Addition of probenecid to oral $\beta$-lactam antibiotics: a systematic review and meta-analysis

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Objectives: To explore the literature comparing the pharmacokinetic and clinical outcomes from adding probenecid to oral $\beta$-lactams.

Methods: Medline and EMBASE were searched from inception to December 2021 for all English language studies comparing the addition of probenecid (intervention) with an oral $\beta$-lactam [flucloxacillin, penicillin V, amoxicillin (+ clavulanate), cefalexin, cefuroxime axetil] alone (comparator). ROBINS-I and ROB-2 tools were used. Data on antibiotic therapy, infection diagnosis, primary and secondary outcomes relating to pharmacokinetics and clinical outcomes, plus adverse events were extracted and reported descriptively. For a subset of studies comparing treatment failure between probenecid and control groups, meta-analysis was performed.

Results: Overall, 18/295 (6%) screened abstracts were included. Populations, methodology and outcome data were heterogeneous. Common populations included healthy volunteers (9/18; 50%) and those with gonococcal infection (6/18; 33%). Most studies were crossover trials (11/18; 61%) or parallel-arm randomized trials (4/18; 22%). Where pharmacokinetic analyses were performed, addition of probenecid to oral $\beta$-lactams increased total AUC (7/7; 100%), $C_{\text{max}}$ (5/8; 63%) and serum $t_{1/2}$ (6/8; 75%). Probenecid improved PTA (2/2; 100%). Meta-analysis of 3105 (2258 intervention, 847 control) patients treated for gonococcal disease demonstrated a relative risk of treatment failure in the random-effects model of 0.33 (95% CI 0.20–0.55; $I^2 = 7\%$), favouring probenecid.

Conclusions: Probenecid-boosted $\beta$-lactam therapy is associated with improved outcomes in gonococcal disease. Pharmacokinetic data suggest that probenecid-boosted oral $\beta$-lactam therapy may have a broader application, but appropriately powered mechanistic and efficacy studies are required.

Introduction

Probenecid, $p$-(di-$n$-propylsulphamyl)-benzoic acid, was developed in 1949 with the purpose of decreasing the renal clearance of penicillin.$^1$ Its mechanism of action is through competitive inhibition of organic anion transporters, which are responsible for excretion of organic agents, such as penicillin.$^2$ Reduction in renal clearance of penicillin with probenecid demonstrated significant increases in serum exposure, meaning that lower doses of drug were required for similar pharmacokinetic/pharmacodynamic (PK/PD) target attainment. Probenecid’s influence on penicillin clearance became mainly academic in the post-war era as the capability to produce more diverse, cheaper and safer $\beta$-lactam antibiotics rapidly expanded.$^3$ Probenecid remains a recommended adjunct in the management of some sexually transmitted infections to support therapeutic target attainment in compartments, such as CSF in neurosyphilis.$^4$ However, its potential important and broader role in preserving the effectiveness of $\beta$-lactams through the optimization of $\beta$-lactam PK and dosing schedules needs to be considered, as well as possible adverse events associated with its use, such as nausea and unfavourable drug–drug interactions.

Globally, the WHO Access, Watch and Reserve (AWaRe) criteria require narrow-spectrum antimicrobials, such as the penicillins,
to be available in appropriate type, dose and duration to treat common infections.\(^4\) With increasing drug resistance within common causative organisms, such as in streptococci, new methods to optimize the delivery of Access agents and protect the use of broader Watch and Reserve antimicrobials are required.\(^4,5\)

It is not always possible to administer higher doses of an oral antibiotic to achieve an optimal PK/PD profile. In some instances, oral drug absorption or gastrointestinal side effects are associated with high doses and limit escalation of therapy. In other situations, augmented renal clearance may make achieving optimal drug exposure difficult. Some agents are not licensed for use at oral doses that would be required to obtain acceptable PK/PD target attainment. Opportunities to deliver oral narrow-spectrum agents in an optimized format may offer an attractive opportunity within local antimicrobial stewardship agendas and support the avoidance of prolonged courses of IV treatment in certain infections.\(^6,7\)

We explored current and historical literature that compared the use of probenecid with an oral \(\beta\)-lactam antibiotic versus the \(\beta\)-lactam antibiotic alone, describing its impact on PK, clinical outcomes and reported adverse events. The aim was to describe the current literature in support of this approach and identify gaps in knowledge that can be addressed by future mechanistic and efficacy-based research.

