycin

Drug	Proposed MIC cut-off points (mg/l)			
	UK Gonococcal Resistance to Antimicrobials Surveillance Programme[3]	European Committee on Antimicrobial Susceptibility Testing[53]	US Centers for Disease Control and Prevention[54]	Other[29,52]
Gentamicin	–	–	–	> 16
Ceftriaxone	> 0.064[a]	> 0.12	> 0.25	–
Azithromycin	> 0.5	> 0.5	–	–

a Decreased susceptibility.

In summary, we did not find that gentamicin MICs, as assessed by in vitro antimicrobial susceptibility testing, accurately predicted treatment failure. This suggests that in vitro laboratory assessment of MICs for gentamicin is not likely to be helpful in selecting those patients with gonorrhoea who can be successfully treated with gentamicin.

Reinfection

If a patient is reinfected after treatment, then their follow-up test for gonorrhoea will be positive even after successful initial therapy. If this occurs following sex with an existing infected partner, then it is likely that the same subtype of *N. gonorrhoeae* will be present at baseline and follow-up. If sexual contact was with a new partner, then the same subtype of *N. gonorrhoeae* could be present at follow-up (e.g. if this is a common subtype within the population) or a different subtype may occur.

Sexual contact following treatment for gonorrhoea was well balanced between the treatment groups: it was reported by 37% (118/322) of participants receiving ceftriaxone [15% (47/322) of whom reported not using condoms] and 34% (104/302) receiving gentamicin [16% (47/302) of whom reported not using condoms]. For both groups, a median of two episodes of sexual contact occurred in the interval between treatment and follow-up. There were similar clearance rates for participants who had and those who had not had sex following randomisation, and these rates appeared to be similar between treatment groups.

Reinfection of participants with gonorrhoea is, therefore, not likely to explain the difference in treatment success between participants receiving ceftriaxone and those receiving gentamicin.

Interval between treatment and follow-up assessment

Microbiological cure following treatment was assessed using NAAT and occurred at ≤ 21 days in 81% of participants in both treatment groups. The median time to assessment of cure did not differ between the two treatment groups (ceftriaxone 16 days, gentamicin 15 days). The median time to follow-up was 15 days from randomisation for those who were cleared of infection and 15.5 days for those who were not cleared of infection.

Persistence of bacterial nucleic acid following effective treatment, even in the absence of viable bacteria, has the potential to cause false-positive test results. Current UK national guidance is to assess cure by performing a NAAT 2 weeks after treatment, by which time a false-positive result is unlikely.[56–60] It has been suggested that pharyngeal infection may take longer to clear following treatment, with a greater possibility of a false-positive result 2 weeks after therapy.[61] The high treatment success rate at all anatomical sites in participants receiving ceftriaxone [genital 98% (151/154), pharyngeal 96% (108/113) and rectal 98% (134/137)] suggests that persistence of bacterial nucleic acid (in the absence of viable bacteria) leading to false-positive results did not occur frequently in the G-TOG trial participants. However, the pharmacodynamics of gentamicin for the treatment of pharyngeal gonorrhoea are largely unknown and it remains possible that the rate of bacterial clearance may be slower with gentamicin than with ceftriaxone.

Negative interaction between gentamicin and azithromycin

An antagonistic interaction between gentamicin and azithromycin could potentially reduce the efficacy of the combination of these two drugs. However, in vitro testing suggests that there is neither antagonism nor synergy when the two antibiotics are combined;[62] furthermore, a recent trial using this combination demonstrated the potential for a high cure rate using dual therapy, at least in a subset of patients with genital infection diagnosed by culture.[25] An antagonistic interaction between gentamicin and azithromycin would, therefore, be an unlikely explanation for the difference in cure rates between ceftriaxone and gentamicin.

Protocol deviations

The proportion of participants reporting protocol deviations was similar between treatment groups and most deviations were considered to be minor. There was an imbalance in the proportion of participants who did not receive their randomised medication. However, it was considered unlikely that this was as a

result of selection bias or knowledge of the treatment allocation. It is therefore believed that the protocol deviations did not affect the validity of the trial.

Results in context

Two systematic reviews[23,24] have reported wide variation in the efficacy of gentamicin for the treatment of gonorrhoea and highlighted the low quality of the previous studies, which had a significant risk of bias. A more recent high-quality non-comparative trial evaluated i.m. gentamicin (240 mg) combined with oral azithromycin (2 g) and reported a cure rate of 100% (lower 95% CI 98.5%).[25] The design of this trial is compared with that of the G-TOG trial in *Table 33*. An updated literature search (see *Appendix 2*) was performed but no further studies evaluating gentamicin for the treatment of gonorrhoea were identified.

There are a number of possible explanations for the higher cure rate reported by Kirkcaldy *et al.*[25] In the diagnosis of gonorrhoea, culture is less sensitive (≈80%) than NAAT; this is most apparent for pharyngeal infections (30% sensitivity) and rectal infections (50% sensitivity).[63,64] This reduced ability to isolate extragenital *N. gonorrhoeae* is likely to be the reason for the small number of pharyngeal and rectal infections that met the inclusion criteria for the Kirkcaldy *et al.*[25] study.

In the G-TOG trial, we found the efficacy of gentamicin to be higher for genital infections (94%) than for extragenital infections (pharynx 80% and rectum 90%), which may partially explain the higher overall cure rate in the Kirkcaldy *et al.*[25] study (100%, 95% CI 98.5% to 100%), in which the majority of infections were genital.

There is also a theoretical possibility that the lower sensitivity of culture could fail to identify persistent infection following unsuccessful treatment if transient suppression of *N. gonorrhoeae* occurred (below the level detectable by culture) but without cure.

The role of azithromycin in the treatment of gonorrhoea

Participants in the G-TOG trial received dual treatment: 1 g of azithromycin combined with either ceftriaxone or gentamicin. Azithromycin has previously been shown to be effective for the treatment of gonorrhoea using a single dose of either 1 g or 2 g,[65–68] although these previous studies used culture to diagnose infection and assess cure, which, as outlined in the previous section, is less sensitive than NAAT.

TABLE 33 Study design for Kirkcaldy *et al.*[25] compared with the G-TOG trial

	Study	
Design	Kirkcaldy *et al.*[25]	G-TOG trial
Number of participants assigned to gentamicin treatment	309	358
Number of participants receiving gentamicin who were included in the primary analysis	157	292
Gentamicin dose (mg)	240	240
Azithromycin dose (g)	2	1
Diagnostic criteria	Positive culture for *N. gonorrhoeae*	Positive NAAT for *N. gonorrhoeae* or positive Gram stain on microscopy
Primary end point	Negative culture 10–17 days after treatment	Negative NAAT 14 days after treatment
Number of participants with pharyngeal infection receiving gentamicin	10	128
Number of participants with rectal infection receiving gentamicin	1	147

Azithromycin resistance and treatment failure has subsequently been reported in a number of geographical locations.[69–73] In the UK, azithromycin-resistant *N. gonorrhoeae* has been detected intermittently since 2004,[74,75] with an ongoing outbreak of high-level azithromycin-resistant isolates identified in England since 2014.[76] The Gonococcal Resistance to Antimicrobials Surveillance Programme reported that 10% of gonococcal isolates in England and Wales had a MIC of > 0.5 mg/l in 2015, indicating probable resistance.[3]

In the G-TOG trial, participant treatment failure occurred in 6% of genital infections, 10% of rectal infections and 20% of pharyngeal infections in those who received gentamicin plus azithromycin, suggesting that oral azithromycin given as a 1-g dose may be suboptimal, particularly for extragenital gonorrhoea. The large majority of gonococcal isolates from participants in the G-TOG trial [290/305 (95%)] had azithromycin MICs within the non-resistant range (≤ 0.5 mg/l). Of the 15 isolates with a MIC of > 0.5 mg/l, two (13%) were from participants who had treatment failure. The majority of treatment failures overall [14/20 (70%)] occurred in participants who had isolates with a MIC of ≤ 0.25 mg/l. Sixty participants harboured an isolate with an azithromycin intermediate MIC of 0.5 mg/l, of whom four (7%) had treatment failure. Thus, we found in vitro azithromycin resistance was only partially predictive of treatment failure. The limited association between MIC and treatment efficacy has been reported by others.[77,78] It is possible that a higher dose of azithromycin (2 g), as was used in the Kirkcaldy *et al.*[25] study, would have been more effective, although without a direct comparative study this is speculative, especially for the treatment of pharyngeal gonorrhoea.

The use of a 1-g dose of azithromycin as monotherapy has also been reported to potentially induce resistance in *N. gonorrhoeae*, with a substantial increase in the MIC following treatment.[79,80]

The use of a 2-g dose of azithromycin combined with gentamicin was associated with a high incidence of gastrointestinal side effects in the Kirkcaldy *et al.*[25] study, with nausea reported by 26% of participants and vomiting by 10%. In the G-TOG trial, the 1-g dose was better tolerated: 14% of participants reported nausea and 4% reported vomiting, which is consistent with previous studies.[68] An extended-release formulation of azithromycin is available that may reduce the incidence of side effects and improve tolerability but there are limited data directly comparing its AE profile with that of the immediate-release formulation.[81,82]

The current UK and US gonorrhoea treatment guidelines recommend dual therapy with a regimen containing oral azithromycin as a 1-g single dose.[6] Our findings, which are the first to use the more sensitive NAATs to assess microbiological clearance, suggest that this component of treatment may be suboptimal, particularly for extragenital gonococcal infections.

Injection site pain

Participants receiving gentamicin reported more severe injection site pain than those receiving ceftriaxone (median VAS score 31.5 and 15.0, respectively), with resolution of pain occurring within a median of 1 hour for ceftriaxone and 1.5 hours for gentamicin. The site of injection and the needle gauge were not prespecified in the trial but would usually be the same for both antibiotics. Ceftriaxone is manufactured as a powder preparation that is reconstituted with lidocaine, resulting in an injection volume of approximately 2 ml for a 500-mg dose.[83] Gentamicin is manufactured as a solution: a 240-mg dose equates to an injection volume of 6 ml.[84] It is likely that this larger volume of injection led to participants who received gentamicin reporting more severe local site pain. In addition, the local anaesthetic effect of lidocaine in those receiving ceftriaxone is likely to have reduced the discomfort following injection.

Safety

Ceftriaxone and gentamicin were generally well tolerated; with a similar proportion of AEs reported in both treatment arms. Gastrointestinal side effects were the most commonly reported: nausea was reported by 12% (38/320) of those who received ceftriaxone and 14% (41/298) of those who received gentamicin. The majority of these side effects were classified as grade 1 (able to eat normally), with only 2% in each treatment group (ceftriaxone 8/320, gentamicin 5/298) being classified as grade 2 (oral intake significantly

decreased). There were no grade 3 events (no significant oral intake or requiring intravenous fluids) and nausea resolved within a median of 3 hours following treatment in both treatment groups. Vomiting was reported by 1% (3/320) of those who received ceftriaxone and 4% (12/298) of those who received gentamicin.

Ceftriaxone and gentamicin are licensed medications that have well-recognised safety profiles. Nausea and vomiting are uncommon side effects of ceftriaxone (range of incidence rate: ≥ 1/1000 to < 1/100)[83] and have been reported in association with gentamicin,[84] but are common following the use of oral azithromycin (≥ 1/100 to < 1/10).[85] It is, therefore, probable that the gastrointestinal side effects reported were principally caused by azithromycin, although the higher reported rate of vomiting in those receiving gentamicin (4%, compared with 1% for ceftriaxone) suggests that gentamicin may also have been a contributing factor.

Dizziness or unsteadiness was reported in 7% of participants who received their allocated treatment (ceftriaxone 24/302, gentamicin 21/298) but was classified as grade 1 (not interfering with function) in the large majority (ceftriaxone 20/24, gentamicin 19/21). One participant who received ceftriaxone reported grade 4 dizziness (bedridden or disabled).

