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Developing a model to predict individualised treatment for gonorrhoea: a modelling study

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ABSTRACT

Objective To develop a tool predicting individualised treatment for gonorrhoea, enabling treatment with previously recommended antibiotics, to reduce use of last-line treatment ceftriaxone.

Design A modelling study.

Setting England and Wales.

Participants Individuals accessing sentinel health services.

Intervention Developing an Excel model which uses participants' demographic, behavioural and clinical characteristics to predict susceptibility to legacy antibiotics. Model parameters were calculated using data for 2015–2017 from the Gonococcal Resistance to Antimicrobials Surveillance Programme.

Main outcome measures Estimated number of doses of ceftriaxone saved, and number of people delayed effective treatment, by model use in clinical practice. Model outputs are the predicted risk of resistance to ciprofloxacin, azithromycin, penicillin and cefixime, in groups of individuals with different combinations of characteristics (gender, sexual orientation, number of recent sexual partners, age, ethnicity), and a treatment recommendation.

Results Between 2015 and 2017, 8013 isolates were collected: 64% from men who have sex with men, 18% from heterosexual men and 18% from women. Across participant subgroups, stratified by all predictors, resistance prevalence was high for ciprofloxacin (range: 11%–51%) and penicillin (range: 6%–33%). Resistance prevalence for azithromycin and cefixime ranged from 0% to 13% and for ceftriaxone it was 0%. Simulating model use, 88% of individuals could be given cefixime and 10% azithromycin, saving 97% of ceftriaxone doses, with 1% of individuals delayed effective treatment.

Conclusions Using demographic and behavioural characteristics, we could not reliably identify a participant subset in which ciprofloxacin or penicillin would be effective. Cefixime resistance was almost universally low; however, substituting ceftriaxone for near-uniform treatment with cefixime risks re-emergence of resistance to cefixime and ceftriaxone. Several subgroups had low azithromycin resistance, but widespread azithromycin monotherapy risks resistance at population level. However, this dataset had limitations; further exploration of individual characteristics to predict resistance to a wider range of legacy antibiotics may still be appropriate.

Strengths and limitations of this study

- ► Model predicts individual susceptibility to legacy antibiotics for gonorrhoea and provides treatment recommendation.
- ► Estimates number of doses of last-line treatment ceftriaxone saved if model used in clinical practice.
- ► Uses contemporary surveillance data on antibiotic resistance.
- ► Simple, user-friendly Excel model could be updated with more recent surveillance data or additional risk factors.
- ► Small sample sizes limited the choice and number of risk factors in the model and the reliability of prevalence estimates used.

INTRODUCTION

Gonorrhoea is the second most common bacterial sexually transmitted infection (STI) diagnosed in the UK. In 2018, 56 259 diagnoses were reported in England, which is 26% more than in 2017.[1 2] If untreated, gonorrhoea can lead to urethritis, cervicitis, pelvic inflammatory disease and infertility.[3 4] *Neisseria gonorrhoeae* has developed resistance to all antibiotics previously used to treat it.[3 5] From sulfonamides, penicillin, tetracycline, azithromycin and ciprofloxacin to cefixime, the bacterium has become resistant to each new treatment in turn, including, in rare cases, to current and last-line treatment ceftriaxone.[6 7] In the UK, individuals diagnosed with gonorrhoea are prescribed 1 g of ceftriaxone administered by intramuscular injection; in other countries, dual therapy of ceftriaxone (250–500 mg) with oral azithromycin (1–2 g) is recommended.[8–10]

The Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP), a sentinel surveillance scheme, has been monitoring antimicrobial resistance (AMR) in *N. gonorrhoeae* in England and Wales since 2000 (figure 1).[8 11] Several cases of ceftriaxone-resistant gonorrhoea have been reported as

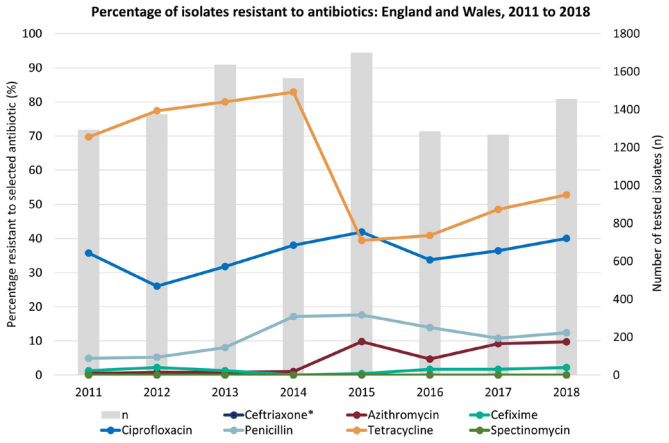

Figure 1 Trends in gonococcal antibiotic resistance, 2011–2018. Data extracted from Public Health England.[8] *The percentage of isolates resistant to ceftriaxone was 0% from 2011 to 2018.

well as an increase in the proportion of isolates with a higher minimum inhibitory concentration (MIC) for ceftriaxone, indicating a reduction in sensitivity to the antibiotic. over time, this upwards drift in MIC is likely to result in ceftriaxone resistance.[8 12 13]

