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Systematic Review and Meta-Analysis to Estimate the Treatment Effect and Inform a Noninferiority Margin for a Phase 3 Noninferiority Trial in Uncomplicated Urogenital Gonorrhea

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Background: Active-controlled noninferiority studies are used to investigate novel agents for uncomplicated urogenital gonorrhea (uUGC) as placebo-controlled trials are unethical. A systematic literature review and meta-analysis were conducted to estimate the ceftriaxone and proxy-for-placebo microbiological treatment effect and determine an appropriate noninferiority margin for phase 3 trials.

Methods: Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed. To account for interstudy variability, a weighted, noniterative random-effects model was fitted using "R" software to estimate the microbiological response rate and 95% confidence intervals (CIs) for ceftriaxone and proxy-for-placebo (treatment with an antibiotic the isolate was subsequently confirmed resistant to, or spontaneous resolution without treatment). I^2, τ^2, and P values were computed and included in the meta-analysis forest plot.

Results: Seventeen studies were included in the meta-analysis; 14 reported ceftriaxone response in micro-intent-to-treat and microbiologically evaluable populations, and 3 reported proxy-for-placebo treatment response in uUGC (microbiologically evaluable population only). Microbiological treatment effect was estimated by subtracting the upper end of the CI for placebo from the lower end of the CI for ceftriaxone. Overall microbiological response was 98% (95% CI, 97–99) for ceftriaxone and 44% (95% CI, 34–54) for proxy-for-placebo, resulting in a microbiological treatment effect of 43%. A noninferiority margin of 15% preserved 65% of the ceftriaxone treatment effect, exceeding the 50% recommended per US Food and Drug Administration guidance for noninferiority studies.

Conclusions: Results of this systematic literature review and meta-analysis could help inform the design, conduct, and analysis of future clinical studies in uUGC.

Uncomplicated urogenital gonorrhea (uUGC) is an acute sexually transmitted infection (STI) of the reproductive tract caused by *Neisseria gonorrhoeae* that results in urethritis and endocervicitis in men and women, respectively.[1] *Neisseria gonorrhoeae* infects mucosal membranes, with the infection detectable at multiple sites including the vagina, penis, pharynx, and rectum. Transmission is estimated to be between 20%–50% for each episode of unprotected sexual contact, with more efficient spread from males.[2]

In the United States (US), over 615,000 cases of gonorrhea were reported in 2019, equating to approximately 188.4 cases per 100,000 persons.[3] In Europe (EU), more than 110,000 cases were reported in 2019, with a notification rate of approximately 32 cases per 100,000 individuals.[4] While this is a reportable STI in both the US and EU, it is posited that the annual cases reported in the US are a fraction of total gonorrhea cases, with underestimation likely in the EU as well. Undetected or inadequately treated uUGC can lead to complications such as epididymitis, infertility, and epididymo-orchitis in men, and salpingitis, pelvic inflammatory disease, tubal infertility, and ectopic pregnancy in women.[1,5]

Antibacterial susceptibility testing and surveillance data for *N. gonorrhoeae* have continued to evolve, with the identification of more isolates that are either antibiotic resistant or have reduced susceptibility (elevated minimum inhibitory concentrations to extended-spectrum cephalosporins) to the current standard of care (ceftriaxone) over time and resistance to previous standard of care drugs (azithromycin, fluoroquinolones, tetracyclines, penicillin, etc.).[5–10] *Neisseria gonorrhoeae* has the potential to become resistant to all currently available antibiotics, highlighting the need for new antibiotics to treat gonorrhea,[11] and was listed as an urgent threat by the US Centers for Disease Control and Prevention in 2019.[12] World Health Organization, US Centers for Disease Control and Prevention, and European STI Guidelines Editorial Board 2010 consensus treatment guidelines recommended intramuscular ceftriaxone combined with a single oral dose of azithromycin[1,13,14]; this was updated in 2020 to intramuscular ceftriaxone alone.[15–17] While these guidelines may delay the emergence of cephalosporin-resistant *N. gonorrhoeae*, the threat remains. Several cases of *N. gonorrhoeae* with high-level

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resistance to azithromycin and resistance to ceftriaxone have been detected in Australia, Canada, and across the EU.[2]

Several promising novel antibiotics with high activity against *N. gonorrhoeae* are in late-stage clinical development for the treatment of uUGC and have been reviewed elsewhere.[18–20] Solithromycin, a fourth-generation macrolide class oral antibiotic and the first fluoroketolide, has shown high efficacy in a phase 2 study and an open-label, randomized, phase 3 study (NCT02210325) but failed to demonstrate noninferiority (10% margin) versus ceftriaxone plus azithromycin in the latter. Zoliflodacin is a first-in-class oral spiropyrimidinetrione antibiotic that inhibits bacterial DNA biosynthesis through a mechanism distinct from that of fluoroquinolones. Efficacy has been demonstrated in a phase 2 study, with the completion of an open-label, randomized, active-comparator (ceftriaxone plus azithromycin), noninferiority, phase 3 study (NCT03959527) expected in 2023. Gepotidacin is a novel, first-in-class, triazaacenaphthylene antibiotic that inhibits bacterial DNA replication by a distinct mechanism of action,[21] which confers activity against most strains of *N. gonorrhoeae*, including those resistant to current antibiotics.[22–24] A randomized, parallel-group, noninferiority (10% margin), phase 3 study of gepotidacin versus active control (ceftriaxone plus azithromycin; NCT04010539) was initiated before the release of the updated treatment guidelines in 2020 and is currently underway.

Active-controlled noninferiority trials are typically used to study the efficacy and safety of new agents for uUGC because placebo-controlled trials are no longer considered ethical. An estimate of the treatment effect of a planned antimicrobial comparator derived from historical studies is necessary to design a noninferiority trial.[25,26] The US Food and Drug Administration (FDA) and European Medicines Agency (EMA)-preferred primary efficacy end point for a phase 3 study in uUGC is microbiologic response at the test-of-cure (TOC) visit (3–7 days after treatment initiation) in the micro-intent-to-treat population (micro-ITT), defined as the subset of the ITT population with culture-confirmed *N. gonorrhoeae* at a urogenital site at baseline, with a noninferiority margin of 10%.[26,27]

The objective of this systematic review and meta-analysis was to assess historical clinical trials and observational studies to determine the microbiological treatment effect and the justifiable noninferiority margin for future phase 3 studies in uUGC.