Dizziness is uncommon (≥ 1/1000 to < 1/100) following treatment with azithromycin or ceftriaxone.[83,85] Gentamicin is potentially vestibulotoxic;[86] it can cause damage to the vestibular apparatus, initially affecting the cristae and progressing to the striolar regions of the maculae,[87] and can cause dizziness, ataxia and nystagmus. Most gentamicin studies have used a prolonged course of treatment and the safety of a single dose is less well characterised, but a recent systematic review of single-dose therapy found vestibulotoxicity to be rare,[88] which is consistent with the G-TOG trial findings.

Gentamicin can also cause renal impairment following reuptake of the drug in the proximal renal tubule, where it leads to a locally high renal drug concentration.[89] The recent review of AEs of gentamicin reported that a transient rise in creatinine was common following a single dose of gentamicin, although many of the relevant studies were in elderly, surgical patients, which may not be directly applicable to the G-TOG trial population.[88] In the G-TOG trial participants, we found a median change in eGFR that was similar in both treatment groups [ceftriaxone –1.3 ml/minute/1.73 m^2 (IQR –6.7–4.3 ml/minute/1.73 m^2), gentamicin –1.4 ml/minute/1.73 m^2 (IQR –6.9–3.8 ml/minute/1.73 m^2)]. This magnitude of change is not considered to be of clinical importance. A small number of participants (2%) experienced a change of > 30% in creatinine level following treatment but, despite this, remained within or just above the upper limit of normal.

The results of the trial were presented to the PPI representatives and their feedback was sought. They considered the study results to be reassuring regarding the safety of gentamicin and that using gentamicin as a second-line therapy in those unable to receive ceftriaxone would be acceptable.

Strengths and limitations

The G-TOG trial was delivered through a registered clinical trials unit and had a robust design resulting in well-balanced treatment arms and a low risk of bias. The trial was pragmatic in design and likely to be relevant to clinical practice in the UK and other countries with similar health-care systems. It included symptomatic and asymptomatic patients, patients with a wide age range, HIV-positive and HIV-negative individuals, men and women, heterosexual men and MSM and a wide variety of ethnic groups, which provides generalisability for our findings. Recruitment was completed to time and target and the sample size was large enough to provide a clear result.

The potential for treatment unblinding was low. It is possible that a participant who had previously received treatment with ceftriaxone (41% of participants were known to have had at least one previous episode of gonorrhoea) may have recognised their therapy and that this could have affected the reporting of subjective outcomes. However, both treatments were given by injection and we would consider it unlikely that participants distinguished between treatments based on their preparation or administration.

The reporting of side effects was similar in both treatment arms. We were not aware of any clinicians being unblinded.

The trial design allowed for a loss to follow-up of ≤ 10% of participants (90% of participants were to be available for analysis) but data were available for analysis of the primary end point in only 85% (306/362) of participants allocated to ceftriaxone and 82% (292/358) of those allocated to gentamicin. The sample size for the trial had been calculated to provide 90% power and it was felt that, despite fewer participants having data for the primary outcome measure, the result was robust as all sensitivity analyses were supportive. The G-TOG trial was designed and powered as a non-inferiority trial, which prevents us making a firm conclusion about the superiority of ceftriaxone, but the size of the risk difference and consistency of our findings in secondary sensitivity analyses suggest that it is likely that gentamicin is less effective than ceftriaxone. The pre-trial estimate of 10% for loss to follow-up was based on a patient return rate of 80–85% in routine clinical practice, with an expectation that with closer monitoring, visit reminders and a monetary incentive this could be increased to 90%. Our experience suggests that during trial design greater allowance should have been made for incorrect sampling at follow-up when estimating the number of patients with available primary end-point data.

The main factor limiting recruitment was research capacity within sexual health centres, for example availability of research nurses and experienced PIs, which was exacerbated by widespread structural reform in the clinical service that occurred during the time of the G-TOG trial. This resulted in some centres not meeting their pre-trial estimates for recruitment. The trial has demonstrated a need to improve engagement in research and increase research expertise in the area of sexual health.

Unexpectedly, a number of participants who were recruited to the trial were found to have a negative AC2 NAAT at their baseline visit [ceftriaxone arm 12% (45/362); gentamicin arm 12% (42/358)]. These were all individuals who had been previously tested and found to be positive on NAAT, but who had not yet received treatment and had been recalled to the clinic to be given antibiotic therapy. In normal clinical practice, a repeat NAAT would not be performed before treatment if a previous test result was positive. The apparently spontaneous reversion from positive to negative NAAT observed in some trial participants could result from one of the following:

- An initial false-positive NAAT before trial entry. NAAT for *N. gonorrhoeae* has a high specificity, particularly for genital specimens, which makes this unlikely.[90]
- A false-negative NAAT at the baseline trial visit. NAAT for *N. gonorrhoeae* has a high sensitivity, which makes this also unlikely.[90]
- Natural clearance of gonorrhoea without antibiotic therapy. It is not known how often this occurs because it would be unethical to knowingly leave gonorrhoea untreated and, as noted above, repeat testing following a positive test result before treatment is not routine practice. In one natural history study, none of 16 women with gonorrhoea had spontaneous clearance over a 5- to 11-week period.[91] In contrast, van Liere *et al.*[92] reported natural clearance of 20% (5/25) of gonococcal infections in a median interval of 11 days between initial testing and returning for follow-up.

The occurrence of 12% of participants with negative tests at their baseline visit does not bias our results since they were equally distributed between the treatment arms. A lack of bias is also supported by the secondary sensitivity analysis that excluded these participants and that was consistent in demonstrating that gentamicin was not non-inferior to ceftriaxone (risk difference –7.1%, 95% CI –11.4% to –2.8%).

The efficacy of antibiotic therapy for gonorrhoea varies over time as different resistant subtypes of infection develop and circulate within a population. Our findings are therefore applicable only to the UK or similar settings at the present time; any future interpretation will need to account for changes in antimicrobial susceptibility. For example, if high-level resistance to ceftriaxone subsequently develops, resulting in a high rate of treatment failure, then gentamicin may become appropriate first-line therapy. Equally, if future circulating subtypes of gonorrhoea become highly resistant to gentamicin, its use would be inappropriate.

Chapter 6 Conclusions

The G-TOG trial compared single-dose gentamicin (240 mg) with single-dose ceftriaxone (500 mg) for the treatment of gonorrhoea and found that non-inferiority of gentamicin to ceftriaxone could not be demonstrated. Gentamicin led to microbiological cure in 94% of participants with genital infection, suggesting that its use would be appropriate as second-line therapy, but cure rates were lower for infections in the rectum (90% cure rate) and pharynx (80% cure rate). Single-dose gentamicin was well tolerated.

Implications for health care

The G-TOG trial has clearly demonstrated that gentamicin cannot be considered to be non-inferior to ceftriaxone, with the largest risk differences in cure being observed in patients with extragenital gonorrhoea. It is, therefore, probable that clinicians will wish to continue to use ceftriaxone (plus azithromycin) as their preferred first-line therapy. However, gentamicin (plus azithromycin) achieved a cure rate of 94% for genital gonorrhoea and its use in patients who are allergic, intolerant or resistant to ceftriaxone would be acceptable. The lower cure rates for rectal (90%) and pharyngeal (80%) infections make gentamicin a less attractive treatment option, but antibiotics are generally less effective at these sites and gentamicin may still be useful as a second- or third-line therapy. A repeat test for gonorrhoea to ensure microbiological cure would be advisable following gentamicin therapy.

The lack of correlation between gentamicin MIC values, obtained on in vitro sensitivity testing, and microbiological cure suggests that these should be interpreted with caution and that they have limited predictive value in clinical practice. There were too few failures with ceftriaxone to comment on any association with in vitro MIC testing. For azithromycin, there was an association between treatment failure and in vitro MICs but it was relatively weak, which limits its utility in clinical practice.

A clinically significant proportion of participants in the gentamicin treatment arm failed therapy, despite also receiving 1 g of oral azithromycin; this suggests that, independent of the efficacy of gentamicin, azithromycin at this dose may be suboptimal, especially for extragenital gonorrhoea. Although the number of culture isolates was limited, a modest trend towards a higher azithromycin MIC in this group suggests that a higher dose of azithromycin (e.g. 2 g) might be more effective but with the caveat that the tolerability of this dose is poor as a result of gastrointestinal side effects. Azithromycin is currently used to reduce the development of resistance and 'protect' ceftriaxone by providing microbiological cover if cephalosporin resistance develops. The observation in the G-TOG trial that a 1-g dose of azithromycin, even in combination with gentamicin, has a significant failure rate raises concerns about the effectiveness of this approach.

The results of the economic evaluation demonstrate that gentamicin is likely to be more costly than ceftriaxone in the treatment of gonorrhoea. This means that there is no evidence that gentamicin is non-inferior to ceftriaxone in the treatment of gonorrhoea, nor is there evidence that it is cost neutral. However, the economic analysis was necessarily restricted because it was not possible to fully take into account the potential costs associated with AMR in gonorrhoea, nor the potential value associated with preserving the effectiveness of ceftriaxone.

A single dose of 240 mg of gentamicin was found to cause few AEs and had a safety profile comparable to that of ceftriaxone. In particular, there was no increase in the frequency of vestibulocochlear or renal side effects, which have been associated with prolonged courses of gentamicin. This provides reassurance for the safe use of gentamicin in clinical practice. Participants receiving i.m. gentamicin reported more injection site pain than those receiving ceftriaxone, most probably related to the larger volume of injection. The pain resolved fully within a few hours for the majority of individuals but an alternative would be to give two separate 3-ml injections of gentamicin intramuscularly into each buttock rather than a single 6-ml injection, although PPI input during trial design suggested that a single injection might be preferred.

Recommendations for research

The lack of a strong association between the in vitro assessment of gonococcal resistance to gentamicin and clinical response highlights a need to explore further why gentamicin treatment is not effective in some patients and whether or not its efficacy can predicted. Whole-genome sequencing will allow the identification of specific subtypes of *N. gonorrhoeae*, which may provide insights into the mechanisms of resistance and detect potential markers of resistance.

Antibiotic resistance in *N. gonorrhoeae* is common and treatment options remain limited. The development of a preventative or therapeutic vaccine is therefore a priority and greater understanding of the immune response to infection is required to facilitate this. The collection and storage of before-and-after serum samples, and matched NAAT and culture samples in the G-TOG trial, will facilitate this future work.

The role of multiple different gonococcal infections within a single individual in the transmission of resistance is poorly understood. Transfer of resistance genes between *N. gonorrhoeae* is common and the archive of isolates collected in the G-TOG trial will allow an exploration of how frequently multiple infections occur and their potential role in the spread of resistance.

Azithromycin used as a 1-g dose to treat gonorrhoea was associated with a significant treatment failure rate, suggesting that it is not the optimal antibiotic to use as part of dual therapy designed to slow the spread of resistance. Further studies are required to evaluate alternative 'second agents', including a 2-g dose of azithromycin using an extended spectrum formulation that might improve tolerability.

Further research is needed to evaluate the potential costs associated with AMR in gonorrhoea. In addition, there needs to be further development of appropriate methods for economic evaluations when AMR is likely to be an issue. Such work will benefit from case studies, and examining the wider implications associated with alternative treatments for gonorrhoea would provide a valuable exemplar to aid in the development of general approaches.

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Health economics

Louise Jackson and Tracy Roberts at the University of Birmingham provided health economics expertise to the trial.

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Publications

Ross JD, Lewis DA. Cephalosporin resistant *Neisseria gonorrhoeae*: time to consider gentamicin? *Sex Transm Infect* 2012;**88**:6–8.

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Data-sharing statement

All requests for anonymised data should be addressed to the corresponding author.

Patient data

This work uses data provided by patients and collected by the NHS as part of their care and support. Using patient data is vital to improve health and care for everyone. There is huge potential to make better use of information from people's patient records, to understand more about disease, develop new treatments, monitor safety, and plan NHS services. Patient data should be kept safe and secure, to protect everyone's privacy, and it's important that there are safeguards to make sure that it is stored and used responsibly. Everyone should be able to find out about how patient data are used. #datasaveslives You can find out more about the background to this citation here: https://understandingpatientdata.org.uk/data-citation.

