CoLab Network

Health Technology Review

Efficacy and Safety of Treatment Options for Uncomplicated Gonococcal Infections

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Rapid Review With Expert Input

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Key Messages

Gonorrhea is the second most common sexually transmitted infection in Canada. It is caused by the bacteria *Neisseria gonorrhoeae* and can be treated with antibiotics, but rising antimicrobial resistance makes implementing the current treatment guidance challenging.

We aimed to identify and summarize the literature since 2016 comparing the clinical effectiveness and safety of treatments for uncomplicated *N. gonorrhoeae* infections of the urethra, cervix, rectum, pharynx, and eye in adolescents and adults, including pregnant people. We searched key resources, including journal citation databases, and conducted a focused internet search for relevant evidence.

This Rapid Review includes 4 randomized controlled trials and 1 companion report, all published since 2019. The studies evaluated the following treatments: gentamicin plus azithromycin compared to ceftriaxone plus azithromycin, gentamicin monotherapy compared to ceftriaxone monotherapy, and ceftriaxone monotherapy compared to ceftriaxone plus azithromycin.

There is a lack of comparative evidence evaluating the clinical effectiveness and safety of antibiotics for *N. gonorrhoeae* infections.

The included studies had mostly cisgender men as participants, so women and people with diverse gender identities were not well represented. Additionally, adolescents younger than 16 years of age and pregnant people were not included in any study.

All the studies were conducted in Europe, so their applicability to the Canadian clinical context is unclear.

Further randomized controlled trials with diverse participant populations are needed to evaluate the safety and efficacy of gentamicin, cefixime, and ciprofloxacin (monotherapy or in combination with azithromycin). Further research is required to evaluate the clinical effectiveness and safety of single-dose versus multidose cefixime.

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Abbreviations

AMR	antimicrobial resistance
CI	confidence interval
IM	intramuscular
IQR	interquartile range
MIC	minimum inhibitory concentration
NAAT	nucleic acid amplification test
PHAC	Public Health Agency of Canada
RCT	randomized controlled trial
RD	risk difference
SD	standard deviation
STI	sexually transmitted infection
TOC	test of cure

Introduction and Rationale

Background

Gonorrhea is a sexually transmitted infection (STI) caused by the gram-negative diplococcus, *Neisseria gonorrhoeae*,[1] which infects genital and extragenital (oropharyngeal, conjunctival, and anorectal) mucosa.[2] Gonorrhea is associated with significant morbidity.

N. gonorrhoeae infections may be classified as:

- **uncomplicated *N. gonorrhoeae* infections** — asymptomatic infections that occur in the endocervical canal in females and in the urethral, pharyngeal, and rectal sites in both males and females (e.g., urethritis, cervicitis, pharyngitis, and proctitis)
- **complicated *N. gonorrhoeae* infections** — local complications that extend locally beyond the primary site of infection (e.g., epididymitis, pelvic inflammatory disease)
- **disseminated infections** — systemic complications from infection, which may include arthritis-dermatitis syndrome and rarely endocarditis or meningitis.[3]

Gonorrhea remains 1 of the most common STIs worldwide. In 2016, WHO estimated there were 86.9 million new cases of *N. gonorrhoeae* infections worldwide in persons aged 15 to 49 years.[4] Gonorrhea is the second most common reportable STI in Canada. There has been a gradual and steady increase in reported cases since 1997. Although the younger age groups have the highest infection rates, the greatest increase in infection rates has been seen in the 30 to 39 years age group, with a 154% increase from 2013 to 2017.[5]

Some international guidelines, including the Public Health Agency of Canada (PHAC) Sexually Transmitted and Blood-Borne Infections guides for health professionals as well as other provincial and territorial guidelines, recommend combination therapy for *N. gonorrhoeae* infections.[6-8] These recommendations are based on early clinical efficacy trials, pharmacokinetic studies or pharmacodynamic simulations, antimicrobial resistance (AMR) surveillance data, anticipated trends in AMR, case reports of treatment failures, and expert opinion. All guidelines that recommend combination therapy include ceftriaxone plus azithromycin as first-line treatment. WHO and PHAC also recommend cefixime plus azithromycin as a first-line treatment for anogenital infection, except in gay, bisexual, and other men who have sex with men [wording from original source]. The recommended doses of ceftriaxone and azithromycin vary between guidelines, and there is a lack of clinical data to support these differences and the superiority of combination therapy over monotherapy. Due to the emergence of azithromycin resistance and concerns regarding antimicrobial stewardship, some guideline developers or organizations have replaced combination therapy with ceftriaxone monotherapy.

Policy Issue

Treatment recommendations for gonococcal infections have changed repeatedly in response to increasing AMR, including multidrug resistance and changing resistance profiles. Rates of gonorrhea are also increasing in Canada. Thus, a review of the evidence for treatment options is required to inform further treatment recommendations.

In September 2023, CADTH completed a technology review that described systematic reviews and guidelines pertaining to the efficacy of antimicrobials for uncomplicated *N. gonorrhoeae* infection. To supplement the technology review, this Rapid Review addresses the following policy questions.

Policy Questions

1. Which antimicrobial (ceftriaxone, cefixime, gentamicin, or ciprofloxacin), with or without azithromycin, should be recommended to treat uncomplicated gonorrhea in adolescents and adults?
2. What dosing regimen should be recommended for cefixime to treat uncomplicated gonorrhea in adolescents and adults?

Main Take-Aways

In response to growing antibiotic resistance and rising gonorrhea rates in Canada, there is a need to reassess treatment options. This involves determining which antibiotics (e.g., ceftriaxone, cefixime, gentamicin, or ciprofloxacin), either alone or in combination with azithromycin, are best for treating uncomplicated infections in adolescents and adults. It is also important to determine the most effective and safe dosing regimen for cefixime in this context.

Purpose

We prepared this Rapid Review to summarize and critically appraise the evidence identified from medical databases and grey literature regarding the clinical effectiveness and safety of treatments for uncomplicated *N. gonorrhoeae* infections of the urethra, cervix, rectum, pharynx, and eye in adolescents and adults, including pregnant people.

Research Questions

This Rapid Review will address the policy questions by exploring the following research questions:

1. What is the efficacy or effectiveness and safety of ceftriaxone, cefixime, gentamicin, or ciprofloxacin (in any dosing regimen either as monotherapy or combination therapy with azithromycin) to treat uncomplicated gonorrhea in adolescents and adults?
2. What is the efficacy or effectiveness and safety of cefixime:
    a) administered as a single dose compared with multiple doses to treat uncomplicated gonorrhea in adolescents and adults
    b) administered as a single dose or multiple doses administered over several days compared with single dose or multiple doses of ceftriaxone to treat uncomplicated gonorrhea in adolescents and adults?

Methods

The Rapid Review was informed by guidance in the WHO guide to rapid reviews.[9] A brief protocol was developed and approved by CADTH.

Literature Search Methods

An information specialist developed and conducted a literature search for clinical studies. Published literature was identified by searching the following bibliographic databases: MEDLINE via Ovid, Embase via Ovid, the Cochrane Database of Systematic Reviews via Wiley, and the Cochrane Central Register of Controlled Trials via Wiley. Duplicates were removed manually in EndNote. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. Search concepts were developed based on the elements of the PICOS (population, intervention, comparison, outcomes, and study) framework and research questions. The main search concepts were gonorrhea and at least 1 of ceftriaxone, cefixime, gentamicin, ciprofloxacin, or synonyms. The US National Institutes of Health's clinical trials registry, ClinicalTrials.gov was searched.

Search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, or indirect treatment comparisons, any types of clinical trials or observational studies. The search was completed on January 16, 2024, and limited to English- or French-language documents published since January 1, 2016. Conference abstracts were excluded from the search results.

Grey literature (literature that is not commercially published or available) was identified by key sources listed in relevant sections of *Grey Matters: A Practical Tool For Searching Health-Related Grey Literature*, including the International Health Technology Assessment (HTA) Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The grey literature search was updated before the completion of the report.

We ensured literature saturation by scanning the reference lists of studies included in the September 2023 technology review and in the current Rapid Review, and potentially relevant systematic reviews, health technology assessments, meta-analyses, and indirect treatment comparisons identified in the September 2023 technology review.

Selection Criteria and Methods

The inclusion criteria (Table 1) were pilot-tested by the research team on a random sample of 50 titles and abstracts (or citations) for the first level of screening and 25 full-text articles in the second level of screening. Once a minimum agreement of 75% was achieved, 1 reviewer (JD, YL, or JPS) screened citations in the first round of screening. In the second round of screening, potentially relevant articles were retrieved and assessed for inclusion by 1 reviewer (JD, YL, or JPS). If stratified data and results were not reported, study investigators were contacted to retrieve any additional information with up to 3 reminders. The final selection of full-text articles was based on the inclusion criteria presented in Table 1. Reference lists of included studies from the September 2023 technology review and this report, as well as relevant systematic reviews,

HTAs, meta-analyses, or indirect treatment comparisons identified during screening were screened using the same study selection process.

Screening was conducted in Synthesi.SR, a proprietary review software developed by the Knowledge Translation Program, St. Michael's Hospital, Unity Health Toronto.

Table 1: Selection Criteria

Elements	Research question 1	Research question 2a	Research question 2b
Population	Adolescents and adults (aged 10 years and older) with uncomplicated laboratory-confirmed *N. gonorrhoeae* infections or clinical syndrome compatible with *N. gonorrhoeae* infection		
Subgroups	Pregnant persons, gbMSM, persons with suspected or confirmed infection, persons coinfected with another STI, site of infection (e.g., eyes, endocervical canal, urethral, pharyngeal, or rectal sites)		
Interventions	Any of the following dosing regimens administered as monotherapy or in combination therapy with azithromycin: • ceftriaxone • cefixime • gentamicin • ciprofloxacin	Cefixime administered as single dose	Cefixime administered as single dose or administered over multiple doses
Comparators	Any of the following dosing regimens administered as monotherapy or combination therapy with azithromycin: • ceftriaxone • cefixime • gentamicin • ciprofloxacin No comparator (case series and single-arm trials will be listed in Appendix 5)	Cefixime administered over multiple doses	Ceftriaxone administered in a single dose or administered over multiple doses
Outcomes	• Clinical cure • Microbiological cure • Treatment failure • Resistance • Serious adverse events • Adverse events[a] • Withdrawal due to adverse events • Allergic or anaphylactic reactions • Adherence to treatment (completion of full treatment course) • Loss to follow-up	• Clinical cure • Microbiological cure • Treatment failure • Resistance • Serious adverse events • Adverse events[a] • Withdrawal due to adverse events • Allergic or anaphylactic reactions • Partner transmission • HIV transmission and acquisition • Loss to follow-up	
Setting	High-income countries (as defined by the World Bank [2024][10])		

Elements	Research question 1	Research question 2a	Research question 2b
Study designs	Randomized controlled trials and nonrandomized (observational) comparative studies		

gbMSM = gay, bisexual, and other men who have sex with men; *N. gonorrhoeae* = *Neisseria gonorrhoea;* STI = sexually transmitted infection.

Note: For research question 1, case series and single-arm trials will be listed in Appendix 5.

[a]The inclusion criteria were amended to consider adverse events as an outcome.

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or they were published before 2016.

Data Abstraction and Critical Appraisal of Individual Studies

Prior to data abstraction, all members of the research team completed a calibration exercise of the data abstraction form using a predefined form on a random sample of 2 included studies. Following calibration, 1 reviewer (JD, YL, or JPS) independently abstracted data from the included studies.

The included publications were critically appraised by a single reviewer (JD or YL) using the Cochrane Risk of Bias 2 tool for randomized controlled trials as a guide.

Data Synthesis

The results were summarized descriptively. The summary of findings is organized based on the research question, the intervention and comparator, and outcomes.

Summary of Evidence

Quantity of Research Available

Main Take-Aways

From a total of 736 identified articles published since 2016, 5 publications from 4 randomized controlled trials were included in this Rapid Review.[11-15] We also identified 11 noncomparative single-arm studies[16-26] and 1 case series[27] that did not meet our eligibility criteria but provided context relevant to the research questions.

A total of 736 citations were identified in the literature search. Following screening of titles and abstracts, 605 were excluded, and 131 potentially relevant studies were retrieved for full-text review. A total of 63 potentially relevant citations were retrieved from the grey literature search, reference scanning, and from subject-matter experts. Of the potentially relevant publications, 189 publications were excluded for various reasons. This report includes 4 unique randomized studies[12-15] and 1 companion report.[11] Study selection details are presented in Appendix 1.

We also identified 11 noncomparative single-arm studies[16-26] and 1 case series.[27] Although these studies did not meet the study design eligibility criteria for this report and were not formally included, they provided

context relevant to the research questions. The characteristics and key findings of these studies are summarized in Appendix 5.

Study Characteristics

We identified 4 unique RCTs[12-15] and 1 companion report[11] relevant to research question 1. There were no reports identified based on the inclusion criteria for research questions 2a and 2b.

Additional details regarding the characteristics of the included publications are provided in Appendix 2.

