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Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics

--Manuscript Draft--

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Corresponding Author:	S Tariq Sadiq St George's, University of London London, UNITED KINGDOM
Corresponding Author's Institution:	St George's, University of London
First Author:	Emma Harding-Esch, Ph.D
Order of Authors:	Emma Harding-Esch, Ph.D
	Susie E Huntington
	Michael J Harvey
	Georgie Weston
	Claire E Broad
	Elisabeth J Adams
	S Tariq Sadiq

Abstract:	Introduction Antimicrobial resistance (AMR) threatens successful Neisseria gonorrhoeae (NG) treatment, with few practical alternatives should ceftriaxone resistance become widespread. AMR point-of-care tests (AMR-POCTs), currently being developed, would allow selection of appropriate treatment regimens (including previously abandoned regimens), thereby sparing ceftriaxone use. We assessed cost-effectiveness of five hypothetical AMR-POCT strategies (second antibiotic alongside ceftriaxone (Strategies A-C); single antibiotic alternative to ceftriaxone (Strategies D and E)) compared with Standard Care (SC; ceftriaxone and azithromycin dual-therapy), to inform appropriate implementation. Aim To assess the costs and effectiveness of these AMR-POCT strategies to optimise treatment regimen choice and reduce selection pressure on ceftriaxone. Methods Decision tree model simulating a cohort of 38,870 NG-diagnosed England sexual health clinic (SHC) attendees. AMR-POCT strategies and associated treatment options costed were: A) ciprofloxacin only (ciprofloxacin preferred over azithromycin as second agent if susceptible); B) azithromycin and ciprofloxacin (azithromycin preferred); C) ciprofloxacin and azithromycin (ciprofloxacin preferred); D) azithromycin AMR-POCT; E) ciprofloxacin AMR-POCT. A micro-costing approach, representing the cost to the SHC (for the year 2015/16), was employed. The time horizon was one year for initial patient treatment only. Primary outcomes were: total costs; percentage of people given optimal treatment (mono- or dual-therapy curing NG and not containing an antibiotic against which there was resistance); percentage of people given non-ceftriaxone optimal treatment; cost-effectiveness (cost per optimal treatment gained). Results All AMR-POCT strategies cost more than SC. Strategy B avoided most sub-optimal treatments (n=48) but cost most to implement (£4,093,844 [5,474,656 EUR]). Strategy D was most cost-effective for both cost per optimal treatments gained (£414.67 [554.5 EUR] per optimal treatment gained) and ceftriaxone avoidance (£11.29 [15.10 EUR] per ceftriaxone-sparing treatment) but resulted in treatment failures (n=34) and sub-optimal treatments (n=706). Conclusions AMR-POCTs can enable correct antibiotic therapy at diagnosis and improved antibiotic stewardship, but may require net health-system investment. However, a relatively small reduction in test cost would enable monotherapy AMR-POCT strategies to be cost-saving.
Suggested Reviewers:	Malcolm Price m.price.2@bham.ac.uk Biostatistician, with research interests including infectious disease models, including a model for the natural history of chlamydia.
	Nichola Naylor Nichola.Naylor@lshtm.ac.uk Health economics analyst with experience evaluating the potential impact of interventions to reduce antimicrobial use.
	Julie Robotham j.robotham@imperial.ac.uk Leads the programme of healthcare-associated infections and antimicrobial resistance modelling and economics research within the Modelling and Economics Unit at Public Health England.
	Susi Sadler S.E.Sadler@exeter.ac.uk Health economist with experience of health technology appraisal and modelling public health interventions for NICE, NHS England and Public Health England.
Opposed Reviewers:	
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Has informed consent has been obtained from persons whose details are described in your manuscript (or from the persons' guardians) that this information may be published?	Not relevant
If the answer to the above question is no, explain here why informed consent was not obtained.	
Please copy/paste your covering letter here.	Professor Tariq Sadiq MD FRCP Professor of Molecular Medicine Consultant in Sexual Health and HIV Medicine St George's, University of London Cranmer Terrace London, SW17 0RE Dr Ines Steffens MD, MPH and DTM&PH Editor-in-Chief Eurosurveillance Dear Dr Steffens, Re: Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics. Harding-Esch EM et al. Following your response to our pre-submission enquiry that this manuscript falls within the scope of Eurosurveillance, thank you for considering it for publication as part of the special issue focusing on how point of care/point of impact testing (POCT/POIT) and self-testing impact surveillance and public health. Antimicrobial resistance (AMR) has developed to every class of antibiotic used for the treatment of gonorrhoea. In 2018, gonorrhoea was classified as a "Priority 2" microorganism by the WHO in its "Global Priority List of Antibiotic-Resistant Bacteria" [1]. There are few practical alternatives if widespread resistance develops to ceftriaxone, the last remaining effective treatment for empirical therapy. New rapid diagnostics that detect antibiotic resistance have been identified as a key strategy for tackling AMR. We assessed the cost-effectiveness of five hypothetical treatment strategies using point-of-care tests (POCTs) for gonorrhoea antimicrobial resistance (AMR-POCTs). We demonstrate that these AMR-POCTs can result in optimal treatments gained and ceftriaxone use avoidance, compared with standard care. These AMR-POCT strategies also enable the re-use of antibiotics, previously abandoned for the treatment of gonorrhoea. We believe this manuscript would be of interest to your readership, reporting on the public health impact, and cost considerations, of AMR-POCTs. We very much look forward to your response. Yours sincerely, Professor Tariq Sadiq MD FRCP 1. WHO. Global priority list of antibiotic-resistant bacteria to guide research, discovery, and development of new antibiotics. World Health Organization: Geneva. https://www.who.int/medicines/publications/WHO-PPL-Short_Summary_25Feb-ET_NM_WHO.pdf, 2018.

If a collective author is included (e.g. a working group or disease-specific network) and if the persons comprising the group are to be included at the end of the article, please list each person here. The contribution of the collective author should be stated in the relevant section.	N/A
Authors' contributions: the contribution of each author to the article, including collective author if applicable, should be described here. This information will appear at the end of the published article.	Designed the model: EMHE, SEH, MJH, CEB, EJA, STS. Ran the model: MJH and GW. Wrote the first draft of the paper: EMHE, SHE, MJH, STS. All authors edited the manuscript and read and approved the final version of the paper.
Please include any acknowledgements here. You may acknowledge anyone who has helped you with any aspect of the report, but it is always the corresponding author's responsibility to obtain permission from anyone being acknowledged.	
Have these findings already been published or is publication of these findings planned in a different format (e.g.: national or European report)?	Rio de Janeiro, Brasil, World STI & HIV Congress 2017 (with IUSTI World), 9-12 July 2017. https://sti.bmj.com/content/93/Suppl_2/A34.3
Do you have any conflicts of interest regarding your manuscript? If yes, please specify. If no, enter 'None'.	SEH, MJH, GW and EJA are employees of Aquarius Population Health (APH) which reports grants on STI and POC research outside the submitted work from Innovate UK, Cepheid, St Georges University of London, Enigma Diagnostics, and AstraZeneca. EHE, CEB and STS are members of the Applied Diagnostic Research and Evaluation Unit at St George's, University of London, which has received funding from Binx Health, Alere, Cepheid, SpeeDx and Sekisui.
Have the nucleic acid sequence data been deposited in sustainable, public, and open access, databases?	
Manuscript Classifications:	United Kingdom; sexually transmitted infections; gonorrhoea; antimicrobial resistance; men who have sex with men - MSM; epidemiology; modelling
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Title: Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics

Authors: Emma M Harding-Esch[1,2], Susie E Huntington[3], Michael J Harvey[3], Georgie Weston[3], Claire E Broad[1], Elisabeth J Adams[3], S Tariq Sadiq[1,2,4]*

[1] Applied Diagnostic Research and Evaluation Unit, Institute for Infection and Immunity, St George's University of London, London, SW17 0RE, UK

[2] National Infection Service, Public Health England, London, NW9 5EQ, UK

[3] Aquarius Population Health, London, N6 5HX, UK

[4] St George's University Hospitals NHS Foundation Trust, London, SW17 0QT, UK

***Correspondence to:** Prof Tariq Sadiq, Institute for Infection and Immunity, St George's University of London, Cranmer Terrace, London, SW17 0RE. Email: ssadiq@sgul.ac.uk Telephone: +44 (0)20 8725 5740.

ABSTRACT

Introduction

Antimicrobial resistance (AMR) threatens successful *Neisseria gonorrhoeae* (NG) treatment, with few practical alternatives should ceftriaxone resistance become widespread. AMR point-of-care tests (AMR-POCTs), currently being developed, would allow selection of appropriate treatment regimens (including previously abandoned regimens), thereby sparing ceftriaxone use. We assessed cost-effectiveness of five hypothetical AMR-POCT strategies (second antibiotic *alongside* ceftriaxone (Strategies A-C); single antibiotic *alternative* to ceftriaxone (Strategies D and E)) compared with

Standard Care (SC; ceftriaxone and azithromycin dual-therapy), to inform appropriate implementation.

Aim

To assess the costs and effectiveness of these AMR-POCT strategies to optimise treatment regimen choice and reduce selection pressure on ceftriaxone.

Methods

Decision tree model simulating a cohort of 38,870 NG-diagnosed England sexual health clinic (SHC) attendees. AMR-POCT strategies and associated treatment options costed were: A) ciprofloxacin only (ciprofloxacin preferred over azithromycin as second agent if susceptible); B) azithromycin and ciprofloxacin (azithromycin preferred); C) ciprofloxacin and azithromycin (ciprofloxacin preferred); D) azithromycin AMR-POCT; E) ciprofloxacin AMR-POCT. A micro-costing approach, representing the cost to the SHC (for the year 2015/16), was employed. The time horizon was one year for initial patient treatment only. Primary outcomes were: total costs; percentage of people given optimal treatment (mono- or dual-therapy curing NG and not containing an antibiotic against which there was resistance); percentage of people given non-ceftriaxone optimal treatment; cost-effectiveness (cost per optimal treatment gained).

Results

All AMR-POCT strategies cost more than SC. Strategy B avoided most sub-optimal treatments (n=48) but cost most to implement (£4,093,844 [5,474,656 EUR]). Strategy D was most cost-effective for both cost per optimal treatments gained (£414.67 [554.5 EUR] per optimal treatment gained) and ceftriaxone avoidance (£11.29 [15.10 EUR] per ceftriaxone-sparing treatment) but resulted in treatment failures (n=34) and sub-optimal treatments (n=706).

Conclusions

AMR-POCTs can enable correct antibiotic therapy at diagnosis and improved antibiotic stewardship, but may require net health-system investment. However, a relatively small reduction in test cost would enable monotherapy AMR-POCT strategies to be cost-saving.

Key words:

Neisseria gonorrhoeae; Sexually transmitted infection; antimicrobial resistance; point-of-care test; cost-effectiveness; ceftriaxone; ciprofloxacin; azithromycin

Conflict of Interest Statement:

SEH, MJH, GW and EJA are employees of Aquarius Population Health (APH) which reports grants on STI and POC research outside the submitted work from Innovate UK, Cepheid, St Georges University of London, Enigma Diagnostics, and AstraZeneca. EHE, CEB and STS are members of the Applied Diagnostic Research and Evaluation Unit at St George's, University of London, which has received funding from Binx Health, Alere, Cepheid, SpeeDx and Sekisui.

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Professor Tariq Sadiq MD FRCP
Professor of Molecular Medicine
Consultant in Sexual Health and HIV Medicine
St George's, University of London
Cranmer Terrace
London, SW17 0RE

Dr Ines Steffens MD, MPH and DTM&PH
Editor-in-Chief
Eurosurveillance

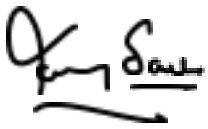
Dear Dr Steffens, 17th March 2020

Re: **Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics.** Harding-Esch EM *et al.*

Many thanks to the editor and reviewers for their comments on the above manuscript. We have provided a point-by-point response to the comments in our "Response to Reviewers", and hope that these adequately address the points raised.

We look forward to hearing from you.

Yours sincerely,



Professor Tariq Sadiq MD FRCP

Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics

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Key words:

Neisseria gonorrhoeae; Sexually transmitted infection; antimicrobial resistance; point-of-care test; cost-effectiveness; ceftriaxone; ciprofloxacin; azithromycin

Introduction

Antimicrobial resistance (AMR) has developed to every class of antibiotic used for treatment of the bacterial sexually transmitted infection (STI) *Neisseria gonorrhoeae* (NG) [1], with increasing reports of multi-drug resistant strains [2]. NG, the second most prevalent bacterial STI globally [3], is associated with serious long-term reproductive health complications if left untreated.

World Health Organization (WHO) guidelines [4] recommend a treatment regimen that treats at least 95% of circulating NG strains, ~~for which the proportion of resistant gonococci does not constitute more than 5% of circulating strains,~~ as monitored through antibiotic surveillance programmes~~,~~ such as Public Health England's national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) [1]. Dual-therapy with ceftriaxone and azithromycin is recommended in Europe [5], and was in the UK until 2019 [6] when it was ~~but has been~~ replaced with 1g ceftriaxone monotherapy ~~in the UK~~ due to the emergence of azithromycin resistance [7]. AMR to ceftriaxone, an extended-spectrum cephalosporin, is the most urgent threat [8],[9] with few practical alternatives immediately available if widespread resistance develops.

Rapid diagnostics have been identified as a key approach to tackling AMR [10]. Rapid tests are those that have a two-hour turnaround, whereas point-of-care tests (POCTs) enable test, results and treatment to be conducted in the same clinical visit [11]. A principal feature of an NG-AMR diagnostic is to assess antibiotic susceptibility at the time of NG diagnosis. A test that combines both NG diagnosis and AMR prediction at the point-of-care (AMR-POCTs) would allow the selection of appropriate treatment regimens for significant numbers of NG infections, including safe use of antimicrobials which have been abandoned for widespread use due to circulating resistance, but which would be effective for a significant proportion of infections [12]. For example, in the UK in 2018~~5~~, 60~~1~~% of NG infections were susceptible to ciprofloxacin, 90% to azithromycin and 88~~76~~% to penicillin [1]. The ability to use these antibiotics to treat NG may in turn reduce AMR selection pressure on ceftriaxone [13].