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Appendix 1 Summary of trial amendments

Amendment reference and date	Amendment details	Previous version number and date	New version number and date
Substantial amendment 06, 18 June 2015	Removal of PK substudy and amendment to eligibility criteria	1.0, 27 May 2014	2.0, 17 June 2015
	PIS	1.0, 4 July 2014	2.0, 4 June 2015
	Informed consent form	1.0, 27 May 2014	2.0, 4 June 2015
Substantial amendment 08, 22 October 2015	Change of RSI	80 mg of cidomycin or a 2-ml solution for injection (date of revision of text: 19 June 2013)	80 mg of cidomycin or a 2-ml solution for injection (date of revision of text: 29 June 2015)
Substantial amendment 09, 21 December 2015	Amendment to PIS to clarify sending of AC2 NAAT swabs to STBRU[a]	2.0, 4 June 2015	3.0, 21 December 2015

PK, pharmacokinetics; RSI, Reference Safety Information; STBRU, Sexually Transmitted Bacteria Reference Unit.
a Owing to STBRU closure during the trial, swabs were analysed by PHE.

Appendix 2 Search strategy for studies assessing the treatment of gonorrhoea with gentamicin

MEDLINE and EMBASE

Date range searched: 1 March 2013 to 22 April 2017.

Date searched: 22 April 2017

One hundred and fifty-six references identified and reviewed

Search strategy

1. gonorrhoea.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
2. gonorrhea.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
3. Neisseria gonorrhoeae.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
4. N gonorrhoeae.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
5. 1 or 2 or 3 or 4
6. gentamicin.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
7. gentamycin.mp. [mp = ti, ab, sh, hw, tn, ot, dm, mf, dv, kw, nm, kf, px, rx, an, ui]
8. 6 or 7
9. 5 and 8
10. limit 9 to yr = '2013-Current'
11. remove duplicates from 10

Appendix 3 Additional tables, listings and figures

TABLE 34 Genital clearance of *N. gonorrhoeae*, by sex

	Sex, *n* (%)			
	Male		Female	
Clearance	Ceftriaxone	Gentamicin	Ceftriaxone	Gentamicin
Number with infection at genital site	107	142	47	32
Cleared of *N. gonorrhoeae*	106 (99)	132 (93)	45 (96)	31 (97)
Not cleared of *N. gonorrhoeae*	1 (1)	10 (7)	2 (4)	1 (3)

TABLE 35 Summary of symptom resolution

	Treatment group, *n* (%)					
	Ceftriaxone (*N* = 362)			Gentamicin (*N* = 358)		
	Symptom present at baseline			Symptom present at baseline		
Symptom	No	Yes	Not known	No	Yes	Not known
Genital discharge at 2 weeks						
No	191 (53)	122 (34)	0 (0)	154 (43)	139 (39)	0 (0)
Yes	1 (< 0.5)	7 (2)	0 (0)	1 (< 0.5)	8 (2)	0 (0)
Not known	17 (5)	24 (7)	0 (0)	24 (7)	32 (9)	0 (0)
Dysuria at 2 weeks						
No	214 (59)	104 (29)	0 (0)	174 (49)	116 (32)	0 (0)
Yes	1 (< 0.5)	2 (1)	0 (0)	0 (0)	12 (3)	0 (0)
Not known	22 (6)	19 (5)	0 (0)	30 (8)	26 (7)	0 (0)
Anorectal pain at 2 weeks						
No	306 (85)	12 (3)	0 (0)	294 (82)	5 (1)	0 (0)
Yes	2 (1)	1 (< 0.5)	0 (0)	1 (< 0.5)	2 (1)	0 (0)
Not known	39 (11)	2 (1)	0 (0)	55 (15)	1 (< 0.5)	0 (0)
Rectal discharge at 2 weeks						
No	308 (85)	11 (3)	0 (0)	294 (82)	6 (2)	0 (0)
Yes	1 (< 0.5)	1 (< 0.5)	0 (0)	0 (0)	2 (1)	0 (0)
Not known	41 (11)	0 (0)	0 (0)	54 (15)	2 (1)	0 (0)
Sore throat at 2 weeks						
No	269 (74)	42 (12)	0 (0)	253 (71)	42 (12)	0 (0)
Yes	5 (2)	5 (1)	0 (0)	4 (1)	3 (1)	0 (0)
Not known	35 (10)	6 (2)	0 (0)	49 (14)	7 (2)	0 (0)

continued

TABLE 35 Summary of symptom resolution (*continued*)

	Treatment group, *n* (%)					
	Ceftriaxone (*N* = 362)			Gentamicin (*N* = 358)		
	Symptom present at baseline			Symptom present at baseline		
Symptom	No	Yes	Not known	No	Yes	Not known
Rectal bleeding at 2 weeks						
No	310 (86)	7 (2)	0 (0)	294 (82)	7 (2)	0 (0)
Yes	3 (1)	1 (< 0.5)	0 (0)	1 (< 0.5)	0 (0)	0 (0)
Not known	40 (11)	1 (< 0.5)	0 (0)	55 (15)	1 (< 0.5)	0 (0)
Tenesmus at 2 weeks						
No	313 (86)	7 (2)	0 (0)	298 (83)	3 (1)	0 (0)
Yes	0 (0)	1 (< 0.5)	0 (0)	1 (< 0.5)	0 (0)	0 (0)
Not known	41 (11)	0 (0)	0 (0)	55 (15)	1 (< 0.5)	0 (0)
Constipation at 2 weeks						
No	302 (83)	10 (3)	0 (0)	293 (82)	3 (1)	0 (0)
Yes	8 (2)	1 (< 0.5)	0 (0)	5 (1)	1 (< 0.5)	0 (0)
Not known	41 (11)	0 (0)	0 (0)	56 (16)	0 (0)	0 (0)
Intermenstrual bleeding at 2 weeks						
No	53 (15)	8 (2)	1 (< 0.5)	41 (11)	5 (1)	0 (0)
Yes	2 (1)	1 (< 0.5)	0 (0)	2 (1)	0 (0)	0 (0)
Not known	4 (1)	0 (0)	0 (0)	15 (4)	2 (1)	0 (0)
Post-coital bleeding at 2 weeks						
No	58 (16)	5 (1)	0 (0)	40 (11)	5 (1)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	6 (2)	0 (0)	0 (0)	18 (5)	2 (1)	0 (0)

TABLE 36 Summary of symptom resolution for females

	Treatment group, *n* (%)					
	Ceftriaxone (*N* = 69)			Gentamicin (*N* = 65)		
	Symptom present at baseline			Symptom present at baseline		
Symptom	No	Yes	Not known	No	Yes	Not known
Genital discharge at 2 weeks						
No	35 (51)	24 (35)	0 (0)	30 (46)	15 (23)	0 (0)
Yes	1 (1)	5 (7)	0 (0)	1 (2)	4 (6)	0 (0)
Not known	3 (4)	1 (1)	0 (0)	8 (12)	7 (11)	0 (0)
Dysuria at 2 weeks						
No	45 (65)	20 (29)	0 (0)	42 (65)	6 (9)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	2 (3)	0 (0)
Not known	3 (4)	1 (1)	0 (0)	11 (17)	4 (6)	0 (0)

TABLE 36 Summary of symptom resolution for females (*continued*)

	Treatment group, *n* (%)					
	Ceftriaxone (*N* = 69)			Gentamicin (*N* = 65)		
	Symptom present at baseline			Symptom present at baseline		
Symptom	No	Yes	Not known	No	Yes	Not known
Anorectal pain at 2 weeks						
No	63 (91)	1 (1)	0 (0)	48 (74)	2 (3)	0 (0)
Yes	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	0 (0)	0 (0)
Rectal discharge at 2 weeks						
No	64 (93)	1 (1)	0 (0)	49 (75)	1 (2)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	0 (0)	0 (0)
Sore throat at 2 weeks						
No	56 (81)	8 (12)	0 (0)	41 (63)	9 (14)	0 (0)
Yes	1 (1)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	12 (18)	3 (5)	0 (0)
Rectal bleeding at 2 weeks						
No	63 (91)	2 (3)	0 (0)	50 (77)	0 (0)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	0 (0)	0 (0)
Tenesmus at 2 weeks						
No	64 (93)	1 (1)	0 (0)	49 (75)	0 (0)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	1 (2)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	0 (0)	0 (0)
Constipation at 2 weeks						
No	58 (84)	4 (6)	0 (0)	48 (74)	0 (0)	0 (0)
Yes	3 (4)	0 (0)	0 (0)	1 (2)	1 (2)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	0 (0)	0 (0)
Intermenstrual bleeding at 2 weeks						
No	53 (77)	8 (12)	1 (1)	41 (63)	5 (8)	0 (0)
Yes	2 (3)	1 (1)	0 (0)	2 (3)	0 (0)	0 (0)
Not known	4 (6)	0 (0)	0 (0)	15 (23)	2 (3)	0 (0)
Post-coital bleeding at 2 weeks						
No	58 (84)	5 (7)	0 (0)	40 (62)	5 (8)	0 (0)
Yes	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Not known	6 (9)	0 (0)	0 (0)	18 (28)	2 (3)	0 (0)

TABLE 37 Summary of symptom resolution for males

	Treatment group, *n* (%)			
	Ceftriaxone (*N* = 293)		Gentamicin (*N* = 292)	
	Symptom present at baseline		Symptom present at baseline	
Symptom	No	Yes	No	Yes
Genital discharge at 2 weeks				
No	156 (53)	98 (33)	123 (42)	124 (42)
Yes	0 (0)	2 (1)	0 (0)	4 (1)
Not known	14 (5)	23 (8)	16 (5)	25 (9)
Dysuria at 2 weeks				
No	169 (58)	84 (29)	131 (45)	110 (38)
Yes	1 (< 0.5)	2 (1)	0 (0)	10 (3)
Not known	19 (6)	18 (6)	19 (7)	22 (8)
Anorectal pain at 2 weeks				
No	243 (83)	11 (4)	245 (84)	3 (1)
Yes	1 (< 0.5)	1 (< 0.5)	1 (< 0.5)	2 (1)
Not known	35 (12)	2 (1)	40 (14)	1 (< 0.5)
Rectal discharge at 2 weeks				
No	244 (83)	10 (3)	244 (84)	5 (2)
Yes	1 (< 0.5)	1 (< 0.5)	0 (0)	2 (1)
Not known	37 (13)	0 (0)	39 (13)	2 (1)
Sore throat at 2 weeks				
No	213 (73)	34 (12)	211 (72)	33 (11)
Yes	4 (1)	5 (2)	4 (1)	3 (1)
Not known	31 (11)	6 (2)	37 (13)	4 (1)
Rectal bleeding at 2 weeks				
No	247 (84)	5 (2)	243 (83)	7 (2)
Yes	3 (1)	1 (< 0.5)	1 (< 0.5)	0 (0)
Not known	36 (12)	1 (< 0.5)	40 (14)	1 (< 0.5)
Tenesmus at 2 weeks				
No	249 (85)	6 (2)	248 (85)	3 (1)
Yes	0 (0)	1 (< 0.5)	0 (0)	0 (0)
Not known	37 (13)	0 (0)	40 (14)	1 (< 0.5)
Constipation at 2 weeks				
No	244 (83)	6 (2)	244 (84)	3 (1)
Yes	5 (1)	1 (< 0.5)	4 (1)	0 (0)
Not known	37 (13)	0 (0)	41 (14)	0 (0)