Study Design

The studies by Rob et al. (2020),[13] Ross et al. (2019),[11,12] de Vries et al. (2022),[14] and Vanbaelen et al. (2023)[15] were RCTs, of which 3 were noninferiority trials.[11-14] The RCT by Vanbaelen et al. was not an efficacy trial, but rather a study to monitor treatment effects on the microbiome and resistome.[15]

Study Setting and Country of Origin

All included RCTs were conducted in Europe; the RCT by de Vries et al. was conducted in the Netherlands,[14] the Rob et al. trial was conducted in the Czech Republic,[13] the Ross et al. (2019) trial was conducted in the UK,[11] and the RCT by Vanbaelen et al. was conducted in Belgium.[15]

With the exception of the Ross et al. RCT, all included RCTs were single-centre studies conducted at a public health service clinic,[14] a dermatovenerology department of a hospital,[13] or an HIV and STI clinic.[15] The Ross et al. study was a multicentre trial conducted across 14 sexual health clinics.[11]

The study periods of the included publications varied. The included RCTs were conducted in the following time periods: 2014 to 2016,[11] 2016 to 2019,[13] 2017 to 2020,[14] and 2022.[15]

Patient Population

The study by Ross et al. included participants aged 16 to 70 years with a diagnosis of untreated genital, pharyngeal, or rectal *N. gonorrhoeae* infection.[11] In total, they included 720 participants; 358 were randomized to the gentamicin plus azithromycin arm and 362 to the ceftriaxone plus azithromycin arm.[11] Of the included patients, approximately 81% were male and 19% were female.[11] One participant was identified within the "other" [wording from original source] gender category. Age was reported as a mean by treatment arm.[11] The mean age of participants was 30.4 years (standard deviation [SD] = 9.9 years) and 30.2 years (SD = 10.1 years) in the gentamicin plus azithromycin and ceftriaxone plus azithromycin groups, respectively.[11] With respect to participants' HIV status, the treatment groups appeared to be balanced; 15% and 12% of participants were self-reported to be HIV-positive in the ceftriaxone plus azithromycin and gentamicin plus azithromycin groups, respectively.[11]

The study by Rob et al. enrolled men and women (aged 18 to 75 years) with a diagnosis of uncomplicated *N. gonorrhoeae* infection of the rectum or pharynx.[13] A total of 145 patients were included, of whom the majority (97%) were male.[13] Seventy-three participants were randomized to the gentamicin plus azithromycin arm, and 72 participants were randomized to the ceftriaxone plus azithromycin arm. Across both treatment arms, most patients were men who have sex with men [wording from original source], with 88.9% in the gentamicin

plus azithromycin arm and 88.7% in the ceftriaxone plus azithromycin arm.[13] The mean age of participants was 32.9 years (range, 18 to 68 years). Most infections were asymptomatic; among patients in both arms, rectal infections were the most common (55.6% in the gentamicin plus azithromycin group; 53.5% in the ceftriaxone plus azithromycin group).[13] However, there were more pharyngeal infections in the gentamicin plus azithromycin group (23.6%) compared to the ceftriaxone plus azithromycin group (19.7%).[13] Rob et al. also reported that the representation of *Chlamydia trachomatis* infection and people living with HIV was similar in both groups.[13]

The de Vries et al. RCT enrolled adults aged 18 years and older with confirmed anorectal or urogenital *N. gonorrhoeae* infection.[14] The study included a total of 346 participants;103 randomized to the ceftriaxone arm and 102 to the gentamicin arm. Of the participants, 95% were male, 5% were female, and less than 1% were transgender.[14] Age was reported as a median for each treatment arm; the median age was 32 years (interquartile range [IQR], 27 to 40 years) and 35 years (IQR, 26 to 42 years) in the ceftriaxone and gentamicin arms, respectively.[14] In 85% of participants, the anus was the primary site of infection.[14] Among patients who experienced symptoms of infection at baseline, urethral discharge (25%) and dysuria (25%) were the most commonly reported.[14] In the study, 21% of participants were people living with HIV and 90% were men who have sex with men [wording from original source].[14]

The study by Vanbaelen et al. included cisgender men who have sex with men [wording from original source] with a confirmed diagnosis of urethral, anorectal, or pharyngeal *N. gonorrhoeae* infection.[15] In total, 42 patients were included in the study; 20 randomized to the ceftriaxone plus azithromycin arm and 22 to the ceftriaxone arm.[15] The median age of participants was 40 years (IQR, 29 to 44 years).[15] Regarding the characteristics of the *N. gonorrhoeae* infection, 71% of participants were infected at all 3 sites (pooled: urethral, anorectal, pharyngeal), and the majority of participants (69%) were symptomatic.[15] In addition, 21% of participants were HIV-positive.[15]

Interventions and Comparators

The included publications evaluated the following treatments for uncomplicated *N. gonorrhoeae* infection in adolescents and adults:

- Two RCTs investigated combination therapy using gentamicin plus azithromycin versus ceftriaxone plus azithromycin.[11,13] In the RCT by Rob et al., patients were randomized to treatment with gentamicin 240 mg single dose intramuscularly (IM) plus azithromycin 2 g single dose orally or treatment with ceftriaxone 500 mg single dose IM plus azithromycin 2 g single dose orally.[13] In the Ross et al. RCT, participants were randomized to treatment with gentamicin 240 mg single dose IM plus azithromycin 1 g single dose orally or treatment with ceftriaxone 500 mg single dose IM plus azithromycin 1 g single dose orally.[11]
- One RCT compared gentamicin monotherapy with ceftriaxone monotherapy.[14] Specifically, de Vries et al. randomly assigned participants to treatment with either ceftriaxone 500 mg single dose IM or gentamicin 5 mg/kg body weight (to a maximum of 400 mg) single dose IM.[14]

- One RCT evaluated ceftriaxone monotherapy with ceftriaxone plus azithromycin.[15] In the Vanbaelen et al. study, patients were randomized to treatment with ceftriaxone 1 g single dose IM or ceftriaxone 1 g single dose IM plus azithromycin 2 g single dose orally.[15]

Outcomes

Outcomes assessed in the studies included:

- Microbiological cure was defined as the proportion of patients with a nucleic acid amplification test (NAAT)–negative test of cure (TOC) for *N. gonorrhoeae* at treatment follow-up.[11,13,14] Rob et al. also defined microbiological cure as a negative culture test for *N. gonorrhoeae* at follow-up.[13]
- Clinical cure was defined as the resolution of symptoms present at baseline in 2 RCTs.[11,13] In 1 RCT, the duration of symptoms from baseline to TOC visit was a secondary outcome.[14]
- Treatment failure was defined by 1 study as NAAT-positive TOC for *N. gonorrhoeae* at treatment follow-up.[14] In addition, although Ross et al. did not define this outcome, they reported data on treatment failures.[11]
- Resistance was inconsistently defined across 3 RCTs.[11,14,15] Ross et al. evaluated resistance as the relationship between clearance of *N. gonorrhoeae* and in vitro measurement of antibiotic minimum inhibitory concentration (MIC).[11] The RCT by de Vries et al. defined resistance as a predictor variable, rather than an outcome variable. They measured the MICs of all 4 antibiotics on isolates at baseline and the TOC visit.[14] Vanbaelen et al. defined resistance as the proportion of participants carrying macrolide resistance genes.[15]
- A serious adverse event was defined as the frequency and severity of known antibiotic side effects (e.g., nausea, vomiting, hearing loss, dizziness, rash) and frequency and severity of any other adverse events reported by participants. Rob et al. and Ross et al. also assessed the tolerability of the treatment injection, measured on a visual analogue scale.[11,13]

Critical Appraisal

Randomized Controlled Trials

The risk-of-bias assessments according to outcomes for the included RCTs are reported in Appendix 3 (Table 3).

There were some concerns across all outcomes assessed for the Ross et al. RCT.[11] This was due to 2 major protocol deviations, in which 14 participants (4 allocated to ceftriaxone and 10 allocated to gentamicin, both in combination with azithromycin) did not receive treatment according to randomization and 18 participants (5 allocated to ceftriaxone and 13 allocated to gentamicin, (both in combination with azithromycin) who did not fulfill the eligibility criteria. The authors reported that it was unlikely that the imbalance in the proportion of major protocol violations was caused by selection bias or knowledge of treatment allocation, and thus were believed to not affect the trial's validity. The Rob et al. RCT was assessed as having some concerns because the study was not blinded.[13] However, microbiological cure was evaluated based on laboratory tests performed by a microbiologist who was not aware of the patient's treatment, and participants subjectively reported secondary outcomes (i.e., clinical cure and adverse events).[13] We assessed the RCT by Vanbaelen

et al. to have some concerns for risk of bias because participants and physicians were not blinded, which might have contributed to altered behaviour between treatment and follow-up visits.[15] In addition, adverse events were subjectively reported by participants.[15] We also assessed the RCT by de Vries et al. to broadly have a low risk of bias across all outcomes.[14]

Findings

Main Take-Aways

Two RCTs compared gentamicin plus azithromycin versus ceftriaxone plus azithromycin. Both treatments showed high microbiological cure rates and similar clinical outcomes, but gentamicin plus azithromycin had slightly higher treatment failure rates and more adverse events reported by patients. Another RCT compared gentamicin monotherapy with ceftriaxone monotherapy, and showed slightly lower microbiological cure rates with gentamicin. In addition, an RCT compared ceftriaxone monotherapy with ceftriaxone plus azithromycin, and found similar rates of multidrug resistance and adverse events between the 2 treatments.

Appendix 4 presents the main study findings.

Research Question 1

Clinical Efficacy of Gentamicin-Azithromycin Versus Ceftriaxone-Azithromycin

We identified 2 RCTs that compared combination therapy using gentamicin plus azithromycin with ceftriaxone plus azithromycin.[11-13]

Microbiological Cure

Across the 2 RCTs, the proportion of microbiological cure in both treatment arms was high.[11,13] Rob et al. reported that 100% of patients achieved microbiological cure in both the gentamicin plus azithromycin and ceftriaxone plus azithromycin treatment arms for all sites of infection.[13]

The Ross et al. RCT also showed that when gentamicin or ceftriaxone was combined with a single dose of azithromycin,[11] the reported microbiological clearance was 91% and 98% for participants in the gentamicin plus azithromycin and ceftriaxone plus azithromycin groups, respectively. The risk difference (RD) adjusted for clinic site and baseline outcome measure was −6.4 (95% confidence interval [CI], −10.4 to −2.4).[11]

For specific infection sites, Ross et al. reported that 96% of participants with a pharyngeal infection had microbiological clearance in the ceftriaxone plus azithromycin group, compared to 80% of patients in the gentamicin plus azithromycin group (adjusted RD = −15.3; 95% CI, −24.0 to −6.5).[11] For participants with a rectal infection, a greater proportion had clearance in the ceftriaxone plus azithromycin group (98%) compared to the gentamicin plus azithromycin group (90%; adjusted RD = −7.8; 95% CI, −13.6 to −2.0).[11]

Clinical Cure

In the RCT by Rob et al., clinical cure was evaluated in 36 patients with symptomatic infections at the start of the study.[13] In both treatment groups, all patients exhibited symptom resolution at 1 week posttreatment.[13]

Results from the Ross et al. RCT showed there was no difference between treatment groups in resolution of multiple assessed symptoms.[11]

Treatment Failure

Ross et al. found that in participants who received gentamicin plus azithromycin, treatment failure occurred in 6% of genital infections, 10% of rectal infections, and 20% of pharyngeal infections.[11] In the ceftriaxone plus azithromycin group, treatment failure occurred in 2% of genital infections, 2% of rectal infections, and 4% of pharyngeal infections.[11]

Resistance

In the RCT by Ross et al., they found that in vitro azithromycin resistance was only partially predictive of treatment failure.[11] Specifically, 95% (290 of 305) of gonococcal isolates from participants in the Ross et al. trial had azithromycin MICs within the nonresistant range (≤ 0.5 mg/L).[11] Of the 15 isolates with a MIC of greater than 0.5 mg/L, 2 (13%) were from participants who had treatment failure.[11] The majority of treatment failures overall (14 of 20; 70%) occurred in participants who had isolates with a MIC of 0.25 mg/L or less.[11] Sixty participants harboured an isolate with an azithromycin intermediate MIC of 0.5 mg/L, of whom 4 (7%) had treatment failure.[11]

Serious Adverse Events and Adverse Events

Overall, few serious adverse events were reported in both studies evaluating treatment of *N. gonorrhoeae* infection with gentamicin plus azithromycin compared to treatment with ceftriaxone plus azithromycin.[11,13] Most adverse events reported by participants in the RCT by Rob et al. were considered mild in both treatment arms.[13] In the study, 3% of participants experienced a serious adverse event in the gentamicin plus azithromycin group, while 1% of participants in the ceftriaxone plus azithromycin group reported a serious adverse event.[13] Specifically, in the gentamicin plus azithromycin group, 1 participant experienced severe nausea and 1 participant reported severe diarrhea. In the ceftriaxone plus azithromycin group, 1 patient experienced severe diarrhea.[13] Of note, nephrotoxicity and ototoxicity are known side effects of gentamicin, although these are rare with a single dose.[28] Rob et al. reported that no cases of ototoxicity occurred and acknowledged a limitation of their trial: it included only patients without chronic kidney disease, a group for which the risk of gentamicin nephrotoxicity is significantly lower.[13]

Ross et al. defined adverse events as the frequency of known side effects for antibiotics (i.e., nausea, vomiting, hearing loss, dizziness, rash) and the frequency of any other adverse events reported by participants. They found that 1 participant reported experiencing a serious adverse event (grade 4 dizziness) in the ceftriaxone plus azithromycin treatment arm, whereas no participants in the gentamicin plus azithromycin treatment group reported experiencing a serious adverse event.[11] A similar proportion of participants in both treatment arms reported at least 1 adverse event (13% in the gentamicin plus azithromycin group and 15% in the ceftriaxone plus azithromycin group).[11]

Almost all participants in both treatment groups in the Ross et al. RCT reported injection-site pain during IM administration.[11] However, the mean pain score was reported to be higher for gentamicin injections than with

ceftriaxone.[11] Patients in the Rob et al. RCT reported a higher mean pain score for ceftriaxone injections than with gentamicin.[11]

Clinical Efficacy of Gentamicin Monotherapy Versus Ceftriaxone Monotherapy

One RCT that compared gentamicin monotherapy with ceftriaxone monotherapy met the inclusion criteria.[14]

Microbiological Cure

In their primary per-protocol analysis, de Vries et al. reported that microbiological cure was observed in 100% of the participants in the ceftriaxone group compared with 93% in the gentamicin group (RD = −0.07; 95% CI, −0.16 to −0.01).[14]

Clinical Cure

Although the RCT by de Vries et al. did not evaluate clinical cure as an outcome, they reported symptom duration of *N. gonorrhoeae* infection from baseline to TOC visit.[14] In both the ceftriaxone and gentamicin groups, most symptoms disappeared at the TOC visit that was conducted 7 to 14 days after treatment.[14]

Treatment Failure

The de Vries et al. RCT defined treatment failure as a NAAT-positive TOC for *N. gonorrhoeae* at treatment follow-up.[14] In addition, participants without a TOC visit were considered to have treatment failure.[14] Although 100% of patients in the ceftriaxone group were cleared of *N. gonorrhoeae* infection, treatment failure was observed in 6 patients in the gentamicin group.[14] Of these 6 patients, 4 participants who did not have a TOC within 14 days after treatment were excluded from the primary per-protocol analysis.[14]

Resistance

De Vries et al. tested the MICs of ceftriaxone and gentamicin at baseline and TOC and found no association between ceftriaxone and gentamicin MICs and treatment failure.[14] In the study population, all *N. gonorrhoeae* strains isolated from the vagina-cervix, urethra, anus, and pharynx did not exhibit a change in MIC results between baseline and TOC in the ceftriaxone and gentamicin groups.