METHODS

Systematic Literature Review

Study Design

A systematic review was designed and executed in compliance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines,[28–30] which incorporated recommendations for standardized data quality assessment and results reporting. A protocol summary was posted before study initiation (study 217017) on the GlaxoSmithKline study register in accordance with disclosure requirements and is available at: https://www.gsk-studyregister.com/en/trial-details/?id=217017.

Two reviewers independently conducted literature searches and systematic reviews using the PubMed (United States National Library of Medicine, National Institutes of Health; http://ncbi.nlm.nih.gov) and Embase (https://www.embase.com/#search) search engines to identify historical studies of ceftriaxone and/or placebo/proxy-for-placebo that assessed the microbiological treatment response at TOC in participants with uUGC or spontaneous resolution in participants with confirmed uUGC without treatment (proxy-for-placebo). This was followed by screening, determining eligibility, and selecting representative studies for inclusion in the meta-analysis, with the aim of identifying all relevant English language publications. Search strings were used with Boolean operators; combinations of search terms produced 11 search algorithms for ceftriaxone, placebo, and proxy-for-placebo treatment effect in uUGC (Supplementary Table 1, http://links.lww.com/OLQ/A835). Studies were restricted to publication dates before February 3, 2021, for PubMed and before February 5, 2021, for Embase. Published studies were limited to English-language publications with no limits set for study year or geographical location. Additional studies were identified outside of the PubMed and Embase searches via evaluation of published literature cited in the articles that were eligible for full-text review.

Identification of Studies and Full-Text Review for Eligibility

Two reviewers independently identified publications via title and abstract screening. All identified publications underwent abstract review, and eligible studies were considered for full-text review and categorized for inclusion in or exclusion from the meta-analysis based on clinical criteria (target population, entry criteria, microbiological end point at TOC) and study quality. A third assessor adjudicated any discrepancies that could not be resolved after discussion. Publications were eligible for full-text review if at least 1 of the following criteria were met:

1. Clinical trial in participants 12 years or older with uUGC evaluating the efficacy of ceftriaxone via microbiological response at TOC in the micro-ITT and/or microbiologically evaluable (ME) population OR clinical trial in participants 12 years or older with uUGC evaluating either placebo treatment or a proxy-for-placebo via microbiological response or molecular microbiological response
2. Observational study that evaluated placebo/proxy-for-placebo response via spontaneous resolution of infection or molecular microbiological response in participants with confirmed uUGC without treatment

Full-text publications of selected abstracts were reviewed and categorized for inclusion in, or exclusion from, the meta-analysis based on target population, entry criteria, and microbiological end point at TOC. After full-text review, studies not included in the meta-analysis were assigned a categorical explanation for exclusion. Publications were eligible for inclusion in the meta-analysis if the following criteria were met: participants were 12 years or older with uUGC; studies with participants who had uUGC at other body sites were eligible if efficacy data were reported separately for each body site and the primary efficacy end point was microbiological response at the urogenital site only; ceftriaxone alone or ceftriaxone plus azithromycin; placebo or proxy-for-placebo; microbiological response or success at TOC visit per FDA and EMA guidance on gonorrhea studies; randomized, double-blind clinical studies, randomized clinical studies, open-label studies, or observational studies (proxy-for-placebo only); and studies with ≥3 days of follow-up per FDA and EMA guidance on TOC.

The following variables were extracted from each publication and included in the meta-analysis: author, publication date, country, number of centers, number of enrolled participants, study population, demographics, baseline characteristics, study drug, dose and duration of therapy, timing of end point measurement, and microbiological cure endpoints.

Meta-Analysis

End Points

The primary endpoint was the percentage of participants with microbiological success in the micro-ITT population (urological) at the TOC visit. Microbiological success was defined as

no growth of *N. gonorrhoeae* in urogenital culture at TOC. The micro-ITT population was a subset of the ITT population who had urogenital culture-confirmed *N. gonorrhoeae* at baseline. Total number of participants treated in each study arm, number with microbiological success and failure per arm, and number lost to follow-up for active comparator and placebo separately were extracted from each study. For proxy-for-placebo studies, the primary endpoint was microbiological success among participants with confirmed ceftriaxone resistance in clinical studies and spontaneous resolution among those with confirmed baseline uUGC with no active treatment (observational studies). Bacterial eradication rate for the micro-ITT population (urological) was calculated as the number of participants with urological microbiologic success at TOC visit divided by the number of participants with confirmed *N. gonorrhoeae* at a urogenital site at baseline. The secondary endpoint was microbiological response in the ME population. The ME population was defined as those in the micro-ITT population with culture-confirmed *N. gonorrhoeae* at baseline who followed essential protocol criteria. Bacterial eradication rate for the ME population was calculated as for the micro-ITT population, with the denominator being the number of participants with confirmed *N. gonorrhoeae* at a urogenital site at baseline and a urogenital specimen collected at TOC visit with available culture results.

Assessment of Study Heterogeneity and Publication Bias

Each publication eligible for inclusion in the meta-analysis was further assessed by the reviewers for risk of bias using the Cochrane risk-of-bias tool for clinical trials and the Newcastle-Ottawa Scale for observational studies.[31s,32s] A third assessor adjudicated any discrepancies that could not be resolved after discussion. Studies were assessed for clinical, methodological, and statistical heterogeneity. Clinical heterogeneity was defined by participant selection, dose and duration of interventions, and timing of end point measurement and was characterized descriptively. Methodological heterogeneity was defined by the study design and execution and assessed to understand how these could have contributed to selection, performance, detection, attrition, and reporting bias. Statistical heterogeneity was defined as variation in results beyond sampling variability. Patients lost to follow-up were classed as microbiological failures in the micro-ITT population (urological); no imputations were performed for missing data.

Studies that classified participants lost to follow-up as treatment failures were included in the micro-ITT meta-analysis. Among studies not reporting microbiological efficacy (success) in the micro-ITT population, this was derived from the ME population by counting losses to follow-up in the ME population as treatment failures. These assessments were used to descriptively characterize heterogeneity and guide decisions around sensitivity analyses.

Data Analysis

Given the paucity of placebo-controlled trials in this setting (unethical by current standards), the treatment effect of the active comparator and proxy-for-placebo was estimated through cross-trial comparison. Ceftriaxone studies (including ceftriaxone plus azithromycin) were used to estimate microbiological response at TOC in the micro-ITT and ME populations among participants with uUGC. Proxy-for-placebo clinical and observational studies were used to estimate microbiological response for proxy-for-placebo at TOC in the ME population among participants with uUGC; there were no eligible clinical studies assessing proxy-for-placebo response in the micro-ITT population.