Rapid tests ~~(with a two-hour turnaround~~ [11]~~)~~ are already being used for NG in some sexual health clinics (SHCs) [14]. While laboratory-based NG fluoroquinolone susceptibility tests exist [15]~~(https://plexpcr.com/resistanceplus-gc/)~~, rapid NG-AMR tests are in development and being clinically evaluated, including an NG fluoroquinolone susceptibility AMR-POCT, developed within the Precise Study [16] ~~(preciseresearch.co.uk)~~ using the io® platform (Binx Health Limited (formerly Atlas Genetics), Boston, USA), already CE-marked for *Chlamydia trachomatis* detection [12, 17]. Costs and short-term clinical impacts of these tests are used in procuring sexual health services provision for a region (known as sexual health commissioning in England) and adoption into SHCs' decision-making [18].

In this analysis, we assessed the cost-effectiveness in English SHCs of five hypothetical AMR-POCT strategies for the treatment of NG, which enable use of ciprofloxacin and/or azithromycin, either alongside, or as an alternative to, ceftriaxone. Potential diagnostic resistance-determinants of these antibiotics are small in number (*gyrA* for ciprofloxacin; *23S rRNA* and *mtrCDE* transporter for azithromycin), are relatively well-understood, and their absence predictive of susceptibility (particularly for ciprofloxacin). The development of molecular AMR-POCTs for detection of these determinants are thus technically feasible and therefore more likely to be immediately available [19-21].

Methods

This report was written following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [22].

Model structure

We compared Standard Care (SC) for NG treatment in the UK (at the time of investigation, ceftriaxone 500mg and azithromycin 1g dual-therapy [6]) with five different AMR-POCT strategies (Supplementary

Figure S1), where the AMR-POCT was used as a reflex test to inform antibiotic selection, irrespective of which test was used to diagnose NG initially. The AMR-POCT strategies were chosen to either facilitate optimised choice of a second antibiotic *alongside* ceftriaxone (dual-therapy), or enable a single antibiotic *alternative* to ceftriaxone (monotherapy) (Box 1).

The rationale for the monotherapy strategies is that an AMR-POCT enables effective treatment of the known resistance profile, sparing the use of ceftriaxone. The rationale for dual-therapy strategies is based on the assumption that combination therapy is more effective at preventing emergence or spread of AMR and thereby preserves the use of ceftriaxone [23].

Each strategy consisted of a series of *intended treatment regimens*, contingent on the results of the AMR-POCT used. For example, in strategy B, the earliest *intended treatment regimen* was SC; where the AMR-POCT indicated azithromycin resistance, the second *intended treatment regimen* was ceftriaxone and ciprofloxacin; where the AMR-POCT then indicated ciprofloxacin resistance, the third *intended treatment regimen* was ceftriaxone monotherapy.

Box 1. Summary of AMR-POCT strategies

Standard Care (SC)

Standard care with dual-therapy of intramuscular ceftriaxone (500mg) and oral azithromycin (1g single dose).

Dual-therapy, including ceftriaxone

A) AMR-POCT for ciprofloxacin resistance only; infections identified as not resistant to ciprofloxacin are given oral ciprofloxacin (500mg) plus ceftriaxone (500mg). Infections identified as ciprofloxacin resistant are given SC.

B) Dual AMR-POCT for azithromycin and ciprofloxacin resistance; if no azithromycin resistance is identified, SC is given. If azithromycin resistant, ciprofloxacin (500mg) and ceftriaxone (500mg) are given unless there is ciprofloxacin resistance, in which case ceftriaxone (500mg) is given alone.

C) Dual AMR-POCT for ciprofloxacin and azithromycin resistance; if no ciprofloxacin resistance is identified, ciprofloxacin (500mg) and ceftriaxone (500mg) are given. If ciprofloxacin resistant, SC is given, unless there is also azithromycin resistance, when ceftriaxone (500mg) is given alone.

Monotherapy optimisation

D) AMR-POCT for azithromycin resistance: if no azithromycin resistance is identified, azithromycin (2g) is given. If azithromycin resistant, ceftriaxone (500mg) and ciprofloxacin (500mg) dual-therapy is given. If the AMR-POCT incorrectly shows no resistance (false negative for AMR), it is assumed the treatment fails. The treatment failure would be identified in the test-of-cure (TOC) and the patient would then receive 500mg ceftriaxone.

E) AMR-POCT for ciprofloxacin; if no ciprofloxacin resistance is identified, 500mg ciprofloxacin monotherapy is given. If ciprofloxacin resistant, SC is given. If the AMR-POCT incorrectly shows no resistance, monotherapy is assumed to fail, the patient returns and receives 500mg ceftriaxone alone.

Strategy	Antibiotic(s) for which resistance is tested		Intended Treatment Regimen based on test result		
	A	B	No resistance to A	Resistance to A	Resistance to A + B
Strategy A	Ciprofloxacin		Ciprofloxacin + Ceftriaxone	Azithromycin + Ceftriaxone	
Strategy B	Azithromycin	+ Ciprofloxacin	Azithromycin + Ceftriaxone	Ciprofloxacin + Ceftriaxone	Ceftriaxone
Strategy C	Ciprofloxacin	+ Azithromycin	Ciprofloxacin + Ceftriaxone	Azithromycin + Ceftriaxone	Ceftriaxone
Strategy D	Azithromycin		Azithromycin[a,b]	Ciprofloxacin + Ceftriaxone	
Strategy E	Ciprofloxacin		Ciprofloxacin[b]	Azithromycin + Ceftriaxone	
Standard Care	No resistance testing is done. Standard Care (SC) is ceftriaxone 500mg and azithromycin 1g dual-therapy [6]				

Unless otherwise stated, doses are: Ceftriaxone 500mg; Azithromycin 1g; Ciprofloxacin (500mg)

Shaded areas indicate Standard Care (SC) i.e. azithromycin and ceftriaxone dual-therapy

[a]2g dose given

[b]If incorrect test result and treatment fails, ceftriaxone is given

A decision tree model was constructed using TreeAge Pro (v.2017) to simulate a hypothetical cohort of 38,870 NG-diagnosed SHC attendees (21,915 men-who-have-sex-with-men [MSM], 8,488 women and 8,467 men-who-have-sex-with-women [MSW]), representing the total number of NG diagnoses in England SHCs in 2015, obtained from national surveillance data (GUMCAD) [24]. Our assumptions regarding AMR-POCT use meant the model could not be used when considering presumptive, e.g. for sexual contacts of NG-positive patients initially negative by microscopy but subsequently positive by NAAT testing. Approximately 10% of NG diagnoses are in contacts [25] but the epidemiological breakdown of these patients (e.g. women, MSW, MSM) and the nature of their NG diagnoses (e.g. microscopy negative and NAAT positive) is not reported. Therefore, contacts could not be removed from the hypothetical cohort.

~~Model assumptions are provided in Supplementary Table S1.~~ Key model assumptions include: 100% compliance with test protocols; all patients entering the model are NG true-positives; dual AMR-POCTs results are available simultaneously; there is no ceftriaxone resistance (supported by England's national NG AMR sentinel surveillance system data [1]) so patients with monotherapy treatment failure would return and be successfully treated with ceftriaxone only. Model assumptions are provided in Supplementary Table S1.

Outcomes

~~Model definitions are provided in Supplementary Table S2.~~ We aimed to assess the costs and effectiveness of these AMR-POCT strategies to optimise treatment regimen choice and reduce selection pressure on ceftriaxone. The primary outcomes were the total costs (2015/16 GB £), the percentage of people given *optimal treatment*, and the percentage of people given non-ceftriaxone optimal treatment. '*Optimal treatment*' was defined as one which cured NG and did not contain an antibiotic against which there was resistance. Model definitions are provided in Supplementary Table S2. These data were used to calculate incremental cost-effectiveness ratios (ICERs, see equation) for

the cost per additional optimal treatment gained and the cost per additional ceftriaxone treatment avoided. This was chosen as the measure of cost-effectiveness rather than other measures, such as cost per Quality Adjusted Life Years (QALYs), because little data exist on the consequence of optimal versus suboptimal NG treatment on long-term outcomes, such as mortality or lifetime costs.

$$ICER = \frac{Cost_B - Cost_A}{Effectiveness_B - Effectiveness_A}$$

Secondary outcomes were the percentage of people given a 'missed earlier *intended treatment regimen*' (MEITR), and the percentage of people failing treatment due to resistance. 'MEITR' was defined as the use of a treatment regimen which cured NG, but where an earlier intended treatment regimen would have provided optimal treatment because susceptible infections had been misclassified as resistant by the AMR-POCT. MEITRs were independent of treatment effectiveness.

Treatment

AMR-POCT strategy treatment regimens were developed with input from three senior clinicians at St George's University Hospitals NHS Foundation Trust, London, who outlined current and hypothetical AMR-POCT patient pathways (Supplementary Figure S1). The purpose of the work was to determine AMR-POCT strategy for short-term clinical impacts, because these are the data used for sexual health service provisioning and decision-making for adoption into SHCs ~~for sexual health service provisioning purposes~~ [18]. Furthermore, progression to longer-term clinical impacts from suboptimally treated infection is poorly defined [26]. Therefore, the time horizon was that of initial patient treatment, and complications associated with STIs such as pelvic inflammatory disease (PID) in women, and adverse drug events associated with treatment, were not considered.

Model parameters

Model epidemiology parameters are presented in Table 1, and cost parameters in Table 2 and Supplementary Table S3. The hypothetical AMR-POCT sensitivity and specificity were based on other NAAT-based rapid and POC tests [27-29], and altered in sensitivity analyses. Antibiotic resistance prevalences were obtained from national surveillance of SHC attendees (GRASP, 2017) [30]. GRASP is England's national sentinel surveillance system that detects and monitors AMR in NG and records potential treatment failures. As the time horizon was that of initial patient treatment, discounting rates were not applied.

Table 1. Epidemiology parameters used in the model

Variable	Percentage (%)						Number						Comments, Reference
	MSM		W		MSW		MSM		W		MSW		
	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	
1 Initial clinic attendances	56.4	N/A	21.8	N/A	21.8	N/A	21,915		8,488		8,467		GUMCAD, 2015 [24]
2 Resistance to azithromycin[a]	4.7	3.3, 6.1	2.7	1.9, 3.5	5.3	3.7, 6.9	285 1,030	723, 1,337	42 229	161, 297	0 449	313, 584	GRASP, 2017 [30]
3 Resistance to ceftriaxone	0.0	0.0, 0.0	0.0	0.0, 0.0	0.0	0.0, 0.0	0	0, 0	0	0, 0	0	0, 0	GRASP, 2017 [30]
4 Resistance to ciprofloxacin[b]	36.2	25.3, 47.1	20.1	14.1, 26.1	32.5	22.8, 42.3	9,555 7,933	5,544, 10,322	1,282 706	1,197, 2,215	2,371 752	1,930, 3,582	GRASP, 2017 [30]
5 Sensitivity of AMR-POCT	98	90, 100	98	90, 100	98	90, 100	N/A	N/A	N/A	N/A	N/A	N/A	Assumption

6	Specificity of AMR-POCT	99	90, 100	99	90, 100	99	90, 100	N/A-	N/A	N/A-	N/A	N/A-	N/A	Assumption

MSM, men-who-have-sex-with-men; W, women; MSW, men-who-have-sex-with-women; N/A, Not Applicable; GUMCAD, genitourinary medicine clinical activity dataset; GRASP, gonococcal resistance to antimicrobial surveillance programme; AMR, antimicrobial resistance; POCT, point-of-care test.

[a] The azithromycin resistance ranges were extended further to 1-10% for all population groups in one way azithromycin resistance analysis so that the effect of more extreme values could be explored.

[b] The ciprofloxacin resistance ranges were extended further to 0-50% in one way ciprofloxacin resistance analysis so that the effect of more extreme values could be explored

Table 2. Cost parameters used in the model

Cost input	Cost[a]		Comments and references
	Base case value	Range (low, high)	
Management of NG (oral medication/IM injection)	£53.00/£62.74 70.88 EUR/83.90 EUR	£37.1, £68.9 / £43.92, £81.56 49.6, 92.1 EUR / 58.73, 109.07 EUR	[a]Adapted [b]Adapted from previous model. Adams, 2014 [31]
Additional cost of performing AMR-POCT	£4.81	[a]Adapted from previous model. Adams, 2014 [31]	
Test of cure for NG (using POCT for NG)	£52.97	[a]Includes cost of POCT for NG estimated at £24. Adapted from previous model. Adams, 2014 [31]	
Return visit due to treatment failure	£48.01 64.20 EUR	£33.61, £62.41 44.95, 83.46 EUR	[a],[b],[c] Adapted from previous model. Adams, 2014 [31]
Single AMR-POCT	£29.00 38.78 EUR	£20, £40 26.75, 53.49 EUR	Estimate [32]
Dual AMR-POCT	£31.90 42.66 EUR	£29, £58 38.78, 77.56 EUR	Estimate - 10% more than price of single AMR POCT (multiplier 1.1, range 1.0-2.0)
Dual AMR-POCT	£31.90 42.66 EUR	£22, £44 29.42, 58.84 EUR	Estimate – single AMR-POCT is varied, multiplier remains at

			1.1 (10% more than price of single AMR POCT)
Azithromycin ~~1g[c]~~ 1g[d]	£1.16 1.55 EUR	£0.81, £1.51 1.08, 2.02 EUR	BNF, 2016 [33]
Azithromycin ~~2g[c]~~ 2g[d]	£2.32 3.10 EUR	£1.62, £3.02 2.17, 4.04 EUR	BNF, 2016 [33]
~~Penicillin: amoxycillin 3g plus probenecid 1g[c]~~	~~£1.73~~	~~BNF, 2016~~ [33]	
Ceftriaxone 500mg ~~[d]~~[e]	£9.58 12.81 EUR	£6.71, £12.45 8.97, 16.65 EUR	BNF, 2016 [33]
Ciprofloxacin ~~500mg[3]~~ 500mg[d]	£0.07 0.09 EUR	£0.05, £0.09 0.07, 0.12 EUR	BNF, 2016 [33]

NG, *Neisseria gonorrhoeae*; IM, intramuscular; AMR, antimicrobial resistance; POCT, point-of-care test; BNF, British National Formulary.