**Methods**

**Search criteria**

We performed a search of MEDLINE and Embase using the search terms outlined in Table S1, available as Supplementary data at JAC Online. Studies in English reporting direct comparison of probenecid plus an oral \(\beta\)-lactam versus the \(\beta\)-lactam alone in human subjects were included. Common oral \(\beta\)-lactam antibiotics used in the UK were selected for inclusion. These were flucloxacinil, penicillin V, amoxicillin, ampicillin, amoxicillin/clavulanate, cefalexin and cefuroxime axetil. Only full-text, original research articles comparing the addition of probenecid with the same oral \(\beta\)-lactam antibiotic were included. Articles were required to describe PK/PD, microbiology or adverse event outcomes to be included. Anything published before December 2021 was included and no prior time limit was set. Studies were excluded if they were not in English, were reviews and letters, compared different antimicrobial agents or routes of delivery, or reported on non-human subjects. This review was registered on the PROSPERO database prior to data extraction (registration number: CRD42021298765).

**Study selection**

Specific literature review software (Covidence, Australia) was used. Two authors (T.M.R. and R.C.W.) independently reviewed abstracts and full texts against inclusion and exclusion criteria. Articles that met screening and eligibility checks were carried forward for full-text review. References of published literature were also reviewed to identify further full texts for inclusion.

**Data extraction**

Data were extracted by one researcher (T.M.R.), with cross-checking independently performed by a second author (R.C.W. or M.G.). Data extracted included publication details (authors, journal, year of publication), study details (participants, study design, intervention, control, dosing schedules), primary and secondary outcomes (including PK data and/or clinical outcomes) and reported adverse events/toxicity.

**Risk of bias**

Risk of bias for individual studies was assessed in line with Cochrane recommendations. For non-randomized studies, the Risk Of Bias in Non-randomized Studies of Interventions (ROBINS-I) assessment tool was used.\(^6\) For randomized studies, the Risk of Bias for randomized studies 2 (RoB 2) tool was used.\(^9\) Risk of bias was assessed by two reviewers (T.M.R. and R.C.W.) independently of each other. Where disagreement in domain scoring occurred, a third reviewer assessed the study and differences were discussed to reach consensus.

**Data analysis**

Data were analysed descriptively in line with the aims of this review. For a subset of studies comparing treatment failure between probenecid and control groups, meta-analysis was performed using the ‘metabin’ function from the ‘meta’ package (version 4.11-0) in R (version 3.5.1).\(^5\) Treatment failure was defined in these studies as microbiological failure, with growth of Neisseria gonorrhoeae during follow-up visit after treatment and not associated with self-reported history of re-exposure. Study findings were displayed in forest plots demonstrating the relative risk determined using the Mantel–Haenszel method. Heterogeneity was visually assessed using funnel plots and the \(I^2\) statistic. As study quality was expected to be highly variable, an a priori decision was made to proceed with meta-analysis as part of the subgroup analysis despite an expected moderate-to-high risk of bias within studies. Bias plots were generated using the ‘robvis’ package in R.\(^9\)

**Results**

**Study selection**

Figure 1 outlines the study selection process. In total, 340 references were identified, with 45 (13%) duplicates removed. Of the 295 titles and abstracts screened, 100 (34%) were carried forward for full-text review. On full-text review, a further 81/100 (81%) were excluded. Common reasons for exclusion were use

![Figure 1](https://example.com/figure1.png)
of a wrong intervention/comparator agent (56/81; 69%) and wrong outcome measures described (9/81; 11%). One manuscript was not accessible. Therefore, 18/295 (6%) manuscripts were included in the review.\(^{11,12}\)

**Study characteristics**

Table 1 summarizes studies included. Studies were reported from 1969 to 2021. Populations, methodology and outcome measures were heterogeneous. Most studies were in healthy volunteers\(^{12,14,16,19,20,23–25,27}\) (9/18; 50%) or in patients with gonococcal infection\(^{13,15,17,21,22,26}\) (6/18; 33%). Additional studies reported on patients with bronchiectasis (1/18; 6%),\(^{11}\) biliary pathology (1/18; 6%)\(^{18}\) and invasive Staphylococcus aureus infection (1/18; 6%).\(^{26}\) Crossover trials (11/18; 61%), parallel-arm randomized trials (4/18; 22%), observational (2/18; 11%) and dose-escalation (1/18; 6%) studies were reported.