Given the reduction in sensitivity to ceftriaxone and multiple reports of treatment failure, alternative treatment strategies should be considered to prepare for the emerging threat of ceftriaxone resistance.[8 12] This could involve treating cases with previously recommended antibiotics to prolong the lifetime of ceftriaxone as an effective treatment. Current therapy with ceftriaxone tends to be based empirically rather than on individual isolate susceptibility, often because no culture result is available at the time of treatment; this approach assumes all infections are resistant to previous treatments, which in most cases is untrue.[2] In addition, resistance prevalence for some legacy antibiotics has decreased as their usage has decreased, for example, for cefixime. The prevalence of AMR is also likely to vary in different subgroups of individuals. For example, antibiotic-susceptible strains are thought to be circulating in low-risk groups, such as those who are less likely to be exposed to antibiotics.[14] This means many people who are currently treated with last-line therapy could potentially be treated with legacy antibiotics.[7 14]

This study aimed to develop an Excel model predicting susceptibility to legacy antibiotics, based on individual demographic, behavioural and clinical characteristics. This could enable individualised treatment of gonorrhoea with legacy antibiotics for people with a very low estimated risk of resistance. GRASP data were used to estimate the prevalence of AMR in different groups of individuals, attempting to identify groups with a very low prevalence of AMR through an exploratory approach. These estimates were fed into the model, which provides the individual's risk of AMR and a recommended treatment option. Using the tool in clinical practice to guide treatment could reduce the number of doses of ceftriaxone given and preserve its use for strains requiring last-line therapy. This could prolong the lifetime of ceftriaxone as an effective antibiotic by reducing selection pressure and delaying the emergence of resistance.

METHODS

Data sources

The study used pseudonymised, individual-level data from the GRASP surveillance dataset, between 2015 and 2017. The GRASP programme involves collecting clinical isolates from consecutive patients diagnosed with gonorrhoea each year between July and September, from sentinel sexual health clinics in England and Wales. The isolates are tested for antimicrobial susceptibility and MICs are recorded. The data are matched to demographic, clinical and behavioural characteristics submitted by the clinics.[12 15] The Diagnostic Sensitivity Test agar, the medium used by GRASP for susceptibility testing of isolates, was changed in 2015; this affected the MICs for azithromycin and tetracycline.[16 17] To avoid difficulties interpreting data from across this period, we used data from 2015 onwards.

Data analysis

We explored the association between participant characteristics and AMR to decide which risk factors to include in the model. GRASP data extraction and analyses were conducted in STATA V.13. This study used the MIC thresholds chosen by GRASP to define gonococcal resistance, which align with the breakpoints used by the European Committee on Antimicrobial Susceptibility (EUCAST) in 2018. (table 1)[16 18] It is worth noting that the EUCAST breakpoint for azithromycin has since been replaced with an epidemiological cut-off value of 1.0 mg/L, but the previous breakpoint of 0.5 mg/L has been retained in GRASP reports for continuity.[19 20] We investigated risk factors which have been shown or are suspected to be associated with reduced antimicrobial susceptibility: for example, men who have sex with men (MSM) have been found to have higher rates of AMR than heterosexual men, bearing in mind that there may not always be truthful disclosure of sexual orientation in healthcare settings.[14 21 22] Other characteristics such as age and gender have also been proposed as a risk factors associated with

Table 1 Breakpoints used to define antimicrobial resistance

Antimicrobial	Resistance definition (MIC)
Ceftriaxone	>0.125 mg/L
Azithromycin	>0.5 mg/L
Cefixime	>0.125 mg/L
Ciprofloxacin	>0.06 mg/L
Penicillin	>1 mg/L

MIC, minimum inhibitory concentration.

resistance.[14] Overall, we investigated the characteristics: gender, sexual orientation, age, ethnicity and number of recent sexual partners (within the previous 3 months), as well as HIV status, previous gonorrhoea and concurrent STIs, and their correlation with each other. We conducted logistic regression to determine ORs for the associations between antibiotic resistance and participant characteristics. Stratified analysis was conducted to obtain estimates of the prevalence of resistance in subgroups of individuals with different combinations of the characteristics found to be associated with resistance.

We chose to investigate resistance to the antibiotics ciprofloxacin, azithromycin, penicillin and cefixime, as they have all been previously recommended to treat gonorrhoea, and resistance to each is well described in the GRASP dataset. Although azithromycin is used alongside ceftriaxone as first-line therapy worldwide, this is not currently recommended in the UK; therefore, we classed azithromycin as a legacy antibiotic.