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

~~[a]~~ [b] Includes staff time and consumables but not antibiotic costs. Costs were inflated to 2015/16 costs using the Hospital and Community Health Services (HCHS) Inflation Indices 2015 produced by the Personal Social Services Research Unit [35]. No data were available for inflation from 2014/15 to 2015/16 so it was assumed to be the same as between 2013/2014 and 2014/15. The UK hospital consumer price index for health services shows similar annual growth in this sector from 2014 (93.2

in 2013, 97.1 in 2014 and 100 in 2015), which validates this assumption [36]. GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP. A further breakdown of cost data is provided in Supplementary Table S3.

~~b~~ c Within the context of this model, treatment failure due to resistance to a monotherapy would result in a return visit. No repeat culture would be taken and no repeat diagnostic tests would occur. The patient would be successfully treated using ceftriaxone, administered via injection.

~~c~~ d Oral medication.

~~d~~ e Administered via intramuscular injection. The price quoted is for 1g vial of ceftriaxone, the smallest non-proprietary vial available (10) - the remaining 500mg is then discarded.

A micro-costing approach was employed, considering only costs incurred to the healthcare provider (i.e. SHC). Costs to those procuring sexual health services provision, ~~commissioners of health services~~ or to health systems as a whole, were not considered. Costs were estimated by adapting an existing model [31], and included: laboratory equipment, POCTs and antibiotics, AMR-POCTs, NG treatment implementation (e.g. staff time and consumables, including partner notification and health promotion) (S~~s~~upplementary Table S3). It was assumed the AMR-POCTs produced results in 30 minutes (maximum acceptable POCT run-time for service users [37, 38]) and that in all strategies, NG-positive samples would still be sent to the laboratory for culture and phenotypic resistance testing. Costs are given in 2015/16 prices (GB £) and inflated when based on old estimates [35]. Antibiotic prices were extracted from the British National Formulary (BNF) website (September 2016), with the cheapest formulation being used including non-proprietary costs where available [33]. Initial costs of diagnosing NG were not considered as people only entered the model after an NG diagnosis. The cost of implementing a change to clinical practice was also not considered.

Sensitivity analyses

We conducted one-way analyses for each of the model parameters by varying them independently at the ends of their ranges to examine the effect on the primary outcome (~~Supplementary~~ Table ~~S4~~1). These analyses identified which model parameters results were most sensitive to. Each sensitivity analysis compared one of the five AMR-POCT strategies with SC, across three population groups (women, MSW, and MSM). Probabilistic sensitivity analyses (PSA) were not performed because our analysis was a cost-effectiveness analysis with the outcome as cost per event avoided, rather than a cost acceptability or cost utility analysis exploring the likelihood that the technology is cost-effective at different willingness to pay (WTP) thresholds. There is no commonly agreed WTP for our outcome, and therefore presenting PSA results would likely not have yielded additional beneficial information.

Results

Overall AMR-POCT strategy costs, treatments used, and treatment outcomes compared with SC in all groups are presented in Table 3. Breakdowns by population group are presented in Supplementary Tables ~~S5~~S4, ~~S6~~ S5 and ~~S7~~S6.

~~***Costs***~~

~~The cost of SC-NG management was £2,856,168 for the total cohort (Table 3). All AMR-POCT strategies cost more than SC, with dual therapy AMR-POCT strategies more expensive than monotherapy strategies. Strategy D was the least expensive AMR-POCT strategy, costing £3,271,684, 14.5% more than SC. Strategy B was the most expensive, costing £4,093,844, 43% more than SC. This was consistent across all population groups.~~

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Table 3. Total costs, treatments used and treatment outcomes for Standard Care and AMR-POCT strategies: all groups (n=38,870)

Strategy	Total cost[a]	Number of Aantibiotics used to treat NG			Number of Ooptimal treatment[a] treatments[b]	Number of Ssub-optimal treatment[b] treatments[c]	Number of MEITR[c] MEITR[d]	Number of Ttreatment failures[d] failures[e]
		Ceftriaxone	Azithromycin	Ciprofloxacin				
Standard care	£2,856,168 3,819,524 EUR	38,870	38,870	0	37,162	1,708	-	-
A) Single POCT for ciprofloxacin; dual-therapy	£3,954,554 5,288,385 EUR	38,870	12,408	26,462	38,057	813	265	-
B) Dual POCT for azithromycin and ciprofloxacin; dual-therapy	£4,093,844 5,474,656 EUR	38,870	36,825	1,373	38,822	48	267	-

C) Dual POCT for ciprofloxacin and azithromycin; dual-therapy	£4,066,498 5,438,086 EUR	38,870	11,736	26,462	38,611	259	912	-
D) Single POCT for azithromycin; monotherapy	£3,271,684 4,375,189 EUR	2,080	36,825	2,045	38,164	706	372	34
E) Single POCT for ciprofloxacin; monotherapy	£3,457,581 4,623,788 EUR	12,656	12,408	26,462	38,057	813	265	248

AMR, antimicrobial resistance; POCT, point-of-care test; NG, *Neisseria gonorrhoeae*; MEITR, missed earlier intended treatment regimen

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

~~[a]~~[b]'optimal' refers to a treatment regimen which cures the NG infection and does not contain any antibiotic against which there is resistance

~~[b]~~[c]'sub-optimal' refers to a treatment regimen which contains antibiotics against which there is NG resistance - if the treatment is a monotherapy it will result in treatment failure

~~c~~d‘missed earlier intended treatment regimen’ (MEITR) refers to a treatment regimen which cures the NG infection and does not contain any antibiotic against which there is resistance, but a treatment regimen was used when an earlier intended treatment regimen would have provided optimal treatment – a MEITR is due to a false-resistant AMR-POCT result

~~d~~e‘treatment failure’ refers to failure to cure an NG infection due to resistance to an antibiotic given as monotherapy and is due to a false-susceptible AMR-POCT result

Costs

The cost of SC NG management was £2,856,168 (3,819,524 EUR) for the total cohort (Table 3). All AMR-POCT strategies cost more than SC, with dual-therapy AMR-POCT strategies more expensive than monotherapy strategies. Strategy D was the least expensive AMR-POCT strategy, costing £3,271,684 (4,375,189 EUR), 14.5% more than SC. Strategy B was the most expensive, costing £4,093,844 (5,474,656 EUR), 43% more than SC. This was consistent across all population groups.

Optimal treatment

All AMR-POCT strategies provided more optimal treatments than SC, in all population groups. Strategy B provided most optimal (n=38,822) and least sub-optimal (n=48) treatments. Strategies A and E equally provided the least optimal treatments (Supplementary Tables ~~S5~~S4, ~~S6~~ S5 and ~~S7~~S6) and the most sub-optimal (n= 813) (Table 3).

Ceftriaxone-sparing treatments given

Since all dual-therapy strategies used ceftriaxone, only monotherapy strategies provided ceftriaxone-sparing options. Strategy D reduced ceftriaxone use by 95% compared to SC (Table 3).

MEITRs given

A MEITR refers to a treatment regimen being used when an earlier intended treatment regimen would have provided optimal treatment. In all population groups, the fewest were in Strategies A and E (n=265), and B (n=267), and the most were in Strategy C (n=912) (Table 3, Supplementary Tables ~~S5~~S4, ~~S6~~ S5 and ~~S7~~S6).

Treatment failures

There were some treatment failures in each monotherapy strategy due to false-susceptible AMR-POCT results: strategy D had 34 (0.09% of treatments) and Strategy E had 248 (0.64% of treatments) (Table 3). There were no treatment failures with SC or dual-therapy strategies (A, B and C) because they all

included ceftriaxone. This was consistent across all population groups (Supplementary Tables ~~S5~~S4, ~~S6~~ S5 and ~~S7~~S6).

Cost-effectiveness analysis (CEA)

The cost-effectiveness analysis (CEA) results are presented in Table 4. When avoidance of sub-optimal treatments was considered, Strategy D was most cost-effective relative to SC, costing £414.67 (554.53 EUR) per optimal treatment gained. Strategy A was least cost-effective overall, whereas Strategy B was the most-cost effective dual-therapy strategy.

Table 4. Cost effectiveness analysis (CEA) for SC and AMR-POCT strategies

Sub-group	Comparison	Total additional cost[a]	Additional cost per patient[a]	Number of optimal treatments gained	Additional cost per optimal treatment gained[a]	Number of ceftriaxone treatments avoided	Additional cost per ceftriaxone-sparing treatment [a]
All	AMR-POCT A vs SC	£1,098,386 1,468,860 EUR	£28.26 37.79 EUR	895	£1,226.97 1,640.81 EUR	0	Dominated
	AMR-POCT B vs SC	£1,237,676 1,655,131 EUR	£31.84 42.58 EUR	1,660	£745.44 996.87 EUR	0	Dominated
	AMR-POCT C vs SC	£1,210,330 1,618,562 EUR	£31.14 41.64 EUR	1,449	£835.39 1,117.16 EUR	0	Dominated
	AMR-POCT D vs SC	£415,516	£10.69 14.30 EUR	1,002	£414.67 554.53 EUR	36,790	£11.29 15.09 EUR

		555,665.3 EUR					
		£601,414	£15.47	895	£671.82	26,214	£22.94
		804,264.8 EUR	20.69 EUR		898.42 EUR		30.68 EUR
	AMR-POCT E vs SC						
		£620,274	£28.30	499	£1,242.13	0	
		829,486.1 EUR	37.85 EUR		1,661.09 EUR		
	AMR-POCT A vs SC						Dominated
		£697,730	£31.84	1,001	£697.32	0	
		933,067.2 EUR	42.58 EUR		932.52 EUR		
	AMR-POCT B vs SC						Dominated
MSM		£683,317	£31.18	864	£790.97	0	
		913,792.8 EUR	41.70 EUR		1,057.76 EUR		
	AMR-POCT C vs SC						Dominated
		£235,532	£10.75	568	£414.38	20,676	£11.39
	AMR-POCT D vs SC		14.38 EUR		554.15 EUR		15.23- EUR

		314,974.5 EUR					
		£358,920	£16.38	499	£718.75	13,842	£25.93
	AMR-POCT E vs SC	479,980 EUR	21.90 EUR		961.18 EUR		34.68- EUR
		£239,316	£28.26	248	£965.92		
		320,034.8 EUR	37.79 EUR		1,291.72 EUR	0	
	AMR-POCT A vs SC						Dominated
		£269,519	£31.83	436	£617.60		
	AMR-POCT B vs SC	360,425 EUR	42.57 EUR		825.91 EUR	0	Dominated
		£263,674	£31.14	391	£674.71		
		352,608.5 EUR	41.64 EUR		902.28 EUR	0	
MSW	AMR-POCT C vs SC						Dominated
		£91,956	£10.86	271	£339.59		£11.58
		122,971.8 EUR	14.52 EUR		454.13 EUR	7,938	15.49- EUR
	AMR-POCT D vs SC						
	AMR-POCT E vs SC	£132,108	£15.60	248	£533.21	5,658	£23.35

		176,666.7 EUR	20.86 EUR		713.06 EUR		31.23- EUR
		£238,796	£28.13	148	£1,612.62	0	
		319,339.4 EUR	37.62 EUR		2,156.54 EUR		
	AMR-POCT A vs SC						Dominated
		£270,428	£31.86	223	£1,210.74	0	
		361,640.6 EUR	42.61 EUR		1,619.11 EUR		
	AMR-POCT B vs SC						Dominated
		£263,339	£31.02	194	£1,356.61	0	
		352,160.5 EUR	41.48 EUR		1,814.18 EUR		
	AMR-POCT C vs SC						Dominated
Women		£88,028	£10.37	163	£540.55	8,176	£10.77
		117,718.9 EUR	13.87 EUR		722.87 EUR		14.40- EUR
	AMR-POCT D vs SC						
		£110,386	£13.00	148	£745.45	6,714	£16.44
	AMR-POCT E vs SC		17.38 EUR		996.88 EUR		21.99- EUR

	147,618.1 EUR					

AMR-POCT, antimicrobial resistance point-of-care test; MSM, men-who-have-sex-with-men; MSW, men-who-have-sex-with-women; SC, standard care.

A strategy is 'dominated' if it is more expensive and provides fewer/equivalent benefits.

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34].

For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

When avoidance of ceftriaxone use was considered, Strategy D was most cost-effective relative to SC, costing £11.29 (15.10 EUR) per ceftriaxone-sparing treatment gained. These findings were consistent across all population groups.

Sensitivity analyses

In one-way sensitivity analyses, the following four parameters had the greatest impact on cost-effectiveness per optimal treatment gained for all AMR-POCT strategies and across all population groups: prevalence of azithromycin resistance; AMR-POCT sensitivity; prevalence of ciprofloxacin resistance; and the cost of single detection AMR-POCT. In monotherapy strategies, the cost-effectiveness model was additionally sensitive to cost of clinical management (both with and without injection), cost of ceftriaxone, and AMR-POCT specificity (for strategy D). The cost multiplier for a dual detection AMR-POCT impacted on AMR-POCT cost-effectiveness for Strategies B and C. Tornado plots from these analyses are presented in Supplementary Figure S2.

For all strategies, variation of ICER in relation to azithromycin resistance prevalence was minimal until prevalence fell to or below 3%, at which point it increased (Supplementary Figure S3). These rises in ICERs were least for strategies B and D. With the exception of strategy B where ICERs were consistent for all population groups, these increases in ICER were most limited in women.