Studies compared different oral β-lactam antibiotics with and without probenecid. These were ampicillin (3/18; 17%), amoxicillin (6/18; 33%), amoxicillin/clavulenate (1/18; 6%), fluclucxacillin (2/18; 11%), cefalexin (4/18; 22%), cefuroxime axetil (2/18; 11%) and penicillin V (1/18; 6%). Doses of β-lactam and frequency of treatment varied between study. Most studies described single doses of β-lactam with or without probenecid (15/18; 83%). Probenecid dosing varied between 250 and 1000 mg per single dose in these studies. Primary outcome measures differed between studies, with the effect of probenecid on oral β-lactam PK reported in 12/18 (67%) studies and treatment outcomes (failure of therapy) reported in 6/18 (33%) studies.

**Risk of bias in studies**

Figure S1 summarizes the risk of bias for both randomized and non-randomized studies included within this review. Overall, there was a moderate-to-high risk of bias in most studies, with low overall risk in 2/18 (11%) studies only.

**Studies reporting β-lactam PK**

Despite variable β-lactam choice and dose, methods of β-lactam quantification and methods of data analysis, common observations were present. Of 12 studies reporting the effect of probenecid on β-lactam PK as a primary outcome, 7/12 (58%) described the influence on AUC, 8/12 (67%) on serum \(t_{\text{max}}\), and 8/12 (67%) on peak observed serum concentration (C\(_{\text{max}}\)). Two of 12 studies (17%) reported the use of Monte Carlo simulation to estimate PTA. Addition of probenecid to oral β-lactam antibiotics increased total AUC in 7/7 (100%) studies reporting it. β-Lactam C\(_{\text{max}}\) was significantly increased in 5/8 (63%) and \(t_{\text{max}}\) in 6/8 (75%) of studies reporting these variables. Both studies assessing PTA (2/2; 100%) demonstrated a significant increase in target attainment with the addition of probenecid to β-lactam therapy.

**Studies reporting treatment failure**

Of the 6/18 (33%) studies reporting on treatment failure as a primary outcome, 4/6 (67%) were included in a meta-analysis comparing the addition of probenecid to an oral β-lactam antibiotic of the same dose on treatment outcome (Figure 2).\(^{15,17,21,26}\) One study (17%) could not be included as different doses of ampicillin were used in the intervention and control arms.\(^{15}\) A further study (1/6; 17%) could not be included due to different dosing schedules between intervention and control arms. All four included studies reported on the outcome of treating gonococcal disease, with microbiological failure at follow-up used to define treatment failure. Three (75%) were randomized studies and one (25%) was observational in design. They contained seven direct comparisons of addition of probenecid to an oral β-lactam antibiotic of fixed dose on treatment outcome in 3105 (2258 intervention and 847 control) patients. The relative risk of treatment failure in the random-effects model was 0.33 (95% CI 0.20–0.55; \(I^2 = 7\%\)), favouring the addition of probenecid to oral β-lactam regimens.

**Side effects and toxicity**

The assessment of side effects/toxicity was reported in 11/18 (61%) studies. Of these, 4/11 (36%) observed side effects, with 7/11 (64%) not reporting any observed adverse events. One randomized study identified a higher rate of reported nausea for 1 g cefuroxime axetil with 1 g probenecid (7/57; 12%) versus 1 g cefuroxime axetil alone (1/52; 2%).\(^{17}\) Within this study, rates of vomiting and diarrhoea were similar. A further study highlighted an increase in observed reports of nausea and dizziness associated with 1 g probenecid twice a day in patients receiving 7 days of treatment for furunculosis.\(^{28}\) Unfortunately, the observed rate was not quantified by the authors. Allen and colleagues\(^{11}\) reported one case of nausea associated with an arm containing 1 g of probenecid twice a day in their study of amoxicillin PK in patients with bronchiectasis. The final study to observe side effects reported six patients with nausea from their entire cohort. The authors do not differentiate between those receiving β-lactam antibiotic alone versus β-lactam antibiotic with probenecid.\(^{15}\) PK data for probenecid and/or β-lactam antibiotics were not provided or not available in a way that allowed evaluation of the impact of drug exposure on these reported outcomes.

**Discussion**

This review highlights the current paucity of evidence for the use of probenecid to optimize the delivery of oral β-lactam antibiotics. Current data are heterogeneous, use historical methods of drug quantification, and focus predominantly on the management of gonococcal disease. Current evidence suggests that addition of probenecid to oral β-lactam therapy reduces microbiological treatment failures in gonococcal disease compared with use of single doses of an oral β-lactam antibiotic alone. In addition, the influence of probenecid on oral β-lactam PK leads to potentially favourable drug exposures that may enhance target attainment for other infective aetiologies requiring longer courses of antimicrobial therapy, including S. aureus infection.