TABLE 38 Baseline data by treatment arm and availability of primary outcome

Characteristic	Treatment group			
	Ceftriaxone		Gentamicin	
	Without clearance data ($N = 56$)	With clearance data ($N = 306$)	Without clearance data ($N = 66$)	With clearance data ($N = 292$)
Age at randomisation (years)				
Mean (SD)	28.6 (8.9)	30.5 (10.3)	27.8 (8.7)	31.1 (10.1)
Median (25th percentile, 75th percentile)	26.2 (22.2, 32.1)	27.7 (22.7, 35.2)	25.8 (21.7, 31.6)	29 (23.2, 35.9)
Minimum, maximum	18.7, 57.4	16.1, 70.2	16.5, 51.1	17.1, 68.4
Sex, *n* (%)				
Male	50 (89)	243 (79)	47 (71)	245 (84)
Female	6 (11)	63 (21)	19 (29)	46 (16)
Other	0 (0)	0 (0)	0 (0)	1 (< 0.5)
Ethnicity, *n* (%)				
White	34 (61)	207 (68)	47 (71)	208 (71)
Black	11 (20)	42 (14)	9 (14)	39 (13)
Asian	5 (9)	21 (7)	3 (5)	15 (5)
Mixed race	4 (7)	23 (8)	7 (11)	19 (7)
Other	2 (4)	13 (4)	0 (0)	11 (4)
Country of birth, *n* (%)				
UK	38 (68)	220 (72)	51 (77)	202 (69)
Other	18 (32)	86 (28)	15 (23)	90 (31)
If other, region				
Europe (non-UK)	4 (7)	14 (5)	4 (6)	10 (3)
North America	1 (2)	17 (6)	3 (5)	11 (4)
Asia Pacific	8 (14)	43 (14)	5 (8)	51 (17)
Latin America	1 (2)	6 (2)	1 (2)	10 (3)
Middle East	1 (2)	1 (< 0.5)	1 (2)	4 (1)
Africa	3 (5)	5 (2)	1 (2)	4 (1)
Creatinine level (μmol/l)				
Mean (SD)	78.6 (18)	78.6 (14.9)	74.2 (13)	79.1 (16.2)
Median (25th percentile, 75th percentile)	76 (67, 87)	78 (69, 88)	72 (63.5, 84)	77 (69, 87)
Minimum, maximum	42, 124	45, 137	51, 104	26, 154
n	51	292	52	280
Medical history, *n* (%)				
Diabetes mellitus	0 (0)	3 (1)	0 (0)	1 (< 0.5)
Otitis media	0 (0)	9 (3)	1 (2)	6 (2)
Renal disease	0 (0)	3 (1)	1 (2)	3 (1)
Liver disease	1 (2)	7 (2)	2 (3)	3 (1)
Immunodeficiency	5 (9)	29 (9)	2 (3)	22 (8)
Any known drug allergies	2 (4)	15 (5)	7 (11)	18 (6)

continued

TABLE 38 Baseline data by treatment arm and availability of primary outcome (*continued*)

Characteristic	Treatment group			
	Ceftriaxone		Gentamicin	
	Without clearance data (*N* = 56)	With clearance data (*N* = 306)	Without clearance data (*N* = 66)	With clearance data (*N* = 292)
Participants with infection at each site, *n* (%)				
Genital	36 (64)	154 (50)	45 (68)	174 (60)
Pharyngeal	15 (27)	113 (37)	26 (39)	102 (35)
Rectal	22 (39)	137 (45)	28 (42)	119 (41)

SD, standard deviation.

TABLE 39 Adverse events

Description	Severity	Outcome	Treatment group
Pain radiating down left leg since injection. Difficulty standing	Moderate	Recovered/resolved	Ceftriaxone
Folliculitis	Mild	Recovered/resolved	Ceftriaxone
Very strong stomach ache	Mild	Recovered/resolved	Ceftriaxone
Ear pain	Mild	Unknown	Ceftriaxone
Right inner ear pain	Mild	Recovered/resolved	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Dyspepsia	Mild	Ongoing	Ceftriaxone
Occasional diarrhoea	Mild	Ongoing	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Cold/flu-like symptoms	Mild	Ongoing	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Diarrhoea	Moderate	Ongoing	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Tinitus	Mild	Recovered/resolved	Ceftriaxone
Creatinine level increased from 87 µmol/l in v1 on 15 January 2016 to 123 µmol/l in v2 on 3 February 2016	Mild	Ongoing	Ceftriaxone
Vulval thrush (candida)	Mild	Ongoing	Ceftriaxone
Loose stools	Mild	Recovered/resolved	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Diarrhoea	Mild	Recovered/resolved	Ceftriaxone
Grade 4 dizziness	Severe	Recovered/resolved	Ceftriaxone
Felt like been kicked by a horse	Mild	Recovered/resolved	Ceftriaxone
Bell's palsy	Mild	Ongoing	Ceftriaxone
Tonsillitis	Mild	Recovered/resolved	Ceftriaxone
Discomfort in left upper abdomen	Mild	Recovered/resolved	Ceftriaxone
Lethargy	Moderate	Recovered/resolved	Ceftriaxone

TABLE 39 Adverse events (*continued*)

Description	Severity	Outcome	Treatment group
Nausea	Mild	Recovered/resolved	Ceftriaxone
Running nose for 2 days	Mild	Recovered/resolved	Ceftriaxone
Fatigue	Moderate	Ongoing	Ceftriaxone
Chesty cough	Moderate	Ongoing	Ceftriaxone
Fatigue	Mild	Recovered/resolved	Ceftriaxone
Cellulitis	Mild	Ongoing	Ceftriaxone
Skin itch and bumps	Moderate	Ongoing	Ceftriaxone
Septic tonsillitis	Moderate	Recovered/resolved	Ceftriaxone
Pregnancy at visit 2	Mild	Recovered/resolved	Ceftriaxone
High creatinine level	Mild	Ongoing	Ceftriaxone
Migraine	Mild	Ongoing	Ceftriaxone
Diarrhoea	Mild	Ongoing	Ceftriaxone
Toothache	Mild	Ongoing	Ceftriaxone
Rectal bleeding	Mild	Recovered/resolved	Ceftriaxone
Right lower-leg cellulitis	Moderate	Ongoing	Ceftriaxone
Diarrhoea	Mild	Recovered/resolved	Ceftriaxone
Aching back	Mild	Ongoing	Ceftriaxone
Aching neck	Mild	Ongoing	Ceftriaxone
Bleeding on wiping post-BO (perianal warts)	Mild	Ongoing	Ceftriaxone
Fever (39.6 °C)	Mild	Recovered/resolved	Ceftriaxone
Loose stool	Mild	Recovered/resolved	Ceftriaxone
Increased anxiety	Mild	Recovered/resolved	Ceftriaxone
Flu-like symptoms	Mild	Recovered/resolved	Ceftriaxone
Sore throat	Mild	Recovered/resolved	Ceftriaxone
Headache	Mild	Recovered/resolved	Ceftriaxone
Creatinine level increased from 76 to 124 mg/dl	Mild	Recovered/resolved	Ceftriaxone
Raised creatinine level	Mild	Recovered/resolved	Ceftriaxone
Anorectal pain	Mild	Recovered/resolved	Ceftriaxone
Deranged creatinine level	Mild	Ongoing	Ceftriaxone
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Cold symptoms	Mild	Ongoing	Gentamicin
Abdominal pain	Mild	Recovered/resolved	Gentamicin
Lethargy	Mild	Recovered/resolved	Gentamicin
Mouth ulcers	Mild	Ongoing	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin

continued

TABLE 39 Adverse events (*continued*)

Description	Severity	Outcome	Treatment group
Headache	Moderate	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Bloated	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Severe	Recovered/resolved	Gentamicin
Viral URTI	Mild	Ongoing	Gentamicin
Visit 2 bloods: hyperkalaemia (potassium level 6.1). Rpt = 5.1. Likely to be artefactual	Moderate	Recovered/resolved	Gentamicin
Nausea	Mild	Recovered/resolved	Gentamicin
Dizziness	Mild	Recovered/resolved	Gentamicin
Nausea	Mild	Recovered/resolved	Gentamicin
Rash	Mild	Ongoing	Gentamicin
Sore throat	Mild	Ongoing	Gentamicin
Raised creatinine level at visit 2: 106 umol/l (grade: mild)	Mild	Ongoing	Gentamicin
Raised potassium level result at visit 1: 5.6 mmol/l	Mild	Recovered/resolved	Gentamicin
Rectal itching	Mild	Recovered/resolved	Gentamicin
Stomach cramps	Mild	Recovered/resolved	Gentamicin
Heartburn	Mild	Recovered/resolved	Gentamicin
Pain at injection site (buttock)	Mild	Ongoing	Gentamicin
Sickness	Severe	Recovered/resolved	Gentamicin
Pain at site of injection	Mild	Ongoing	Gentamicin
Raised creatinine level	Mild	Ongoing	Gentamicin
Left eye conjunctivitis	Mild	Unknown	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Ongoing	Gentamicin
Tonsillitis	Moderate	Recovered/resolved	Gentamicin
URTI	Moderate	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Stiff arms	Moderate	Ongoing	Gentamicin
Diarrhoea (one episode, type 6, no blood or mucous)	Mild	Recovered/resolved	Gentamicin
Diarrhoea (one episode, type 7, no blood or mucous)	Mild	Recovered/resolved	Gentamicin
Myalgia	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Diarrhoea	Mild	Recovered/resolved	Gentamicin
Bilateral flank pain – intermittent/stabbing	Mild	Recovered/resolved	Gentamicin
Back pain	Moderate	Recovered/resolved	Gentamicin

BO, bowel opening; URTI, upper respiratory tract infection.

TABLE 40 Concomitant medications

Drug name	Treatment group
Ceftriaxone, 500 mg stat	Gentamicin
Azithromycin, 1 g stat p.o.	Ceftriaxone
Azithromycin, 1 g p.o.	Ceftriaxone
Doxycycline	Ceftriaxone
Doxycycline	Ceftriaxone
Doxycycline	Gentamicin
Trimethoprim	Gentamicin
Ceftriaxone	Gentamicin
Doxycycline	Gentamicin
Doxycycline	Gentamicin
Doxycycline, 100 mg	Ceftriaxone
Metronidazole	Gentamicin
Ceftriazone	Gentamicin
Clarithromycin	Ceftriaxone
Doxycycline	Ceftriaxone
Doxycycline	Ceftriaxone
Ofloxacin	Gentamicin
Doxycycline	Ceftriaxone
Doxycycline	Gentamicin
Doxycycline, 100 mg b.i.d.	Gentamicin
Doxycycline	Gentamicin
Doxycycline	Gentamicin
Doxycycline	Ceftriaxone
Doxycycline	Ceftriaxone
Doxycycline	Gentamicin
Metronidazole, 400-mg tablet	Ceftriaxone
Azithromycin	Gentamicin
Doxycycline	Gentamicin
Doxycycline	Ceftriaxone

b.i.d., bis in die (twice a day); p.o., per os (by mouth); stat, statim.

TABLE 41 Protocol deviations recorded on the protocol deviation log

Details	Treatment group
Participant is heterosexual and a rectal swab was taken and there were no indications to take this	Gentamicin
Participant is heterosexual & a pharyngael swab was taken and there were no indications to take this	Gentamicin
wrong blood test requested = no creatinine done on pt	Ceftriaxone
No microscopy done on FU- NAAT and cultures taken only which were negative	Ceftriaxone
Creatinine not done as wrong test requested on form- too late to add on as blood destroyed after 7d	Ceftriaxone
Patient did not have full examiniation done at FU as was only oral GC pos	Gentamicin
Clinical examination not done at FU appt as patient asymptomatic needed for all patients though	Ceftriaxone
Examination not performed on Follow Up Visit	Ceftriaxone
Rectal GC culture not obtained on Visit 2	Ceftriaxone
Pt allergic to penicillin wrongly randomized	Ceftriaxone
Pt withdrawn due to change of clinicians decision. Pt treated for PID	Gentamicin
All tests on V1 obtained as per protocol partly discarded as Pt could not continue the study	Gentamicin
Pt randomized into the trial before microscopy results available – not eligible due to BV infection	Ceftriaxone
Creatinine test not performed by LAB CK done instead. Called the Lab the samples already destroyed	Gentamicin
Creatinine blood test not performed by Lab CK test done instead-contacting the Lab-sample destroyed	Ceftriaxone
oral NAAT & culture tests obtained on Visit 2 – while not required	Gentamicin
participant declined clinical examination at follow-up	Gentamicin
Creatinin result unavailable due to unlabled specimen	Ceftriaxone
Dose Administration Details not entered on Randomisation system by the injecting nurse	Ceftriaxone
isolate not saved	Gentamicin
VAS not done at baseline	Ceftriaxone
test result of recal culture not obtainable from lab	Gentamicin
test result of pharyngeal culture not obtainable from lab	Gentamicin
isolate not saved	Ceftriaxone
isolate not saved	Ceftriaxone
Pt declined urethral GC culture test on FU visit	Ceftriaxone
Gc not isolated	Ceftriaxone
Incorrect labelling of sample	Ceftriaxone
Oral NAAT not repeated on visit 2	Gentamicin
Oral Culture not taken on 2nd visit	Gentamicin
no creatinine results sample request lost in transit	Ceftriaxone
Patient declined rectal swab as no risk of infection he percieved	Gentamicin
Visit 2 culture sample not taken	Ceftriaxone
Creatine result unavailable sample not recieved by QEHB lab	Ceftriaxone
Study team aware pregnancy test not taken before randomisation. Patient given treatment when pregna[nt]	Gentamicin
unable to obtain blood samples creatinine result available from 05.10.16 = 80	Ceftriaxone
only creatinine blood taken unable to bleed patient for immune response samples	Ceftriaxone