Serious Adverse Events and Adverse Events

De Vries et al. evaluated the number, type, and severity of treatment-related adverse events (e.g., nausea, vomiting, diarrhea, upper abdominal pain, dizziness, headache, skin rash) until 30 days after treatment, as defined by Common Terminology Criteria for Adverse Events (CTCAE) version 4.03.[14] They reported that there were there were no serious adverse events reported for patients in the gentamicin and ceftriaxone monotherapy groups.[14] In both groups, a similar proportion of patients reported at least 1 adverse event, with 23% of participants in the ceftriaxone treatment arm and 22% in the gentamicin treatment arm.[14]

Clinical Efficacy of Ceftriaxone Monotherapy Versus Ceftriaxone-Azithromycin

One RCT that compared ceftriaxone monotherapy with ceftriaxone plus azithromycin was included in our study.[15] This RCT did not evaluate microbiological cure, clinical cure, or treatment failure.[15]

Resistance

Vanbaelen et al. found that the prevalence of multidrug resistance on day 14 after treatment was similar between both the ceftriaxone monotherapy and ceftriaxone plus azithromycin treatment arms.[15]

Serious Adverse Events and Adverse Events

In the RCT by Vanbaelen et al., there were no serious adverse events reported, and no difference was found in terms of adverse events between both treatment arms.[15]

Research Question 2a

We did not identify any relevant studies evaluating the efficacy, effectiveness, or safety of cefixime administered as a single dose compared with administration across multiple doses for treating uncomplicated *N. gonorrhoeae* infection in adolescents and adults.

Research Question 2b

We did not identify any relevant studies evaluating the efficacy, effectiveness, or safety of cefixime administered as a single dose or as multiple doses compared with ceftriaxone administered as a single dose or as multiple doses.

Limitations

All included RCTs had majority cisgender men as participants; as such, women and diverse gender identities were underrepresented. Although the study populations of all included RCTs were mixed between adults and adolescents, they did not include adolescent populations younger than 16 years of age. Moreover, pregnant people were not included in any study. No comparative studies evaluating cefixime or ciprofloxacin (monotherapy or in combination with azithromycin) were identified (research question 1). We also did not identify any comparative studies evaluating cefixime administered as multiple doses or as a single dose (research questions 2a and 2b). None of the included studies evaluated outcomes such as allergic or anaphylactic reactions, adherence to treatment, partner transmission, and HIV transmission and acquisition.

In addition to the methodological limitations of the included studies described in the Critical Appraisal section, the external validity of results was low. All included RCTs were conducted in Europe, and thus generalizability to the Canadian health care landscape is unclear. Furthermore, the sample sizes in the RCTs by Vanbaelen et al. and Rob et al. were low, which may affect the precision of the studies.[13,15]

Conclusions and Implications for Decision- or Policy-Making

Main Take-Aways

Results from 2 RCTs indicate high microbiological cure rates with both gentamicin plus azithromycin and ceftriaxone plus azithromycin, with similar clinical outcomes observed. One RCT showed 100% microbiological cure rates for both gentamicin monotherapy and ceftriaxone monotherapy. However, the authors of the 3 RCTs could not conclude that gentamicin is not worse than ceftriaxone. Overall, the clinical evidence suggests that ceftriaxone therapies are better at treating gonorrhea. Although IM injections of both antibiotics were generally well tolerated, differences in injection-site pain between gentamicin and ceftriaxone highlight the importance of considering patient preferences. Further research is needed to better understand treatment effectiveness and safety, particularly with larger sample sizes and diverse populations.

Summary of Evidence

In this report, we aimed to summarize and critically appraise the evidence regarding the clinical effectiveness and safety of treatments for uncomplicated *N. gonorrhoeae* infections of the urethra, cervix, rectum, pharynx, and eye in adolescents and adults, including pregnant people. We included 4 RCTs plus 1 companion report in this review. Specifically, 2 RCTs[11-13] compared gentamicin and ceftriaxone (both in combination with azithromycin), 1 RCT[14] compared gentamicin and ceftriaxone monotherapies, and 1 RCT[15] evaluated ceftriaxone monotherapy and ceftriaxone plus azithromycin. We also included study characteristics and results of 10 single-arm studies that evaluated ceftriaxone monotherapy,[17,18,22,24,25] ceftriaxone in combination with azithromycin,[16,21] ciprofloxacin monotherapy,[19,23] and gentamicin monotherapy[20] in Appendix 5 as additional information.

We did not identify any comparative studies comparing cefixime or ciprofloxacin (monotherapy or in combination with azithromycin) or comparing cefixime administered as multiple doses and as a single dose. In addition, we did not identify any comparative studies evaluating single-dose or multidose cefixime compared to single-dose or multidose ceftriaxone. We also did not identify comparative evidence regarding clinical effectiveness and safety outcomes for allergic or anaphylactic reactions, adherence to treatment, partner transmission, and HIV transmission and acquisition.

Across the 2 RCTs that evaluated treatment with gentamicin plus azithromycin compared to ceftriaxone plus azithromycin, microbiological cure rates were high for all sites of infection. Of participants treated with gentamicin plus azithromycin, 91%[11,12] to 100%[13] exhibited microbiological cure, while 98%[11,12] to 100%[13] of participants treated with ceftriaxone plus azithromycin cleared their *N. gonorrhoeae* infection. Because the microbiological cure rate was lower for patients treated with gentamicin plus azithromycin in the Ross et al. RCT, the authors were unable to conclude that gentamicin plus azithromycin was noninferior to ceftriaxone plus azithromycin.[11,12] In the RCT that evaluated gentamicin and ceftriaxone monotherapies, 93% of participants treated with gentamicin had microbiological clearance at all sites compared to 100% of participants treated with ceftriaxone.[9] Gentamicin did not meet the noninferiority threshold that was

predefined by the authors of this study, indicating that gentamicin was not noninferior to ceftriaxone monotherapy.[14] Clinical cure was observed for the majority of patients in 3 RCTs.[11-14]

Treatment with gentamicin and ceftriaxone (monotherapy or each in combination with azithromycin) was well tolerated. In participants treated with gentamicin plus azithromycin, none[11,12] to 3%[13] reported a serious adverse event, such as severe nausea or severe diarrhea. In those participants treated with ceftriaxone plus azithromycin, 1%[13] or less[11,12] reported a serious adverse event. Injection-site pain was also prevalent in both studies, with higher mean pain scores reported for gentamicin in the Ross et al.[11,12] RCT and for ceftriaxone in the Rob et al.[13] RCT. Similarly, gentamicin and ceftriaxone monotherapies were also well tolerated, with no serious adverse events reported for patients in both groups.[14] There were also no serious adverse events reported in the RCT that evaluated ceftriaxone monotherapy compared to ceftriaxone in combination with azithromycin.[15] Resistance was inconsistently defined across 3 RCTs.[11,12,14,15] There was no clear association found between treatment failure and resistance to gentamicin, ceftriaxone, or azithromycin.

Implications for Clinical Practice

Overall, the included studies were unable to conclude that treatment with gentamicin alone or with azithromycin was noninferior to ceftriaxone (with or without azithromycin) for the clearance of *N. gonorrhoeae* infection, with the important caveat that these findings are from limited evidence. Amid changes in the AMR profile among gonococci, increasing azithromycin resistance, and decreasing susceptibility of ceftriaxone, decision-makers should consider local resistance patterns in developing treatment guidelines. Clinicians should also be aware that MICs are not always predictive of *N. gonorrhoeae* treatment failure, especially for azithromycin and gentamicin, which has implications for resistance-guided therapy.[29] Furthermore, considering the varying degrees of IM injection-site pain reported between gentamicin and ceftriaxone, it is important to consider patient acceptability and tolerability when selecting treatment options. Shared decision-making between patients and clinicians could help ensure patients receive treatment that aligns with their values and preferences.

Considerations for Future Research

Further high-quality RCTs with larger sample sizes, blinding, and diverse patient populations (e.g., adolescents, pregnant people, and transgender and nonbinary individuals) that evaluate gentamicin, cefixime, and ciprofloxacin (monotherapy or in combination with azithromycin or other antibiotics), as well as single versus multidose cefixime would help to provide more accurate findings on clinical effectiveness and safety. Future studies that assess the utility of an oral option for reducing overall *N. gonorrhoeae* prevalence and community burden should also be considered. Future work should also focus on patient-important outcomes, such as preferences, acceptability, tolerability, and barriers and facilitators to treatment.

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Clinical Review

Jasmeen Dourka coordinated the study and drafted the first version of the report. Jasmeen screened articles, abstracted data, and contributed to the report's revision and interpretation of findings. Jasmeen also carried out risk-of-bias assessments and quality assessments.

Yonda Lai screened articles, abstracted data, and contributed to the report's revision and interpretation of findings. Yonda also carried out risk-of-bias assessments and quality assessments.

Jane Pearson Sharpe screened articles, abstracted data, and contributed to the report's revision and interpretation of findings.

Sharon E. Straus provided oversight and leadership responsibility for all research activities and contributed to the report's revision and interpretation of findings.

Andrea C. Tricco provided oversight and leadership responsibility for all research activities and contributed to the report's revision and interpretation of findings.

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Conflicts of Interest

Andrea Tricco disclosed the following:

- Presented to CDEC in November 2016 on anti-VEGF medications

Darrell Tan disclosed the following:

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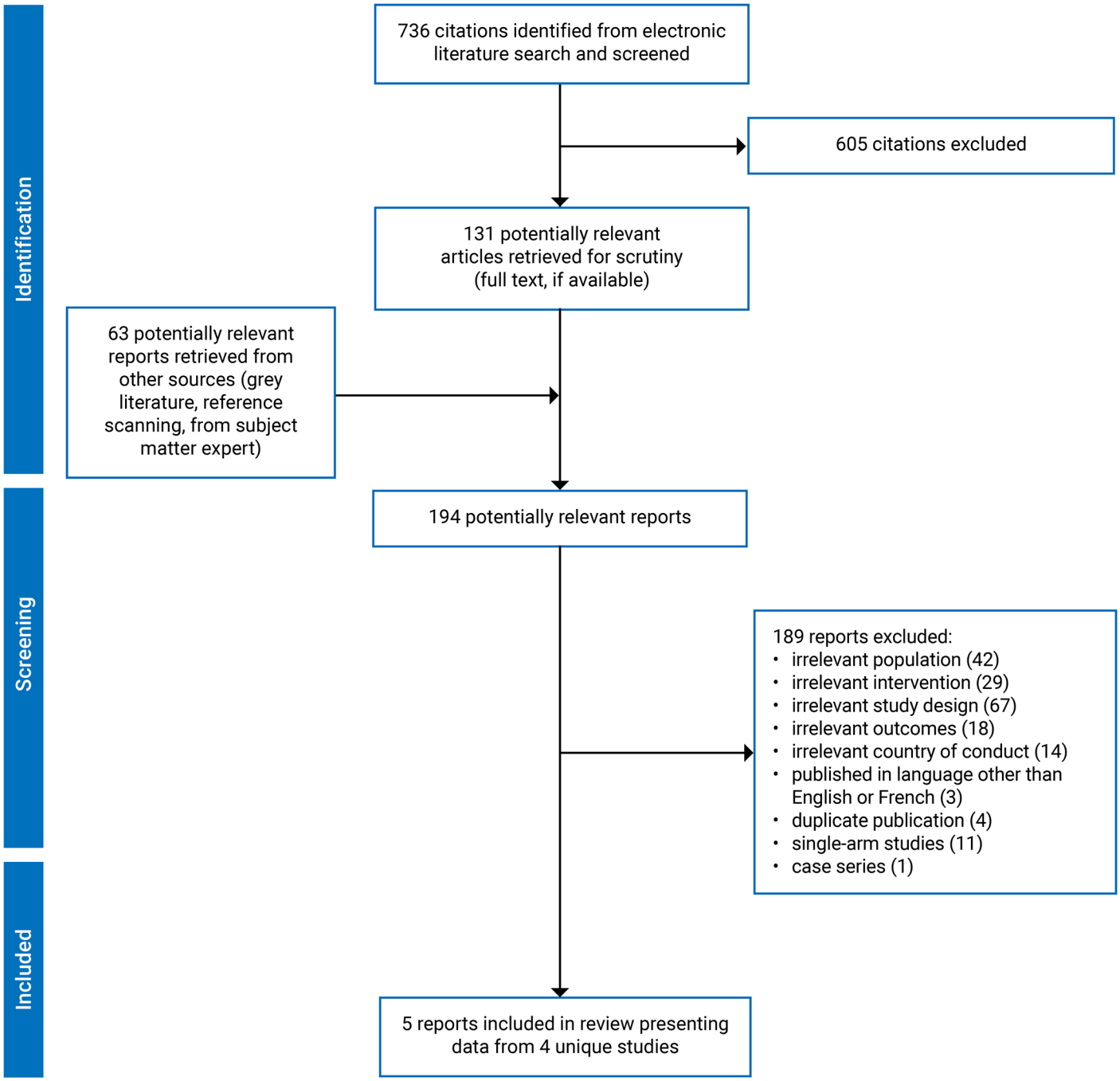
- Gilead — HIV PrEP and PEP
- Glaxo Smith Kline — Antiretroviral therapy for HIV
- CIHR Canadian HIV Trials Network — Canadian guidelines on HIV pre-exposure and postexposure prophylaxis 2017 and current (2022 to 2024)
- NACI — NACI guidance on Imvamune vaccine for mpox (2023 to 2024)

No other conflicts of interest were declared.