Variation in AMR-POCT accuracy also showed similar patterns across all population groups. Apart from Strategy D, variation in specificity had very little effect on cost per optimal treatment gained. In contrast, as sensitivity decreased to a minimum of 90%, particularly towards the lower range, the cost per optimal treatment gained increased exponentially, except for strategy B where the relationship was linear. Strategy B also had the smallest change in ICER between maximum (100%) and minimum (90%) sensitivity (maximum difference of £169.21 (226.28 EUR) per optimal treatment gained in women) compared with other strategies where the difference was in the thousands. For Strategy D, change in sensitivity had little impact on cost per optimal treatment gained, whereas when specificity

decreased to below around 95.5%, the cost per optimal treatment gained started to increase exponentially. The sensitivity analyses are presented in Supplementary Figure S4.

The prevalence of ciprofloxacin resistance had very little effect on cost per optimal treatment gained in Strategies B, C and D (Supplementary Figure S5). For Strategies A and E, as ciprofloxacin resistance increased from about 20%, there was an exponential increase in cost per optimal treatment gained for women only.

The relationship between ICER and cost of a single target AMR-POCT was linear. Interestingly, as the cost of the single target AMR-POCT increased, the two dual-target AMR-POCTs diverged, with strategy B costing less per optimal treatment gained relative to strategy C.

For the three single target AMR-POCTs (A, D and E), reducing the cost of the test had the greatest impact on cost per treatment gained. Monotherapy strategies became cost-saving (ICER <0) for all population groups when AMR-POCT cost was ≤£18 (24.07 EUR) for Strategy D, and ≤£16 (21.40 EUR) for Strategy E (Supplementary Figure S6). Strategy B had lowest costs per additional optimal treatment for dual-therapy strategies.

Discussion

This is the first study to assess the cost-effectiveness and impacts of deploying AMR-POCTs for gonorrhoea. All AMR-POCT strategies assessed resulted in more optimal treatments compared with SC. Monotherapy AMR-POCT strategies provided ceftriaxone-sparing options, with Strategy D reducing the use of ceftriaxone by 95%. Both outcomes are important in promoting antibiotic stewardship by minimising risks of breakthrough with ceftriaxone-resistant circulating strains, and reducing selection pressure for resistance developing to ceftriaxone, respectively.

Our cost-effectiveness analysis adapted a previously published cost-effectiveness model of introducing a dual CT/NG POCT into a SHC [29, 31], and was populated using available published data, and where unavailable, using unpublished data and expert opinion. By employing a decision tree

model approach we could account for sufficient complexity without over-building. This approach is, however, unable to assess outcomes that a transmission-dynamic model would be required for, such as that developed by Fingerhuth *et al*. [39], including impact AMR-POCTs could have on re-infection in a previously treated patient, on population prevalence or burden of disease, or on AMR evolution.

Turner *et al*. have adapted the same CT/NG POCT cost-effectiveness model we used for our analysis [29, 31] to analyse the potential clinical and overall economic impact of an NG AMR-POCT [40]. Whilst theirs was not a cost-effectiveness analysis, and different model assumptions and parameters from ours were used, they also demonstrated that AMR-POCTs could lead to overall reductions in ceftriaxone use, but that introduction of AMR-POCTs incurred increased costs. Using an individual-based dynamic transmission model that incorporated partner treatment and which was applied to a London MSM population, Zienkiewicz *et al.* [41] also demonstrated that AMR-POCTs for NG ciprofloxacin sensitivity reduced ceftriaxone use, by 70% compared with the reference scenario. An individual-based model of molecular NG-AMR test-use compared with culture within an NG surveillance system in remote settings found that they substantially improve the timeliness of NG-AMR detection, facilitating a faster change in recommended treatment, with potential for decreasing NG-AMR impact on the wider population [42]. Fingerhuth *et al.* [39] developed a compartmental transmission model of antibiotic-sensitive and antibiotic-resistant NG to look at proportion of resistant infections and cases averted. They showed that the clinical pathway that included an AMR-POCT resulted in the lowest proportion of resistant infections after 30 years, whereas the clinical pathway with a POCT that did not test for AMR resulted in the highest. They also noted that test diagnostic performance is key for AMR-POCTs to have a beneficial public health impact. The potential public health impact of AMR-POCTs was confirmed by Tuite *et al.*, with AMR-POCTs delaying the proportion of isolates reaching >5% resistance compared with empiric treatment [43]. However, it was highlighted that the AMR-POCT must test for resistance to multiple anitimicrobials, otherwise non-tested, resistant, strains will be selected for. Thus, continued surveillance, including culture, must be continued. Together, these health economic and modelling evaluations highlight the possible

beneficial impacts of implementing AMR-POCTs on reducing ceftriaxone use and decreasing NG-AMR prevalence at the population level, but the design and implementation of the tests should also be carefully considered.

As with all mathematical models, several assumptions were made (Supplementary Table S1), including AMR-POCT diagnostic accuracy - a necessity as these tests are currently in early phases of development [16]~~(preciseresearch.co.uk)~~. Future performance estimates will need to ~~take~~ consider two elements: predictive accuracies of any biomarkers used to detect AMR; the performance of platforms and chemistries used to detect them. Variations in both may independently affect outcomes.

Our analysis had some limitations. We used the most recent NG-AMR data available from GRASP at the time [30], but AMR rates constantly change and, in the sensitivity analyses, AMR prevalence alterations had the greatest impact on AMR-POCT cost-effectiveness (Supplementary Figure S2). This may limit the generalisability of our results, as it is not possible to know future resistance profiles. However, the results should be generalisable to the ranges used in the sensitivity analyses. In addition, as AMR-POCTs are still in development, some of the model's other epidemiological parameters will have changed by the time the AMR-POCTs are available for use in routine practice, which may further limit the analyses' applicability in the longer term. This highlights the need to continually conduct analyses such as these, to enhance our ability to predict and understand future trends. Our anlayses are also limited to data from England, with results perhaps less generalisable to other countries. This will be exacerbated by the 2019 change to 1g ceftriaxone monotherapy, further setting it aside from guidelines in other European countries [7]. Our model also did not consider NG-positive patients co-infected with another organism, such as *Chlamydia trachomatis*, which would affect patient pathways and treatment options. Additional factors not considered were costs associated with treating long-term NG infection sequelae [44], costs incurred outside of the SHC, and costs or cost-savings

associated with changing clinical pathways in order to accommodate the AMR-POCTs. Thus the time horizon for the costs and consequences was of initial patient treatment only.

Strategy B was most effective for avoiding sub-optimal treatments but the most costly to implement. Strategy D was the most cost-effective for both effectiveness outcomes (optimal treatments gained and ceftriaxone avoidance), but resulted in treatment failures, as well as nearly 15-fold higher sub-optimal treatments compared to Strategy B. Both strategies B and D enabled the re-use of ciprofloxacin, previously abandoned for the treatment of NG in the UK [6].

All AMR-POCT strategies were more expensive than SC, with dual-therapy AMR-POCT strategies more expensive than monotherapy strategies, suggesting that short-term net financial investments in AMR-POCT adoption are required to gain long-term antimicrobial stewardship benefits. Interestingly, our sensitivity analysis suggested that even if AMR-POCT costs were significantly reduced, perhaps through production scale-up, dual-therapy AMR-POCT strategies would still not be cost-saving. However, a relatively small reduction to <£18 (24.07 EUR) per test would enable the monotherapy AMR-POCT strategies to be cost-saving.

The monotherapy strategies resulted in treatment failures due to false-susceptible AMR-POCT results, although minimal relative to SC. Since we assumed ceftriaxone treated 100% of NG infections, there were no treatment failures for SC or dual-therapy strategies. The most recent GRASP data suggest that ceftriaxone resistance remains low (no ceftriaxone resistance reported, ~~but~~ although there is a reduction in susceptibility with 24.6% of isolates with~~the~~ minimum inhibitory concentrations (MICs) ~~was at the breakpoint (~~≥0.03~~125~~ mg/L~~) for 7/1268 gonococcal isolates~~ in 2018 compared with 16.6% in 2017 [1]), but there are increasing concerns regarding international ceftriaxone-resistant strains [45-47]. This potentially undermines our assumption and the resulting lack of treatment failures from dual-therapy AMR-POCT strategies.

Most MEITRs (treatment regimen used when an earlier intended treatment regimen would have provided optimal treatment) were in Strategy C, and the least in Strategies A, B and E. Avoiding MEITRs

is important because it maximises the ability to use ciprofloxacin (in Strategies A, C and E), or reduces the need for ceftriaxone use (Strategies B and D). These numbers were small compared to actual patient numbers in whom a MEITR might be used if these AMR-POCTs were available more generally. For example, using national surveillance data [24, 48], we estimated that over 25,000 of the 38,870 NG-–diagnosed SHC patients assumed to have been treated with SC in 2015 would have had ciprofloxacin-susceptible NG. Strategies A and E would have enabled all, except 265 (Table 3), of these patients to be treated with ciprofloxacin, a 100-fold reduction in these missed opportunities.

Since a MEITR is due to susceptible infections misclassified as resistant by the AMR-POCT, test specificity is key. In sensitivity analyses of AMR-POCT accuracy, Strategy D was the only strategy where cost per optimal treatment gained was affected by changes in specificity. In all other strategies, cost per optimal treatment gained increased as sensitivity decreased. This is because these strategies contained an AMR-POCT that included ciprofloxacin testing, so resistance (20-36%, dependent on population group [30]) was detected and optimal treatment could be given. In contrast, if AMR-POCT sensitivity in these strategies fell, true ciprofloxacin-resistant cases were missed and the patient sub-optimally treated. Strategy D, where the AMR-POCT was for azithromycin only, was the only strategy where ciprofloxacin was given without resistance-testing - as the specificity decreased, more patients received false-positive azithromycin resistance results and were treated with ciprofloxacin. Due to high ciprofloxacin resistance prevalence, this treatment was sub-optimal in a large number of cases. Following the logic of the other strategies, if azithromyin resistance prevalence increased, cost per optimal treatment gained in Strategy D would become sensitive to both AMR-POCT specifity and sensitivity.

Thus, prevalence of resistance has important implications for AMR-POCT accuracy requirements and ICERs of optimal treatments gained. In the azithromycin resistance sensitivity analyses, ICERs increased when resistance fell below about 3% (well below current UK azithromycin resistance prevalence, reported at approximately 9.7% [1]), primarily because when azithromycin resistance is

low, there is little value in testing for it (Strategies B, C and D) and there will be few treatment failures from background resistance (Strategies A and E). In the ciprofloxacin resistance sensitivity analysis, an effect on ICERs was only seen in women in strategies A and E (because of lower baseline ciprofloxacin resistance prevalence).

From a population-level antimicrobial stewardship public health perspective, increasing the number of sub-optimal treatments may eventually lead to an increased number of resistant infections [39]. The relative public health importance of a smaller total number of sub-optimal treatments with a few treatment failures versus a higher number of sub-optimal treatments with no failures, warrants further investigation, and could be included in future transmission model analyses. Furthermore, the long-term public health impact of preserving ceftriaxone use whilst increasing the risk of treatment failures from monotherapy strategies (versus maintaining ceftriaxone in the earlier intended treatment regimen with an increase in sub-optimal treatments and no adequate treatment alternative), should also be investigated.

Conclusion

Once developed, AMR-POCTs could have wide-ranging implications for clinical decision-making globally, including the re-use of antibiotics previously abandoned for the treatment of NG, ensuring the right treatment is given to the right person, at the right time (precision medicine) [9, 12]. The O'Neill review of AMR [10] noted that accepting the initial expense of new test introduction may enable longer-term societal pay-offs by reducing infection rates and maintaining effective NG treatments. However, a relatively small reduction in test cost could enable some AMR-POCT strategies to be cost-saving.

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Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics

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ABSTRACT

Introduction

Antimicrobial resistance (AMR) threatens successful *Neisseria gonorrhoeae* (NG) treatment, with few practical alternatives should ceftriaxone resistance become widespread. AMR point-of-care tests (AMR-POCTs), currently being developed, would allow selection of appropriate treatment regimens (including previously abandoned regimens), thereby sparing ceftriaxone use. We assessed cost-effectiveness of five hypothetical AMR-POCT strategies (second antibiotic *alongside* ceftriaxone (Strategies A-C); single antibiotic *alternative* to ceftriaxone (Strategies D and E)) compared with Standard Care (SC; ceftriaxone and azithromycin dual-therapy), to inform appropriate implementation.

Aim

To assess the costs and effectiveness of these AMR-POCT strategies to optimise treatment regimen choice and reduce selection pressure on ceftriaxone.

Methods

Decision tree model simulating a cohort of 38,870 NG-diagnosed England sexual health clinic (SHC) attendees. AMR-POCT strategies and associated treatment options costed were: A) ciprofloxacin only (ciprofloxacin preferred over azithromycin as second agent if susceptible); B) azithromycin and ciprofloxacin (azithromycin preferred); C) ciprofloxacin and azithromycin (ciprofloxacin preferred); D) azithromycin AMR-POCT; E) ciprofloxacin AMR-POCT. A micro-costing approach, representing the cost to the SHC (for the year 2015/16), was employed. The time horizon was one year for initial patient treatment only. Primary outcomes were: total costs; percentage of people given optimal treatment (mono- or dual-therapy curing NG and not containing an antibiotic against which there was resistance); percentage of people given non-ceftriaxone optimal treatment; cost-effectiveness (cost per optimal treatment gained).

Results

All AMR-POCT strategies cost more than SC. Strategy B avoided most sub-optimal treatments (n=48) but cost most to implement (£4,093,844 [5,474,656 EUR]). Strategy D was most cost-effective for both cost per optimal treatments gained (£414.67 [554.5 EUR] per optimal treatment gained) and ceftriaxone avoidance (£11.29 [15.10 EUR] per ceftriaxone-sparing treatment) but resulted in treatment failures (n=34) and sub-optimal treatments (n=706).