Microbiological response was presented as raw frequencies, percentages, and 95% confidence intervals (CIs) for each individual study and were reported for the primary efficacy endpoint in the micro-ITT and ME populations. Individual results within each treatment group were synthesized to obtain a pooled point estimate for response rate at the primary end point. A weighted, noniterative, random-effects model (DerSimonian-Laird) was fit using "R" software to obtain estimates of microbiological response rates and corresponding 95% CIs for ceftriaxone and proxy-for-placebo treatment to account for interstudy variability. I^2 was used to describe the percentage variation across studies due to heterogeneity rather than chance; τ^2 was used to estimate the degree of heterogeneity variance. Overall microbiological response rate and 95% CIs based on random-effects model, I^2, τ^2, and P values for heterogeneity were computed and presented in forest plots. Microbiological treatment effect was obtained based on an indirect method, that is, the difference between the lower 95% CI for ceftriaxone and the upper 95% CI for proxy-for-placebo. For sensitivity, a direct comparison approach was also used to estimate microbiological treatment effect using the lower 95% CI of the difference between ceftriaxone and proxy-for-placebo in microbiological treatment effect estimation, targeting a noninferiority margin of 10% to 15% on the absolute scale, or preserving >50% of the microbiological treatment effect on the absolute scale, per FDA guidance.[25] Confidence intervals of the difference were calculated as follows: if the estimate (E) for ceftriaxone and proxy-for-placebo is E1 and E2, respectively, with standard errors SE(E1) and SE(E2), then the difference (d = E1 − E2) has standard error:

$$\mathrm{SE}(d) = \sqrt{\left(S\mathrm{E}[\mathrm{E1}]^2 + \mathrm{SE}[\mathrm{E2}]^2\right)}$$

with the 95% CI for the difference equal to $d - 1.96\mathrm{SE}(d)$ to $d + 1.96\mathrm{SE}(d)$.

Sensitivity Analyses

The following methods were used to assess the robustness of the primary DerSimonian-Laird random-effects model: (1) fixed-effects model assuming the true proportion of responders is the same for all studies; (2) generalized linear mixed model assuming binomial likelihood for the proportion of responders from each study and normal random-effects distribution for the logit-transformed proportions; and (3) Bayesian random-effects model assuming a weakly informative prior for the heterogeneity between-study variance.

RESULTS

Systematic Review

Literature searches in PubMed and Embase identified 127 and 170 results, respectively, resulting in 231 unique publications. Of these, 154 (66.7%) were excluded during first-round abstract screening (Fig. 1). Of the 77 publications that progressed to full-text review, 68 were excluded. Adjudication by a third assessor was not required for any of the publications that were screened/reviewed. An additional 8 studies were identified for inclusion in the meta-analysis from the referenced literature of the 9 studies that satisfied all inclusion criteria. Among the final 17 clinical studies included in the meta-analysis, 14 informed on ceftriaxone treatment response in the micro-ITT and ME populations (Table 1), with 5 studies[33s–37s] and 14 studies[33s–46s] informing on treatment response in the micro-ITT and ME populations, respectively. Three studies (1 prospective clinical trial and 2 observational studies) informed on proxy-for-placebo treatment response in uUGC (Table 2).[47s–49s]

Among the included ceftriaxone studies reporting microbiological response in the micro-ITT population, clinical heterogeneity was seen across ceftriaxone dose (250–500 mg), proportion of male