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
BD NAATs from × 3 sites accidently discarded at baseline	Ceftriaxone
Pharangeal culture not sent at baseline in error	Ceftriaxone
There were not freezing isolates at this particular time	Gentamicin
U + E not sent for serum creatinine in error	Ceftriaxone
Urethral and rectal cultures not sent in error	Ceftriaxone
No throat NAAT/culture sent at visit 2 in error	Ceftriaxone
lab stopped freezing isolate at this time	Ceftriaxone
Visit 1 U + E sample not labelled so result unavailable	Gentamicin
Immune samples not sent at visit 2 as no kits available	Ceftriaxone
Aptima combo samples not sent at visit 2 in error	Ceftriaxone
VAS not completed by patient at visit 1 in error	Ceftriaxone
Lab was not keeping isolates	Gentamicin
U + E not sent at visit 2 in error	Gentamicin
VAS not done at visit 2 in error	Gentamicin
Urethral GC culture unable to exclude GC due to lab error	Gentamicin
follow-up was performed 13 post baseline thus fell before the 14 days post baseline required	Ceftriaxone
U + Es not taken. Pt IVDU and refused after immune samples taken	Gentamicin
Lab was not keeping isolates	Gentamicin
lab Stopped frezzing isolate at this tiem	Ceftriaxone
RECTAL SAMPLING NOT SEN IN ERROR	Gentamicin
Rectal testing not done at baseline in error	Gentamicin
rectal sampling not done in error	Ceftriaxone
VAS not completed at visit 2 in error	Ceftriaxone
Clinical lab did not save	Ceftriaxone
Patients clinic number not on tracking sheet so lab could not follow up result	Gentamicin
lost on subculture	Gentamicin
VAS not completed at visit 1 in error	Gentamicin
VAS not complete	Gentamicin
immune response not taken	Gentamicin
creatinine not taken	Gentamicin
Sample left in incubator for too long – unable to process in lab	Gentamicin
v 2 ocurred day12 as patietn unable to coemanother day	Gentamicin
Creatinine resutls not available due to lab error	Gentamicin
Follow up: incorrectly sampled pharynx in place of rectum	Ceftriaxone
Visual Analogue Scale not done at this visit	Ceftriaxone
Visit 2 2 weeks post visit 1 but not scheduled. No G-TOG delegated Dr available. Seen by clinic staf	Ceftriaxone
Immune study bloods not performed in error	Ceftriaxone

continued

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
Couldnt access MACRO db. Paper CRF not available some data not collected. Immune visit 2 blood ND	Ceftriaxone
Culture sample was not transferred to STBRU[a] – lab error	Ceftriaxone
No Side effects or use of NHS service info collected in error	Gentamicin
No Visit 2 immune study bloods collected in error	Gentamicin
baseline NAAT tests not obtained only pre-trial rectal NAAT +ve for GC. baseline culture was taken	Gentamicin
Culture sample was not transferred to STBRU[a] – lab error	Gentamicin
Throat sample not taken. Rectal sample not taken as patient did not admit to anal sex	Ceftriaxone
VAS not completed in error	Ceftriaxone
doxycycline prescribed in addition to azithromycin	Gentamicin
Doxycycline erroneously prescribed in addition to G-TOG drug/azithromycin	Gentamicin
failed to send urine sample for lab analysis	Ceftriaxone
Full sampling profile not taken on baseline visit. Rectal and urethral NAAT and cultures missing	Ceftriaxone
Culture sample was not transferred to STBRU.[a] Lab error	Gentamicin
rectal and urethral NAAT/ culture not taken at baseline. PI error	Gentamicin
Full sampling profile on baseline incomplete. Pharynx and urine NAAT/cultures missing. PI error	Ceftriaxone
Culture sample was not transferred to STBRU.[a] Lab error	Ceftriaxone
Full sampling profile on visit 1 incomplete. Urine and rectal NAAT/culture not taken	Ceftriaxone
rectal and throat culture not taken at baseline	Gentamicin
urine NAAT was missing. No results from the laboratory	Gentamicin
at TOC visit throat culture but not TMA was obtained. Pt was recalled TMA taken 4 days later	Gentamicin
lost to follow up. pt reattended for screen 23/1/16 but too late for study. All GC swabs negative	Gentamicin
urine sample was missing from the laboratory	Gentamicin
patient not keen on signing pt. 5 of consent. Discussed with [name] happy for data to be included	Ceftriaxone
incomplete sampling profile. Rectal NAAT/ culture not taken	Ceftriaxone
Culture sample was not transferred to STBRU[a] – lab error	Gentamicin
lost to follow up	Ceftriaxone
sampling error. rectal sample was not taken by mistake	Ceftriaxone
Culture sample was not transferred to STBRU[a] – lab error	Ceftriaxone
Culture sample was not transferred to STBRU[a] – lab error	Gentamicin
Patient decline rectal swab to be taken as never had rectal swabs before. No history of anal sex	Gentamicin
Culture sample was not transferred to STBRU[a] – lab error	Gentamicin
Culture sample was not transferred to STBRU.[a] Lab error	Ceftriaxone
lost to follow up	Ceftriaxone
lost to follow up	Gentamicin
patient declined rectal sample to be taken. no rectal contact on baseline	Gentamicin
Prescribed doxcycline from [clinic name]. Has had 3 doses before coming for G-TOG follow up appt	Gentamicin
lost to follow up	Gentamicin
Patient withdrew consent for study	Ceftriaxone

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
patient declined questionnaire and bloods at follow up visit due to time constraints	Ceftriaxone
pt received doxycyline for 1 week due to rectal chlamydia positive result	Ceftriaxone
Pt DNA TOC visit. emaield and siad he went to [clinic name] for tests on 17/8/16 & was all clear. No SEs	Gentamicin
Blood sample taken from participant on 20-FEB-2015 and deliverd to the lab for creatinine testing. M	Gentamicin
Some culture plates were incorrectly discarded in the laboratory and this subjects plate was amongst	Gentamicin
rectal culture sample was not transferred to STBRU.[a] ISOLATE WAS NOT SAVED	Gentamicin
NO CREATINE RESULT MARKED AS DONE	Gentamicin
NO REPEAT VVS DONE AT FOLLOW UP	Gentamicin
No result for urethral culture as marked as done but no result on server	Ceftriaxone
PHARYNX POSITIVE ON RESULT BUT ISOLOTE WAS NOT SAVED BY THE LABORATORY	Gentamicin
no result for creatitine marked as done but no result on server	Ceftriaxone
uretral sample not done two cultures were sent for pharynx both were reported as negative	Ceftriaxone
THE ISOLATE WAS NOT SAVED BY THE LAB FOROM THE CERVIX CULTURE THAT CAME BACK POSITIVE FOR GC	Gentamicin
patient did not attend follow up	Gentamicin
Blood sample too old to process	Ceftriaxone
pharynx result culture not available lab had discarded sample and apologized as this was a mistake	Ceftriaxone
CREATITINE BLOOD TOO OLD TO PROCESS	Gentamicin
culture not obtained at visit 2 my mistake sorry	Gentamicin
NO BLOOD KITS AVAILABLE FOR IMMUNE RESPONSE	Ceftriaxone
patient reattended on the 3NOV 2015 as she tested too early on follow up her results came back NEG	Ceftriaxone
Isolate was not saved from the cervix and sent to STBRU[a]	Ceftriaxone
DID NOT ATTEND HIS FOLLOW UP APPOINTMENT	Gentamicin
Did not attend follow up appointment	Gentamicin
NO BLOOD KITS AVAILABLE SO BLOODS NOT DONE FOR IMMUNE RESPONSE	Gentamicin
NO RESULT ON SERVER FOR CREATITNE BLOODS	Gentamicin
culture only taken from Pharynx at this visit	Gentamicin
patient attended follow up at 13 days as she could not attend aftre this date	Ceftriaxone
vvs not repeated as already had a positive result now aware a n additional one should have been don	Ceftriaxone
culture not repeated at follow up as all were negative sorry should have repeated	Ceftriaxone
natts were not repeated at this visit as were all done 05-10-2015 al cultures were done	Gentamicin
urethral sample positive but isilate was not saved by the labs and sent to mSTBTU	Ceftriaxone
NO RESULT AVAIALBLE FOR UREATHRAL CULTURE AS PLATE WAS UNLABELED	Ceftriaxone
creatitne blood taken but reported as too old to test	Ceftriaxone
ISOLATE WAS NOT SAVED BY THE LABS AND WAS NOT SENT TO STBRU[a]	Ceftriaxone
lost to follow up	Gentamicin
INSUFFICIENT SAMPLE FOR CREATITINE PATIENT DIFFICULT TO BLEED	Ceftriaxone
only pharynx sample was obtained at visit 1	Ceftriaxone

continued

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
sample lost in transport. Urine	Gentamicin
BLOODS DISPOSED AS UNBLINDED	Gentamicin
PROBLEM AT FIRST VISIT WITH CULTURES NOT INCUBATED FOR THE RIGHT AMOUNT OF TIME SO THESE WERE REPEAT	Ceftriaxone
result not available reported as plate not inoculated	Ceftriaxone
rectal sample not done	Ceftriaxone
did not attend follow up	Gentamicin
sample reported as unlabelled so not processed creatitine creatitne sample	Ceftriaxone
UREATHRAL SAMPLE ISOLATE WAS NOT SAVED AND SENT TO STBRU[a]	Ceftriaxone
RECTAL CULTURE ISOLATE WAS NOT SAVED AND SENT TO STBRU[a] BY THE LABS	Gentamicin
unable to obtain bloods 2 × attempts .Follow up visit 28-JAN-2016 CREATITNE AND IMMUNE RESPONSE BLOO	Ceftriaxone
creatine kinase result given not creatitne as requested	Ceftriaxone
THE ISOLATE WAS NOT SAVED BY THE LAB	Ceftriaxone
BLOOD WAS TAKEN BUT NOT PROCESSED AS ARRIVED AT LAB LATE	Ceftriaxone
no immune kits available	Gentamicin
creatitine result not available as wasnt recieved in lab for 24 hours and too old to process	Gentamicin
no culture result for cervix report states plate not innoculated	Gentamicin
At visit 1 patient left department with his urine so no sample collected at this visit	Gentamicin
lost to follow up	Gentamicin
the pharyngeal culture isolate was not saved by the lab	Ceftriaxone
DID NOT ATTEND FOLLOW UP	Ceftriaxone
patient declined to have bloods done	Ceftriaxone
patient declined to have bloods done	Ceftriaxone
did not attend follow up	Ceftriaxone
no creatitine result as patient declined bloods	Gentamicin
did not attend follow up	Ceftriaxone
did not attend follow up	Gentamicin
blood creatitine taken but no result on server	Gentamicin
did not attend follow up	Gentamicin
PATIENT ATTENDED FOR TOC AT 7 DAYS THEN ATTENDED DAY AFTER THAT AND WAS RETREATED AS HAD SEXUAL CON	Gentamicin
no creatitne result on server sample lost in transit or not processed	Gentamicin
unable to obtain bloods 3 attempts became distressed	Ceftriaxone
CREATITINE TOO OLD TO TEST BY THE TIME IT REACHEDCTHE LAB	Ceftriaxone
NO BLOOD KITS AVAILABLE	Gentamicin
NO BLOOD KITS AVAILABLE	Ceftriaxone
no blood kits available	Gentamicin
patient did not attend follow up	Gentamicin