Conclusions

AMR-POCTs can enable correct antibiotic therapy at diagnosis and improved antibiotic stewardship, but may require net health-system investment. However, a relatively small reduction in test cost would enable monotherapy AMR-POCT strategies to be cost-saving.

Key words:

Neisseria gonorrhoeae; Sexually transmitted infection; antimicrobial resistance; point-of-care test; cost-effectiveness; ceftriaxone; ciprofloxacin; azithromycin

Introduction

Antimicrobial resistance (AMR) has developed to every class of antibiotic used for treatment of the bacterial sexually transmitted infection (STI) *Neisseria gonorrhoeae* (NG) [1], with increasing reports of multi-drug resistant strains [2]. NG, the second most prevalent bacterial STI globally [3], is associated with serious long-term reproductive health complications if left untreated.

World Health Organization (WHO) guidelines [4] recommend a treatment regimen that treats at least 95% of circulating NG strains, as monitored through antibiotic surveillance programmes such as Public Health England's national Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) [1]. Dual-therapy with ceftriaxone and azithromycin is recommended in Europe [5], and was in the UK until 2019 [6] when it was replaced with 1g ceftriaxone monotherapy due to the emergence of azithromycin resistance [7]. AMR to ceftriaxone, an extended-spectrum cephalosporin, is the most urgent threat [8],[9] with few practical alternatives immediately available if widespread resistance develops.

Rapid diagnostics have been identified as a key approach to tackling AMR [10]. Rapid tests are those that have a two-hour turnaround, whereas point-of-care tests (POCTs) enable test, results and treatment to be conducted in the same clinical visit [11]. A principal feature of an NG-AMR diagnostic is to assess antibiotic susceptibility at the time of NG diagnosis. A test that combines both NG diagnosis and AMR prediction at the point-of-care (AMR-POCTs) would allow the selection of appropriate treatment regimens for significant numbers of NG infections, including safe use of antimicrobials which have been abandoned for widespread use due to circulating resistance, but which would be effective for a significant proportion of infections [12]. For example, in the UK in 2018, 60% of NG infections were susceptible to ciprofloxacin, 90% to azithromycin and 88% to penicillin [1]. The ability to use these antibiotics to treat NG may in turn reduce AMR selection pressure on ceftriaxone [13].

Rapid tests are already being used for NG in some sexual health clinics (SHCs) [14]. While laboratory-based NG fluoroquinolone susceptibility tests exist [15], rapid NG-AMR tests are in development and

being clinically evaluated, including an NG fluoroquinolone susceptibility AMR-POCT, developed within the Precise Study [16] using the io® platform (Binx Health Limited (formerly Atlas Genetics), Boston, USA), already CE-marked for *Chlamydia trachomatis* detection [12, 17]. Costs and short-term clinical impacts of these tests are used in procuring sexual health services provision for a region (known as sexual health commissioning in England) and adoption into SHCs' decision-making [18].

In this analysis, we assessed the cost-effectiveness in English SHCs of five hypothetical AMR-POCT strategies for the treatment of NG, which enable use of ciprofloxacin and/or azithromycin, either alongside, or as an alternative to, ceftriaxone. Potential diagnostic resistance-determinants of these antibiotics are small in number (*gyrA* for ciprofloxacin; *23S rRNA* and *mtrCDE* transporter for azithromycin), are relatively well-understood, and their absence predictive of susceptibility (particularly for ciprofloxacin). The development of molecular AMR-POCTs for detection of these determinants are thus technically feasible and therefore more likely to be immediately available [19-21].

Methods

This report was written following the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist [22].

Model structure

We compared Standard Care (SC) for NG treatment in the UK (at the time of investigation, ceftriaxone 500mg and azithromycin 1g dual-therapy [6]) with five different AMR-POCT strategies (Supplementary Figure S1), where the AMR-POCT was used as a reflex test to inform antibiotic selection, irrespective of which test was used to diagnose NG initially. The AMR-POCT strategies were chosen to either facilitate optimised choice of a second antibiotic *alongside* ceftriaxone (dual-therapy), or enable a single antibiotic *alternative* to ceftriaxone (monotherapy) (Box 1).

The rationale for the monotherapy strategies is that an AMR-POCT enables effective treatment of the known resistance profile, sparing the use of ceftriaxone. The rationale for dual-therapy strategies is based on the assumption that combination therapy is more effective at preventing emergence or spread of AMR and thereby preserves the use of ceftriaxone [23].

Each strategy consisted of a series of *intended treatment regimens*, contingent on the results of the AMR-POCT used. For example, in strategy B, the earliest *intended treatment regimen* was SC; where the AMR-POCT indicated azithromycin resistance, the second *intended treatment regimen* was ceftriaxone and ciprofloxacin; where the AMR-POCT then indicated ciprofloxacin resistance, the third *intended treatment regimen* was ceftriaxone monotherapy.

Box 1. Summary of AMR-POCT strategies

Standard Care (SC)

Standard care with dual-therapy of intramuscular ceftriaxone (500mg) and oral azithromycin (1g single dose).

Dual-therapy, including ceftriaxone

A) AMR-POCT for ciprofloxacin resistance only; infections identified as not resistant to ciprofloxacin are given oral ciprofloxacin (500mg) plus ceftriaxone (500mg). Infections identified as ciprofloxacin resistant are given SC.

B) Dual AMR-POCT for azithromycin and ciprofloxacin resistance; if no azithromycin resistance is identified, SC is given. If azithromycin resistant, ciprofloxacin (500mg) and ceftriaxone (500mg) are given unless there is ciprofloxacin resistance, in which case ceftriaxone (500mg) is given alone.

C) Dual AMR-POCT for ciprofloxacin and azithromycin resistance; if no ciprofloxacin resistance is identified, ciprofloxacin (500mg) and ceftriaxone (500mg) are given. If ciprofloxacin resistant, SC is given, unless there is also azithromycin resistance, when ceftriaxone (500mg) is given alone.

Monotherapy optimisation

D) AMR-POCT for azithromycin resistance: if no azithromycin resistance is identified, azithromycin (2g) is given. If azithromycin resistant, ceftriaxone (500mg) and ciprofloxacin (500mg) dual-therapy is given. If the AMR-POCT incorrectly shows no resistance (false negative for AMR), it is assumed the treatment fails. The treatment failure would be identified in the test-of-cure (TOC) and the patient would then receive 500mg ceftriaxone.

E) AMR-POCT for ciprofloxacin; if no ciprofloxacin resistance is identified, 500mg ciprofloxacin monotherapy is given. If ciprofloxacin resistant, SC is given. If the AMR-POCT incorrectly shows no resistance, monotherapy is assumed to fail, the patient returns and receives 500mg ceftriaxone alone.

Strategy	Antibiotic(s) for which resistance is tested		Intended Treatment Regimen based on test result		
	A	B	No resistance to A	Resistance to A	Resistance to A + B
Strategy A	Ciprofloxacin		Ciprofloxacin + Ceftriaxone	Azithromycin + Ceftriaxone	
Strategy B	Azithromycin	+ Ciprofloxacin	Azithromycin + Ceftriaxone	Ciprofloxacin + Ceftriaxone	Ceftriaxone
Strategy C	Ciprofloxacin	+ Azithromycin	Ciprofloxacin + Ceftriaxone	Azithromycin + Ceftriaxone	Ceftriaxone
Strategy D	Azithromycin		Azithromycin[a,b]	Ciprofloxacin + Ceftriaxone	
Strategy E	Ciprofloxacin		Ciprofloxacin[b]	Azithromycin + Ceftriaxone	
Standard Care	No resistance testing is done. Standard Care (SC) is ceftriaxone 500mg and azithromycin 1g dual-therapy [6]				

Unless otherwise stated, doses are: Ceftriaxone 500mg; Azithromycin 1g; Ciprofloxacin (500mg)

Shaded areas indicate Standard Care (SC) i.e. azithromycin and ceftriaxone dual-therapy

[a]2g dose given

[b]If incorrect test result and treatment fails, ceftriaxone is given

A decision tree model was constructed using TreeAge Pro (v.2017) to simulate a hypothetical cohort of 38,870 NG-diagnosed SHC attendees (21,915 men-who-have-sex-with-men [MSM], 8,488 women and 8,467 men-who-have-sex-with-women [MSW]), representing the total number of NG diagnoses in England SHCs in 2015, obtained from national surveillance data (GUMCAD) [24]. Our assumptions regarding AMR-POCT use meant the model could not be used when considering presumptive, e.g. for sexual contacts of NG-positive patients initially negative by microscopy but subsequently positive by NAAT testing. Approximately 10% of NG diagnoses are in contacts [25] but the epidemiological breakdown of these patients (e.g. women, MSW, MSM) and the nature of their NG diagnoses (e.g. microscopy negative and NAAT positive) is not reported. Therefore, contacts could not be removed from the hypothetical cohort.

Key model assumptions include: 100% compliance with test protocols; all patients entering the model are NG true-positives; dual AMR-POCTs results are available simultaneously; there is no ceftriaxone resistance (supported by England's national NG AMR sentinel surveillance system data [1]) so patients with monotherapy treatment failure would return and be successfully treated with ceftriaxone only. Model assumptions are provided in Supplementary Table S1.

Outcomes

We aimed to assess the costs and effectiveness of these AMR-POCT strategies to optimise treatment regimen choice and reduce selection pressure on ceftriaxone. The primary outcomes were the total costs (2015/16 GB £), the percentage of people given *optimal treatment*, and the percentage of people given non-ceftriaxone optimal treatment. '*Optimal treatment*' was defined as one which cured NG and did not contain an antibiotic against which there was resistance. Model definitions are provided in Supplementary Table S2. These data were used to calculate incremental cost-effectiveness ratios (ICERs, see equation) for the cost per additional optimal treatment gained and the cost per additional ceftriaxone treatment avoided. This was chosen as the measure of cost-effectiveness rather than

other measures, such as cost per Quality Adjusted Life Years (QALYs), because little data exist on the consequence of optimal versus suboptimal NG treatment on long-term outcomes, such as mortality or lifetime costs.

$$ICER = \frac{Cost_B - Cost_A}{Effectiveness_B - Effectiveness_A}$$

Secondary outcomes were the percentage of people given a 'missed earlier *intended treatment regimen*' (MEITR), and the percentage of people failing treatment due to resistance. 'MEITR' was defined as the use of a treatment regimen which cured NG, but where an earlier intended treatment regimen would have provided optimal treatment because susceptible infections had been misclassified as resistant by the AMR-POCT. MEITRs were independent of treatment effectiveness.

Treatment

AMR-POCT strategy treatment regimens were developed with input from three senior clinicians at St George's University Hospitals NHS Foundation Trust, London, who outlined current and hypothetical AMR-POCT patient pathways (Supplementary Figure S1). The purpose of the work was to determine AMR-POCT strategy for short-term clinical impacts, because these are the data used for sexual health service provisioning and decision-making for adoption into SHCs [18]. Furthermore, progression to longer-term clinical impacts from suboptimally treated infection is poorly defined [26]. Therefore, the time horizon was that of initial patient treatment, and complications associated with STIs such as pelvic inflammatory disease (PID) in women, and adverse drug events associated with treatment, were not considered.

Model parameters

Model epidemiology parameters are presented in Table 1, and cost parameters in Table 2 and Supplementary Table S3. The hypothetical AMR-POCT sensitivity and specificity were based on other

NAAT-based rapid and POC tests [27-29], and altered in sensitivity analyses. Antibiotic resistance prevalences were obtained from national surveillance of SHC attendees (GRASP, 2017) [30]. GRASP is England's national sentinel surveillance system that detects and monitors AMR in NG and records potential treatment failures. As the time horizon was that of initial patient treatment, discounting rates were not applied.

Table 1. Epidemiology parameters used in the model

Variable	Percentage (%)						Number						Comments, Reference
	MSM		W		MSW		MSM		W		MSW		
	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	Base case value	Range (low, high)	
1 Initial clinic attendances	56.4	N/A	21.8	N/A	21.8	N/A	21,915		8,488		8,467		GUMCAD, 2015 [24]
2 Resistance to azithromycin[a]	4.7	3.3, 6.1	2.7	1.9, 3.5	5.3	3.7, 6.9	1,030	723, 1,337	229	161, 297	449	313, 584	GRASP, 2017 [30]
3 Resistance to ceftriaxone	0.0	0.0, 0.0	0.0	0.0, 0.0	0.0	0.0, 0.0	0	0, 0	0	0, 0	0	0, 0	GRASP, 2017 [30]
4 Resistance to ciprofloxacin[b]	36.2	25.3, 47.1	20.1	14.1, 26.1	32.5	22.8, 42.3	7,933	5,544, 10,322	1,706	1,197, 2,215	2,752	1,930, 3,582	GRASP, 2017 [30]
5 Sensitivity of AMR-POCT	98	90, 100	98	90, 100	98	90, 100	N/A	N/A	N/A	N/A	N/A	N/A	Assumption

6	Specificity of AMR-POCT	90, 99 100	99	90, 99 100	99	90, 99 100	N/A	N/A	N/A	N/A	N/A	N/A		Assumption

MSM, men-who-have-sex-with-men; W, women; MSW, men-who-have-sex-with-women; N/A, Not Applicable; GUMCAD, genitourinary medicine clinical activity dataset; GRASP, gonococcal resistance to antimicrobial surveillance programme; AMR, antimicrobial resistance; POCT, point-of-care test.

[a] The azithromycin resistance ranges were extended further to 1-10% for all population groups in one way azithromycin resistance analysis so that the effect of more extreme values could be explored.