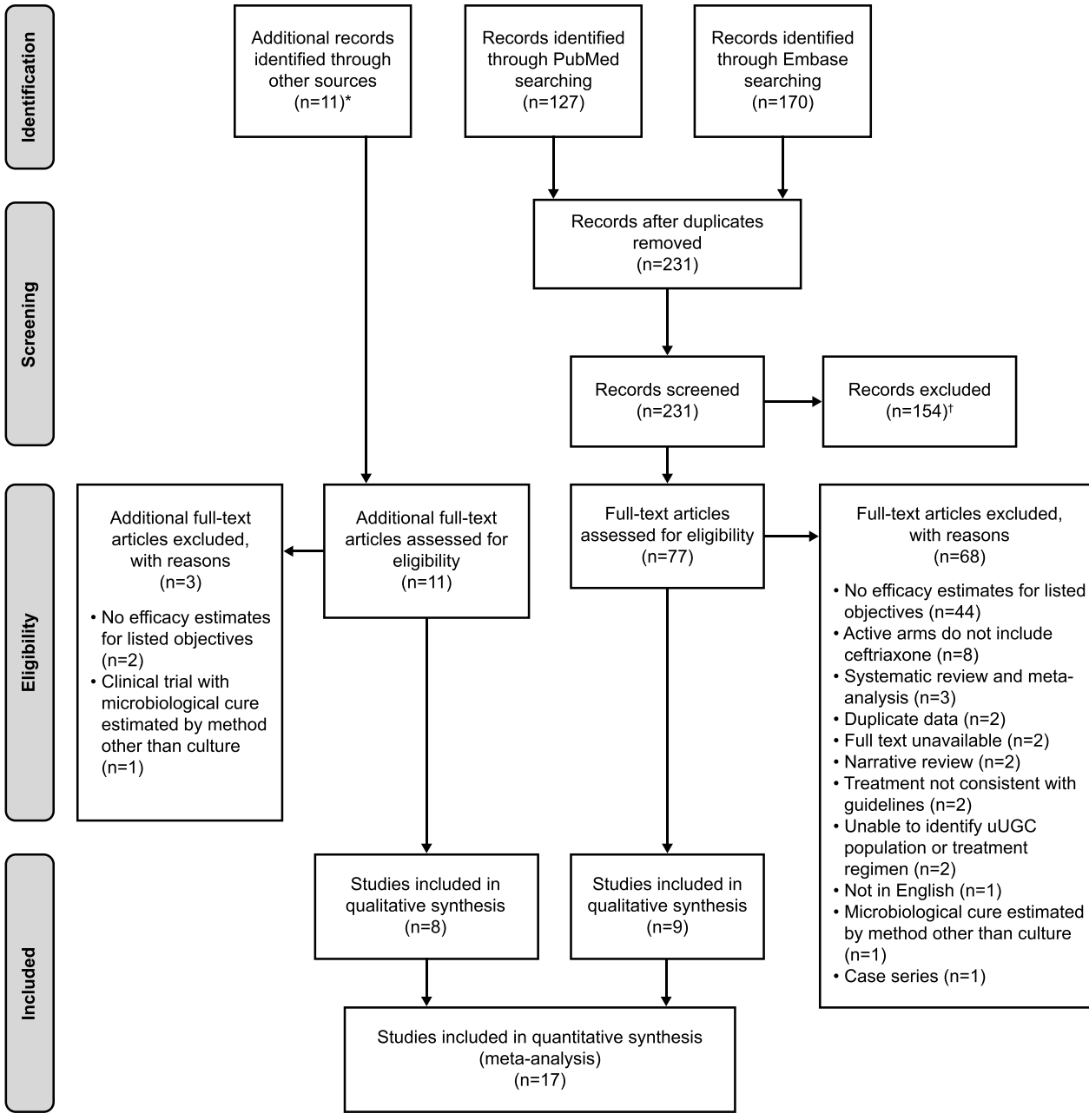


Figure 1. Flowchart depicting the systematic literature search for treatment effect estimation in uUGC: publication identification, screening, eligibility, and meta-analysis inclusion. *The 11 additional records were identified from the referenced literature cited in the publications identified by the primary searches. †Reasons for exclusion were as follows: narrative reviews (gonorrhea, STDs, PID, HIV; n = 36); unrelated to gonorrhea and no information on primary objectives (n = 33); microbiology surveillance in vitro gonorrhea susceptibility (n = 17); HIV/STD studies and not informing on primary objectives (n = 17); STD/gonorrhea prevention studies (n = 13); STD mathematical modeling studies (n = 8); case reports for other STDs (n = 7); gonorrhea RCTs not reporting on efficacy of ceftriaxone, placebo, or proxy-for-placebo (n = 5); observational studies for STDs, not gonorrhea-specific (*Mycoplasma genitalium* and bacterial vaginosis; n = 4); RCTs unrelated to gonorrhea (n = 3); complicated gonorrhea case reports (n = 3); gonorrhea antibody study and adherence to treatment guidelines (n = 2); STD surveillance studies (n = 2); PID etiology/microstudy (n = 1); STD case series, not gonorrhea (n = 1); systematic review and meta-analysis not reporting on efficacy of ceftriaxone, placebo, or proxy-for-placebo (n = 1); and letter to the editor (n = 1). HIV, human immunodeficiency virus; PID, pelvic inflammatory disease; RCT, randomized controlled trial; STD, sexually transmitted disease; uUGC, uncomplicated urogenital gonorrhea.

participants (45.6%–95%), and timing of microbiological response end point (4–10 days). Among ceftriaxone studies reporting microbiological response in the ME population, clinical heterogeneity was seen across ceftriaxone dose (125 mg to 1 g), proportion of male participants (0%–100%), and timing of microbiological response end point (3–10 days). Of the 3 studies reporting proxy-for-placebo response, 1 study reported microbiological response in participants randomized to an active treatment to which their *N.*

TABLE 1. Study Characteristics of 14 Published Ceftriaxone Studies Identified in a Systematic Review That Assessed Microbiological Response of Success in Patients ≥12 Years of Age With uUGC in the Micro-ITT and ME Populations

				Demographics			Timing of End Point	Analysis Populations	
Author, Year	Study Design (Comparator)	Region	Ceftriaxone Dose (Route)*	N	Age, Mean (SD) or Range, y	Male, %	Microresponse (TOC), d	Micro-ITT Responder, %	ME Responder, %
Chen, 2019[33s]	OL RCT Ph 3 (solithromycin)	USA/ Australia	500 mg (IM) + 1000 mg azithromycin (PO)†	131	29.4 (10.3)	95.0	7 ± 2	84.5	100‡
Hook, 2019[34s]	OL RCT Ph 3 (delafloxacin)	USA	250 mg (IM)	154	28.7 (10.0)	77.3	7 ± 3	91.0	96.8‡
Taylor, 2018[35s]	OL RCT (zoliflodacin)	USA	500 mg (IM)	180	28.8 (8.2)	93.2	6 ± 2	100	100‡
Muratani, 2008[38s]	OL study (none)	Japan	1 g (IV)	67	28.1 (9.8)	40	3–14	NR	100
Ramus, 2001[39s]	OL RCT (cefixime)	USA	125 mg (IM)	43	18.9 (2.7)	0	7 ± 3	NR	95
Rompalo, 1994[40s]	OL RCT (trospectomycin sulfate)	USA	250 mg (IM)	22	NR (range, 15–60)	52.8	4–8§	NR	100
Plourde, 1992[36s]	OL RCT (cefixime)	Kenya	250 mg (IM)	63	NR (range, 18–65)	82.0	4–7§	85.1‡	100
Portilla, 1992[41s]	OL RCT (cefixime)	USA	250 mg (IM)	47	23.3 (NR; range, 18–44)	33.3	4–9	NR	100
Handsfield, 1991[42s]	OL RCT (cefixime)	USA	250 mg (IM)	94	27.1 (7.8)	65.0	3–10	NR	98.9
Bryan, 1990[43s]	DB RCT (ciprofloxacin)	Zambia	250 mg (IM)	82	28.0 (5.6)	100	7–10	NR	100
Albrecht, 1989[37s]	OL RCT (enoxacin)	USA	250 mg (IM)	25	NR	45.6	5–9	96.2‡	100
Christophersen, 1989[44s]	OL RCT (pivampicillin)	Denmark	250 mg (IM)	170	24.5 (NR)	84.0	7–14	NR	99.3
Dixon, 1986[45s]	OL RCT (penicillin)	UK	250 mg (IM) 500 mg (IM)	93 50	NR	52.4 NR	3–9	NR 100	100
Handsfield, 1983[46s]	OL RCT (spectinomycin)	USA	125 mg (IM) 250 mg (IM)	31 28	26.9 (8.1) 27.7 (6.7)	100	3–8	NR NR	100 100

Micro-ITT population included participants with a positive culture from a urogenital site who received another therapy for uUGC before the TOC visit (losses to follow-up were included in this efficacy assessment as failures). ME participants were those in the micro-ITT population who received study drug, had no important protocol deviations, and had an efficacy assessment (losses to follow-up not included).

*Single IM dose on day 1.

†Single oral dose on day 1.

‡Derived based on data reported in publication on loss to follow-up for participants with uUGC only.