Appendix 1: Selection of Included Studies

Figure 1: PRISMA Flow Chart of Selected Reports



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Primary Clinical Studies

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up

Vanbaelen et al. (2023)[15]
Trial Name: ResistAZM
Country: Belgium
Funding source: Institute of Tropical Medicine
	RCT
	Setting: HIV/STI Clinic at the Institute of Tropical Medicine (Antwerp, Belgium), between January 2022 and May 2022
		Cisgender MSM (aged 18 years or older) with a confirmed diagnosis or urethral, anorectal, or pharyngeal NG infection
		Total number of participants, N = 42
		• Allocated to ceftriaxone monotherapy, n = 22
		• Allocated to ceftriaxone plus azithromycin, n = 20
		Age (years), median (IQR)
		• Total sample (n = 42): 40 (29.3 to 44.0)
		• Ceftriaxone group (n = 22): 40 (28.5 to 41.8)
		  ◦ Lost to follow-up: n = 2 (n = 1 quarantined due to COVID-19; n = 1 was ill)
		• Ceftriaxone plus azithromycin group (n = 20): 41.5 (29.8 to 45.0)
		  ◦ Lost to follow-up: n = 0
		HIV status, n (%)
		• Total sample (n = 42)
		  ◦ Positive: 9 (21.4)
		  ◦ Negative: 33 (78.6)
		• Ceftriaxone group (n = 22)
		  ◦ Positive: 5 (22.7)
		  ◦ Negative: 17 (77.3)
		• Ceftriaxone plus azithromycin group (n = 20)
		  ◦ Positive: 4 (20.0)
		  ◦ Negative: 33 (78.6)
		NG infection, n (%)
		• Total sample (n = 42)
			Intervention: Ceftriaxone 1 g IM single dose
			Comparator: Ceftriaxone 1 g IM single dose plus azithromycin 2g PO single dose
				Outcomes: Resistance, serious adverse events
				Follow-up: 14 days after treatment

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		◦ Symptomatic: 13 (31.0) ◦ Asymptomatic: 29 (69.0) • Ceftriaxone group (n = 22) ◦ Symptomatic: 7 (31.8) ◦ Asymptomatic: 15 (68.2) • Ceftriaxone plus azithromycin group (n = 20) ◦ Symptomatic: 6 (31.0) ◦ Asymptomatic: 29 (69.0) NG infection site, n (%) • Total sample (n = 42) ◦ Anorectal: 3 (7.1) ◦ Urethral: 9 (21.4) ◦ Pooled (urethral, anorectal, pharyngeal): 30 (71.4) • Ceftriaxone group (n = 22) ◦ Anorectal: 2 (9.1) ◦ Urethral: 4 (18.2) ◦ Pooled (urethral, anorectal, pharyngeal): 16 (72.7) • Ceftriaxone plus azithromycin group (n = 20) ◦ Anorectal: 1 (5.0) ◦ Urethral: 5 (25.0) ◦ Pooled (urethral, anorectal, pharyngeal): 14 (70.0)		
de Vries et al. (2022)[14] Trial Name: NABOGO Country: Netherlands **Funding source:** ZonMw and GGD-Amsterdam	RCT (noninferiority trial) Setting: Centre for Sexual Health of the Public Health Service (Amsterdam, Netherlands), between	Adults (aged 18 years or older) with confirmed anorectal or urogenital NG infection Total number of participants, N = 346 **Allocated to ceftriaxone, n = 103:** • n = 8 negative NAAT at baseline • n = 2 only pharyngeal NG	**Intervention:** Ceftriaxone 500 mg IM single dose **Comparator:** Gentamicin 5 mg/kg body weight (maximum of 400 mg) IM single dose	Outcomes: Microbiological cure, clinical cure, treatment failure, serious adverse events, resistance

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
	September 2017 and June 2020	◦ n = 93 analyzed microbiological ITT ▪ n = 0 no TOC dose ▪ n = 0 TOC ≥ 14 days ◦ n = 93 analyzed PP ▪ n = 0 use of unpermitted antibiotic ▪ n = 12 condomless sexual contact involving primary infection site ◦ n = 81 analyzed strict PP **Allocated to gentamicin, n = 102:** • n = 9 negative NAAT at baseline • n = 4 only pharyngeal NG ◦ n = 89 analyzed microbiological ITT ▪ n = 3 no TOC dose ▪ n = 1 TOC ≥ 14 days ◦ n = 85 analyzed PP ▪ n = 1 use of unpermitted antibiotic ▪ n = 3 condomless sexual contact involving primary infection site ◦ n = 81 analyzed strict PP Age (years), median (IQR) • Ceftriaxone group: 32 (27 to 40) • Gentamicin group: 35 (26 to 42) Sex, n (%) • Ceftriaxone group (n = 103): ◦ Male: 98 (95) ◦ Female: 5 (5) ◦ Transgender: 0 (0) • Gentamicin group (n = 102) ◦ Male: 96 (94)		Follow-up: 7 to 14 days after treatment

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		◦ Female: 5 (5) ◦ Transgender: 1(1) Sexual behaviour or gender group, n (%) • Ceftriaxone group (n = 103): ◦ MSM: 95 (92) ◦ Men who have sex with women: 3 (3) ◦ Women: 5 (5) ◦ Transgender: 0 (0) • Gentamicin group (n = 102) ◦ MSM: 92 (90) ◦ Men who have sex with women: 3 (3) ◦ Women: 5 (5) ◦ Transgender: 1 (< 1) HIV status, n (%) • Ceftriaxone group (n = 103): ◦ Negative: 82 (80) ◦ Positive: 21 (20) ◦ Missing: 0 (0) • Gentamicin group (n = 102) ◦ Negative: 78 (76) ◦ Positive: 24 (24) ◦ Missing: 0 (0) Location of NG infection *Vaginal or cervical infection,* n (%)[a] • Ceftriaxone group (n = 103): ◦ No: 93/95 (98) ◦ Yes: 2/95 (2) • Gentamicin group (n = 102): • No: 89/93 (96)		

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		• Yes: 2/93 (4) *Urethral infection,* n (%)[a] • Ceftriaxone group (n = 103): ◦ No: 66/95 (69) ◦ Yes: 29/95 (31) • Gentamicin group (n = 102): ◦ No: 62/93 (67) ◦ Yes: 31/93 (33) *Anal infection,* n (%)[a] • Ceftriaxone group (n = 103): ◦ No: 10/95 (11) ◦ Yes: 85/95 (89) • Gentamicin group (n = 102): ◦ No: 18/93 (19) ◦ Yes: 75/93 (81) *Pharyngeal infection,* n (%)[a] • Ceftriaxone group (n = 103): ◦ No: 53/95 (56) ◦ Yes: 42/95 (44) • Gentamicin group (n = 102): ◦ No: 59/93 (63) ◦ Yes: 34/93 (37)		
Rob et al. (2020)[13] Trial Name: NR Country: Czech Republic **Funding source:** Grant Agency of Czech Ministry of Health	RCT (noninferiority trial) Setting: Dermatovenerology Department of Na Bulovce Hospital (Prague, Czech Republic) between June 2016 and January 2019	People (aged 18 to 75 years) with a diagnosis of uncomplicated rectal or pharyngeal NG infection Total number of participants, N = 145 • Allocated to gentamicin plus azithromycin, n = 73 ◦ Lost to follow-up: n = 0 ◦ Excluded from analysis (failure to comply with sexual abstinence until TOC): n = 1	**Intervention:** Gentamicin 240 mg IM single dose plus azithromycin 2 g PO single dose **Comparator:** Ceftriaxone 500 mg IM single dose plus azithromycin 2 g PO single dose	Microbiological cure, clinical cure, serious adverse events Follow-up: 1 week (microbiological cure, clinical cure, adverse events) and 3 weeks after treatment (microbiological cure)

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up

		• Allocated to ceftriaxone plus azithromycin, n = 72
		  ◦ Lost to follow-up: n = 1 (reason NR)
		Age (years), mean (range)
		• Gentamicin plus azithromycin group (n = 72): 31.6 (18 to 46)
		• Ceftriaxone plus azithromycin group (n = 71): 34.3 (19 to 68)
		Gender, n (%)
		• Gentamicin plus azithromycin group (n = 72):
		  ◦ Male: 70 (97.2)
		  ◦ Female: 2 (2.8)
		• Ceftriaxone plus azithromycin group (n = 71):
		  ◦ Male: 68 (95.8)
		  ◦ Female: 3 (4.2)
		Sexual orientation, n (%)
		• Gentamicin plus azithromycin group (n = 72):
		  ◦ Heterosexual: 8 (11.1)
		  ◦ MSM: 64 (88.9)
		• Ceftriaxone plus azithromycin group (n = 71):
		  ◦ Heterosexual: 8 (11.3)
		  ◦ MSM: 63 (88.7)
		HIV status, n (%)
		• Gentamicin plus azithromycin group (n = 72):
		  ◦ Negative: 24 (33.3)
		  ◦ Positive: 48 (66.7)
		• Ceftriaxone plus azithromycin group (n = 71):
		  ◦ Negative: 22 (31.0)
		  ◦ Positive: 49 (69.0)
		Infection site, n (%)
		• Gentamicin plus azithromycin group (n = 72):		

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		◦ Pharyngeal: 17 (33.3) ◦ Rectal: 40 (55.6) ◦ Pharyngeal + rectal: 15 (20.8) ◦ Urogenital: 14 (19.4) • Ceftriaxone plus azithromycin group (n = 71): ◦ Pharyngeal: 14 (19.7) ◦ Rectal: 38 (53.5) ◦ Pharyngeal + rectal: 19 (26.8) ◦ Urogenital: 20 (28.2) Symptoms at site of infection, n (%) • Gentamicin plus azithromycin group (n = 72): ◦ None: 52 (72.2) ◦ Sore throat: 3 (4.2) ◦ Anal pain/discharge: 17 (23.6) • Ceftriaxone plus azithromycin group (n = 71): ◦ None: 55 (77.5) ◦ Sore throat: 1 (1.4) ◦ Anal pain/discharge: 15 (21.1) Chlamydial coinfection, n (%) • Gentamicin plus azithromycin group (n = 72): ◦ No: 48 (◦ Yes: 24 (33.3) • Ceftriaxone plus azithromycin group (n = 71): ◦ No: 45 (63.4) ◦ Yes: 26 (36.6)		
Ross et al. (2019)[11] Trial Name: G-ToG Country: UK	RCT (noninferiority trial) Setting: 14 sexual health clinics, between October 2014 and November 2016	Adults (aged 16 to 70 years) with diagnosis of untreated genital, pharyngeal, or rectal NG infection Total number of participants, N = 720 • Allocated to gentamicin plus azithromycin, n =	**Intervention:** Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose **Comparator:** Gentamicin	Outcomes: Microbiological cure, clinical cure, treatment failure, serious adverse events, resistance

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
Funding source: UK National Institute for Health Research		358 ◦ n = 66 excluded ▪ n = 10 incorrectly sampled at follow-up ▪ n = 56 did not attend follow-up • Allocated to ceftriaxone plus azithromycin, n = 362 ◦ n = 56 excluded ▪ n = 16 incorrectly sampled at follow-up ▪ n = 1 withdrew consent ▪ n = 39 did not attend follow-up Age (mean), years (SD) • Gentamicin plus azithromycin group (n = 358): 30.4 (9.9) • Ceftriaxone plus azithromycin group (n = 362): 30.2 (10.1) Gender, n (%) • Gentamicin plus azithromycin group (n = 358): ◦ Female: 65 (18) ◦ Male: 292 (82) ◦ Other: 1 (< 1) • Ceftriaxone plus azithromycin group (n = 362): ◦ Female: 69 (19) ◦ Male: 293 (81) ◦ Other: 0 (0) Ethnicity, n (%) • Gentamicin plus azithromycin group (n = 358): ◦ White: 255 (71) ◦ Black: 48 (13) ◦ Asian: 18 (5) ◦ Mixed race: 26 (7)	240 mg IM single dose plus azithromycin 1 g PO single dose	Follow-up: 2 weeks after treatment

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		◦ Other: 11 (3) • Ceftriaxone plus azithromycin group (n = 362): ◦ White: 241 (67) ◦ Black: 53 (15) ◦ Asian: 26 (7) ◦ Mixed race: 27 (7) ◦ Other: 15 (4) HIV status (participant self-report), n (%) • Gentamicin plus azithromycin group (n = 358): ◦ Positive: 43 (12) ◦ Unknown: 8 (2) • Ceftriaxone plus azithromycin group (n = 362): ◦ Positive: 53 (15) ◦ Unknown: 10 (3) Site of infection, n (%) • Gentamicin plus azithromycin group (n = 358): ◦ Genital: 219 (61) ◦ Pharyngeal: 128 (36) ◦ Rectal: 147 (41) • Ceftriaxone plus azithromycin group (n = 362): ◦ Genital: 190 (52) ◦ Pharyngeal: 128 (35) ◦ Rectal: 159 (44) Number of sites infected, n (%) • Gentamicin plus azithromycin group (n = 358): ◦ One: 180 (50) ◦ Two: 94 (26) ◦ Three: 42 (12) • Ceftriaxone plus azithromycin group (n = 362):		

Study citation, trial name, country, funding source	Study design, setting	Population characteristics	Intervention and comparator(s)	Clinical outcomes, length of follow-up
		◦ One: 189 (52) ◦ Two: 96 (27) ◦ Three: 32 (9)		

g = grams; HIV = HIV; IM = intramuscular; IQR = interquartile range; miTT = microbiological intention to treat; mg = milligrams; MIC = minimum inhibitory concentration; MSM = men who have sex with men; NG = *Neisseria gonorrhoeae*; NR = not reported; PO = "per os" - oral administration; PP = per protocol; RCT = randomized controlled trial; STI = sexually transmitted infection.