Model

We developed a user-friendly model in Microsoft Excel (2016 version) to predict individualised treatment for gonorrhoea. It consists of an input table to enter individual characteristics; a lookup table containing estimates of the prevalence of resistance derived from GRASP data; and an output table providing the risk of resistance to multiple antibiotics and a recommended treatment. We developed the treatment recommendation algorithm based on the WHO guidelines.[23]

Simulation

We estimated the impact of using the tool in clinical practice in a hypothetical population, estimating the number of doses of ceftriaxone saved and number of people delayed effective treatment. We incorporated the predicted outcome at test-of-cure (TOC) at the 2-week follow-up consultation recommended in BASHH treatment guidelines.[4] We assumed that the treatment failure rate was equal to the estimated risk of resistance for that subgroup, and that if treatment was found to be unsuccessful after the TOC, the individual would then be prescribed ceftriaxone. We estimated the total number of doses of ceftriaxone saved by calculating the doses saved initially by prescribing legacy antibiotics instead of ceftriaxone, minus doses of ceftriaxone given at follow-up if treatment was unsuccessful. Other assumptions were that treatment failure was only due to resistance, rather than other factors such as non-adherence; there was no re-infection; and all individuals attended follow-up.

We simulated use of the model at the 5% threshold as the highest acceptable risk of resistance in a legacy antibiotic for it to be prescribed, as well as at the 10% and 20% thresholds as a sensitivity analysis to explore a less cautious approach. We also repeated the simulation using the upper and lower bounds of the CIs for the estimates of the risk of resistance in each subgroup, allowing us to investigate the impact of a higher or lower prevalence of resistance than predicted. For groups in which the prevalence of resistance was estimated to be zero, the lower bound was taken to be 0, and a value of 0.25 was selected as the upper bound, based on a similar approach used in other studies.[24]

Patient and public involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

RESULTS

Sample characteristics

Between 2015 and 2017, 8013 isolates were collected by GRASP, along with characteristics such as gender and sexual orientation, and tested for antimicrobial susceptibility. Isolates were collected from 29 free at the point of use, specialist sexual health clinics across England and Wales.[8] The average number of samples submitted by each clinic was 276, ranging from 18 to 1567 samples per clinic. In total, 63.5% of isolates were from MSM, 18.4% were from heterosexual men and 18.1% were from heterosexual women. Overall, 39.5% of isolates were resistant to ciprofloxacin; 8.2% to azithromycin; 14.1% to penicillin; and 1.2% to cefixime. Data cleaning was conducted prior to analysis: for the 8494 recorded observations, there were 8014 attendances where both patient information and isolates were collected; removing a duplicated observation left 8013 observations remaining. Clinic re-attendance was explored during analysis, identified by duplication of clinic-specific patient ID codes with different accompanying information, for example dates of visit. A total of 8013 clinic attendances occurred in 7765 individuals, due to re-attendance. In total, 224 people attended the same clinic twice (2.9%); 12 people attended the same clinic three times (0.2%). The remaining 7529 people did not re-attend (97.0%). Re-attendances were not removed from analysis but retained, acting as separate treatment episodes. Cases where the same people attended different clinics could not be identified as patient ID codes were clinic specific.

Relationships between risk factors and antibiotic resistance

We explored associations between individual characteristics and AMR to determine which variables should be included in the model, using GRASP surveillance data from 2015 to 2017. We combined gender and sexual orientation into a single variable grouped into women, heterosexual men and MSM; this was due to very low numbers of women identifying as bisexual or homosexual. We could not conduct logistic regression for certain variables, for example, concurrent STIs, due to missing data.

The odds of AMR, calculated with univariate ORs, were greater in men than women for all antibiotics, and greater in MSM than heterosexual men for all antibiotics except cefixime, for which MSM had significantly reduced odds of resistance (OR 0.24, 95% CI 0.11–0.50, p=0.000)

(table 2). The odds of AMR were greater in older than younger individuals for all antibiotics except cefixime, where older individuals had lower odds. The same pattern was observed for ethnicity: white individuals had higher odds of AMR for all antibiotics except cefixime. Having more than two recent sexual partners was associated with greater odds of ciprofloxacin resistance and reduced odds of resistance to azithromycin, penicillin or cefixime.

Subgroup-specific analysis

We conducted stratified analysis to estimate the prevalence of resistance in participant subgroups based on combinations of risk factors associated with AMR: age, number of sexual partners in the previous 3 months, gender, sexual orientation and ethnicity (figure 2). These variables were chosen because of their association with higher or lower prevalence of AMR. We also described the correlation of these variables with each other (online supplemental table A1). High levels of missing data for variables such as HIV status and previous gonorrhoea infection prohibited their inclusion in stratified analysis.[12] Notably, the variable for the site of infection (eg, urethral, cervical or pharyngeal) was not included in the model as it was missing or unknown for 41% of observations in the dataset; the variable for geographic region was also excluded as it was missing for 64% of observations (online supplemental tables A2 and A3). Some variables were converted to binary variables for the stratified analysis, as including more categories led to low numbers of individuals per stratum. The cut-off points chosen for binarisation were aimed to be discriminatory, resulting in a large difference in the prevalence of AMR between groups, while remaining clinically relevant. Therefore, the cut-offs chosen were as follows: number of partners (<2 or ≥2 partners), age (<25 or ≥25 years), ethnicity (white or other). Importantly, missing data and low numbers of individuals per stratum limited the choice and number of variables included in the stratified analysis. Of 8494 total sample observations, 4944 were included in the stratified analysis (58.2%).