§Postenrollment.

d indicates days; DB, double-blind; IM, intramuscular; IV, intravenous; ME, microbiologically evaluable population; micro-ITT, microbiological intent-to-treat population; NR, not reported; OL, open-label; Ph, phase; PO, orally (per os); RCT, randomized controlled trial; TOC, test of cure; UK, United Kingdom; USA, United States of America; uUGC, uncomplicated urogenital gonorrhea; y, years.

gonorrhoeae isolate was later confirmed to be resistant. Two observational studies assessed rates of spontaneous resolution or clearance of uUGC via a molecular microbiological nucleic acid amplification test among participants with microbiological confirmation of *N. gonorrhoeae* at baseline and no antibiotic treatment. There was minimal methodological heterogeneity among studies reporting efficacy in the micro-ITT and ME populations.

Meta-Analysis

No studies for proxy-for-placebo treatment response were identified in the micro-ITT population; therefore, the primary comparison was based on ceftriaxone and proxy-for-placebo treatment response in the ME population. Given that the key difference between the micro-ITT and ME populations was how missing samples and participants lost to follow-up were incorporated in the analyses (for ME, these were not included in the analysis; for micro-ITT, any losses to follow-up were counted as treatment failures), it was expected that the effect of ceftriaxone versus placebo would be similar to the ME population, but with equally lower microbiological response rates (success) in both groups. Therefore, it was reasonable to apply the same microbiological treatment effect and noninferiority margin for both the ME and micro-ITT populations. The random-effects meta-analysis for ceftriaxone in the ME population estimated the pooled rate of microbiological success to be 98% (95% CI, 97%–99%; Fig. 2A). For proxy-for-placebo, the random-effects meta-analysis in the ME population estimated the rate of microbiological success to be 44% (95% CI, 34%–54%; Fig. 2B). Microbiological treatment effect was calculated as 43%: this is derived from the difference between the upper 95% CI for proxy-for placebo, which was 54%, and the lower 95% CI for ceftriaxone, which was 97% (Table 3). A noninferiority margin of 15% preserved 65% of the ceftriaxone treatment effect per FDA guidance for noninferiority studies, which requires >50% of the treatment effect to be preserved. Some statistical heterogeneity was detected in both the ceftriaxone and proxy-for-placebo groups, but it was not considered statistically significant (Fig. 2).

Risk of Bias

Two independent reviewers used the Cochrane risk-of-bias tool to assess risk of bias for ceftriaxone and proxy-for-placebo

TABLE 2. Study Characteristics of 3 Published Ceftriaxone and Proxy-for-Placebo Studies Identified in a Systematic Review That Assessed Microbiological Response of Success in Patients ≥12 Years of Age With uUGC in the Micro-ITT and ME Populations

Proxy-for-Placebo

				Demographics			Timing of End Point	Analysis Populations	
Author, Year	Study Design	Region	Ciprofloxacin Dose (Route)	N	Age, Mean (SD), y	Male, %	Microresponse (TOC), d	Micro-ITT Responder, %	ME Responder, %
Aplasca de Los Reyes, 2001[47s]	OL RCT	Philippines	500 mg (PO)	207	NR; ≥16	0	4–7	NR	53.3

Observational Cohort Studies Reporting Spontaneous Resolution of uUGC

Author, Year	Study Design	Region	Baseline Measure	N	Age, Mean (SD) or Range, y	Male, %	Follow-up Timing (Range), d	Primary Outcome	Micro-ITT Responder, %
Mensforth, 2020[48s]	Observational prospective cohort nested within RCT	UK	Positive NAAT uUGC	83	30.4 (9.7)	77.0	10 (7–15)	Clearance*	41.1
van Liere, 2019[49s]	Prospective cohort GC clearance	The Netherlands	Positive NAAT uUGC	38	22 (NR) range: 21–24	30.0	10 (7–14)	Spontaneous clearance†	30.8

Micro-ITT population included participants with a positive culture from a urogenital site who received another therapy for uUGC before the TOC visit (losses to follow-up were included in this efficacy assessment as failures). ME participants were those in the micro-ITT population who received study drug, had no important protocol deviations, and had an efficacy assessment (losses to follow-up not included).

*Positive uUGC NAAT at preenrollment sample and negative at enrollment without antibiotics.

†Positive preenrollment NAAT and negative enrollment NAAT at the same anatomical site in the absence of antibiotics.

d indicates days; GC, gonorrhea; ME, microbiologically evaluable population; micro-ITT, microbiological intent-to-treat population; NAAT, nucleic acid amplification test; NR, not reported; OL, open-label; PO, orally (per os); RCT, randomized controlled trial; TOC, test of cure; UK, United Kingdom; uUGC, uncomplicated urogenital gonorrhea; y, years.

clinical trials (Supplementary Table 2, http://links.lww.com/OLQ/A835). One study had low risk of bias across all domains.[35s] Two studies had high risk of bias in one domain due to study attrition (incomplete outcome data).[33s,34s] Eleven studies had uncertain risk of bias due to attrition and high risk of bias due to selective reporting, as results were for the ME population only.[36s–46s] For the proxy-for-placebo clinical trial included, risk of bias was uncertain for attrition and high for selection reporting because the micro-ITT response was not reported for the urogenital site.[47s] For proxy-for-placebo observational studies, 2 independent reviewers used the Newcastle-Ottawa Scale for assessing risk of bias (Supplementary Table 3, http://links.lww.com/OLQ/A835). Both studies had low risk of bias, scoring 10 out of 12.[48s,49s]