Notes: We have retained the original terms that study authors used when describing sex, gender, and sexual orientation.

This table has not been copy-edited.

[a]Among participants with a NAAT-confirmed NG infection

Appendix 3: Critical Appraisal of Included Publications

Note this appendix has not been copy-edited.

Table 3: Risk-of-Bias Assessment per Outcome Within Each RCT Using RoB2

First author (year)	Risk-of-bias domain[a]					Overall risk of bias
	Randomization	Deviation	Missing data	Measurement	Results selection	
Microbiological cure						
De Vries 2022[14]	Low	Low	Low	Low	Low	Low
Rob 2020[13]	Low	Some[c]	Low	Low	Low	Some
Ross 2019[11]	Low	Some[b]	Low	Low	Low	Some
Clinical cure						
De Vries 2022[14]	Low	Low	Low	Low	Low	Low
Rob 2020[13]	Low	Some[c]	Low	Some[c]	Low	Some
Ross 2019[11]	Low	Some[b]	Low	Low	Low	Some
Treatment failure						
De Vries 2022[14]	Low	Low	Low	Low	Low	Low
Ross 2019[11]	Low	Some[b]	Low	Low	Low	Some
Serious adverse events and adverse events						
Vanbaelen 2023[15]	Low	Some[d]	Low	Some[d]	Low	Some
De Vries 2022[14]	Low	Low	Low	Low	Low	Low
Rob 2020[13]	Low	Some[c]	Low	Some[c]	Low	Some
Ross 2019[11]	Low	Some[b]	Low	Low	Low	Some
Resistance						
Vanbaelen 2023[15]	Low	Some[d]	Low	Low	Low	Some
De Vries 2022[14]	Low	Low	Low	Low	Low	Low
Ross 2019[11]	Low	Some[b]	Low	Low	Low	Some

RoB2 = Cochrane Risk of Bias tool, version 2

[a]**Randomization**: bias arising from the randomization process; **Deviation**: bias due to deviations from the intended intervention; **Missing data**: bias due to missing outcome data; **Measurement**: bias in the measurement of the outcome; **Results selection**: bias in the selection of the reported results. Judgment scale: Low, some, high, unclear.

[b]Rated as "some concern" due to 2 major protocol violations – not receiving treatment according to randomization (4 allocated to ceftriaxone, 10 to gentamicin) and not fulfilling eligibility criteria (5 allocated to ceftriaxone and 13 to gentamicin).

[c]Rated as "some concern" as the study was not blinded, but the primary outcome was evaluated based on laboratory tests performed by microbiologist who was not aware of patient's treatment and secondary outcomes were subjectively reported by the patients.

[d]Rated as "some concern" as neither participants nor physicians were blinded, which might have led to altered behaviour between the study visits.

Appendix 4: Main Study Findings

Table 4: Summary of Findings by Outcome — Microbiological Cure

Population	de Vries et al. (2022)[14]		Rob et al. (2020)[13]		Ross et al. (2019)[11]	
	Gentamicin 5 mg/kg body weight (max. 400 mg) IM	Ceftriaxone 500 mg IM	Gentamicin 240 mg IM plus azithromycin 2 g PO	Ceftriaxone 500 mg IM plus azithromycin 2 g PO	Gentamicin 240 mg IM plus azithromycin 1 g PO	Ceftriaxone 500 mg IM plus azithromycin 1 g PO
Total study population, N	102	103	73	72	358	362
Participants with NG infection cleared at all sites, n of N (%; 95% CI)	79 of 85 (93%; 85 to 97)	93 of 93 (100%; 96 to 100)	72 of 72 (100%; 95 to 100)	71 of 71 (100%; 95 to 100)	267 of 292 (91%; 88 to 94)	299 of 306 (98%; 95 to 99)
Participants with genital infection cleared, n of N (%; 95% CI)	3 of 4 [a] (75%; 19 to 99)	2 of 2 [a] (100%; 16 to 100)	NA	NA	163 of 174 (94%; 90 to 97)	151 of 154 (98%; 96 to 100)
Participants with anorectal infection cleared, n of N (%; 95% CI)	68 of 72 (87%; 86 to 98)	82 of 84 (98%; 92 to 100)	40 of 72 (55.6%) [b]	38 of 71 (53.5%) [b]	107 of 119 (90%; 84 to 95)	134 of 137 (98%; 95 to 100)
Participants with pharyngeal infection cleared, n of N (%; 95% CI)	9 of 34 (26%; 13 to 44)	38 of 42 (90%; 77 to 97)	17 of 72 (23.6%) [b]	14 of 71 (19.7%) [b]	82 of 102 (80%; 72 to 88)	108 of 113 (96%; 92 to 99)
Participants with concurrent rectal and pharyngeal infections cleared, n of N (%; 95% CI)	NA	NA	15 of 72 (20.8%) [b]	19 of 71 (26.8%) [b]	NA	NA
Participants with urethral infection cleared, n of N (%; 95% CI)	26 of 30 (87%; 69 to 96)	29 of 29 (100%; 88 to 100)	NA	NA	NA	NA

CI = confidence interval; DNA = DNA; g = grams; IM = intramuscular; mg = milligrams; NA = not applicable; NG = *Neisseria gonorrhoeae*; PO = "per os"- oral administration; RNA = ribonucleic acid; SD = single dose.

Notes: Data are reported from the per-protocol analysis population, unless otherwise stated. This table has not been copy-edited.

[a]Genital infections for the de Vries et al. study were specific to the vagina and cervix.

[b]In the Rob et al. RCT, data are presented as the proportion of participants with anorectal, pharyngeal, or concurrent rectal and pharyngeal infections.

Table 5: Summary of Findings by Outcome — Clinical Cure

Study citation and study design	Method of measurement	Intervention/Comparator	Result
de Vries et al. (2022)[14] RCT	Participant reported	Ceftriaxone 500 mg IM single dose	Symptoms at T_0, n (%): • Urethral discharge: 26 (28%) • Dysuria: 28 (30%) • Anal discharge: 7 (8%) • Pain/itching anus: 10 (11%) • Discharge, unknown location: 1 (1%) • Other symptoms: 11 (12%) Symptoms at TOC, n (%): • Urethral discharge: 1 (1%) • Dysuria: 2 (2%) • Anal discharge: 0 (0%) • Pain/itching anus: 0 (0%) • Discharge, unknown location: 0 (0%) • Other symptoms: 0 (0%)
		Gentamicin 5 mg/kg body weight (maximum of 400 mg) IM single dose	Symptoms at T_0, n (%): • Urethral discharge: 23 (27%) • Dysuria: 21 (25%) • Anal discharge: 9 (11%) • Pain/itching anus: 9 (11%) • Discharge, unknown location: 4 (5%) • Other symptoms: 9 (11%) Symptoms at TOC, n (%): • Urethral discharge: 3 (4%) • Dysuria: 3 (4%) • Anal discharge: 1(1%) • Pain/itching anus: 1 (1%)

Study citation and study design	Method of measurement	Intervention/Comparator	Result	
			• Discharge, unknown location: 1 (1%) • Other symptoms: 1 (1%)	
Rob et al. (2020)[13] RCT	Participant reported	Gentamicin 240 mg IM single dose + Azithromycin 2g PO single dose (combination therapy)	Clinical cure (evaluated in the 36/143 (25.2%) patients symptomatic at baseline) was observed in all patients at the first week follow-up examination.	
		Ceftriaxone 500 g IM single dose + azithromycin 2g PO single dose (combination therapy)		
Ross et al. (2019)[11] RCT	Participant reported	Ceftriaxone 500 mg IM single dose + Azithromycin 1 g PO single dose (combination therapy)	Resolution of symptoms present at baseline, n: • Genital discharge: 129 • Dysuria: 106 • Sore throat: 47 • Anorectal pain: 13 • Rectal bleeding: 8 • Rectal discharge: 12 • Tenesmus: 7 • Constipation 11 • Intermenstrual bleeding (women only): 9	**AJD (95% CI) between groups:** • Genital discharge: −0.1% (−5.5 to 5.2) • Dysuria: −7.7 (−13.6 to 1.9) • Sore throat: 4.0% (−7.4 to 15.4) • Anorectal pain: −24.4% (−62.5 to 13.7) • Rectal bleeding: 12.5% (−10.4 to 35.4) • Rectal discharge: −9.9% (−43.7 to 23.9) • Tenesmus: 12.5% (−10.4 to 35.4) • Constipation −12.6% (−57.8 to 32.6) • Intermenstrual bleeding (women only): 11.1% (−9.4 to 31.6)

Study citation and study design	Method of measurement	Intervention/Comparator	Result	
		Gentamicin 240 mg IM single dose + Azithromycin 1 g PO single dose (combination therapy)	Resolution of symptoms present at baseline, n: • Genital discharge: 147 • Dysuria: 128 • Sore throat: 45 • Anorectal pain: 7 • Rectal bleeding: 7 • Rectal discharge: 8 • Tenesmus: 3 • Constipation: 4 • Intermenstrual bleeding (women only): 5	

AJD = adjusted risk difference; CI = confidence interval; g = grams; IM = intramuscular; mg = milligrams; NA = not applicable; PO = "per os"- oral administration; RCT = randomized controlled trial; T_0 = baseline; TOC = test of cure
Note: This table has not been copy-edited.

Table 6: Summary of Findings by Outcome — Treatment Failure

Study citation and study design	Method of measurement	Intervention/Comparator	Result
de Vries et al. (2022)[14] RCT	NAAT-positive TOC (7 to 14 days after treatment), or administering rescue medication for persisting symptoms in combination with a positive Gram-stain result, or a positive NG culture (3 to 6 days after treatment)	Ceftriaxone 500 mg IM single dose	0 participants in the ceftriaxone group experienced treatment failure
		Gentamicin 5 mg/kg body weight (maximum of 400 mg) IM single dose	In the primary per-protocol analysis 6 participants (of 85) in the gentamicin group did not achieve microbiological clearance (7 to 14 days after treatment)
Ross et al. (2019)[11] RCT	NAAT-positive TOC	Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose (combination therapy)	Participant treatment failure occurred in 2% of genital infections, 2% of rectal infections, and 4% of pharyngeal infections in those who received ceftriaxone plus azithromycin
		Gentamicin 240 mg IM single dose plus azithromycin 1 g PO single dose (combination therapy)	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

g = grams; IM = intramuscular; mg = milligrams; NA = not applicable; NAAT = nucleic acid amplification test; NG; *Neisseria gonorrhoeae*; NR = not reported; PO = "per os"- oral administration; RCT = randomized control trial; TOC = test of cure

Note: This table has not been copy-edited.

Table 7: Summary of Findings by Outcome — Serious Adverse Events and Adverse Events

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result

Vanbaelen et al. (2023)[15]
RCT
	Participant-reported[a]	Ceftriaxone 1 g IM single dose plus azithromycin 2g PO single dose (combination therapy)	• Any adverse event: n = 4
			  ◦ Abdominal pain: 25% (1/4)
			  ◦ Nausea: 75% (3/4)
			  ◦ Pain at injection site: 25% (1/4)
			• Presyncope: 25% (1/4)

		Ceftriaxone 1 g IM single dose	• Any adverse event: n = 2
			  ◦ Abdominal pain: 0% (0/2)
			  ◦ Nausea: 0% (0/4)

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			◦ Pain at injection site: 100% (2/2) • Presyncope: 0% (0/2)
de Vries et al. (2022)[14] RCT	Participant reported	Ceftriaxone 500 mg IM single dose	• Participants with at least 1 adverse event: 23% (24/103) • Participants with serious adverse events: 0% (0/103) • 25% reduction in eGFR: 4% (4/103) • Nausea: 3% (3/103) • Vomiting: 0% (0/103) • Diarrhea:11% (11/103) • Upper abdominal pain: 4% (4/103) • Dizziness: 2% (2/103) • Headache: 3% (3/103) • Skin rash: 2% (2/103) • Itching: 2% (2/103) • Throat ache: 3% (3/103) • Fatigue: 3% (3/103) • Fever or influenza-like symptoms: 1% (1/103) • Other adverse events: 7% (7/103)
		Gentamicin 5 mg/kg body weight (maximum of 400 mg) IM single dose	• Participants with at least 1 adverse event: 22% (22/102) • Participants with serious adverse events: 0% (0/102) • 25% reduction in eGFR: 3% (3/102) • Nausea: 1% (1/102) • Vomiting: 1% (1/102) • Diarrhea: 2% (2/102) • Upper abdominal pain: 1% (1/102) • Dizziness: 3% (3/102) • Headache: 5% (5/102) • Skin rash: 1% (1/102) • Itching: 2% (2/102)

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			• Throat ache: 3% (3/102) • Fatigue: 3% (3/102) • Fever or influenza-like symptoms: 2% (2/102) • Other adverse events: 12% (12/102)
Rob et al. (2020)[13] RCT	Visual analogue scale	Gentamicin 240 mg IM single dose plus azithromycin 2 g PO single dose	IM injection-site mean pain score (range): 1.8 (1 to 5)
		Ceftriaxone 500 mg IM single dose plus azithromycin 2 g PO single dose	IM injection-site mean pain score (range): 3.4 (0 to 10)

	Participant reported	Gentamicin 240 mg IM single dose plus azithromycin 2 g PO single dose	• Total number of adverse events (n = 32)
			• Participants with at least 1 adverse event: 40% (29/72)
			• Participants with serious adverse events: 3% (2/72)
			• Nausea: 19% (14/72)
			  ◦ Mild: 17% (12/72)
			  ◦ Moderate: 1% (1/72)
			  ◦ Severe: 1% (1/72)
			• Diarrhea: 24% (17/72)
			  ◦ Mild: 14% (10/72)
			  ◦ Moderate: 8% (6/72)
			  ◦ Severe: 1% (1/72)
			• Stomach pain: 3% (2/72)
			  ◦ Mild: 0% (0/72)
			  ◦ Moderate: 1% (1/72)
			  ◦ Severe: 1% (1/72)
			• Vomiting: 0% (0/72)
			  ◦ Mild: 0% (0/72)
			  ◦ Moderate: 0% (0/72)
			  ◦ Severe: 0% (0/72)
			• Rash/edema: 1% (1/72)
			  ◦ Mild: 0% (0/72)