Estimates of the prevalence of resistance were obtained for 24 different participant groups. For ciprofloxacin, resistance was high in all groups, with a median of 31.6%, varying from 11.1% to 54.1%; resistance was lowest in women with at least two recent sexual partners, at least 25 years old and of non-white ethnicity (table 3, figure 2). For azithromycin, the median resistance prevalence was 6.2%, with a maximum value of 12.7%. Five groups (6.3% of participants) had no recorded azithromycin resistance, while multiple groups had a prevalence of resistance less than 5%, the WHO treatment threshold (which made up 18.3% of participants included in the model).[9] For penicillin, resistance was relatively high, with a median of 13.5%; this varied from 5.8% to 33.3% and never fell below the 5% recommended WHO limit, and was lowest in women with at least two recent sexual partners, younger than 25 and of white ethnicity. For cefixime, the median resistance prevalence was 1.9%; nine subgroups had no recorded resistance (making up 33.7% of participants). The highest level of cefixime resistance recorded was 13.3%; otherwise, the estimated prevalence of cefixime resistance was almost universally low. In total, 96.3% of participants fell into groups with an estimated prevalence of cefixime resistance below 5%.

Developing the model

We developed the model as an Excel spreadsheet allowing the input of individual characteristics and providing an output of their predicted risk of resistance to ciprofloxacin, azithromycin, penicillin and cefixime and a treatment recommendation of the lowest-risk antibiotic. The model (Model, online supplemental file) and user guide (Model—user guide, online supplemental file 1) are available as additional files. We developed the recommended treatment algorithm such that if the estimated risk of resistance to an older antibiotic is 5% or less, this antibiotic will be recommended instead of ceftriaxone. This is based on WHO guidelines specifying that a treatment should only be recommended if the chance of success is at least 95%.[23] The threshold used in the model is modifiable to suit the user's judgement.

Simulation of the impact of the model

We simulated the impact of the model if used in routine clinical practice with a hypothetical population of 50 000 individuals diagnosed with gonorrhoea, based on the PHE annual STI data tables for 2018, assumed to have the same distribution of characteristics as the sample included in stratified analysis.[1] We estimated that, using the tool at the 5% resistance threshold for recommending an antibiotic, 98.5% of people (49 252) attending GUM clinics with gonorrhoea could be treated initially with cefixime or azithromycin instead of ceftriaxone (table 4). The prevalence of ciprofloxacin and penicillin resistance was too high for any groups to be treated with these agents. Only heterosexual men aged under 25 years with fewer than two recent sexual partners, of white ethnicity, would be initially given ceftriaxone. Treatment would be unsuccessful for 1.0% of people (519), who would then be prescribed ceftriaxone at follow-up, meaning the cure rate with the model is estimated at 99.0%. This leads to an overall value of 97.47% of doses of ceftriaxone saved (48 733). We repeated this analysis at the 10% and 20% thresholds for antibiotic recommendation to estimate the impact of less cautious approach to prescribing legacy antibiotics; this could save more doses of ceftriaxone, but risks more people being delayed effective treatment due to resistance. At the 10% and 20% levels, all individuals were initially treated with cefixime or azithromycin, as the risk of resistance to these antibiotics was always estimated to be lower than resistance to ciprofloxacin and penicillin. Overall, 98.8% of doses of ceftriaxone (49 422) were saved, while 1.2% of people (578) were delayed effective treatment (cure rate 98.8%). We also repeated the simulation using the upper and lower bounds of the CIs for the estimates of resistance prevalence (table 4),

Table 2 Table showing crude ORs of resistance to ciprofloxacin, azithromycin, penicillin and cefixime for different patient characteristics

	Ciprofloxacin resistance				Azithromycin resistance				Penicillin resistance				Cefixime resistance			
	OR	95% CI	N	P value	OR	95% CI	N	P value	OR	95% CI	N	P value	OR	95% CI	N	P value
Age group																
<25 years old	1				1				1				1			
≥25 years old	1.31*	1.10 to 1.55	2965	0.002	1.05	0.81 to 1.34	4297	0.729	1.07	0.88 to 1.30	4306	0.501	0.58	0.33 to 1.02	4296	0.059
Ethnic group																
Not white	1				1				1				1			
White	1.32*	1.11 to 1.57	2783	0.002	1.48*	1.12 to 1.96	3938	0.006	1.07	0.88 to 1.32	3947	0.493	0.89	0.46 to 1.70	3947	0.718
No of partners in previous 3 months																
<2 partners	1				1				1				1			
≥2 partners	1.2	0.98 to 1.47	1759	0.076	0.8	0.59 to 1.08	2589	0.139	0.98	0.78 to 1.23	2595	0.872	0.52	0.26 to 1.03	2595	0.062
Gender and sexual orientation																
Female	1				1				1				1			
Heterosexual male	2.10*	1.53 to 2.87	2901	0	1.71*	0.03 to 1.05	4167	0.032	1.68*	1.19 to 2.38	4175	0.003	1.2	0.58 to 2.45	4174	0.627
MSM	2.68*	2.04 to 3.50	2901	0	1.88*	0.00 to 1.22	4167	0.004	1.42*	1.05 to 1.93	4175	0.025	0.24*	0.11 to 0.50	4174	0
HIV status																
Negative	1				1				1				1			
Positive	1.23*	1.01 to 1.50	2145	0.036	0.99	0.73 to 1.35	2936	0.953	1.26	1.00 to 1.59	2945	0.051	0.09*	0.01 to 0.67	2945	0.018
Previous gonorrhoea																
No	1				1				1				1			
Yes	1.10*	0.92 to 1.31	2856	0.287	1	0.76 to 1.32	4059	0.982	1.09	0.88 to 1.34	4068	0.442	0.61	0.27 to 1.37	4068	0.233

*Indicates p value below 0.005.
MSM, men who have sex with men.