Sensitivity Analyses

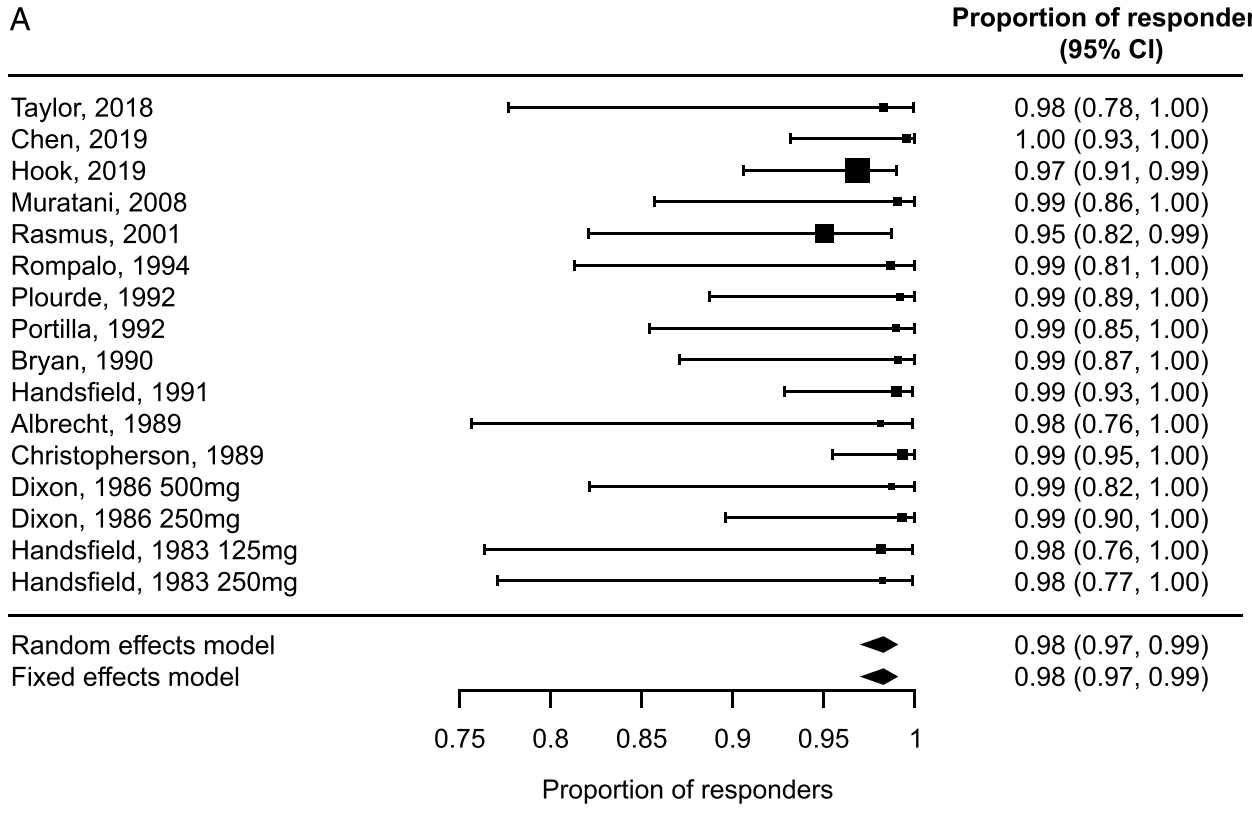
In the ME population, the 4 models produced similar pooled effect sizes for proxy-for-placebo (range, 43% to 44%) and ceftriaxone (range, 98% to >99%; Table 3). Overall, the results supported the choice of model and a noninferiority margin of 15%. The meta-analysis for ceftriaxone in the micro-ITT population estimated the pooled rate of microbiological success to be 88% (95% CI, 82%–92%); the meta-analysis for proxy-for-placebo in the ME population estimated the rate of microbiological success to be 44% (95% CI, 34%–54%), resulting in a microbiological treatment effect of 28% (Supplementary Table 4, http://links.lww.com/OLQ/A835; Supplementary Fig. 1, http://links.lww.com/OLQ/A835). Given the conservative nature of this estimate, a noninferiority margin of 15% is justified. The direct derivation for the microbiological treatment effect was slightly higher than the indirect derivation for all models.

As a conservative sensitivity analysis, the microbiological treatment effect for the micro-ITT population was also explored by comparing the ceftriaxone micro-ITT meta-analysis results with the available proxy-for-placebo data (ME population). Care should be taken when adopting this approach regarding missing data because participants lost to follow-up were included as treatment failures for ceftriaxone, but not for placebo.

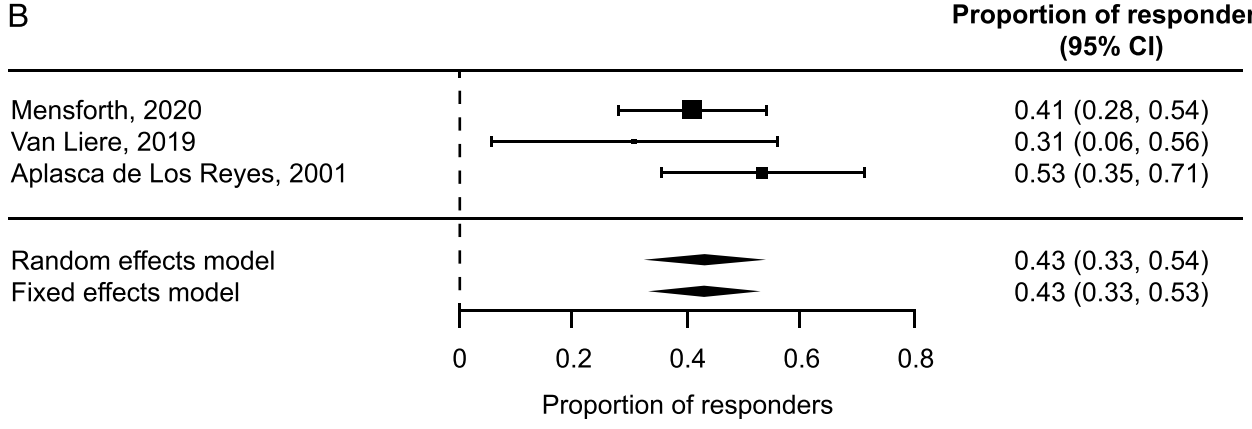
DISCUSSION

The findings from this systematic literature review and meta-analysis were used to estimate the antibacterial treatment effect of ceftriaxone and proxy-for placebo, which was then used to determine the microbiological treatment effect and propose a noninferiority margin.

Food and Drug Administration guidance includes a meta-analysis intended to establish a noninferiority margin for microbiological response in uUGC. The FDA-recommended noninferiority margin for *N. gonorrhoeae* trials is 10% based on (1) 1 study that estimated a proxy-for-placebo response among participants with uUGC resistant to the drug they were randomized to, and (2) 2 studies that estimated a proxy-for-placebo response in subjects randomized to a low dose of an active comparator (third-generation cephalosporin) "deemed less effective."[26,47s,50s,51s] The recommended noninferiority margin is not based on ceftriaxone treatment effect (current standard of care), nor is it based on the contemporary body of literature, which would contribute to estimating proxy-for-placebo treatment effect. This is especially challenging because the minimum inhibitory concentrations of *N. gonorrhoeae* have increased over time[52s]; therefore, participants enrolled in older historical studies may not be wholly reflective of



Random effects model test for heterogeneity: I^2=0.0%, tau²=0 (SE=0.481), p-value=0.963