[b] The ciprofloxacin resistance ranges were extended further to 0-50% in one way ciprofloxacin resistance analysis so that the effect of more extreme values could be explored

Table 2. Cost parameters used in the model

Cost input	Cost[a]		Comments and references
	Base case value	Range (low, high)	
Management of NG (oral medication/IM injection)	£53.00/£62.74 70.88 EUR/83.90 EUR	£37.1, £68.9 / £43.92, £81.56 49.6, 92.1 EUR / 58.73, 109.07 EUR	[b]Adapted from previous model. Adams, 2014 [31]
Return visit due to treatment failure	£48.01 64.20 EUR	£33.61, £62.41 44.95, 83.46 EUR	[b,c] Adapted from previous model. Adams, 2014 [31]
Single AMR-POCT	£29.00 38.78 EUR	£20, £40 26.75, 53.49 EUR	Estimate [32]
Dual AMR-POCT	£31.90 42.66 EUR	£29, £58 38.78, 77.56 EUR	Estimate - 10% more than price of single AMR POCT (multiplier 1.1, range 1.0-2.0)
Dual AMR-POCT	£31.90 42.66 EUR	£22, £44 29.42, 58.84 EUR	Estimate – single AMR-POCT is varied, multiplier remains at 1.1 (10% more than price of single AMR POCT)
Azithromycin 1g[d]	£1.16 1.55 EUR	£0.81, £1.51 1.08, 2.02 EUR	BNF, 2016 [33]
Azithromycin 2g[d]	£2.32 3.10 EUR	£1.62, £3.02 2.17, 4.04 EUR	BNF, 2016 [33]
Ceftriaxone 500mg [e]	£9.58 12.81 EUR	£6.71, £12.45 8.97, 16.65 EUR	BNF, 2016 [33]

Ciprofloxacin	£0.07	£0.05, £0.09	BNF, 2016 [33]
500mg[d]	0.09 EUR	0.07, 0.12 EUR	

NG, *Neisseria gonorrhoeae*; IM, intramuscular; AMR, antimicrobial resistance; POCT, point-of-care test; BNF, British National Formulary.

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

[b] Includes staff time and consumables but not antibiotic costs. Costs were inflated to 2015/16 costs using the Hospital and Community Health Services (HCHS) Inflation Indices 2015 produced by the Personal Social Services Research Unit [35]. No data were available for inflation from 2014/15 to 2015/16 so it was assumed to be the same as between 2013/2014 and 2014/15. The UK hospital consumer price index for health services shows similar annual growth in this sector from 2014 (93.2 in 2013, 97.1 in 2014 and 100 in 2015), which validates this assumption [36]. GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP. A further breakdown of cost data is provided in Supplementary Table S3.

[c] Within the context of this model, treatment failure due to resistance to a monotherapy would result in a return visit. No repeat culture would be taken and no repeat diagnostic tests would occur. The patient would be successfully treated using ceftriaxone, administered via injection.

[d] Oral medication.

[e] Administered via intramuscular injection. The price quoted is for 1g vial of ceftriaxone, the smallest non-proprietary vial available (10) - the remaining 500mg is then discarded.

A micro-costing approach was employed, considering only costs incurred to the healthcare provider (i.e. SHC). Costs to those procuring sexual health services provision, or to health systems as a whole, were not considered. Costs were estimated by adapting an existing model [31], and included: laboratory equipment, POCTs and antibiotics, AMR-POCTs, NG treatment implementation (e.g. staff time and consumables, including partner notification and health promotion) (Supplementary Table S3). It was assumed the AMR-POCTs produced results in 30 minutes (maximum acceptable POCT run-time for service users [37, 38]) and that in all strategies, NG-positive samples would still be sent to the laboratory for culture and phenotypic resistance testing. Costs are given in 2015/16 prices (GB £) and inflated when based on old estimates [35]. Antibiotic prices were extracted from the British National Formulary (BNF) website (September 2016), with the cheapest formulation being used including non-proprietary costs where available [33]. Initial costs of diagnosing NG were not considered as people only entered the model after an NG diagnosis. The cost of implementing a change to clinical practice was also not considered.

Sensitivity analyses

We conducted one-way analyses for each of the model parameters by varying them independently at the ends of their ranges to examine the effect on the primary outcome (Table 1). These analyses identified which model parameters results were most sensitive to. Each sensitivity analysis compared one of the five AMR-POCT strategies with SC, across three population groups (women, MSW, and MSM). Probabilistic sensitivity analyses (PSA) were not performed because our analysis was a cost-effectiveness analysis with the outcome as cost per event avoided, rather than a cost acceptability or cost utility analysis exploring the likelihood that the technology is cost-effective at different willingness to pay (WTP) thresholds. There is no commonly agreed WTP for our outcome, and therefore presenting PSA results would likely not have yielded additional beneficial information.

Results

Overall AMR-POCT strategy costs, treatments used, and treatment outcomes compared with SC in all groups are presented in Table 3. Breakdowns by population group are presented in Supplementary Tables S4, S5 and S6.

Table 3. Total costs, treatments used and treatment outcomes for Standard Care and AMR-POCT strategies: all groups (n=38,870)

Strategy	Total cost[a]	Number of antibiotics used to treat NG			Number of optimal treatments[b]	Number of sub-optimal treatments[c]	Number of MEITR[d]	Number of treatment failures[e]
		Ceftriaxone	Azithromycin	Ciprofloxacin				
Standard care	£2,856,168 3,819,524 EUR	38,870	38,870	0	37,162	1,708	-	-
A) Single POCT for ciprofloxacin; dual-therapy	£3,954,554 5,288,385 EUR	38,870	12,408	26,462	38,057	813	265	-
B) Dual POCT for azithromycin and ciprofloxacin; dual-therapy	£4,093,844 5,474,656 EUR	38,870	36,825	1,373	38,822	48	267	-

C) Dual POCT for ciprofloxacin and azithromycin; dual-therapy	£4,066,498 5,438,086 EUR	38,870	11,736	26,462	38,611	259	912	-
D) Single POCT for azithromycin; monotherapy	£3,271,684 4,375,189 EUR	2,080	36,825	2,045	38,164	706	372	34
E) Single POCT for ciprofloxacin; monotherapy	£3,457,581 4,623,788 EUR	12,656	12,408	26,462	38,057	813	265	248

AMR, antimicrobial resistance; POCT, point-of-care test; NG, *Neisseria gonorrhoeae*; MEITR, missed earlier intended treatment regimen

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

[b]'optimal' refers to a treatment regimen which cures the NG infection and does not contain any antibiotic against which there is resistance

[c]'sub-optimal' refers to a treatment regimen which contains antibiotics against which there is NG resistance - if the treatment is a monotherapy it will result in treatment failure

[d]'missed earlier intended treatment regimen' (MEITR) refers to a treatment regimen which cures the NG infection and does not contain any antibiotic against which there is resistance, but a treatment regimen was used when an earlier intended treatment regimen would have provided optimal treatment – a MEITR is due to a false-resistant AMR-POCT result

[e]'treatment failure' refers to failure to cure an NG infection due to resistance to an antibiotic given as monotherapy and is due to a false-susceptible AMR-POCT result

Costs

The cost of SC NG management was £2,856,168 (3,819,524 EUR) for the total cohort (Table 3). All AMR-POCT strategies cost more than SC, with dual-therapy AMR-POCT strategies more expensive than monotherapy strategies. Strategy D was the least expensive AMR-POCT strategy, costing £3,271,684 (4,375,189 EUR), 14.5% more than SC. Strategy B was the most expensive, costing £4,093,844 (5,474,656 EUR), 43% more than SC. This was consistent across all population groups.

Optimal treatment

All AMR-POCT strategies provided more optimal treatments than SC, in all population groups. Strategy B provided most optimal (n=38,822) and least sub-optimal (n=48) treatments. Strategies A and E equally provided the least optimal treatments (Supplementary Tables S4, S5 and S6) and the most sub-optimal (n= 813) (Table 3).

Ceftriaxone-sparing treatments given

Since all dual-therapy strategies used ceftriaxone, only monotherapy strategies provided ceftriaxone-sparing options. Strategy D reduced ceftriaxone use by 95% compared to SC (Table 3).

MEITRs given

A MEITR refers to a treatment regimen being used when an earlier intended treatment regimen would have provided optimal treatment. In all population groups, the fewest were in Strategies A and E (n=265), and B (n=267), and the most were in Strategy C (n=912) (Table 3, Supplementary Tables S4, S5 and S6).

Treatment failures

There were some treatment failures in each monotherapy strategy due to false-susceptible AMR-POCT results: strategy D had 34 (0.09% of treatments) and Strategy E had 248 (0.64% of treatments) (Table 3). There were no treatment failures with SC or dual-therapy strategies (A, B and C) because they all

included ceftriaxone. This was consistent across all population groups (Supplementary Tables S4, S5 and S6).

Cost-effectiveness analysis (CEA)

The cost-effectiveness analysis (CEA) results are presented in Table 4. When avoidance of sub-optimal treatments was considered, Strategy D was most cost-effective relative to SC, costing £414.67 (554.53 EUR) per optimal treatment gained. Strategy A was least cost-effective overall, whereas Strategy B was the most-cost effective dual-therapy strategy.

Table 4. Cost effectiveness analysis (CEA) for SC and AMR-POCT strategies

Sub-group	Comparison	Total additional cost[a]	Additional cost per patient[a]	Number of optimal treatments gained	Additional cost per optimal treatment gained[a]	Number of ceftriaxone treatments avoided	Additional cost per ceftriaxone-sparing treatment [a]
All	AMR-POCT A vs SC	£1,098,386 1,468,860 EUR	£28.26 37.79 EUR	895	£1,226.97 1,640.81 EUR	0	Dominated
	AMR-POCT B vs SC	£1,237,676 1,655,131 EUR	£31.84 42.58 EUR	1,660	£745.44 996.87 EUR	0	Dominated
	AMR-POCT C vs SC	£1,210,330 1,618,562 EUR	£31.14 41.64 EUR	1,449	£835.39 1,117.16 EUR	0	Dominated
	AMR-POCT D vs SC	£415,516	£10.69 14.30 EUR	1,002	£414.67 554.53 EUR	36,790	£11.29 15.09 EUR

		555,665.3 EUR					
		£601,414	£15.47	895	£671.82	26,214	£22.94
		804,264.8 EUR	20.69 EUR		898.42 EUR		30.68 EUR
	AMR-POCT E vs SC						
		£620,274	£28.30	499	£1,242.13	0	
		829,486.1 EUR	37.85 EUR		1,661.09 EUR		
	AMR-POCT A vs SC						Dominated
		£697,730	£31.84	1,001	£697.32	0	
		933,067.2 EUR	42.58 EUR		932.52 EUR		
	AMR-POCT B vs SC						Dominated
MSM		£683,317	£31.18	864	£790.97	0	
		913,792.8 EUR	41.70 EUR		1,057.76 EUR		
	AMR-POCT C vs SC						Dominated
		£235,532	£10.75	568	£414.38	20,676	£11.39
	AMR-POCT D vs SC		14.38 EUR		554.15 EUR		15.23 EUR

		314,974.5 EUR					
		£358,920	£16.38	499	£718.75	13,842	£25.93
	AMR-POCT E vs SC	479,980 EUR	21.90 EUR		961.18 EUR		34.68 EUR
		£239,316	£28.26	248	£965.92		
		320,034.8 EUR	37.79 EUR		1,291.72 EUR	0	
	AMR-POCT A vs SC						Dominated
		£269,519	£31.83	436	£617.60		
	AMR-POCT B vs SC	360,425 EUR	42.57 EUR		825.91 EUR	0	Dominated
		£263,674	£31.14	391	£674.71		
		352,608.5 EUR	41.64 EUR		902.28 EUR	0	
MSW	AMR-POCT C vs SC						Dominated
		£91,956	£10.86	271	£339.59		£11.58
		122,971.8 EUR	14.52 EUR		454.13 EUR	7,938	15.49 EUR
	AMR-POCT D vs SC						
	AMR-POCT E vs SC	£132,108	£15.60	248	£533.21	5,658	£23.35

		176,666.7 EUR	20.86 EUR		713.06 EUR		31.23 EUR
	AMR-POCT A vs SC	£238,796 319,339.4 EUR	£28.13 37.62 EUR	148	£1,612.62 2,156.54 EUR	0	Dominated
	AMR-POCT B vs SC	£270,428 361,640.6 EUR	£31.86 42.61 EUR	223	£1,210.74 1,619.11 EUR	0	Dominated
	AMR-POCT C vs SC	£263,339 352,160.5 EUR	£31.02 41.48 EUR	194	£1,356.61 1,814.18 EUR	0	Dominated
Women	AMR-POCT D vs SC	£88,028 117,718.9 EUR	£10.37 13.87 EUR	163	£540.55 722.87 EUR	8,176	£10.77 14.40 EUR
	AMR-POCT E vs SC	£110,386	£13.00 17.38 EUR	148	£745.45 996.88 EUR	6,714	£16.44 21.99 EUR

	147,618.1 EUR					

AMR-POCT, antimicrobial resistance point-of-care test; MSM, men-who-have-sex-with-men; MSW, men-who-have-sex-with-women; SC, standard care.

A strategy is 'dominated' if it is more expensive and provides fewer/equivalent benefits.

[a] GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [34].

For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP.

When avoidance of ceftriaxone use was considered, Strategy D was most cost-effective relative to SC, costing £11.29 (15.10 EUR) per ceftriaxone-sparing treatment gained. These findings were consistent across all population groups.

Sensitivity analyses

In one-way sensitivity analyses, the following four parameters had the greatest impact on cost-effectiveness per optimal treatment gained for all AMR-POCT strategies and across all population groups: prevalence of azithromycin resistance; AMR-POCT sensitivity; prevalence of ciprofloxacin resistance; and the cost of single detection AMR-POCT. In monotherapy strategies, the cost-effectiveness model was additionally sensitive to cost of clinical management (both with and without injection), cost of ceftriaxone, and AMR-POCT specificity (for strategy D). The cost multiplier for a dual detection AMR-POCT impacted on AMR-POCT cost-effectiveness for Strategies B and C. Tornado plots from these analyses are presented in Supplementary Figure S2.