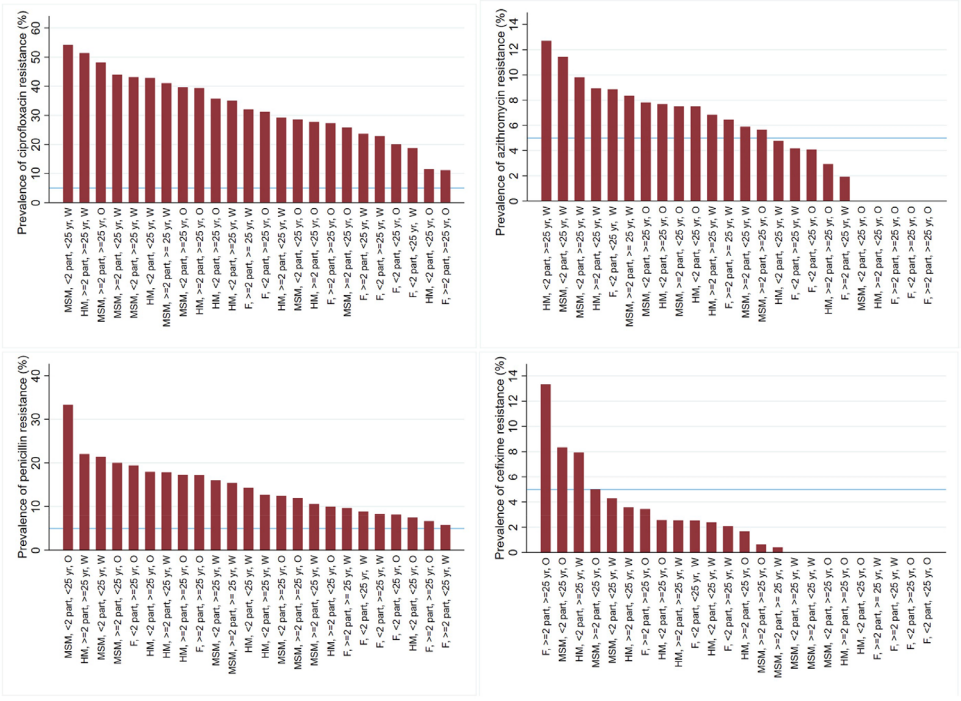

Figure 2 Graphs showing the variation in the prevalence of antibiotic resistance in different patient subgroups. The blue line represents the 5% resistance threshold, below which the antibiotic can be recommended. HM, heterosexual male; MSM, men who have sex with men.

investigating the impact of uncertainty in the prevalence estimates. Using the lower bound (assuming resistance prevalence is lower than predicted), with 5%, 10% or 20% treatment thresholds, 99.7% (49 844) of doses of ceftriaxone were saved. Using the upper bound, with a 5% threshold, 73.4% (36,700) doses of ceftriaxone were saved. This rose to 83.9% at the 10% level and 96.2% at the 20% level.

DISCUSSION

Statement of principal findings

In this study, we developed a model predicting individual susceptibility to antibiotics based on patient characteristics associated with resistance: gender, sexual orientation, age, ethnicity and number of recent sexual partners. This was achieved by calculating estimates of the prevalence of resistance in different participant subgroups, using GRASP data. We estimated that resistance to ciprofloxacin and penicillin was too high for treatment in all groups, never dropping below 11.1% for ciprofloxacin or 5.8% for penicillin.[23] For cefixime and azithromycin, the estimated prevalence of resistance was lower, estimated to be below the WHO 5% treatment recommendation threshold for patients groups making up 96.3% of individuals (cefixime) or 18.3% (azithromycin).

The model could be a novel method of rapidly establishing individual susceptibility to a range of antibiotics, by using population-level data to predict individual susceptibility. However, use of the tool in practice would depend on the prevalence of resistance being sufficiently varied between groups to enable heterogenous antibiotic prescription. If AMR was predicted to be universally low and all participants were prescribed one legacy antibiotic, resistance could rapidly re-emerge. If AMR was universally high, no legacy antibiotics would be prescribed, and the situation would be unchanged. Ideally, a minority of small groups of individuals could be safely treated with a range of different legacy antibiotics without prompting the rapid return of resistance to any one antibiotic. When we simulated routine use of the model in clinical practice, we estimated that 97.5% of doses of ceftriaxone could be saved by treating people almost universally with cefixime (88.2% of participants) or azithromycin (10.3%). However, substituting ceftriaxone for cefixime in the majority of patients would be undesirable as it could prompt the return of widespread cefixime resistance and potentially also select for ceftriaxone resistance, while widespread use of azithromycin monotherapy also risks the return of azithromycin resistance.[25] Therefore, the analysis suggests that there may not be enough variation in patient susceptibility to these antibiotics for this approach to be feasible in the current context.