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			◦ Moderate: 1% (1/72) ◦ Severe: 0% (0/72)
		Ceftriaxone 500 mg IM single dose plus azithromycin 2 g PO single dose	• Total number of adverse events (n = 39) • Participants with at least 1 adverse event: 46% (33/71) • Participants with serious adverse events: 1% (1/71) • Nausea: 27% (19/71) ◦ Mild: 21% (15/72) ◦ Moderate: 6% (4/72) ◦ Severe: 0% (0/72) • Diarrhea: 27% (19/71) ◦ Mild: 18% (13/72) ◦ Moderate: 7% (5/72) ◦ Severe: 1% (1/72) • Stomach pain: 1% (1/71) ◦ Mild: 0% (0/72) ◦ Moderate: 1% (1/72) ◦ Severe: 0% (0/72) • Vomiting: 1% (1/71) ◦ Mild: 1% (1/72) ◦ Moderate: 0% (0/72) ◦ Severe: 0% (0/72) • Rash/edema: 0% (0/71) ◦ Mild: 0% (0/72) ◦ Moderate: 0% (0/72) ◦ Severe: 0% (0/72)
Ross et al. (2019)[11] RCT	Visual analogue scale	Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose	IM injection-site mean pain score: 21/100
		Gentamicin 240 mg IM single dose plus azithromycin 1 g PO single dose	IM injection-site mean pain score: 36/100

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result

	Participant reported	Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose	• Total number of adverse events (n = 54)
			• Participants with at least 1 adverse event: 15% (48/320)
			• Participants with serious adverse events: < 1% (1/320)
			• Nausea: 12% (38/320)
			• Vomiting: 1% (3/320)
			• Reduction in hearing: 2% (5/320)
			• Dizziness or unsteadiness: 7% (24/320)
			• Skin rash: 2% (5/320)
			• IM injection-site pain: 98% (315/320)
			• Most frequently reported adverse events (> 5%)
			  ◦ Gastrointestinal disorders: 14/54
			  ◦ Nervous system disorders: 10/54
			  ◦ General disorders and administration site conditions: 6/54
			  ◦ Infections and infestations: 6/54

		Gentamicin 240 mg IM single dose plus azithromycin 1 g PO single dose	• Total number of adverse events (n = 43)
			• Participants with at least 1 adverse event: 13% (38/298)
			• Participants with serious adverse events: 0% (0/298)
			• Nausea: 14% (41/298)
			• Vomiting: 1% (12/298)
			• Reduction in hearing: 1% (3/298)
			• Dizziness or unsteadiness: 7% (21/298)
			• Skin rash: 4% (5/320)
			• IM injection-site pain: 99% (294/298)
			• Most frequently reported adverse events (> 5%)
			  ◦ Gastrointestinal disorders: 22/43
			  ◦ Nervous system disorders: 3/43
			  ◦ General disorders and administration site conditions:

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			3/43 ◦ Infections and infestations: 5/43

eGFR = estimated glomerular filtration rate; g = grams; IM = intramuscular; mg = milligrams; PO = "per os"= oral administration; RCT = randomized controlled trial

Notes: Data are number of participants or mean (range).

This table has not been copy-edited.

[a]Data for Vanbaelen et al. 2023 are reported as number of events. All other trials consider the number of participants.

Table 8: Summary of Findings by Outcome — Resistance

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
Vanbaelen et al. (2023)[15] RCT	Metagenomic sequencing and resistome profiling of isolates	Ceftriaxone 1 g IM single dose plus azithromycin 2 g PO single dose	Multidrug resistance proportions at day 14 (95% CI): • Aminoglycosides, Beta-lactams, Fluoroquinolones, Tetracyclines: 95% (76.4 to 99.1) • Aminoglycosides, Beta-lactams, Fluoroquinolones, Tetracyclines: 95% (76.4 to 99.1) • Aminoglycosides, Beta-lactams, Fluoroquinolones, Tetracyclines AND macrolides: 95% (76.4 to 99.1)
		Ceftriaxone 1 g IM single dose	Multidrug resistance proportions at day 14 (95% CI): • Aminoglycosides, beta-lactams, Fluoroquinolones, Tetracyclines: 100% (83.9 to 100) • Aminoglycosides, beta-lactams, Fluoroquinolones, Tetracyclines: 100% (83.9 to 100) • Aminoglycosides, beta-lactams, Fluoroquinolones, Tetracyclines AND macrolides: 100% (83.9 to 100)
de Vries et al. (2022)[14] RCT	In vitro measurement of MICs at T_0 and T_7	Ceftriaxone 500 mg IM single dose	Paired MIC results (mg/L) of Neisseria gonorrhoeae isolates per anatomical site at T_0 and TOC patients with MIC results at both time points; N; Median (IQR); p value): • Vagina-cervix ◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA • Urethra

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA • Anus ◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA • Pharynx ◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA
		Gentamicin 5 mg/kg body weight (maximum of 400 mg) IM single dose	Paired MIC results (mg/L) of Neisseria gonorrhoeae isolates per anatomical site at T_0 and TOC from patients with MIC results at both time points; N; Median (IQR); p value) • Vagina-cervix ◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA • Urethra ◦ T_0: 3; 3 (1.5 to 4); NA ◦ TOC: 3; 0.8 (0.8 to 3); NA • Anus ◦ T_0: 1; 3(3 to 3); NA ◦ TOC: 1; 1.5(1.5 to 1.5); NA • Pharynx ◦ T_0: 0 (NA); NA ◦ TOC: 0 (NA); NA
Ross et al. (2019)[11] RCT	In vitro measurement of antibiotic MICs	Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose	Distribution of MICs by treatment response in 145 participants[b] Clearance of NG infection: • 20 at MIC ≤ 0.002mg/L • 66 at 0.004 mg/L • 25 at 0.008 mg/L • 19 at 0.016mg/L

Study citation and study design	Method of measurement	Intervention vs. Comparator	Result
			• 9 at 0.032 mg/L • 1 at 0.064 mg/L • 1 at 0.125 mg/L
		Gentamicin 240 mg IM single dose plus azithromycin 1 g PO single dose	Distribution of MICs by treatment response in 132 participants[c] Clearance of NG infection: • 3 at 1.0 mg/L • 33 at 2.0 mg/L • 81 at 4.0 mg/L • 3 at 8.0 mg/L

g = grams; IM = intramuscular; mg = milligrams; mg/L = milligram per litre; MICs = minimal inhibitory concentrations; NA = not available; PO = "per os"= oral administration; RCT = randomized controlled trial; TOC = test of cure; T_0 = baseline.

Notes: Vanbaelen et al. created 3 indicators of multidrug resistance: The first indicator represented participants who carried resistance genes to > 1 of the following nonmacrolide antibiotics: aminoglycosides, beta-lactams, fluoroquinolones, and tetracyclines. The second indicator was created with the addition of addition of trimethoprim and sulfonamides to the previous indicator. The third indicator represented participants who carried resistance genes to both macrolides and nonmacrolides.

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[a]Multidrug resistance proportions were not reported at T_0

[b]For those who did not clear infection: 1 participant showed an MIC of ≤ 0.002mg/L; 1 with 0.004 mg/L and 2 with 0.008 mg/L. Azithromycin MICs for the 4 participants who did not clear were 0·125 mg/L (cervix), 0·125 mg/L (rectum), 0·125 mg/L (pharynx), and 0·25 mg/L (urethra).

[c]For those who did not clear their infection: 12 showed gentamicin MICs of 4 mg/L.

Appendix 5: Summary of Single-Arm Studies and Case Series

Note this appendix has not been copy-edited.

Table 9: Characteristics of Relevant Single-Arm Studies

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
Bízova et al., (2024)[16] Country: Czech Republic **Funding source:** NR	Study Design: Randomized controlled trial[a] Setting: Two centres in Czech Republic between April 2021-June 2022	Patients 18 to 65 years of age diagnosed with uncomplicated urogenital, rectal, or pharyngeal gonorrhea Total sample: n = 161 Allocated to ceftriaxone plus azithromycin: n = 81 (5 lost to follow-up) Age in years, mean (range): • 32.8 (19 to 55) Gender, n (%): • Female: 4/76 (5.3%) • Male: 72/76 (94.7%) Sexual orientation, n (%): • Heterosexual: 29/76 (38.2%) • MSM: 47/76 (61.8%)	Ceftriaxone 1 g IM single dose plus azithromycin 2 g PO single dose[c]	Microbiological cure (NAAT-negative TOC and culture TOC) Clinical cure (clinical assessment of the patient by the physician) Serious adverse events
Belakebi et al., (2023)[17] Country: France **Funding source:** None declared	Study Design: Prospective cohort study Setting: Single sexual health French centre between April 2021-August 2021	Patients test-screened for *N. gonorrhoeae* and *C. trachomatis* infection from self-collected urinary, pharyngeal, cervicovaginal and anal samples Total sample: n = 122[b] Received ceftriaxone group: n = 63 Age in years, mean (standard deviation): • 32.9 (10.1) Gender, n (%): • Female: 3/122 (2.5%) • Male: 119/122 (97.5%) Sexual orientation, n (%): • Heterosexual: 51/119 (39.8%) • MSM: 68/119 (60.2%)	Ceftriaxone 1 g IM single dose[c]	Microbiological cure (negative TOC, method NR) Treatment Failure (positive TOC) Serious adverse events
Aoki et al., (2021)[18] Country: Japan **Funding source:** Public and Industry	Study Design: Prospective cohort study Setting: Single	MSM patients aged > 19 years diagnosed with extragenital (rectal or pharyngeal) gonorrhea infection	Ceftriaxone 1 g IV single dose[c]	Microbiological cure (NAAT- negative TOC) Treatment Failure (positive TOC)

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
	Sexual Health Clinic between January 2017-December 2020	Total sample: n = 376 Allocated to ceftriaxone: n = 208 Age in years, mean (standard deviation): • 32.9 (10.1) Gender, n (%): • Male: 208/208 (100%) Sexual orientation, n (%): • MSM: 208/208 (100%)		Resistance (determine MICs, method NR)
Klausner et al., (2020)[19] Country: US **Funding source:** Public	Study Design: Single-arm clinical trial Setting: Eight sexual health clinics in 7 cities between October 2016-December 2018	Patients age ≥ 18 years, provided informed consent, had untreated urogenital or rectal N. gonorrhea infection, no contraindications to ciprofloxacin treatment, and were willing to abstain from sexual intercourse or use condoms during any sexual contact until the test of cure visit Total sample: n = 106 Allocated to ciprofloxacin: n = 106 Age in years, mean (standard deviation): • 28.1 (7.9) Gender, n (%): • Female: 8/106 (7.5%) • Male: 98/106 (92.5%) Sexual orientation, n (%): • Heterosexual: 16/106 (15.1%) • Homosexual/gay/lesbian: 73/106 (68.9%) • Bisexual: 14/106 (13.2%) • Other/refused to answer: 3/106 (2.8%) Race, n (%): • American Indian/Alaskan Native: 2/106 (1.9%) • Asian: 7/106 (6.6%) • Hawaiian/Pacific Islander: 1/106 (0.9%) • African American/Black: 29/106 (27.4%)	Ciprofloxacin 500 mg PO single dose	Microbiological cure (negative culture)

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
		• White: 57/106 (53.8%) • Multiracial: 5/106 (4.7%) • Other/unknown: 5/106 (4.7%)		
Barbee et al., (2019)[20] Country: US **Funding source:** Public	Study Design: Single-arm clinical trial Setting: A sexually transmitted diseases centre between September 2018-March 2019	MSM patients who screened positive for pharyngeal gonorrhea, had not yet received treatment, and presented to the sexually transmitted diseases clinic for treatment Total sample: n = 13 Allocated to gentamicin: n = 13 Age in years, mean (range): • 29.3 (21 to 44) Gender, n (%): • Male: 13/13 (100%) Sexual orientation, n (%): • MSM: 13/13 (100%) Race, n (%): • White: 3/13 (23%) • Black/African American: 1/13 (7.7%) • Asian/Pacific Islander: 3/13 (23%) • Other: 6/13 (46.2%)	Gentamicin 260 mg IM single dose	Microbiological cure (negative culture) Treatment Failure (positive culture for gonorrhea) Resistance (standard antimicrobial MICs by agar dilution) Adverse events (patient reported)
Hook et al., (2019)[22] Country: US **Funding source:** Industry	Study Design: Randomized controlled trial[a] Setting: Twenty-five centres between January 2014-Decemer 2014	Patients 15 years of age with uncomplicated urogenital gonorrhea Total sample: n = 460 Allocated to ceftriaxone: n = 154 Age in years, mean (standard deviation, range): • 28.7 (10.04, 17 to 63) Gender, n (%): • Female: 35/154 (22.7%) • Male: 119/154 (77.3%) Sexual orientation of males, n (%): • Heterosexual: 59/119 (49.6%) • MSM/bisexual: 60/119 (50.4%) Race, n (%):	Ceftriaxone 250mg IM single dose	Microbiological cure (NAAT-negative TOC or culture) Clinical cure (investigator assessment of urogenital site at the TOC visit) Treatment failure (positive culture) Adverse events (patient reported)