For all strategies, variation of ICER in relation to azithromycin resistance prevalence was minimal until prevalence fell to or below 3%, at which point it increased (Supplementary Figure S3). These rises in ICERs were least for strategies B and D. With the exception of strategy B where ICERs were consistent for all population groups, these increases in ICER were most limited in women.

Variation in AMR-POCT accuracy also showed similar patterns across all population groups. Apart from Strategy D, variation in specificity had very little effect on cost per optimal treatment gained. In contrast, as sensitivity decreased to a minimum of 90%, particularly towards the lower range, the cost per optimal treatment gained increased exponentially, except for strategy B where the relationship was linear. Strategy B also had the smallest change in ICER between maximum (100%) and minimum (90%) sensitivity (maximum difference of £169.21 (226.28 EUR) per optimal treatment gained in women) compared with other strategies where the difference was in the thousands. For Strategy D, change in sensitivity had little impact on cost per optimal treatment gained, whereas when specificity

decreased to below around 95.5%, the cost per optimal treatment gained started to increase exponentially. The sensitivity analyses are presented in Supplementary Figure S4.

The prevalence of ciprofloxacin resistance had very little effect on cost per optimal treatment gained in Strategies B, C and D (Supplementary Figure S5). For Strategies A and E, as ciprofloxacin resistance increased from about 20%, there was an exponential increase in cost per optimal treatment gained for women only.

The relationship between ICER and cost of a single target AMR-POCT was linear. Interestingly, as the cost of the single target AMR-POCT increased, the two dual-target AMR-POCTs diverged, with strategy B costing less per optimal treatment gained relative to strategy C.

For the three single target AMR-POCTs (A, D and E), reducing the cost of the test had the greatest impact on cost per treatment gained. Monotherapy strategies became cost-saving (ICER <0) for all population groups when AMR-POCT cost was ≤£18 (24.07 EUR) for Strategy D, and ≤£16 (21.40 EUR) for Strategy E (Supplementary Figure S6). Strategy B had lowest costs per additional optimal treatment for dual-therapy strategies.

Discussion

This is the first study to assess the cost-effectiveness and impacts of deploying AMR-POCTs for gonorrhoea. All AMR-POCT strategies assessed resulted in more optimal treatments compared with SC. Monotherapy AMR-POCT strategies provided ceftriaxone-sparing options, with Strategy D reducing the use of ceftriaxone by 95%. Both outcomes are important in promoting antibiotic stewardship by minimising risks of breakthrough with ceftriaxone-resistant circulating strains, and reducing selection pressure for resistance developing to ceftriaxone, respectively.

Our cost-effectiveness analysis adapted a previously published cost-effectiveness model of introducing a dual CT/NG POCT into a SHC [29, 31], and was populated using available published data, and where unavailable, using unpublished data and expert opinion. By employing a decision tree

model approach we could account for sufficient complexity without over-building. This approach is, however, unable to assess outcomes that a transmission-dynamic model would be required for, such as that developed by Fingerhuth *et al*. [39], including impact AMR-POCTs could have on re-infection in a previously treated patient, on population prevalence or burden of disease, or on AMR evolution.

Turner *et al*. have adapted the same CT/NG POCT cost-effectiveness model we used for our analysis [29, 31] to analyse the potential clinical and overall economic impact of an NG AMR-POCT [40]. Whilst theirs was not a cost-effectiveness analysis, and different model assumptions and parameters from ours were used, they also demonstrated that AMR-POCTs could lead to overall reductions in ceftriaxone use, but that introduction of AMR-POCTs incurred increased costs. Using an individual-based dynamic transmission model that incorporated partner treatment and which was applied to a London MSM population, Zienkiewicz *et al.* [41] also demonstrated that AMR-POCTs for NG ciprofloxacin sensitivity reduced ceftriaxone use, by 70% compared with the reference scenario. An individual-based model of molecular NG-AMR test-use compared with culture within an NG surveillance system in remote settings found that they substantially improve the timeliness of NG-AMR detection, facilitating a faster change in recommended treatment, with potential for decreasing NG-AMR impact on the wider population [42]. Fingerhuth *et al.* [39] developed a compartmental transmission model of antibiotic-sensitive and antibiotic-resistant NG to look at proportion of resistant infections and cases averted. They showed that the clinical pathway that included an AMR-POCT resulted in the lowest proportion of resistant infections after 30 years, whereas the clinical pathway with a POCT that did not test for AMR resulted in the highest. They also noted that test diagnostic performance is key for AMR-POCTs to have a beneficial public health impact. The potential public health impact of AMR-POCTs was confirmed by Tuite *et al.*, with AMR-POCTs delaying the proportion of isolates reaching >5% resistance compared with empiric treatment [43]. However, it was highlighted that the AMR-POCT must test for resistance to multiple anitimicrobials, otherwise non-tested, resistant, strains will be selected for. Thus, continued surveillance, including culture, must be continued. Together, these health economic and modelling evaluations highlight the possible

beneficial impacts of implementing AMR-POCTs on reducing ceftriaxone use and decreasing NG-AMR prevalence at the population level, but the design and implementation of the tests should also be carefully considered.

As with all mathematical models, several assumptions were made (Supplementary Table S1), including AMR-POCT diagnostic accuracy - a necessity as these tests are currently in early phases of development [16]. Future performance estimates will need to consider two elements: predictive accuracies of any biomarkers used to detect AMR; the performance of platforms and chemistries used to detect them. Variations in both may independently affect outcomes.

Our analysis had some limitations. We used the most recent NG-AMR data available from GRASP at the time [30], but AMR rates constantly change and, in the sensitivity analyses, AMR prevalence alterations had the greatest impact on AMR-POCT cost-effectiveness (Supplementary Figure S2). This may limit the generalisability of our results, as it is not possible to know future resistance profiles. However, the results should be generalisable to the ranges used in the sensitivity analyses. In addition, as AMR-POCTs are still in development, some of the model's other epidemiological parameters will have changed by the time the AMR-POCTs are available for use in routine practice, which may further limit the analyses' applicability in the longer term. This highlights the need to continually conduct analyses such as these, to enhance our ability to predict and understand future trends. Our anlayses are also limited to data from England, with results perhaps less generalisable to other countries. This will be exacerbated by the 2019 change to 1g ceftriaxone monotherapy, further setting it aside from guidelines in other European countries [7]. Our model also did not consider NG-positive patients co-infected with another organism, such as *Chlamydia trachomatis*, which would affect patient pathways and treatment options. Additional factors not considered were costs associated with treating long-term NG infection sequelae [44], costs incurred outside of the SHC, and costs or cost-savings associated with changing clinical pathways in order to accommodate the AMR-POCTs. Thus the time horizon for the costs and consequences was of initial patient treatment only.

Strategy B was most effective for avoiding sub-optimal treatments but the most costly to implement. Strategy D was the most cost-effective for both effectiveness outcomes (optimal treatments gained and ceftriaxone avoidance), but resulted in treatment failures, as well as nearly 15-fold higher sub-optimal treatments compared to Strategy B. Both strategies B and D enabled the re-use of ciprofloxacin, previously abandoned for the treatment of NG in the UK [6].

All AMR-POCT strategies were more expensive than SC, with dual-therapy AMR-POCT strategies more expensive than monotherapy strategies, suggesting that short-term net financial investments in AMR-POCT adoption are required to gain long-term antimicrobial stewardship benefits. Interestingly, our sensitivity analysis suggested that even if AMR-POCT costs were significantly reduced, perhaps through production scale-up, dual-therapy AMR-POCT strategies would still not be cost-saving. However, a relatively small reduction to <£18 (24.07 EUR) per test would enable the monotherapy AMR-POCT strategies to be cost-saving.

The monotherapy strategies resulted in treatment failures due to false-susceptible AMR-POCT results, although minimal relative to SC. Since we assumed ceftriaxone treated 100% of NG infections, there were no treatment failures for SC or dual-therapy strategies. The most recent GRASP data suggest that ceftriaxone resistance remains low (no ceftriaxone resistance reported, although there is a reduction in susceptibility with 24.6% of isolates with minimum inhibitory concentrations (MICs) ≥0.03 mg/L in 2018 compared with 16.6% in 2017 [1]), but there are increasing concerns regarding international ceftriaxone-resistant strains [45-47]. This potentially undermines our assumption and the resulting lack of treatment failures from dual-therapy AMR-POCT strategies.

Most MEITRs (treatment regimen used when an earlier intended treatment regimen would have provided optimal treatment) were in Strategy C, and the least in Strategies A, B and E. Avoiding MEITRs is important because it maximises the ability to use ciprofloxacin (in Strategies A, C and E), or reduces the need for ceftriaxone use (Strategies B and D). These numbers were small compared to actual patient numbers in whom a MEITR might be used if these AMR-POCTs were available more generally.

For example, using national surveillance data [24, 48], we estimated that over 25,000 of the 38,870 NG-diagnosed SHC patients assumed to have been treated with SC in 2015 would have had ciprofloxacin-susceptible NG. Strategies A and E would have enabled all, except 265 (Table 3), of these patients to be treated with ciprofloxacin, a 100-fold reduction in these missed opportunities.

Since a MEITR is due to susceptible infections misclassified as resistant by the AMR-POCT, test specificity is key. In sensitivity analyses of AMR-POCT accuracy, Strategy D was the only strategy where cost per optimal treatment gained was affected by changes in specificity. In all other strategies, cost per optimal treatment gained increased as sensitivity decreased. This is because these strategies contained an AMR-POCT that included ciprofloxacin testing, so resistance (20-36%, dependent on population group [30]) was detected and optimal treatment could be given. In contrast, if AMR-POCT sensitivity in these strategies fell, true ciprofloxacin-resistant cases were missed and the patient sub-optimally treated. Strategy D, where the AMR-POCT was for azithromycin only, was the only strategy where ciprofloxacin was given without resistance-testing - as the specificity decreased, more patients received false-positive azithromycin resistance results and were treated with ciprofloxacin. Due to high ciprofloxacin resistance prevalence, this treatment was sub-optimal in a large number of cases. Following the logic of the other strategies, if azithromyin resistance prevalence increased, cost per optimal treatment gained in Strategy D would become sensitive to both AMR-POCT specifity and sensitivity.

Thus, prevalence of resistance has important implications for AMR-POCT accuracy requirements and ICERs of optimal treatments gained. In the azithromycin resistance sensitivity analyses, ICERs increased when resistance fell below about 3% (well below current UK azithromycin resistance prevalence, reported at approximately 9.7% [1]), primarily because when azithromycin resistance is low, there is little value in testing for it (Strategies B, C and D) and there will be few treatment failures from background resistance (Strategies A and E). In the ciprofloxacin resistance sensitivity analysis, an

effect on ICERs was only seen in women in strategies A and E (because of lower baseline ciprofloxacin resistance prevalence).

From a population-level antimicrobial stewardship public health perspective, increasing the number of sub-optimal treatments may eventually lead to an increased number of resistant infections [39]. The relative public health importance of a smaller total number of sub-optimal treatments with a few treatment failures versus a higher number of sub-optimal treatments with no failures, warrants further investigation, and could be included in future transmission model analyses. Furthermore, the long-term public health impact of preserving ceftriaxone use whilst increasing the risk of treatment failures from monotherapy strategies (versus maintaining ceftriaxone in the earlier intended treatment regimen with an increase in sub-optimal treatments and no adequate treatment alternative), should also be investigated.

Conclusion

Once developed, AMR-POCTs could have wide-ranging implications for clinical decision-making globally, including the re-use of antibiotics previously abandoned for the treatment of NG, ensuring the right treatment is given to the right person, at the right time (precision medicine) [9, 12]. The O'Neill review of AMR [10] noted that accepting the initial expense of new test introduction may enable longer-term societal pay-offs by reducing infection rates and maintaining effective NG treatments. However, a relatively small reduction in test cost could enable some AMR-POCT strategies to be cost-saving.

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Dear Editors,

Response to Reviewers

Antimicrobial resistance point-of-care testing for gonorrhoea treatment regimens: cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies compared with standard care in England sexual health clinics. eurosurveillance-D-19-00402

We would like to thank the reviewers for their comments, which have helped improve the clarity of the manuscript and its relevance to the wider NG-AMR literature. We have provided point-by-point responses to the reviewers' comments. Page numbers refer to the clean version. The track changes version, should mirror these page number with the correct 'Review: Mark-up' options.

We would like to note that in order to respond to reviewers' comments, the word counts have increased as follows:
Abstract: 314 words
Text: 4163 words
In addition, the number of references has increased to 48.

Reviewers' comments:

Reviewer #1: General comments
The paper provides an interesting analysis, which is very timely. The paper is well written and easy to read.
There are complex intervention strategies being evaluated, and although this makes it complex for the reader, the authors do well to explain these within the methods with the example given and box 1.
Though some of the standard approaches to cost-effectiveness analysis for wider policy making are not applied, the work has worth in providing information to clinicians and healthcare professionals treating such patients (e.g. by focusing on appropriate treatment). A lot of information is presented. The main assumptions and limitations are discussed within the discussion section, highlighting the author's awareness to the works strengths and limitations.
The CHEERs checklist has been used appropriately.
Thank you for these positive comments.

Points of clarification / suggested revisions
1. Abstract - given that the title and results indicate cost-effectiveness (cost per optimal treatment) this should also be stated as a primary outcome in methods.
Page 2: This has been added to the abstract methods.

It would also benefit from a sentence stating from what perspective this analysis was performed from (e.g. healthcare system or payer etc).
Page 2: This has been added to the abstract methods.

£414.67 could be £414.67 per optimal treatment gained to make more clear.
Page 3: This has been added to the abstract results. We have also added "per ceftriaxone-sparing treatment" after £11.29.

I think it should also be made clear in the abstract that its an annual time horizon and the cost year you're reporting in.

Page 2: This has been added to the abstract methods.

2. Is there a reason websites are not referenced in the standard format? (E.g. https://plexpcr.com/resistanceplus-gc/ could still be referenced [15] with date accessed)
Page 5, paragraph 1: We have added websites as references.