Strengths and weaknesses of the study

We derived model parameters from contemporary data on antibiotic resistance and individual characteristics in England and Wales. The GRASP dataset is considered to have robust methodology for determining AMR and provides a valuable resource in combining resistance data with a variety of individual characteristics.[12 15] This study uses a simple, user-friendly Excel tool to predict treatment. The tool could be modified to be updated with more recent resistance data, different risk factors

Table 3 Patient subgroups included in stratified analysis, stratified by gender and sexual orientation, number of recent partners, age and ethnicity, sorted by the size of subgroup

	Number of individuals (n=4944)		Ciprofloxacin (n=1648)			Azithromycin (n=2430)			Penicillin (n=2436)			Cefixime (n=2436)		
Description	N	%	Res (%)	95% CI	N	Res (%)	95% CI	N	Res (%)	95% CI	N	Res (%)	95% CI	N
Female, <2 partners, <25 yr, other	156	3.2	20	9.3 to 38.0	30	4.1	1.0 to 14.9	49	8.2	3.1 to 19.8	49	0	0.0 to 0.0	49
Female, <2 partners, <25 yr, white	207	4.2	18.8	10.1 to 32.3	48	8.9	4.3 to 17.4	79	8.9	4.3 to 17.5	79	2.5	0.6 to 9.6	79
Female, <2 partners, ≥25 yr, other	88	1.8	31.3	13.6 to 56.7	16	0	0.0 to 0.0	36	19.4	9.6 to 35.5	36	0	0.0 to 0.0	36
Female,<2 partners, ≥25 yr, white	169	3.4	22.9	11.9 to 39.5	35	4.2	1.0 to 15.2	48	8.3	3.2 to 20.2	48	2.1	0.3 to 13.4	48
Female, ≥2 partners, <25 yr, other	68	1.4	27.3	12.8 to 49.0	22	0	0.0 to 0.0	29	17.2	7.4 to 35.3	29	3.5	0.5 to 20.8	29
Female, ≥2 partners, <25 yr, white	146	3	23.7	12.8 to 39.6	38	1.9	0.3 to 12.4	52	5.8	1.9 to 16.4	52	0	0.0 to 0.0	52
Female, ≥2 partners, ≥25 yr, other	39	0.8	11.1	1.5 to 50.0	9	0	0.0 to 0.0	15	6.7	0.9 to 35.2	15	13.3	3.4 to 40.6	15
Female, ≥2 partners, ≥25 yr, white	97	2	32	16.9 to 52.2	25	6.5	1.6 to 22.4	31	9.7	3.2 to 26.1	31	0	0.0 to 0.0	31
HM, <2 partners, <25 yr, other	91	1.8	11.5	3.8 to 30.3	26	7.5	2.4 to 20.8	40	7.5	2.4 to 20.8	40	0	0.0 to 0.0	40
HM, <2 partners, <25 yr, white	74	1.5	42.9	26.2 to 61.3	28	4.8	1.2 to 17.2	42	14.3	6.6 to 28.4	42	2.4	0.3 to 15.1	42
HM, <2 partners, ≥25 yr, other	143	2.9	35.7	22.8 to 51.1	42	7.7	3.5 to 16.1	78	18	10.9 to 28.1	78	2.6	0.6 to 9.7	78
HM, <2 partners, ≥25 yr, white	142	2.9	35	21.9 to 50.8	40	12.7	6.5 to 23.4	63	12.7	6.5 to 23.4	63	7.9	3.3 to 17.7	63
HM, ≥2 partners, <25 yr, other	119	2.4	27.8	15.6 to 44.4	36	0	0.0 to 0.0	60	10	4.6 to 20.5	60	1.7	0.2 to 10.9	60
HM, ≥2 partners, <25 yr, white	121	2.5	29.3	17.4 to 44.8	41	8.9	3.8 to 19.7	56	17.9	9.9 to 30.1	56	3.6	0.9 to 13.2	56
HM, ≥2 partners, ≥25 yr, other	181	3.7	39.3	28.0 to 52.0	61	2.9	1.0 to 8.7	102	17.3	11.2 to 25.8	104	0	0.0 to 0.0	104
HM, ≥2 partners, ≥25 yr, white	213	4.3	51.4	40.1 to 62.5	74	6.8	3.5 to 13.1	117	22	15.5 to 30.4	118	2.5	0.8 to 7.6	118
MSM, <2 partners, <25 yr, other	33	0.7	28.6	7.2 to 67.4	7	0	0.0 to 0.0	12	33.3	13.1 to 62.4	12	8.3	1.2 to 41.3	12