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
		• White: 48/154 (31.2%) • Black/African American: 92/154 (59.7%) • Asian: 1/154 (0.6%) • Other: 13/154 (8.4%)		
Chen et al., (2019)[21] Country: US and Australia **Funding source:** Industry	Study Design: Randomized controlled trial[a] Setting: Three sexual health centres between September 2014- August 2015	Patients aged 15 years or older with untreated uncomplicated genital gonorrhea Total sample: n = 262 Allocated to ceftriaxone plus azithromycin: n = 131 Age in years, mean (standard deviation): • 29.4 (10.3) Gender, n (%): • Female: 7/131 (5.0%) • Male: 124/131 (95.0%) Sexual orientation of males, n (%): • Heterosexual: 29/124 (23.0%) • MSM: 95/124 (77.0%)	Ceftriaxone 500 mg IM single dose plus azithromycin 1g PO single dose	Microbiological cure (negative culture or NAAT-negative TOC) Treatment failure (persistence- positive culture or positive NAAT) Adverse events (patient reported)
Taylor et al., (2018)[24] Country: US **Funding source:** Public and Industry	Study Design: Randomized controlled trial[a] Setting: Five sexual health centres between November 2014-December 2015	Men and non-pregnant women 18 to 55 years of age were eligible to participate if they had signs and symptoms of urogenital gonorrhea, untreated urogenital gonorrhea, or sexual contact in the preceding 14 days with a person who had gonorrhea Total sample: n = 180[b] Allocated to ceftriaxone: n = 40 Age in years, mean (standard deviation): • 28.8 (8.2) Gender, n (%): • Female: 13/180 (7.0%) • Male: 167/180 (93.0%) Sexual partner of males, n (%): • Women only: 90/180 (54.0%) • Men only: 66/180 (40.0%) • Men and women: 11/180 (7.0%) Race, n (%):	Ceftriaxone 500 mg IM single dose	Microbiological cure (NAAT-negative TOC or culture) Clinical cure (investigator's assessment) Adverse events (patient reported)

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
		• Black: 107/180 (59%) • White: 58/180 (32%) • Other, multiracial, or unknown: 15/180 (8%)		
Allan-Blitz et al., (2018)[23] Country: US **Funding source:** Public	Study Design: Retrospective review of patient records Setting: A single sexual health centre between June 2016-September 2017	Participants with wild-type (non-mutated) gyr A genotype gonorrhea infections Total sample: n = 25 Received ciprofloxacin: n = 25	Ciprofloxacin 500 mg PO single dose	Microbiological cure (negative TOC, method NR)
Ito et al., (2016)[25] Country: Japan **Funding source:** Public	Study Design: Prospective cohort study Setting: A single clinic between January 2018-December 2015	Men with gonococcal urethritis Total sample: n = 255 Received ceftriaxone: n = 255	Ceftriaxone 1 g IV single dose	Microbiological cure (NAAT-negative TOC) Resistance (MICs by agar dilution) Adverse events (patient reported)
Wind et al., (2016)[26] Trial Name: NA Country: Netherlands **Funding source:** Public	Study Design: Prospective cohort study Setting: STI Outpatient Clinic from March through October 2014	Patients (aged 18 years or older) with anogenital NG infection to whom routine treatment was prescribed Total number of participants, N = 62 Treatment at inclusion, n (%) • Ceftriaxone monotherapy: 23 (37) • Ceftriaxone plus azithromycin: 27 (44) • n = 1 excluded due to a negative pretreatment result for NG Sex, n (%) • Male: 41 (66) • Female: 21 (34) Age, years, median (IQR): 24 (22 to 34) Sexual risk group, n (%) • MSM: 35 (56) • Heterosexual male: 6 (10) • Female: 21 (34) HIV infected, n (%): 12 (19) NG Infection, n (%) • Urogenital: 41 (66) • Rectal: 31 (50) • Pharyngeal: 14 (23)	Ceftriaxone 500 mg IM single dose Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO single dose [b]	Microbiological cure (RNA and DNA-based NAAT)

Study citation, country, funding source	Study design, setting	Population characteristics	Intervention	Clinical outcomes
		Chlamydia trachomatis coinfection, n (%): 23 (37) Signs or symptoms at examination, n (%): 37 (60) MIC, mg/L, mean (range) • Ceftriaxone: 0.006 (< 0.002 to 0.047) • Azithromycin: 0.142 (< 0.016 to 1)		

IM = intramuscular; mg = milligrams; MICs = minimal inhibitory concentration; MSM = men who have sex with men; NAAT = nucleic acid amplification test; NR = not reported; PO = "per os" - oral administration; RNA = ribonucleic acid; TOC = test of cure

Note: These studies did not meet the eligibility criteria but had 1 relevant treatment group

[a]Only 1 treatment arm in the randomized controlled trial was relevant to our study.

[b]Population characteristics were reported for entire sample and were unavailable for relevant treatment arm.

[c]The following studies included ceftriaxone plus doxycycline as an intervention: Belakabi et al., Aoki et al. and Bízova et al.

[d]In the Wind et al. study, patients received treatment with ceftriaxone plus azithromycin only if they were coinfected with *Chlamydia trachomatis*.

Table 10: Characteristics of Relevant Case Series

Study citation, country, funding source	Study design, setting	Population characteristics	Treatments	Clinical outcomes
Belga et al. (2019)[27] Country: Canada **Funding source:** None declared	Retrospective case series Setting: Acute care centres, community providers, STI clinics, between 2000 and 2016	Adults (≥ 12 years) with a diagnosis of gonococcal conjunctivitis (ocular infection) Total number of patients, N = 45 • TOC data available for n = 7 cases Age, median (IQR) • 24 (20 to 33) Sex, n (%) • Female: 19 (42%) • Male: 26 (58%) Ethnicity, n(%) • White: 13 (28.9) • First Nations: 15 (33.3) • Other: 3 (6.7) • Unknown: 14 (31.1) Sexual partner, n (%) • Bisexual: 2 (4.4) • Opposite sex: 25 (55.6) • Same sex: 6 (13.3) • Unknown: 12 (26.7) HIV status, n (%) • Negative: 33 (73.3)	Cefixime 800 mg PO single dose Ceftriaxone 2 g IV single dose Ceftriaxone < 2 g IV single dose	Outcomes: Microbiological cure

Study citation, country, funding source	Study design, setting	Population characteristics	Treatments	Clinical outcomes
		• Positive: 2 (4.4) • Unknown: 10 (22.2)		

g = grams; HIV = human immunodeficiency virus; IV = intravenous, IQR = interquartile range; mg = milligrams; PO = "per os"- oral administration; TOC = test of cure

Table 11: Summary of Findings of Relevant Single-Arm Studies

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings

Bizova et al., (2024)[16]
Randomized controlled trial[a]
	Ceftriaxone 1 g IM single dose plus azithromycin 2 g PO single dose	Microbiological cure (negative-NAAT TOC and culture TOC)	Per-protocol analysis (n = 76)
			• Gonorrhea overall
			  ◦ Negative culture and NAAT: 76/76 (100.0%; 95% CI, 95 to 100)
			  ◦ Negative culture 1 week: 76/76 (100.0%; 95% CI, 95 to 100)
			  ◦ Negative culture 3 weeks: 76/76 (100.0%; 95% CI, 95 to 100)
			  ◦ Negative NAAT 3 weeks: 76/76 (100.0%; 95% CI, 95 to 100)
			• Urogenital gonorrhea
			  ◦ Negative culture and NAAT 3 weeks: 49/49 (100.0%; 95% CI, 93 to 100)
			• Rectal gonorrhea
			  ◦ Negative culture and NAAT 3 weeks: 37/37 (100.0%; 95% CI, 91 to 100)
			• Pharyngeal gonorrhea
			  ◦ Negative culture and NAAT 3 weeks: 21/21 (100.0%; 95% CI, 84 to 100)
			• *Chlamydia trachomatis*
			  ◦ Negative NAAT after 6 weeks: 23/23 (100.0%; 95% CI, 85 to 100)

		Clinical cure (clinical assessment of the patient by the physician)	Per-protocol analysis (n = 76) • Resolution of symptoms: 76/76 (100.0%; 95% CI, 95 to 100)

		Serious adverse events (NR)	Per-protocol analysis (n = 76)
			• Serious adverse events
			  ◦ None: 76/76 (100.0%; 95% CI, 95 to 100)
			  ◦ At least 1: 0/76 (0%; 95% CI, 0 to 0.05)

Belakebi et al., (2023)[17] Prospective cohort study	Ceftriaxone 1 g IM single dose	Microbiological cure (Negative TOC, method NR)	Ceftriaxone group (n = 63) • Response rate in patients 93.65% (95% CI, 83.75% to 97.95%)
		Treatment Failure (positive TOC)	• Positive TOC: 4/63 (6.3%) patients treated with 1g ceftriaxone alone had a positive TOC after first treatment ◦ 2 were considered as a delayed bacterial clearance because a further TOC was

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
			◦ negative without further treatment ◦ 2 were considered as early re-contaminations
		Serious adverse events	• No serious adverse effect was declared
Aoki et al., (2021)[18] Prospective cohort study	Ceftriaxone 1 g IV single dose	Microbiological cure (NAAT- negative TOC)	• All sites: ◦ 204/208 (98.1%; 95% CI, 95.2% to 99.3%) • Pharyngeal infections: ◦ 135/138 (97.8%; 95% CI, 93.8% to 99.4%) • Rectal infections: ◦ 69/70 (98.6%; 95% CI, 92.3% to 99.9%)
		Treatment Failure (positive TOC)	• Positive TOC: Treatment failure (4 cases) ◦ After re-treatment with a single dose of 1 g IV ceftriaxone (3 cases) or combination therapy of ceftriaxone plus doxycycline (dose, route, and frequency NR), all cases were cleared
		Resistance (determine MICs, method NR)	• MIC: 1 case showed MIC = 0.5 mcg/mL, which was treated successfully
Klausner et al., (2020)[19] Single-arm clinical trial	Ciprofloxacin 500 mg PO single dose	Microbiological cure[b] (negative culture)	Intent to treat [number of infections with cure/ number of infections (%; 95% CI) • All sites: 154/168 (91.7%; 95% CI 87.6 to 100.0) • Cervical/urethral: 38/39 (97.4%; 95% CI 90.4 to 100.0) • Rectal: 81/89 (91%; 95% CI 85.0 to 100.0) • Pharyngeal: 35/40 (87.5%; 95% CI 77.0 to 100.0) Microbiological intent to treat [number of infections with cure/number of infections (%; 95% CI) • All sites: 121/129 (93.8%; 95% CI, 89.6 to 100.0) • Cervical/urethral: 33/34 (97.1%; 95% CI, 89.1 to 100.0) • Rectal: 74/79 (93.7%; 95% CI, 88.0 to 100.0) • Pharyngeal: 14/16 (87.5%; 95% CI, 69.5 to 100.0) Per-protocol [number of infections with cure/ number of infections (%; 95% CI) • All sites: 117/117 (100%; 95% CI, 97.5 to 100.0) • Cervical/urethral: 30/30 (100%; 95% CI, 90.5 to 100.0) • Rectal: 73/73 (100%; 95% CI, 96.0 to 100.0)

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
			• Pharyngeal: 14/14 (100; 95% CI, 80.7 to 100.0)
Barbee et al., (2019)[20] Single-arm clinical trial	Gentamicin 260 mg IM single dose	Microbiological cure (negative culture)	• Cured: 2/10 (20%; 95% CI, 2.5%–55.6%)
		Treatment Failure (positive culture for gonorrhea)	• Treatment failure: 8/10 (80%, 95% CI, NR)
		Resistance (standard antimicrobial MICs by agar dilution)	• MIC thresholds: ◦ Among treatment failures (n = 8), none had a TOC gentamicin MIC > 1 doubling dilution greater than the enrolment MIC o All cultured isolates (enrolment and TOC) had MIC ≤ 8 mg/L
		Adverse events (patient reported)	• Mean injection pain, range: 2 (1 to 7) • Patients reporting any adverse event: 7/13 (53.8%) ◦ Headaches: 6/13 (46.2%) ◦ Hearing changes: 1/13 (7.7%) ◦ Urine changes: 1/13 (7.7%) ◦ Vomiting changes: 1/13 (7.7%) ◦ Fatigue changes: 2/13 (15.4%)
Hook et al., (2019)[22] Randomized controlled trial[a]	Ceftriaxone 250 mg IM single dose	Microbiological cure (NAAT-negative TOC or culture)	Urogenital sites: • All participants: 91/100 (91%) • Women: 16/17 (94.1%) • Men: 75/83 (90.4%) ◦ Heterosexual men: 44/48 (91.7%) ◦ MSM/bisexual men: 31/35 (88.6%)
		Clinical cure (investigator assessment of urogenital site at the TOC visit)	Clinical result at TOC Visit - Ceftriaxone group, n = 95 • Clinical cure: 79/95 (91.9%) • Clinical failure: 7/95 (8.1%) • Had remaining or new signs and symptoms at urogenital site: 7/95 (8.1%) • Missing clinical data from urogenital site: 0/95 (0%)
		Treatment failure (positive culture)	Culture positive at TOC • All anatomical sites: 3 • Urogenital site: 3 • Pharyngeal site: 0 • Rectal site: 0 • Missing TOC culture data: 6 • Additional antimicrobials: 0

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
		Adverse events (patient reported)	AEs Reported by ≥ 2.0% of Participants, Ceftriaxone (N = 154) • Diarrhea: 11/154 (7.1%) • Nausea: 2/154 (1.3%) • Headache: 7/154 (4.5%) • Vomiting: 1/154 (0.6%) • Flatulence: 0/154 (0.0%) • Dizziness: 1/154 (0.6%) • Injection-site pain: 7/154 (4.5%)

Chen et al., (2019)[21]
Randomized controlled trial[a]
	Ceftriaxone 500 mg IM single dose plus azithromycin 1g PO single dose	Microbiological cure (negative culture or NAAT-negative TOC)	• Eradication (negative NG culture)
			  ◦ 109/129 (84%)
			• Indeterminate (culture result not available)
			  ◦ 20/129 (16%)

		Treatment failure (persistence- positive culture or positive NAAT)	• Persistence (positive culture or positive NAAT) ◦ 0/124 (0%)
		Adverse events (patient reported)	Ceftriaxone + azithromycin group, n = 131 • One or more adverse events: 45/131 (34%) • Adverse events related to study drug: 33/131 (25%) • Gastrointestinal disorders: 31/131 (24%) Adverse events in > 2% of patients • Diarrhea: 20/131 (15%) • Nausea: 15/131 (11%) • Abdominal pain: 4/131 (3%) • Abdominal discomfort: 0/131 (0%) • Abdominal distension: 0/131 (0%) • Abdominal pain upper: 0/131 (0%) • Vomiting: 0/131 (0%) • Headache: 7/131 (5%) • Dizziness: 3/131 (2%) • Lethargy: 3/131 (2%) • Trichomoniasis: 0/131 (0%)