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
ISOLATE WAS NOT SAVED AS ORGANISM DIED ON PHARNX PLATE	Gentamicin
no result for creatinine on server may have been lost in transit	Gentamicin
DECLINED BLOODS AT VISIT 2	Gentamicin
VAS SCORE NOT DONE AS PATIENT DECLINED DID NOT HAVE THE INJECTION. DECLINED	Gentamicin
No VAS sheet for visit 2 verbal from patient no change and documented on VAS sheet visit 1 by nurse	Gentamicin
Microscopy not done in error	Gentamicin
NAAT visit1 no result on system & pt notes no longer on site therefore pre randomistion input on mac	Gentamicin
VAS sheet not given @visit2 pt asked by nurse re:changes and written on VAS sheet visit 1	Gentamicin
unable to clarify if doxycycline px and taken notes no longer on site no written info on system	Gentamicin
Urine TMA sample lost so no result	Ceftriaxone
No creatinine result – sent to lab? lost no result	Ceftriaxone
VASsheet visit 2 not given to pt documented on VAS sheet visit 1 same value as per pt says	Ceftriaxone
Visit 2 was done on day 13 and not after day 14 as included day of visit as day1 so visit early	Ceftriaxone
VAS sheet not given @ visit2 documented on VAS sheet visit 1 not change in value as per patient	Ceftriaxone
In error- incorporated pretrial blood with visit1 as complete screen so only NAAT pretrial results	Ceftriaxone
Vas sheet visit 2 not given documented on vas sheet Visit1 same value as per patient stated	Ceftriaxone
Vas score for visit 2 not completed in error	Gentamicin
No creatinine result from visit 1. Lab error they performed hepatic screen and not renal screen	Gentamicin
Vas sheet not given visit 2 written on vas sheet from visit 1 so 1 vas sheet in total	Gentamicin
No creatinine result form baseline visit check with cmft labs no listed sample so ?? lost in transit	Ceftriaxone
No Creatinine result sample not done in error.PI aware	Gentamicin
Urethral microscopy not performed at visit 2 in error	Ceftriaxone
Visual Analogue scale not completed in error	Gentamicin
Retreated for GC by GUM 17/11/2015 as non compliance	Ceftriaxone
Never attended for visit 2	Ceftriaxone
Creatinine not done in error so no result for this visit	Ceftriaxone
Culture plates not taken from sites 5 and 2 dr decision	Ceftriaxone
Naat testinfg not taken from site 2 & 5 dr decision	Ceftriaxone
No NAAT for PHarynx taken at baseline. Unknown reason why as culture was obtained	Ceftriaxone
Culture not taken in error	Gentamicin
No follow up examination made. – patient believed to be a false pos on micro	Gentamicin
No RECtal NAAT or Culture taken at follow up- patient believed to be negative	Gentamicin
dr decision not to test UR culture	Gentamicin
VAS scale not completed by participant at visit 2	Gentamicin
patient declined some baseline swabs -no UR culture taken	Ceftriaxone
Unable to obtain visit 2 immunology bloods due to poor blood flow	Ceftriaxone
source data missing for weight assume visually patient weight greater than 40 kg	Ceftriaxone

continued

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
Clinician unaware immunology samples required at follow up. Education provided	Gentamicin
Patient reports no receptive anal sex therefore original assessing clinician did not take	Ceftriaxone
VAS score not taken at follow up	Ceftriaxone
Immunology bloods not taken at follow up	Gentamicin
VAS not taken at Follow up	Gentamicin
Bacterial Vaginosis at visit 1	Ceftriaxone
Creatinine blood not taken at visit 2	Ceftriaxone
Cultures not taken visit 2 – user error – education provided	Ceftriaxone
VAS score not taken visit 2. Busy clinic	Ceftriaxone
Participant diagnosed with bacterial vaginosis at baseline	Gentamicin
Immunology bloods not taken at visit 2	Gentamicin
Duration of pain not asked of patient. User Error – education provided	Gentamicin
Rectal swabs not taken at baseline- patient declined swabs	Gentamicin
Rectal NAAT not taken and urine taken at drs discretion	Gentamicin
Creatine blood not obtained at visit 1. The request was made but not recieved in labs	Ceftriaxone
Newly trained nurse was not aware that CREATINE WAS required at visit 1 – training provided	Ceftriaxone
Rectal and pharangeal swabs not taken at v1. this was a user error and a reminder was made	Gentamicin
Rec and additional swabs not taken on date of visit 1 – user error and training offered	Gentamicin
Rec and Ph cultures not taken at visit 2. User error and reminders were provided	Ceftriaxone
PH and REC swab not taken at visit 2 in error	Gentamicin
U and E blood taken at visit 1 but not recieved in labs. Local investigation taking place	Ceftriaxone
Rec swabs not taken in error	Gentamicin
Vas score not taken at visit two patient fainted so limited for time	Ceftriaxone
disgnosis of BV	Gentamicin
GRAM STAIN NOT REPEATED FOR RECTAL SLIDE POSITIVE AT BASELINE	Gentamicin
NAAT sample for pharynx result not available ? lost retaken pon 6th may	Gentamicin
Culture sample for phaynx result not available ?lost retaken on 6th May	Gentamicin
urethral culture plate sample not taken	Ceftriaxone
patient disclosed long standing chronic conditon Dr diagnosed PID	Gentamicin
Pharynx naat sample not taken no Oral Sex	Ceftriaxone
Pharynx culture not taken No oral sex	Ceftriaxone
No Rectal Naat done ? No Anal Sex	Gentamicin
No Rectal culture done ? No anal sex	Gentamicin
Urethral swab not done No penetrative sex	Ceftriaxone
NAAT Rectum sample not performed	Ceftriaxone
CULTURE Rectum sample not performed	Ceftriaxone
VISUAL ANALOGUE SCALE NOT COMPLETED	Ceftriaxone
phyical exam not done in error	Gentamicin

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
Pencillin allergy	Gentamicin
Follow-up visual analgue scale not done in error	Ceftriaxone
no rectal Naats result available for visit 1	Gentamicin
pt left clinic before clinical examination swabs and bloods taken	Gentamicin
Rectal Naats and culture was not repeated at Visit 2	Gentamicin
serum creatine not done in error	Gentamicin
The culture sample was not taken at visit 2	Ceftriaxone
Culture not taken at Visit 2	Ceftriaxone
Naat Testing performed as routine clinic appointment and not at V2	Ceftriaxone
Culture testing not performed at routine visit also not performed at V2	Ceftriaxone
Unable to obtain blood sampling at V2 – 3 × attempts	Ceftriaxone
Rectal culture not performed at Baseline	Ceftriaxone
GC culture (R) isolate not saved by laboratory	Ceftriaxone
Positive result for visit 2 Ur GC culture samples reported on Lastword – sample not stored by lab	Gentamicin
No creatinine result available from lab (lab error)	Gentamicin
Noted after patient left that GC diagnosis over 4/52 ago. PI & G-TOG team informed immediately	Ceftriaxone
Cepheid machine error – TH. Previous BD NAAT neg. Culture neg. AC NAAT sent. Will repeat at v2 for safety	Ceftriaxone
Error result on Cepheid machine for GC Th NAAT. Returned 09-May-2016 to repeat	Gentamicin
Triple site AC NAATs and cultures sent at visit 1 but local NAATs not repeated	Gentamicin
Site not clear from culture samples- will repeat triple site at visit 2 for completeness	Gentamicin
AC NAATs and cultures sent at visit 1 on 01-Jul-2016. Local NAATs not repeated	Ceftriaxone
Creatinine result not available-?mismatched sample/labelling error	Ceftriaxone
throat swab result shown as error on 22/08/16 at local lab. patient will be recalled to reswab throa	Ceftriaxone
Patient didnt come for repeat throat swab after multiple attempts to contact as dated on 05/09/16	Ceftriaxone
technical error results with the machine for rectal swabs. patient will be recalled to reswab site	Ceftriaxone
PRE BASELINE SYPHILIS TEST WAS NEGATIVE BUT CONFIRMED RESULTS OF 12/09/2016 CAME AS POSITIVE	Gentamicin
Culture sample not taken from infected site at visit 2 - Oversight by nurse covering study visit	Ceftriaxone
Culture sample not taken at follow-up visit. Oversight by nurse covering visit	Gentamicin
No Creatinine visit 2 - porter failed to deliver sample in time for processing	Gentamicin
CREATININE SAMPLE NOT PROCESSED DUE TO PORTER FAILING TO DELIVER TO LAB	Gentamicin
Porter failed to deliver sample to path intime and sample was no processed	Ceftriaxone
CREATININE NOT TAKEN IN ERROR	Gentamicin
Copy of positive GC lab result not available at time of recruitment as tested at London clinic	Gentamicin
Symptom assessment /Follow up:genital discharge negative but the symptom resolution period unknown	Gentamicin
VISUAL ANALOGUE SCALE WAS NOT DONE ON VISIT 1 – BASELINE	Gentamicin

continued

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
PATIENT ALLERGIC TO AZITHROMYCIN	Gentamicin
BV DIAGNOSED ON LOCAL SLIDE NOT SEEN	Gentamicin
PATIENT DECLINED NAAT AND CULTURE SET OF SCREENING SWABS RECTAL AND PHARYNX ONCE RANDOMISED	Gentamicin
PARTICIPANT DID NOT ATTEND HIS FOLLOW UP VISIT LOST TO FOLLOW UP AS PER PROTOCOL	Ceftriaxone
LOCAL LABORATORY URINE NAAT TEST NOT DONE/BASELINE VISIT	Gentamicin
PHARYNX LOCAL LABORATORY CULTURE TEST/FOLLOW UP VISIT NOT DONE	Gentamicin
FOLLOW UP VISIT DONE 13 DAYS AFTER THE BASELINE VISIT BY MISTAKE	Gentamicin
VISUAL ANALOGUE SCALE NOT DONE AT THE BASELINE VISIT	Ceftriaxone
VISUAL ANALOGUE SCALE AT THE FOLLOW UP VISIT NOT DONE	Ceftriaxone
VISUAL ANALOGUE SCALE NOT DONE	Ceftriaxone
CREATININE RESULT NOT AVAILABLE AT VISIT 1	Gentamicin
NAAT AND CULTURE PHARYNGEAL TESTING NOT DONE IN THE F/U VISITNAAT POSITIVE ONLY IN SCREENING VISIT	Ceftriaxone
Pharynx NAAT negative on visit one retested by mistake in visit 2	Gentamicin
PARTICIPANT WAS NOT ELIGIBLE	Gentamicin
Blood sample for creatinine issed in error. Nurses are aware they need to take this sample for futur	Gentamicin
culture of urethreal sample only taken in error. Aware need sample from all sites for next patient	Gentamicin
NAAT Pharyngeal sample taken in error at baseline visit	Ceftriaxone
Pharyngeal culture omitted in error at Follow up visit	Ceftriaxone
Rectal NAAT sample taken in error at follow up visit. Removed from eCRF as requested	Gentamicin
Visit 1 NAAT samples are missing from local IT system	Ceftriaxone
Pt tested in London told +ve came here for Rx & enrolled.Later found result equivocal	Gentamicin
Samples taken from rectum and pharynx for NAAT testing but no results available from lab	Ceftriaxone
Rectal sample not done	Ceftriaxone
Pharyngeal result not done (NAAT testing)	Ceftriaxone
Baseline urethra sample not available	Ceftriaxone
Blood sample not taken due to venepuncture difficulties	Ceftriaxone
Additional swab not taken for AC testing. Unknown reason	Ceftriaxone
No GC culture taken at Visit 1 from urethral site	Gentamicin
No GC CULTURE AT VISIT 1 FROM THE THROAT	Gentamicin
NO URETHRAL GC CULTURE TAKEN ON VISIT 1	Ceftriaxone
DATE ON CHEMICAL PATHOLOGY REQUEST FORM MISREAD BY LAB STAFF AND SAMPLE NOT PROCESSED	Gentamicin
URETHRAL GC CULTURE NOT TAKEN	Ceftriaxone
THROAT CULTURE NOT TAKEN BY GUM STAFF PRIOR TO RANDOMISATION	Ceftriaxone
AC swab missed and not obtained at Enrolment visit	Gentamicin
Throat swab for NAAT not done at visit 2. Patient came back to have the sample taken on 2 Sept 2016	Gentamicin

TABLE 41 Protocol deviations recorded on the protocol deviation log (*continued*)

Details	Treatment group
VAS not completed on baseline visit	Gentamicin
VAS form missed during the Visit 1	Ceftriaxone
Weight not done on Visit 1	Ceftriaxone

BV, bacterial vaginosis; CK, creatine kinase; CRF, case report form; GUM, genitourinary medicine; IVDU, intravenous drug user; PID, pelvic inflammatory disease; QEHB, Queen Elizabeth Hospital Birmingham; STBRU, Sexually Transmitted Bacteria Reference Unit; U + E, urea and electrolytes.
a Owing to STBRU closure during the trial, swabs were analysed by PHE.
Text is taken directly from source data CRF forms with redactions made to remove staff names and clinic names.