Continued

Table 3 Continued

Description	Number of individuals (n=4944)		Ciprofloxacin (n=1648)			Azithromycin (n=2430)			Penicillin (n=2436)			Cefixime (n=2436)		
	N	%	Res (%)	95% CI	N	Res (%)	95% CI	N	Res (%)	95% CI	N	Res (%)	95% CI	N
MSM, <2 partners, <25 yr, white	124	2.5	54.2	40.1 to 67.6	48	11.4	5.8 to 21.2	70	21.4	13.4 to 32.6	70	4.3	1.4 to 12.5	70
MSM, <2 partners, ≥25 yr, other	121	2.5	39.6	26.9 to 53.9	48	7.8	3.3 to 17.4	64	12.5	6.4 to 23.1	64	0	0.0 to 0.0	64
MSM, <2 partners, ≥25 yr, white	545	11	43.2	36.3 to 50.3	190	9.8	6.8 to 13.9	275	16	12.1 to 20.8	275	0	0.0 to 0.0	275
MSM, ≥2 partners, <25 yr, other	86	1.7	25.8	13.5 to 43.8	31	7.5	2.4 to 20.8	40	20	10.3 to 35.2	40	5	1.3 to 17.9	40
MSM, ≥2 partners, <25 yr, white	289	5.9	44	35.2 to 53.1	116	5.9	3.2 to 10.6	170	10.6	6.8 to 16.2	170	0	0.0 to 0.0	170
MSM, ≥2 partners, ≥25 yr, other	329	6.7	48.2	38.9 to 57.5	108	5.7	3.0 to 10.5	159	12	7.8 to 18.0	159	0.6	0.1 to 4.3	159
MSM, ≥2 partners, ≥25 yr, white	1363	27.6	41	36.9 to 45.3	529	8.3	6.6 to 10.6	743	15.4	13.0 to 18.2	746	0.4	0.1 to 1.2	746
Mean			32.7			5.6			14.4			2.5		
Median			31.7			6.2			13.5			1.9		

HM, heterosexual male; MSM, men who have sex with men; Partners, number of partners in the previous 3 months; 25 yr, refers to 25 years of age.

Table 4 Simulation of the impact of using the Excel tool in practice, using the baseline, lower bound and upper bound of the CIs for the estimated prevalence of resistance in each patient subgroup

		Initial treatment		Follow-up		Overall	
		N	%	N	%	N	%
Baseline							
5% Level	Ceftriaxone given	748	1.5	519	1.04	1267	2.53
	Doses saved	49252	98.5	49481	98.96	48733	97.47
	Cefixime	44094	88.19				
	Azithromycin	5158	10.52				
10% Level	Ceftriaxone given	0	0	578	1.16	578	1.16
	Doses saved	50000	100	49422	98.84	49422	98.84
	Cefixime	44842	89.68				
	Azithromycin	5158	10.32				
20% Level	Ceftriaxone given	0	0	578	1.16	578	1.16
	Doses saved	50000	100	49422	98.84	49422	98.84
	Cefixime	44842	89.68				
	Azithromycin	5158	10.32				
Lower bound of CI							
5% Level	Ceftriaxone given	0	0	156	0.31	156	0.31
	Doses saved	50000	100	49844	99.69	49844	99.69
	Cefixime	46491	92.98				
	Azithromycin	3509	7.02				
10% Level	Ceftriaxone given	0	0	156	0.31	156	0.31
	Doses saved	50000	100	49844	99.69	49844	99.69
	Cefixime	46491	92.98				
	Azithromycin	3509	7.02				
20% Level	Ceftriaxone given	0	0	156	0.31	156	0.31
	Doses saved	50000	100	49844	99.69	49844	99.69
	Cefixime	46491	92.98				
	Azithromycin	3509	7.02				
Upper bound of CI							
5% Level	Ceftriaxone given	12935	25.87	365	0.73	13300	26.6
	Doses saved	37065	74.13	49635	99.27	36700	73.4
	Cefixime	33556	67.11				
	Azithromycin	3509	7.02				
10% Level	Ceftriaxone given	7241	14.48	819	1.64	8060	16.12
	Doses saved	42759	85.52	49181	98.36	41940	83.88
	Cefixime	39250	78.5				
	Azithromycin	3509	7.02				
20% Level	Ceftriaxone given	0	0	1888	3.78	1888	3.78
	Doses saved	50000	100	48112	96.22	48112	96.22
	Cefixime	46491	92.98				
	Azithromycin	3509	7.02				

Follow-up, follow-up consultation 2 weeks after initial treatment.

or other antibiotics. The ability to modify the resistance threshold for prescribing an antibiotic makes the tool more versatile and acceptable. This simple approach to stratifying treatment based on individual characteristics is transferable and could be applied to the management of other infectious diseases, for example urinary

tract infections, provided that high-quality, reliable data are available on the trends of AMR among that population.[5 26] More broadly, an individualised approach to antibiotic prescribing could lead to increased heterogeneity of treatments given, lessening the selection pressure on the emergence of resistance to last-line therapy.[6]