β-Lactam antibiotics exhibit time-dependent mechanisms of action. In the late 20th and early 21st centuries, optimal PK/PD targets for β-lactams have been explored and defined. The time the free (unbound) concentration of β-lactam spends above an organism’s MIC (\(T_{>\text{MIC}}\)) best describes β-lactam PK/PD.\(^{29}\) Traditionally, targets of greater than 40%–50% \(T_{>\text{MIC}}\) are targeted, with evidence that attainment of this target leads to improved patient outcomes.\(^{29}\) For some infections, such
| Paper            | Population                          | Design                     | Intervention                                      | Control                             | Microbiological outcome                                      | Pharmacokinetic data                                      | Adverse events                           |
|------------------|-------------------------------------|----------------------------|--------------------------------------------------|-------------------------------------|--------------------------------------------------------------|-----------------------------------------------------------|------------------------------------------|
| Allen et al.     | 6 patients (4 female) with stable   | Randomized crossover of 3  | Amoxicillin 1 g twice a day plus probenecid 500 mg four times a day OR Amoxicillin 1 g twice a day plus probenecid 1 g twice a day | High-dose amoxicillin 3 g twice a day placebo | Nil                                                          | Probenecid reduced amoxicillin clearance to one-third of that with the placebo. No influence on Cmax or t1/2 identified. | 1 patient in probenecid 1 g twice-a-day arm reported nausea |
| 1990             | bronchiectasis, median age 53.5 years | regimens                   |                                                  |                                     |                                                              |                                                           |                                          |
| Barbhaiya et al. | 8 healthy volunteers, 22–26 years old | Crossover study            | Amoxicillin 3 g with 1 g probenecid              | Amoxicillin 3 g alone               | Nil                                                          | Greater peak amoxicillin concentration and larger AUC with probenecid. | N/A                                      |
| 1979             |                                     |                            |                                                  |                                     |                                                              |                                                           |                                          |
| Bro-Jorgensen    | 1915 men and 921 females with       | Observational study        | Ampicillin 1 g plus 1 g probenecid OR Ampicillin 2 g plus 1 g probenecid | Ampicillin 1 g OR Ampicillin 2 g    | Microbiological failure within 14 days of treatment          | Nil observed                                                                        |                                          |
| and Jensen       | uncomplicated gonorrhoea            | comparing 4 regimens       |                                                  |                                     |                                                              |                                                           |                                          |
| 1971             |                                     |                            |                                                  |                                     | Microbiological failure identified during two follow-up visits Ampicillin plus probenecid treatment failure: 3/24 (13%), Ampicillin: 2/72 (3%), with 3/72 (4%) in this arm also lost to follow-up. | No correlation between serum concentration and recurrent positive culture. | N/A                                      |
| Eriksson         | 96 outpatients with uncomplicated    | Observational study        | Ampicillin 2 g plus 1 g probenecid              | Ampicillin 2 g in divided dose 5 h apart | Microbiological failure                                      | Probenecid increased the free fluocloxacillin AUC and reduced clearance by approximately 53%–55%. 2–5 fold increase in | Nil observed                            |
| 1973             | gonorrhoea                           |                            |                                                  |                                     | identified during two follow-up visits Ampicillin plus probenecid treatment failure: 3/24 (13%), Ampicillin: 2/72 (3%), with 3/72 (4%) in this arm also lost to follow-up. |                                                           |                                          |
| Everts et al.    | 11 healthy volunteers (7 female, 4  | Crossover study            | Fluocloxacillin 1000 mg plus probenecid 500 mg  | Fluocloxacillin 1000 mg             | Nil                                                          | Nil observed                                                                            |                                          |
| 2020             | male)                               |                            |                                                  |                                     |                                                              |                                                           |                                          |