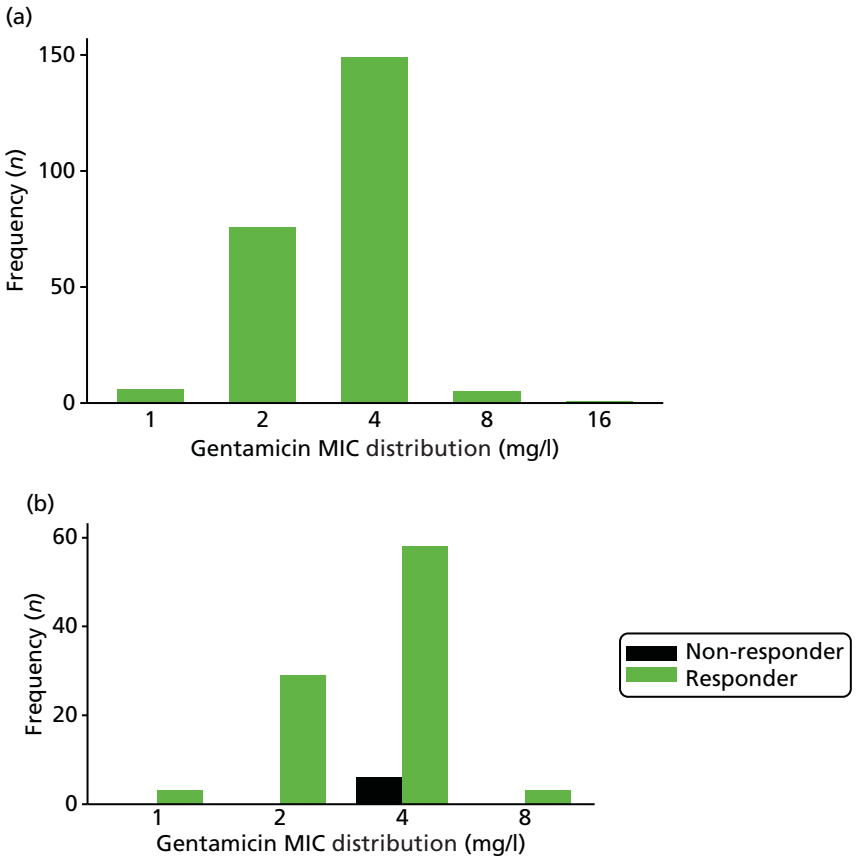

FIGURE 17 Distribution of genital gentamicin MIC. (a) All participants; and (b) by treatment response.

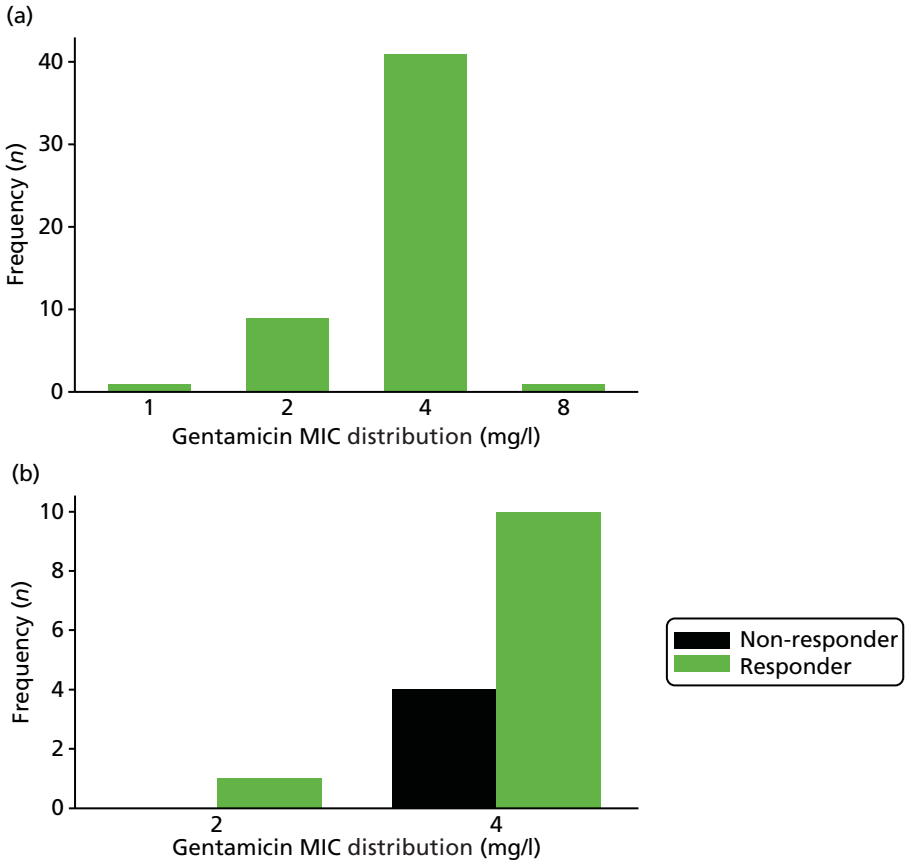

FIGURE 18 Distribution of pharyngeal gentamicin MIC. (a) All participants; and (b) by treatment response.

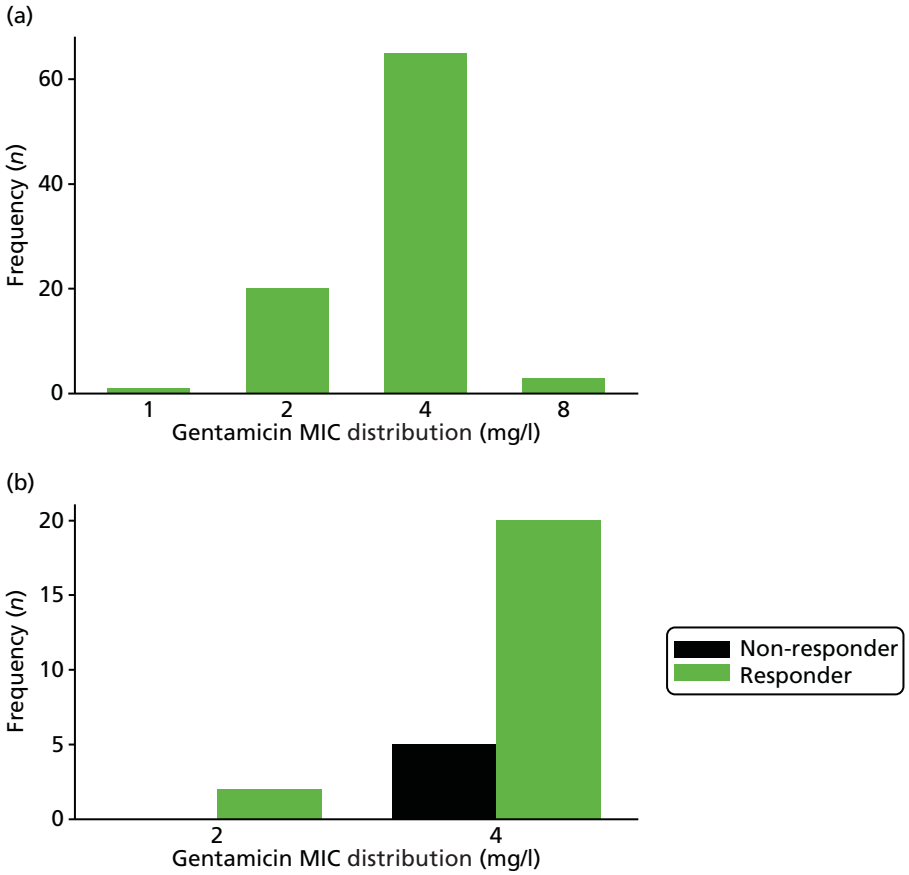

FIGURE 19 Distribution of rectal gentamicin MIC. (a) All participants; and (b) by treatment response.

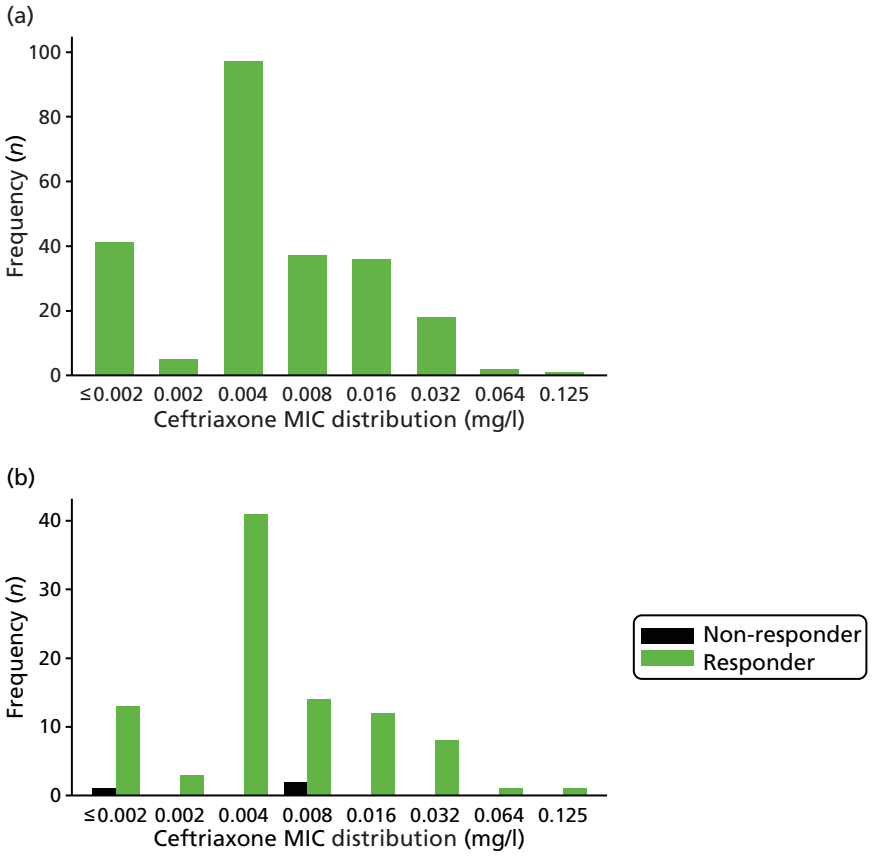

FIGURE 20 Distribution of genital ceftriaxone MIC. (a) All participants; and (b) by treatment response.