Taylor et al., (2018)[24]
Randomized controlled trial[a]
	Ceftriaxone 500 mg IM single dose	Microbiological cure (NAAT-negative TOC or culture)	Microbiological cure % (cure/confirmed infection; 95% CI)
			• Micro-Intention to treat
			  ◦ Urethra or cervix - 100% (28/28; 88 to 100)
			  ◦ Rectum - 100% [3/3; 29 to 100)
			  ◦ Pharynx - 100% [4/4; 40 to 100)
			• Per-protocol
			  ◦ Urethra or cervix - 100% [21/21; 89 to

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
			100) ◦ Rectum - 100% [3/3; 29 to 100) ◦ Pharynx - 100% [4/4; 40 to 100)
		Clinical cure (investigator's assessment)	Cure: • In the micro-ITT population, among participants with signs and symptoms of gonorrhea infection at baseline, cure occurred in 26 of 27 participants (96%; 95% CI, 81 to 100) in the group that received ceftriaxone
		Adverse events (patient reported)	Ceftriaxone group, n = 40 • Any system organ class ◦ Mild: 14/40 (35%) ◦ Moderate: 4/40 (10%) ◦ Severe: 0/40 (0%) ◦ Not Related to Trial Drug: 12/40 (30%) ◦ Related: 6/40 (15%) • Gastrointestinal disorders ◦ Mild: 3/40 (8%) ◦ Moderate: 0/40 (0%) ◦ Severe: 0/40 (0%) ◦ Not Related to Trial Drug: 1/40 (3%) ◦ Related: 2/40 (5%) • General disorders ◦ Mild: 2/40 (5%) ◦ Moderate: 0/40 (0%) ◦ Severe: 0/40 (0%) ◦ Not Related to Trial Drug: 1/40- (3%) ◦ Related: 1/40 (3%) • Investigations ◦ Mild: 0/40 (0%) ◦ Moderate: 1/40 (3%) ◦ Severe: 0/40 (0%) ◦ Not Related to Trial Drug: 1/40 (3%) ◦ Related: 0/40 (0%) • Nervous system disorders ◦ Mild: 2/40 (5%) ◦ Moderate: 0/40 (0%) ◦ Severe: 0/40 (0%) ◦ Not Related to Trial Drug: 1/40 (3%) ◦ Related: 1/40 (3%)

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
Allan-Blitz et al., (2018)[23] Retrospective review of patient records	Ciprofloxacin 500 mg PO single dose	Microbiological cure (negative TOC, method NR)	• Negative TOC result: 25/25 (100%, 95% CI, 83%–100%)
Ito et al., (2016)[25] Prospective cohort study	Ceftriaxone 1 g IV single dose	Microbiological cure (NAAT-negative TOC)	• Negative result for participants followed-up between 5 and 9 days after treatment: 111/111 (100%) • Efficacy against gonococcal urethritis: 100% • Positive test result for participants followed-up between 10 and 18 days after treatment: 3/60 (5%) • Negative result for participants followed-up between 2 and 41 days after treatment: 191/194 (98.5%; 95% CI 96.8% –100%)
		Resistance (MICs by agar dilution)	Ceftriaxone MICs isolates, n = 136 • Persistence according to MIC 0.008 mg/L: 1/136 (0.7%) ◦ evaluated at 13 days after treatment • Persistence where MIC (mg/L) were not determined: 2/136 (1%) ◦ Evaluated at 15 and 17 days, respectively, after treatment
		Adverse events (patient reported)	• Any adverse event: 7/220 (3.2%) • Diarrhea (grade 1): 4/220 (1.8%) • Urticaria (during administration of ceftriaxone): 3/220 (1.3%) ◦ 1 event classified as grade 1, other 2 were grade 3
Wind et al., (2016)[26]	Ceftriaxone 500 mg IM single dose	Microbiological cure (negative RNA and DNA-based NAAT TOC)	All sites of infection (cure/confirmed infection; 95% CI): • DNA clearance: 23/23 (100%; NR) • RNA clearance: 23/23 (100%; NR) By site of infection: Vagina/endocervix (cure/confirmed infection; 95% CI): • DNA clearance: 11/11 (100%; NR) • RNA clearance: 11/11 (100%; NR) Rectum (cure/confirmed infection; 95% CI): • DNA clearance: 9/9 (100%; NR) • RNA clearance: 9/9 (100%; NR) Urethra (cure/confirmed infection; 95% CI): • DNA clearance: 3/3 (100%; NR) • RNA clearance: 3/3 (100%; NR)

Study citation and study design	Intervention	Outcome (method of measurement)	Main study findings
	Ceftriaxone 500 mg IM single dose plus azithromycin 1 g PO[c]		All sites of infection (cure/confirmed infection; 95% CI): • DNA clearance: 26/26 (100%; NR) • RNA clearance: 26/26 (100%; NR) By site of infection: Vagina/endocervix (cure/confirmed infection; 95% CI): • DNA clearance: 8/8 (100%; NR) • RNA clearance: 8/8 (100%; NR) Rectum (cure/confirmed infection; 95% CI): • DNA clearance: 2/2 (100%; NR) • RNA clearance: 2/2 (100%; NR) Urethra (cure/confirmed infection; 95% CI): • DNA clearance: 16/16 (100%; NR) • RNA clearance: 16/16 (100%; NR)

CI = confidence interval; DNA = DNA; IM = intramuscular; mg = milligrams; MICs = minimal inhibitory concentrations; MSM = men who have sex with men; NAAT = nucleic acid amplification test; NR = not reported; PO = "per os"- oral administration; RNA = ribonucleic acid; TOC = test of cure

Note: These studies did not meet the eligibility criteria but had 1 relevant treatment group.

[a]Only 1 treatment arm in the randomized controlled trial was relevant to our study.

[b]The intent-to-treat population included all infections in subjects enrolled who had a culture-positive N. gonorrhea infection at enrolment regardless of repeat gyrA serine 91 N. Gonorrhea result at enrolment. The microbiological intent-to-treat population for the specified anatomical site included only those with a wild-type gyrA serine 91 N. gonorrhoeae culture-positive result at enrolment. The per-protocol population for the specified anatomical site included those in the microbiological intent-to-treat population with a follow-up culture result collected within the protocol-specified follow-up visit window (i.e., 5 to 10 days after enrolment) and who did not receive any contraindicated medication or systemic antibiotical before the follow-up visit.

[c]In the Wind et al. study, patients received treatment with ceftriaxone plus azithromycin only if they were coinfected with *Chlamydia trachomatis*.

Table 12: Summary of Findings of Relevant Case Series

Study citation and study design	Treatments	Outcome (method of measurement)	Main study findings
Belga et al. (2019)[27] Retrospective case series	Cefixime 800 mg PO single dose Ceftriaxone 2 g IV single dose Ceftriaxone < 2 g IV single dose	Microbiological cure (NAAT-negative, culture-only, or culture and NAAT-negative TOC)	• Results of TOC were available for 7 cases – all were negative • TOC cases were treated at baseline with: ◦ Cefixime 800 mg PO single dose (14.3%; n = 1) ◦ Ceftriaxone 2 g IV single dose (42.9%; n = 3) ◦ Ceftriaxone < 2 g IV single dose (42.9%; n = 3)

g = grams; IV = intravenous; mg = milligrams; NAAT = nucleic acid amplification test; PO = "per os"- oral administration; TOC = test of cure

Note: Test of cure (TOC) data were only available for 7 of 45 cases included in the study.

Appendix 6: Nucleic Acid Amplification Test and Culture Methods of Studies

Note this appendix has not been copy-edited.

Table 13: NAAT and Culture Methods of Included Publications

Study citation	NAAT methods	Culture methods
de Vries et al. (2022)[14]	Aptima Combo 2, Hologic, Marlborough, MA, US	Swabs and urethral samples were directly inoculated onto plates with BBL GC-Lect Agar (Becton Dickinson, Franklin Lakes, NJ, US) and incubated for 48 hours. Suspected colonies were identified as NG by a positive oxidase test and matrix-assisted laser desorption ionisation time-of-flight mass spectrometry (MALDI)-TOF (Bruker, Billerica, MA, US). Pure colonies were grown on NG agar plates eDetails NRiched with 1% Iso VitaleX (BioTRADING Benelux, Mijdrecht, Netherlands)
Rob et al. (2020)[13]	GeneProof	Swabs for cultivation of NG were immediately inoculated onto non-selective and selective modified Thayer-Martin agar plates. Inoculated agar plates were transferred to the hospital laboratory within 1 hour for incubation in 48 hours at 36°C in a humid 5% CO_2 eDetails NRiched atmosphere. Suspected gonococcal colonies were species verified using biochemical NEISSERIAtest (LACHEMA, Brno, Czech Republic) and Gram-stained microscopy.
Ross et al. (2019)[11,12]	Aptima Combo 2, Hologic, MA, US. If the local laboratory did not use Aptima Combo 2 NAAT, additional samples were tested at Public Health England (London, UK)	Culture specimens were processed according to local laboratory procedures, and pure viable cultures confirmed to be NG were frozen to −70°C or below and shipped to Public Health England for antimicrobial sensitivity testing

CA = California; CO_2 = Carbon dioxide; Ct = cycle threshold; MA = Massachusetts; NA = Not applicable; NAAT = nucleic acid amplification test; NG = *Neisseria gonorrhoeae*; NJ = New Jersey; PCR = polymerase chain reaction.

Table 14: NAAT and Culture Methods of Relevant Single-Arm Studies

Study citation	NAAT methods	Culture methods
Bizova et al., (2024)[16]	Cobas 4800 CT/NG NAAT assay (Roche Diagnostics)	Swabs for cultivation of NG were sampled and immediately inoculated onto nonselective and selective modified Thayer-Martin agar plates. Inoculated agar plates were directly transferred to the hospital laboratory for incubation at 36C in a humid 5% CO_2-enriched atmosphere for 48 hours. Suspected gonococcal colonies were species verified using the biochemical NEISSERIA test(LACHEMA) or the PolyViteX VCAT3 medium (Biomerieux)

Study citation	NAAT methods	Culture methods
Belakebi et al., (2023)[17]	Details NR	Details NR
Aoki et al., (2021)[18]	TMA (Bio Medical Laboratories, Inc. Tokyo, Japan) was used to detect NG and CT in clinical specimens collected from mouth washing and rectal swabs	NA
Klausner et al., (2020)[19]	NA	Details NR
Barbee et al., (2019)[20]	NA	Specimens for culture were obtained with a polyester swab, plated directly onto selective Thayer-Martin media, and placed in a candle (CO_2) jar in a 37°C incubator within 15 minutes of collection. Plates were transported to the Neisseria Reference Laboratory daily.
Hook et al., (2019)[22]	NAAT (Aptima Combo 2)	Cultures were analyzed by local laboratories for NG and identified isolates were sent to a central laboratory (The University of Alabama Birmingham Infectious Disease STD Program Laboratory) for agar dilution susceptibility testing using standard methods
Chen et al., (2019)[21]	The Cobas 4800 CT/NG test (Roche, Basel, Switzerland; Australian sites) or Aptima Combo 2 Assay (Hologic, Marlborough, MA, US; US site) were used for the detection of NG and CT nucleic acid in genital, pharyngeal, and rectal specimens. For specimens in which NG was detected by the Cobas assay, specimens were considered positive if confirmatory testing with quantitative PCR targeting the *opa* gene was also positive. For extragenital samples in which NG was detected by the Cobas assay, specimens were considered positive if quantitative PCR targeting the *opa* gene and quantitative PCR targeting the *porA* pseudogene were both positive.	NG was cultured and identified using selective agar media (modified Thayer-Martin media or equivalent, incubated overnight at 35 to 37°C in 5% CO_2), colony morphology, Gram stains, oxidase tests, and carbohydrate utilization assays.
Taylor et al., (2018)[24]	NAAT was performed at local laboratories or at the Infectious Diseases Laboratory at the University of Alabama at Birmingham (UAB) with the use of Aptima Combo 2 (Hologic)	Modified Thayer-Martin agar plates were inoculated and immediately placed in a CO_2–enriched environment before transport to local laboratories. Plates were read at 24, 48, and 72 hours after inoculation. Colonies containing oxidase-positive, gram-negative diplococci were presumed to be NG. Isolates were frozen and shipped to the UAB laboratory, where the identification of neisseria, hemophilus, moraxella, and related bacteria was confirmed with the use of the Remel RapID NH System
Allan-Blitz et al., (2018)[23]	Details NR	Details NR

Study citation	NAAT methods	Culture methods
Ito et al., (2016)[25]	First-voided urine specimens were obtained for testing of NG by the APTIMA Combo 2 assay (Gen-Probe Incorporated, San Diego, CA, US)	NA
Wind et al. (2016)[26]	RNA-based NAAT: Samples for RNA-based NAAT were collected using Aptima vaginal swab specimen kits for vaginal and anal samples, and Aptima urine. specimen kits for urine samples. All were tested using the Aptima Combo 2 assay for NG and *C. trachomatis* on the Tigris direct tube sampling system (Hologic, San Diego, CA), and relative light units (RLUs) were reported. Equivocal results were retested using the Aptima GC assay (Hologic). DNA-based NAAT: Samples for DNA-based NAAT were collected using Cobas PCR female swab sample kits for vaginal and anal sampling, and the Cobas PCR urine sample kits for urine samples. All were tested using the Cobas 4800 assay for NG and *C. trachomatis* (Roche, Basel, Switzerland); Ct of positive samples was reported.	NA

CA = California; Ct = cycle threshold; MA = Massachusetts; NA = Not applicable; NAAT = nucleic acid amplification test; NG = *Neisseria gonorrhoeae*; NJ = New Jersey; NR = not reported; PCR = polymerase chain reaction; STD = sexually transmitted disease; TMA = transcription mediated amplification; UAB = University of Alabama at Birmingham.

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