| Paper                      | Population                          | Design                          | Intervention                      | Control       | Microbiological outcome                                      | Pharmacokinetic data                                                                                      | Adverse events                                      |
|---------------------------|-------------------------------------|---------------------------------|-----------------------------------|---------------|---------------------------------------------------------------|----------------------------------------------------------------------------------------------------------|------------------------------------------------------|
| Everts et al. 2021        | 11 healthy volunteers (7 female, 4 male) | Crossover study                 | Cefalexin 1 g plus probenecid 500 mg | Cefalexin 1 g | Nil                                                           | flucloxacillin PK/PD target attainment. Probenecid increased cefalexin AUC, C<sub>max</sub> and t<sub>½</sub>; enhanced PTA for S. aureus. | Nil observed                                        |
| Frisk et al. 1952         | 14 healthy volunteers               | Dose-escalation study           | Penicillin 500000 units with escalating dose of probenecid from 0.25 mg to 1 g | Penicillin 500 mg alone | Nil                                                           | There is a linear relationship between probenecid dose and increase in plasma penicillin concentration in the probenecid dosing range of 0.25–1 g of probenecid. | Nil observed                                        |
| Gottlieb and Mills 1986   | 65 MSM with suspected gonorrhoea    | Randomized, parallel-arms study | Cefuroxime 1 g plus probenecid 1 g | Cefuroxime 1 g | Microbiological failure within 4–7 days of treatment Probenecid arm had 1/36 failures at 4–7 days; control arm had 3/29 failures. | Nil                                                                                                     | N/A                                                  |
| Gower and Dash 1969       | 6 healthy volunteers                | Crossover study                 | Cefalexin 1 g four times a day plus probenecid 500 mg four times a day | Cefalexin 1 g four times a day | Nil                                                           | Probenecid increased peak cefalexin concentration and serum t<sub>½</sub>. Probenecid significantly reduced urinary excretion of cefalexin. | Nil observed                                        |
| Hedström and Kahlmeter 1980 | 6 patients with S. aureus infection (4 male, 2 female) | Crossover study                 | Flucloxacillin 1 g twice a day plus probenecid 1 g twice a day | Flucloxacillin 1 g twice a day | Nil                                                           | Probenecid increased flucloxacillin t<sub>½</sub> and doubled AUC in the central compartment. | Nausea and dizziness reported in ‘a few’ patients receiving probenecid 1 g twice a day in a separate observational phase of the study in 35 patients with furunculosis; 1/35 patients reported urticaria and 4/35 exanthem | N/A                                                  |
| Karney et al. 1974        | 155 patients with anogenital gonorrhoea (80 male, 75 female) | Randomized, double-blind, parallel-arms study | Ampicillin 3.5 g plus 1 g probenecid | Ampicillin 3 g | Microbiological failure within 3–7 days of treatment Probenecid arm had fewer failures at 14 days, with 1/60 (2%) | Nil                                                                                                     | N/A                                                  |
| Study | Year | Participants | Study Design | Treatment 1 | Treatment 2 | Results |
|-------|------|--------------|--------------|-------------|-------------|---------|
| Meyers et al. | 1969 | 10 healthy volunteers (10 male, 4 female) | Crossover study | Cefalexin 500 mg plus 500 mg probenecid | Nil | Probenecid increased the serum t½ of cefalexin. |
| Mitchell and Robson | 1974 | 102 males with urethral discharge | Randomized, parallel-arms study | Amoxicillin 2 g plus probenecid 1 g | Nil | Microbiological failure within 28 days of treatment Cure with probenecid: 50/52 (98%); amoxicillin alone: 39/45 (89%). |
| Paulsen et al. | 1989 | 12 healthy volunteers (7 male, 5 female) | Randomized crossover study | Amoxicillin 1 g plus probenecid 1 g | Nil | Probenecid increased amoxicillin t½ and peak concentration. This led to a doubling of the AUC; no significant difference in PK parameters when compared with 3 g amoxicillin. |
| Reichman et al. | 1985 | 124 patients with uncomplicated gonorrhoea (20 female, 104 male) | Blinded, randomized, parallel-arms study | Cefuroxime axetil 1 g plus probenecid 1 g | Nil | Microbiological failure within 4–7 days of treatment Cure within probenecid arm in 55/56 (98%) versus 50/51 (98%) in control arm. |
| Sales et al. | 1972 | 9 patients with T-tubes in the CBD post cholecystectomy | Crossover study | Cefalexin 1 g plus probenecid 500 mg (n=5 patients) | Nil | Probenecid led to significant increase in observed bile cefalexin concentration. |
| Shanson et al. | 1984 | 10 healthy volunteers | Randomized crossover study | Amoxicillin 3 g plus probenecid 1 g | Nil | Nausea (7/57 versus 1/52) was more predominant with probenecid; vomiting (2/57 versus 1/52) and diarrhoea (6/57 versus 7/52) were similar |
| Staniforth et al. | 1983 | 16 healthy volunteers | Crossover study | Amoxicillin 500 mg plus probenecid 1 g AND Amoxicillin/clavulanate 750 mg plus probenecid 1 g | Nil | Probenecid had no effect on clavulanic acid PK; a small change in renal clearance was noted; amoxicillin AUC, Cmax and t½ were increased. |