Random effects model test for heterogeneity: I^2=6.33%, tau²=0.010 (SE=0.159), p=0.344

Figure 2. Forest plot of the meta-analysis for microbiological response for (A) ceftriaxone and (B) proxy-for-placebo in uUGC among the ME study population. CI, confidence interval; I^2, percentage of variation across studies due to heterogeneity rather than chance (total heterogeneity/total variability); ME, microbiologically evaluable population; τ^2, estimate of the degree of heterogeneity (heterogeneity variance); uUGC, uncomplicated urogenital gonorrhea.

the current target population (isolates) in a clinical trial or those enrolled in current studies.[53s] However, the inclusion of more recent clinical trials allows for reestimation of a noninferiority margin based on ceftriaxone as standard of care and proxy-for-placebo.[53s] European Medicines Agency guidance also supports a noninferiority margin of 10% for *N. gonorrhoeae* studies.[27] Based on our meta-analysis, a noninferiority margin of 10% preserves 77% of the ceftriaxone treatment effect, compared with a 15% noninferiority margin preserving 65% of the ceftriaxone treatment effect. The primary endpoint of microbiological response in the micro-ITT population could not be calculated; however, we believe that using the ME population resulted in the best noninferiority margin approximation possible, given the recent data available.

As antimicrobial resistance becomes more prevalent, it is imperative that new antibacterial agents are approved for the treatment of *N. gonorrhoeae*.[2] More recent clinical trials may include

TABLE 3. Summary of Meta-Analysis Results for the Active Comparator (ME Population) Versus Proxy-for-Placebo (ME Population) in uUGC Studies

	Ceftriaxone ME*		Proxy-for-Placebo ME†		Microbiological Treatment Effect Indirect‡	Microbiological Treatment Effect Direct§
Analysis	Proportion of Responders (95% CI)	Heterogeneity I^2, τ^2 (SE), P Value	Proportion of Responders (95% CI)	Heterogeneity I^2, τ^2 (SE), P Value	Ceftriaxone Lower CI Minus Placebo Upper CI	Lower CI of Difference
Der Simonian-Laird random effects¶	0.98 (0.97–0.99)	0.00%, 0 (0.48), 0.96	0.44 (0.34–0.54)	6.33%, 0.01 (0.16), 0.34	0.43	0.44
Fixed effects	0.98 (0.97–0.99)	0.00%, 0 (NA), 0.96	0.44 (0.34–0.54)	6.33%, 0 (NA), 0.34	0.44	0.45
GLMM	1.00 (0.98–1.00)	41.83%, 0.98 (NA), 1.00‖	0.43 (0.34–0.53)	0.00%, 0 (NA), 0.34‖	0.45	0.46
—	—	τ Mode, Mean (SD) (95% CrI)	—	τ Mode, Mean (SD) (95% CrI)	—	—
Bayesian	0.98 (0.97–0.99)	0, 0.26 (0.19) (0–0.62)	0.43 (0.30–0.58)	0, 0.27 (0.21) (0–0.69)	0.39	0.41

ME population includes all participants with gonorrhea at urethral and cervical sites randomized to treatment and who returned for FU visit; loss to FU not included in analyses.

*Includes Taylor, 2018; Chen, 2019; Hook, 2019; Plourde, 1992; Albrecht, 1989; Muratani, 2008; Ramus, 2001; Rompalo, 1994; Portilla, 1992; Bryan, 1990; Handsfield, 1991; Christophersen, 1989; Dixon, 1986; Handsfield, 1983.

†Includes Aplasca de los Reyes, 2001; Mensforth, 2020; van Liere, 2019.

‡Indirect comparison is the lower 95% CI of ceftriaxone minus upper 95% CI of proxy-for-placebo.

§Direct comparison is the lower 95% CI of difference between ceftriaxone and proxy-for-placebo.

¶DerSimonian, 1986.

‖Wald test.[54s]

CI indicates confidence interval; CrI, credible interval; FU, follow-up; GLMM, generalized linear mixed model; I^2, percentage of variation across studies due to heterogeneity rather than chance (total heterogeneity/total variability); ME, microbiologically evaluable population; NA, not applicable; τ^2, estimate of the degree of heterogeneity (heterogeneity variance); uUGC, uncomplicated urogenital gonorrhea.

N. gonorrhoeae isolates that are resistant or less susceptible to ceftriaxone[2] compared with older trials where resistance to ceftriaxone was not identified. To this end, our literature search used search terms that were purposefully more general in nature to identify all relevant publications, historic and recent. Using only older studies without contemporary isolates showing decreased susceptibility when calculating the ceftriaxone treatment effect may result in an inaccurate noninferiority margin. A noninferiority margin wider than the 10% margin recommended by the FDA and EMA may be warranted in view of the potential benefits (e.g., oral administration, favorable pharmacokinetic/pharmacodynamic profiles) of the newer antibiotics in clinical development, such as zoliflodacin and gepotidacin, and the increasing minimum inhibitory concentrations for oral cephalosporins worldwide. Furthermore, an oral antibiotic may be preferable to many than the current intramuscular ceftriaxone, particularly considering the reluctance many people have with injections. Considering these points alongside our current findings, a noninferiority margin of 15% would accelerate the development of novel oral therapeutics for participants and increase study feasibility in a therapeutic area where participant recruitment and follow-up can be challenging, and where existing drugs will become less effective as antibiotic resistance increases.[53s]

Although inclusion of open-label studies may have introduced bias because the primary endpoint was microbiological cure in the micro-ITT population, low risk of bias was seen across all studies for this endpoint because the microbiological response could not be influenced by the investigators. The studies included in the meta-analysis had a broad range of dosing regimens: only 1 study evaluated azithromycin, and TOC visit timing varied between studies (3–10 days after treatment initiation). However, no statistically significant heterogeneity in the meta-analysis was observed.

We characterized the clinical and methodological heterogeneity across historic uUGC studies of ceftriaxone and proxy-for-placebo and estimated a noninferiority margin based on microbiological response in the ME population. Based on the calculated microbiological treatment effect, a proposed noninferiority margin of 15% preserves 65% of the ceftriaxone treatment effect. Given the need for novel oral treatments for uUGC, the current 10% noninferiority margin requirement may be overly stringent for clinical studies in uUGC. Results of this systematic literature review and meta-analysis could help inform the design, conduct, and analysis of future uUGC studies.