3. It should be mentioned in the methods that the study adheres to the CHEERs checklist
Page 5: This has been added to the beginning of the methods, and a reference to the Husereau *et al.* BMJ article provided as well.

4. The key methodological points should be stated, then the signposting to the supplementary material since the key points should still be presented in the main text. (e.g. line 39, page 9)
Page 10, paragraph 3: The signposting to supplementary material has now been moved to after the key methodological points have been stated.

5. More reasoning on why short term clinical impacts were the aim would be beneficial (line 26, page 10). [The supplementary support material does provide a nice wealth of information though, clearly presented]
Page 11: We have added to the reasoning for the focus on short-term clinical impacts in the proposed location (methods "treatment" section).

6. "there is no ceftriaxone resistance [23]" - can you back this up with any surveillance/resistance epidemiological data, if so please state.
Page 10, paragraph 2: We have updated the reference to the 2019 GRASP report, and made clearer that this supports the assumption that there is no ceftriaxone resistance.

7. Though the seeming reason that "per optimal treatment gained" was chosen as an outcome was to show the reduced selection pressure, was there a reason that there was also not the inclusion of a more standardised measure such as cost per QALY gained? (even in a shorter time horizon). I think the reasons for choosing the main cost-effectiveness measures (e.g. those presented in Table 4) could be further justified.
Page 11, paragraph 1: We have added further explanation where the ICER equation is presented in the methods.

8. Parameter ranges can be placed in the main tables (Table 1 and 2) - e.g. just in brackets next to the base case value
Tables 1 and 2 (pages 13-16) have been modified to add parameter ranges, where appropriate, and we have consequently removed Supplementary Table 4. We have included a column for the ranges, as per the editorial comments below.

9. "No data were available for inflation from 2014/15 to 2015/16 so it was assumed to be the same as between 2013/2014 and 2014/15. The UK consumer price index for health services shows similar annual growth in this sector from 2014 which validates this assumption." - could you add a reference for the last sentence and be make it clearer which period you were looking at e.g. similar annual growth from 2014 to 2015.
Page 16: In footnote [a] of Table 2, we have clarified where the data come from, the time-period looked at, and the data variables used.

10. Are you assuming 100% compliance with test protocols? This could be mentioned in the treatment pathway methods section.

Page 10, paragraph 2: We have added “100% compliance with tests protocols” to the methods model assumptions section.

11. The column headings in Table 3 could be more clear - e.g. "number of optimal cases" instead of just "optimal cases"
Pages 20-22 (Table 3): This change has been made.

12. Was there a reason probabilistic sensitivity analyses were not performed? This could be stated.
Page 17, paragraph 2: We have provided the justification for not conducting a probabilistic sensitivity analysis in the methods “sensitivity analysis” section.

13. Discussion - How generalizable do you think these results are outside of your tested cohort? i.e. in future years? Some discussion of what this means in the longer term.
Page 32, paragraph 3: We have added discussion of generalisability with regards to Europe and the future in the discussion limitations section.

14. Though it may be the first of its kind for this specific problem, some discussion of how this fits into wider health economic or mathematical evaluations in relation to gonorrhoea & AMR (even if just a few sentences) is needed.
Page 31, paragraph 2: We have added a paragraph outlining health economic and modelling work by others.

Reviewer #2: It was interesting to read your paper presenting the results of a modelling study addressing use of antimicrobial resistance (AMR) point-of-care testing (POCT) for infections with Neisseria gonorrhoea (NG) in England sexual health clinics, the objective of which was to assess cost-effectiveness and impact on ceftriaxone use of five hypothetical strategies in comparison to (at the time of the study) standard care for gonorrhoea in England (ceftriaxone 500 mg and azithromycin 1 g dual-therapy).

Since the current standard care for gonorrhoea in England sexual health clinics is 1 g ceftriaxone monotherapy, the public health relevance of the paper is less clear. Also, as the AMR-POCTs are currently in early phases of development and many epidemiology parameters used in the model will have changed by the time AMR-POCTs become available, the paper is probably not so interesting for Eurosurveillance readers.
Page 32, paragraph 3: Thank you for this insight. We have added these points to the limitations paragraph of the discussion.

Reviewer #3: The manuscript was a well written analysis of using various treatment options for gonorrhea in a manner that preserves antimicrobial stewardship. I did not have any specific comments to improve the models or clarity of the information presented.
Thank you for this positive feedback.

Editorial comments:
Thanks again for submitting your contribution to the Eurosurveillance special issue on point-of-care testing.
General: Overall I agree with the reviewers’ pertinent comments and have only few additional points.

The costs should also be expressed in Euro (XX EUR) given that this is the currency used in the majority of EU countries.

Throughout: We have converted all costs into Euros, and added the following explanation for how the conversion was calculated to the main text and each table, as appropriate: "a GBP costs were converted to Euros using a historic currency conversion of an average of 366 days from the 1st July 2015 to 30th June January 2016 [33]. For this time period, 1 GBP = 1.34 Euros, and 1 Euro = 0.75 GBP."

Please provide a general statement as to what you consider POC tests.
Page 4, paragraph 3: A sentence defining rapid and POCTs has been added to the third paragraph of the introduction.

With respect to comment 8 by reviewer 1, I suggest to add a new column for the ranges in the table.
Tables 1 and 2 (pages 13-16): Thank you for this suggestion, we have done this.

Reviewer 2 flagged in comments to us that they missed the citation of the following paper published in 2017: Turner KM1, Christensen H2, Adams EJ3, McAdams D4, Fifer H5, McDonnell A6, Woodford N5,6. Analysis of the potential for point-of-care test to enable individualised treatment of infections caused by antimicrobial-resistant and susceptible strains of Neisseria gonorrhoeae: a modelling study. BMJ Open. 2017 Jun 14;7(6):e015447. doi: 10.1136/bmjopen-2016-015447. Can you ensure that there are no overlaps with the current submission?
Page 31, paragraph 2: We have added a paragraph to reference the Turner et al. 2017 paper, and what that study found, as well as other health economic and modelling studies.

We have outlined the differences with the Turner paper below, but believe this is too extensive to add to the manuscript:

Turner et al. have analysed the potential clinical and overall economic impact of an NG AMR-POCT, adapting the same CT/NG POCT cost-effectiveness model we have adapted for our analysis. In contrast with our approach where patients enter the model with an NG diagnosis with treatment indicated by AMR-POCT results in all cases, Turner et al. considered three different management scenarios (current management; simple POCT management; AMR-POCT management – the only scenario enabling ceftriaxone avoidance), thus enabling the incremental benefit of an AMR-POCT versus a simple POCT to be determined. Their base case was 100% ceftriaxone treatment, with the following AMR-POCT scenarios for non-ceftriaxone dual therapy with azithromycin: 1. POCT for ciprofloxacin resistance; 2. POCT for penicillin resistance. They found that AMR-POCTs could lead to overall reductions in ceftriaxone use by 66% (scenario 1) and 79% (scenario 2), reflecting trends seen for Strategies E and F in our model. Although supporting the rationale to use previously abandoned antibiotics to reduce selection pressure on ceftriaxone AMR, the Turner et al. model does not consider treatment failure of the ciprofloxacin and penicillin monotherapies as an outcome, which could equally have important public health consequences. The Turner et al. economic implications of AMR-POCT implementation was total additional annual cost of testing, as opposed to the ICER and WTP threshold analyses we have conducted. As with our model, there were increased costs associated with introduction of an AMR-POCT (we assumed similar POCT costs: Turner et al. assumed test cost was £25, whereas we assumed £29 for a single-target POCT and £31.90 for a dual-target POCT). Turner et al. used tariff costings (reimbursement based on patient SHC attendance) whereas we employed a micro-costing approach (cost to the SHC), and we have previously shown that tariff costings are more likely to result in POCTs being more cost-effective than SC.

Abstract: Please add a section 'Aim'.
Page 2: This has been done.

Introduction: The first sentence in the second paragraph seems incomplete – please check.
Page 4, paragraph 2: We have modified the sentence to try and make it clearer.

You refer to test results being obtained after 2 hrs as rapid tests. I would expect a much faster time for a result.
Page 4, paragraph 3: This 2 hour turnaround is taken from the definition of rapid and POC tests by WHO. This definition is now provided in the introduction.

Sexual health commissioning seems to be a term that is used specifically in the UK. Can you suggest an alternative for the non-UK readers?
Page 5, paragraph 1; Page 17, paragraph 1: We have replaced this with "procuring sexual health services provision for a region".

Methods: Please reference standard care in table 1.
Box 1, pages 7-9: We believe this is in reference to Box 1, rather than Table 1. We have added a row to depict Standard Care, as well as a reference to Bignell *et al.* (BASHH 2011 treatment guidelines for standard care with ceftriaxone 500mg and azithromycin 1g dual-therapy).

Results: Information from supplementary materials that is mentioned in the discussion needs to be moved to the core of the manuscript.
We have reviewed the discussion and found two references to supplementary materials (see below). Upon review, we think that sufficient information is already provided in the main manuscript and do not think that additional information needs to be added to the manuscript, which is already quite long. Apologies if you are referring to something else that we have missed, in case which case we ask if you can please clarify.

Supplementary materials referred to in the discussion are:

- Page 32: "As with all mathematical models, several assumptions were made (Supplementary Table S1)".
    - Key assumptions are already outlined in the methods, page 10: "Key model assumptions include: 100% compliance with test protocols; all patients entering the model are NG true-positives; dual AMR-POCTs results are available simultaneously; there is no ceftriaxone resistance (supported by England's national NG AMR sentinel surveillance system data [1]) so patients with monotherapy treatment failure would return and be successfully treated with ceftriaxone only. Model assumptions are provided in Supplementary Table S1."
- Page 32 para 3: "AMR prevalence alterations had the greatest impact on AMR-POCT cost-effectiveness (Supplementary Figure S2)."
    - This point is mentioned on page 29: "In one-way sensitivity analyses, the following four parameters had the greatest impact on cost-effectiveness per optimal treatment gained for all AMR-POCT strategies and across all population groups: **prevalence of azithromycin resistance; AMR-POCT sensitivity; prevalence of ciprofloxacin resistance; and the cost of single detection AMR-POCT.** In monotherapy strategies, the cost-effectiveness model was additionally sensitive to cost of clinical management (both with and without injection), cost of ceftriaxone, and AMR-POCT specificity (for strategy D). The cost multiplier for a dual detection AMR-POCT impacted on AMR-POCT cost-effectiveness for Strategies B and C. Tornado plots from these analyses are presented in Supplementary Figure S2."

Under 'Optimal treatment' scenario D seems also critical.

We have chosen not to highlight scenario D under optimal treatments, as it leads to 38,164 optimal treatments – which is less than scenario C (38,611) and only slightly more than A and E (38.057) – but has 706 sub-optimal treatments and 34 treatment failures. Strategy B is the strategy with the most optimal treatments, and least "negative" outcomes, which is why we have chosen to highlight this strategy over the others.

Discussion: please add a limitation section.
Page 32, paragraph 3: We have highlighted the limitations section in the discussion.

Other
- Tables must be created in Word. The full table (title, table, notes) should be inserted in the manuscript directly after the first paragraph in which it is mentioned. As tables must be editable, images are not acceptable. To aid readability in both the online and .pdf versions of the article, portrait-oriented tables are preferred whenever possible (https://www.eurosurveillance.org/for-authors).
We have checked that the tables are directly after the first paragraph in which they are mentioned, they each have titles and notes. They are in portrait orientation wherever possible.

- If you present numbers with percentages in Tables, the percentages need to be in a Table column separate from the numbers. When the sample size is small (less than 60), we would not generally give percentages as they are subject to disproportional change with increasing or decreasing numerator and static denominator. The tables should not have any empty cells as design element or because information is not available (NA can be used for example).
None of the tables contain percentages. We have removed empty cells from tables.

- Figures must be provided in an editable format, i.e. we need to be able to edit text inside the figure (see our instructions for authors: http://www.eurosurveillance.org/for-authors).
The formatting guidelines in the link provided note that: "Figures should always be provided as vector files (.pdf, .eps, .wmf, .emf, .svg) and should not include bitmap elements (i.e. a map as a picture in the background)." We have provided ours as a pdf, exported directly from the programme in which the figure was created. However, the software used means the figures are not editable. All figures are Supplementary Figures, so perhaps they do not need to be editable? Please advise.

- The supplement files should be headed with a short descriptive title and contain the requested disclaimer at the top (https://www.eurosurveillance.org/for-authors).
All the supplementary files contain a short descriptive title and the disclaimer at the top.

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Supplementary material (excluding author information)

CHEERS checklist—Items to include when reporting economic evaluations of health interventions

Section/item	Item No	Recommendation	Reported on page No/ line No
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	Page 1
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	Pages 2-3
Background and objectives	3	Provide an explicit statement of the broader context for the study.	Page 4
		Present the study question and its relevance for health policy or practice decisions.	Page 5
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	Page 9
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	Pages 4, 5, 9 and 10,
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	Pages 12-14
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	Pages 5-10
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	Pages 10 and 24
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	Page 10
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	Pages 1, 9-10, 14
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	Pages 10-11
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	N/A
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate	Pages 12-14, Supplementary Table

Section/item	Item No	Recommendation	Reported on page No/ line No
		resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	S3
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	Pages 12-14, Supplementary Table S3
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	Pages 23-24
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	Pages 6, 9, 11, 24-25, Supplementary Table S1
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	Pages 9, 14, Supplementary Table S4
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	Tables 1 and 2 Supplementary Tables S3 and S4
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	Pages 15-23 Tables 3 and 4 Supplementary Tables S5-S7 Supplementary Figures S2-S6
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	Pages 14, 22 -26 Supplementary Figure S2-S6
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects that are not reducible by more information.	Pages 15, 18, 22, 23, 26
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	Pages 23-27

Section/item	Item No	Recommendation	Reported on page No/ line No
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	Title page
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	Title page

For consistency, the CHEERS statement checklist format is based on the format of the CONSORT statement checklist