N/A, not assessed; CBD, common bile duct.
Probenecid. Furthermore, Grayson and colleagues demonstrated the potential impact of probenecid on free antibiotic concentration, but the true impact of probenecid on free antibiotic concentration remains to be defined in many cases. Finally, probenecid is known to interact with a number of common medications seen in multi-morbid patients, including paracetamol, non-steroidal anti-inflammatory drugs, antipsychotic medications and immunosuppressants. Consideration of these factors on treatment selection and outcomes is lacking from current data.

Future work should focus on characterization of the direct efficacy of addition of probenecid to common oral β-lactam antimicrobial dosing regimens. These studies could include the mechanistic characterization of probenecid’s influence on free chemically active drug and include assessment of clearance, plasma protein binding and target site concentration attainment. As well as demonstrating enhanced antimicrobial PK using probenecid, an impact on antimicrobial PD, clinical outcomes and toxicity must be clearly demonstrated. Future work should include the assessment and definition of probenecid PK/PD. With improved opportunities to provide therapeutic drug monitoring of both oral β-lactams and probenecid,40,41 this will further enhance the clinical acceptability of PK manipulation with probenecid and address concerns surrounding potential toxicity, which has not been reported in studies to date.

Conclusions

Probenecid is associated with improved microbiological cure at follow-up when added to oral β-lactam regimens for the treatment of gonococcal disease. Preclinical and observational data suggest that probenecid-boosted oral β-lactam therapy may have a broader application in the future. To define the potential role of probenecid-boosted oral β-lactam regimens, appropriately powered mechanistic and efficacy-based studies to facilitate direct comparison should be conducted.

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| Study | Experimental Events Total | Control Events Total | Risk Ratio | RR 95%-CI | Weight (common) | Weight (random) |
|-------|---------------------------|----------------------|------------|------------|-----------------|-----------------|
| Ampicillin 1g, males UCG (Bro-Jorgensen) | 12 | 617 | 17 | 161 | 0.18 | [0.09; 0.38] | 34.0% 27.1% |
| Ampicillin 2g, males UCG (Bro-Jorgensen) | 15 | 801 | 22 | 336 | 0.29 | [0.15; 0.54] | 39.1% 30.5% |
| Ampicillin 1g, females UCG (Bro-Jorgensen) | 7 | 303 | 3 | 79 | 0.61 | [0.40; 1.00] | 6.0% 11.5% |
| Ampicillin 2g, females UCG (Bro-Jorgensen) | 9 | 393 | 4 | 146 | 0.84 | [0.32; 2.67] | 7.4% 14.2% |
| Amoxicillin 2g, males UD (Mitchell) | 2 | 52 | 5 | 45 | 0.29 | [0.06; 1.36] | 8.1% 8.9% |
| Cefuroxime axetil 1g, mixed UCG (Reichman) | 1 | 56 | 1 | 51 | 0.94 | [0.06; 14.19] | 1.3% 3.1% |
| Cefuroxime axetil 1g, males G (Gottlieb) | 1 | 36 | 3 | 29 | 0.27 | [0.03; 2.45] | 4.2% 4.7% |

Common effect model
Random effects model
Heterogeneity: I² = 7%, τ² = 0.1047, p = 0.37

Figure 2. Meta-analysis of the relative risk (RR) of microbiological failure of treatment for gonococcal disease for probenecid-boosted oral β-lactams versus oral β-lactam antibiotic alone. UCG, uncomplicated gonococcal disease; UD, urethral discharge of presumed gonococcal disease; G, gonococcal disease (complicated and uncomplicated); I², dispersion of effect size within the meta-analysis; τ², estimated amount of total heterogeneity.
Cambridge and the University of Warwick. The views expressed in this publication are those of the author(s) and not necessarily those of the NHS, the NHHR, the Department of Health & Social Care or the UK Health Security Agency (previously PHE); and (3) Professor Alison H. Holmes is an NHIR Senior Investigator.

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Author contributions
T.M.R. and M.G. developed the concept and methodology for the review. T.M.R., R.C.W. and M.G. undertook data extraction and reviewing. All authors contributed significantly to data interpretation. T.M.R. drafted the initial manuscript. All authors contributed significantly to the revision of the manuscript and finalization for submission.

Data availability
Data and materials are available from the authors on reasonable request.

Supplementary data
Table S1 and Figure S1 are available as Supplementary data at JAC Online.

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