REFERENCES

1. World Health Organization. WHO Guidelines for the Treatment of *Neisseria gonorrhoeae*; 2016. Available at: https://apps.who.int/iris/bitstream/handle/10665/246114/9789241549691-eng.pdf. Accessed June 9, 2022.
2. European Centre for Disease Prevention and Control. Gonorrhoea—Annual Epidemiological Report for 2018; 2020. Available at: https://www.ecdc.europa.eu/en/publications-data/gonorrhoea-annual-epidemiological-report-2018. Accessed June 9, 2022.
3. Centers for Disease Control and Prevention. National Overview—Sexually Transmitted Disease Surveillance, 2019; 2021. Available at: https://www.cdc.gov/std/statistics/2019/overview.htm#Gonorrhea. Accessed June 9, 2022.
4. European Centre for Disease Prevention and Control. Surveillance Atlas of Infectious Diseases; 2019. Available at: https://atlas.ecdc.europa.eu/public/index.aspx. Accessed June 9, 2022.
5. Centers for Disease Control and Prevention. Sexually transmitted infections prevalence, incidence and cost estimates in the United States; 2021. Available at: https://www.cdc.gov/std/statistics/prevalence-2020-at-a-glance.htm. Accessed June 9, 2022.
6. Wi T, Lahra MM, Ndowa F, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Global surveillance and a call for international collaborative action. PLoS Med 2017; 14:e1002344.

7. Kirkcaldy RD, Zaidi A, Hook EW 3rd, et al. *Neisseria gonorrhoeae* antimicrobial resistance among men who have sex with men and men who have sex exclusively with women: The Gonococcal Isolate Surveillance Project, 2005–2010. Ann Intern Med 2013; 158(5 Pt 1):321–328.
8. Unemo M, Del Rio C, Shafer WM. Antimicrobial resistance expressed by *Neisseria gonorrhoeae*: A major global public health problem in the 21st century. Microbiol Spectr 2016; 4.
9. Unemo M, Shafer WM. Antimicrobial resistance in *Neisseria gonorrhoeae* in the 21st century: Past, evolution, and future. Clin Microbiol Rev 2014; 27:587–613.
10. Thomas JC 4th, Joseph SJ, Cartee JC, et al. Phylogenomic analysis reveals persistence of gonococcal strains with reduced-susceptibility to extended-spectrum cephalosporins and mosaic penA-34. Nat Commun 2021; 12:3801.
11. Bolan GA, Sparling PF, Wasserheit JN. The emerging threat of untreatable gonococcal infection. N Engl J Med 2012; 366:485–487.
12. Centers for Disease Control and Prevention. Antibiotic Resistance Threats in the United States. Atlanta, GA: U.S. Department of Health and Human Services, CDC, 2019.
13. Workowski KA, Bolan GA, Centers for Disease Control and Prevention. Sexually transmitted diseases treatment guidelines, 2015. MMWR Recomm Rep 2015; 64(RR-03):1–137.
14. Bignell C, Unemo M, European STI Guidelines Editorial Board. 2012 European guideline on the diagnosis and treatment of gonorrhoea in adults. Int J STD AIDS 2013; 24:85–92.
15. St Cyr S, Barbee L, Workowski KA, et al. Update to CDC's treatment guidelines for gonococcal infection, 2020. MMWR Morb Mortal Wkly Rep 2020; 69:1911–1916.
16. Unemo M, Ross J, Serwin AB, et al. 2020 European guideline for the diagnosis and treatment of gonorrhoea in adults (published online October 29, 2020). Int J STD AIDS. doi:10.1177/0956462420949126.
17. Workowski KA, Bachmann LH, Chan PA, et al. Sexually transmitted infections treatment guidelines, 2021. MMWR Recomm Rep 2021; 70:1–187.
18. Lewis DA. New treatment options for *Neisseria gonorrhoeae* in the era of emerging antimicrobial resistance. Sex Health 2019; 16:449–456.
19. Cristillo AD, Bristow CC, Torrone E, et al. Antimicrobial resistance in *Neisseria gonorrhoeae*: Proceedings of the STAR Sexually Transmitted Infection-Clinical Trial Group Programmatic Meeting. Sex Transm Dis 2019; 46:e18–e25.
20. Yang F, Yan J, van der Veen S. Antibiotic resistance and treatment options for multidrug-resistant gonorrhea. Infect Microbes Dis 2020; 2:67–76.
21. Gibson EG, Bax B, Chan PF, et al. Mechanistic and structural basis for the actions of the antibacterial gepotidacin against *Staphylococcus aureus* gyrase. ACS Infect Dis 2019; 5:570–581.
22. Jacobsson S, Golparian D, Scangarella-Oman N, et al. In vitro activity of the novel triazaacenaphthylene gepotidacin (GSK2140944) against MDR *Neisseria gonorrhoeae*. J Antimicrob Chemother 2018; 73:2072–2077.
23. Farrell DJ, Sader HS, Rhomberg PR, et al. In vitro activity of hepotidacin (GSK2140944) against *Neisseria gonorrhoeae*. Antimicrob Agents Chemother 2017; 61:e02047–e02016.
24. Mushtaq S, Vickers A, Sadouki Z, et al. In vitro activities of gepotidacin, a novel triazaacenaphthylene and topoisomerase IV DNA gyrase inhibitor, against gram-negative bacteria and *Staphylococcus saprophyticus*. Presented at: ECCMID; April 13–16, 2019; Amsterdam, the Netherlands. Poster P1849.
25. Food and Drug Administration. Non-inferiority clinical trials to establishing effectiveness. 2016. Available at: https://www.fda.gov/media/78504/download. Accessed June 9, 2022.
26. Food and Drug Administration. Uncomplicated gonorrhea: Developing drugs for treatment—guidance for industry; 2015. Available at: https://www.fda.gov/files/drugs/published/Uncomplicated-Gonorrhea–Developing-Drugs-for-Treatment.pdf. Accessed June 9, 2022.
27. European Medicines Agency. Guideline on the evaluation of medicinal products indicated for treatment of bacterial infections, Rev 3. 2019. Available at: https://www.ema.europa.eu/en/documents/scientific-guideline/draft-guideline-evaluation-medicinal-products-indicated-treatment-bacterial-infections-revision-3_en.pdf. Accessed June 9, 2022.
28. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: Explanation and elaboration. BMJ 2009; 339:b2700.
29. Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. PLoS Med 2009; 6:e1000097.
30. Moher D, Simera I, Schulz KF, et al. Helping editors, peer reviewers and authors improve the clarity, completeness and transparency of reporting health research. BMC Med 2008; 6:13.

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