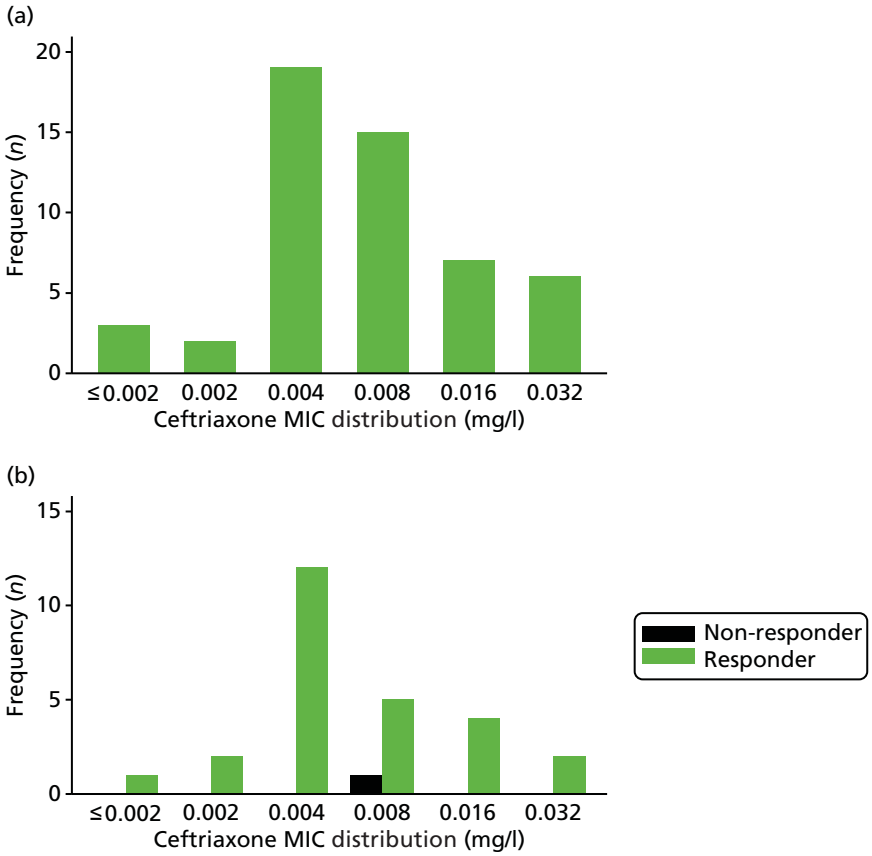

FIGURE 21 Distribution of pharyngeal ceftriaxone MIC. (a) All participants; and (b) by treatment response.

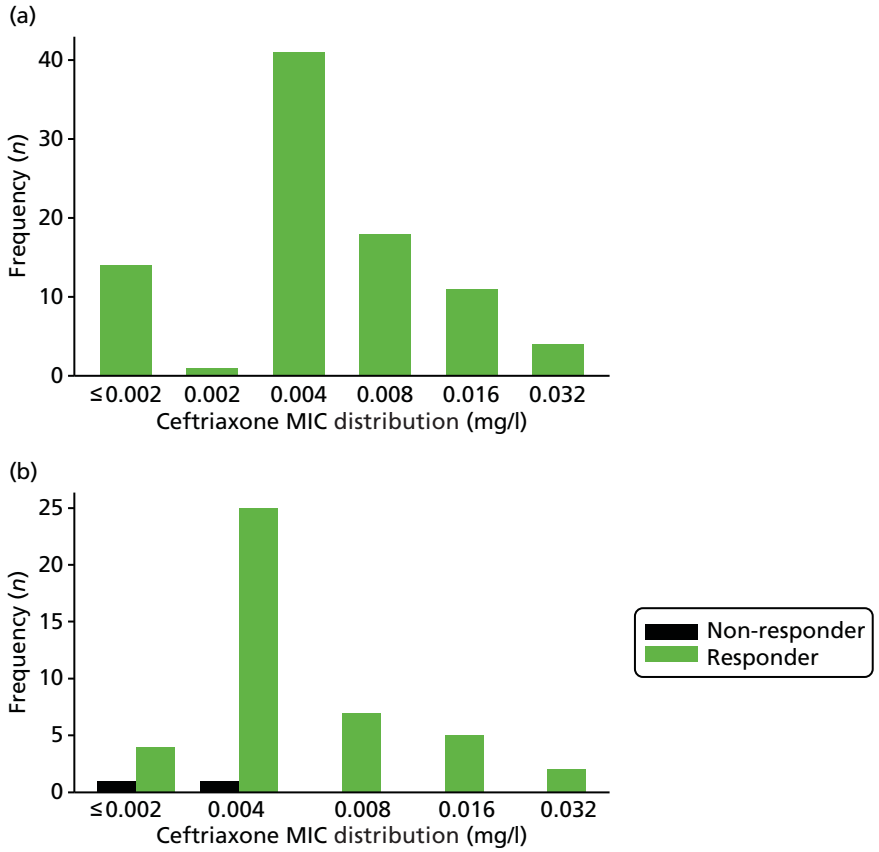

FIGURE 22 Distribution of rectal ceftriaxone MIC. (a) All participants; and (b) by treatment response.

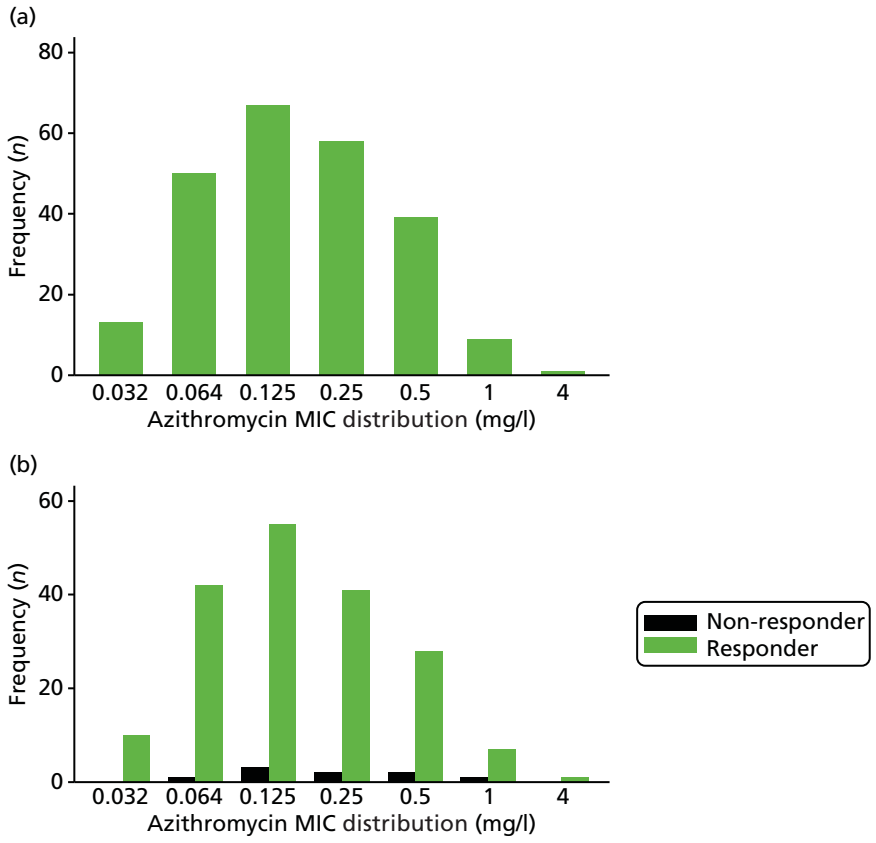

FIGURE 23 Distribution of genital azithromycin MIC. (a) All participants; and (b) by treatment response.

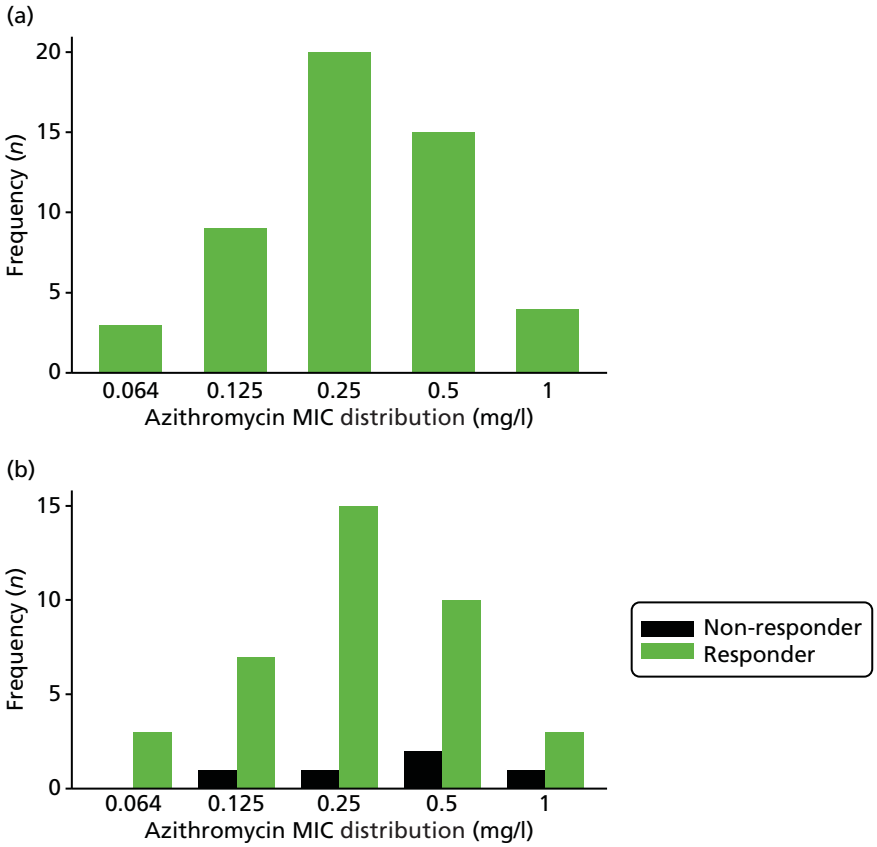

FIGURE 24 Distribution of pharyngeal azithromycin MIC. (a) All participants; and (b) by treatment response.

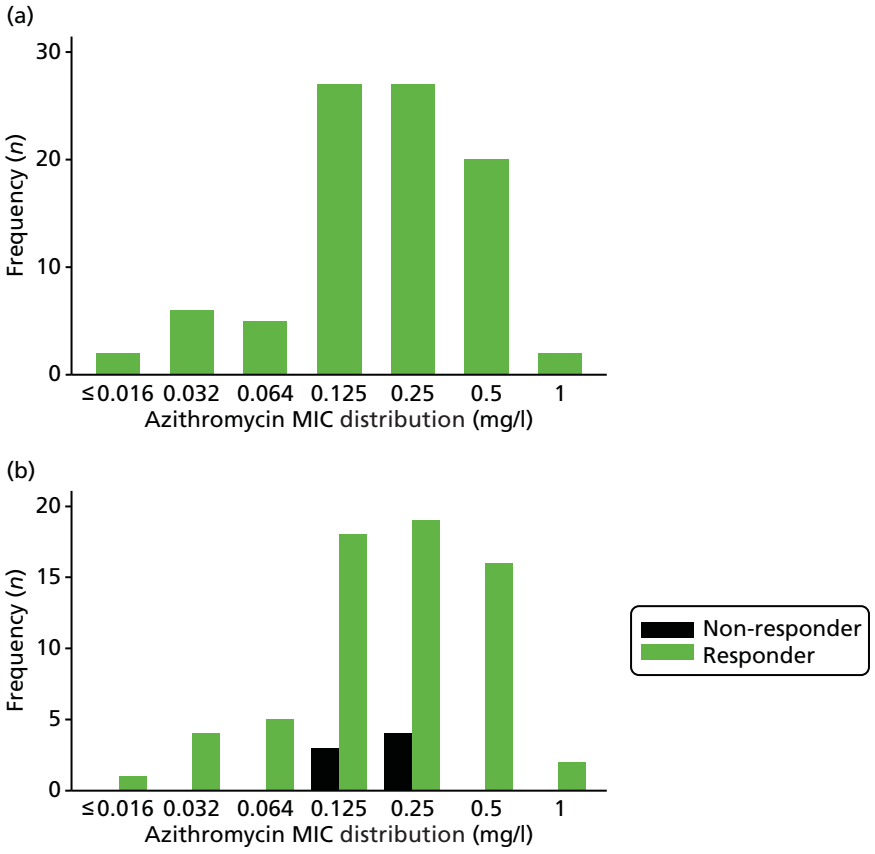

FIGURE 25 Distribution of rectal azithromycin MIC. (a) All participants; and (b) by treatment response.

EME
HS&DR
HTA
PGfAR
PHR

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