Oversampling of some groups in the GRASP dataset may be associated with differences in the prevalence of resistance between participant groups. For example, MSM are more likely to present for treatment at sentinel sites and are a higher-risk group for AMR; this could lead to overestimating the prevalence of resistance in our sample.[15] In addition, small sample sizes were used to obtain subgroup-specific resistance estimates. This is partly because the GRASP dataset was restricted to 3 years of data (2015–2017) due to a change in the medium used for susceptibility testing for some antibiotics in 2015. A smaller dataset and high levels of data non-response for some variables limited the choice and number of risk factors included in the model, due to low numbers of individuals per stratum, which reduces the reliability of the prevalence estimates used. For example, the site of sample origin (such as urethral, cervical or pharyngeal) was not included in the model due to a large amount of missing data for this variable. This may limit the model as infections are known to be more likely to harbour resistance; they can also be more difficult to treat and require ceftriaxone treatment regardless.[4 27 28] Similarly, because only a limited number of variables could be included in the model, this simple approach predicted individual susceptibility based on broad individual categories, which may not be the most acceptable or accurate approach. More broadly, re-introducing old antibiotics could increase the selection pressure for AMR, even if the study aimed to re-introduce these antibiotics conservatively. The simulation may not fully represent the real impact of the tool due to assumptions such as no loss-to-follow-up and no contraindications for any antibiotics.[29]

Strengths and weaknesses in relation to other studies

To enable individualised treatment, other studies have focused on biochemical techniques, such as nucleic acid amplification tests (NAATs), rather than mathematical modelling.[6] Rapid NAAT point-of-care tests are being developed to quickly determine the presence of *N. gonorrhoeae* in clinical isolates and its susceptibility to multiple antibiotics, based on the presence or absence of molecular markers associated with resistance. This could facilitate rapid individualised treatment by providing results within 90 min.[7 30–33] For example, molecular assays can accurately determine resistance to ciprofloxacin by detecting alterations at the gonococcal *GyrA S91* locus, which account for most ciprofloxacin resistance.[34 35] The modelling approach might be less acceptable than biochemical techniques as it relies on population-level assumptions about individual resistance, rather than using specimens from the individuals themselves. However, mathematical modelling could be cheaper, less technically difficult and more applicable worldwide than biochemical techniques as it does not require specialised equipment, only a simple Excel model which provides information instantaneously, provided that local GRASP-like surveillance data are available.[3 36] Other molecular approaches include the use of whole genome sequencing (WGS). Predictive modelling and machine learning algorithms have been developed to predict resistance phenotype from the genetic sequence of *N. gonorrhoeae*.[33 37 38] While this approach incorporates more complex and diverse mechanisms of resistance than NAATs, it is not completely accurate at predicting individual susceptibility.[33 39] Other studies have investigated repurposing older antibiotics or those used for other diseases, such as gentamicin and aztreonam, as widespread gonococcal resistance has not emerged to these treatments.[25 40 41] However, they are unlikely to be recommended as first-line treatments soon due to lower efficacy or a lack of evidence for clinical efficacy. Although resistance has previously emerged to the antibiotics investigated in this study, as previous first-line treatments they are well studied and known to be effective for susceptible infections.[42]

Meaning of the study

In this study, we developed a simple, user-friendly model for predicting individualised treatment for gonorrhoea, which if implemented in practice could enable use of legacy antibiotics in susceptible infections instead of last-line treatment ceftriaxone, which could prolong its effective lifetime. This is in line with UK national strategy on AMR, which aims to optimise use of antibiotics and preserve last-line therapies.[43] However, we found that antibiotic resistance may not be varied enough between participant groups for heterogenous prescription of antibiotics, which is essential for the approach to be feasible. The prevalence of ciprofloxacin and penicillin resistance was too high to permit treatment, while cefixime resistance was found to be universally low across groups. However, our model recommends that almost everyone be treated with cefixime, which would likely lead to the re-emergence of resistance. Nonetheless, treating a minority of individuals with cefixime could be feasible. Azithromycin resistance was potentially varied enough between groups to facilitate heterogenous treatment; azithromycin monotherapy is known to effectively treat susceptible *N. gonorrhoeae,* so this could be a potential option for those with a low predicted risk of resistance.[44 45] However, the 2 g dose of azithromycin necessary to avoid the development of resistance can be associated with adverse gastrointestinal side effects.[4 46 47] Furthermore, this preliminary model only recommends antibiotic monotherapy, which has been associated with the spread of resistance. For example, resistance emerged to cefixime and azithromycin in Japan following the use of cefixime and azithromycin monotherapies[5 48 49] Developing a model which can recommend individualised multi-drug therapies, with the help of clinician guidance, could help to reduce the

risk of resistance emerging and make this approach more effective.[7 41]

This preliminary data analysis was to assess whether a tool using routine patient data to guide treatment could be useful and to stimulate further discussion in the context of growing concern about antibiotic resistance. This may also help to support decision-making around the use of new diagnostic tests to detect resistance as these become more commonly available.

Unanswered questions and future research

Future research could investigate using this approach with more robust estimates of the prevalence of resistance. This could be achieved with a larger dataset, potentially by including more years of GRASP data in the future, although using older data may make the model less reflective of the dynamic nature of changing resistance patterns in the population. Alternatively, the model could be used in conjunction with data from other surveillance systems, for example, data from the Genitourinary Medicine Clinic Activity Dataset or the Second Generation Surveillance System.[50–52] The use of regional data could allow sexual networks to be included in the model and provide greater discriminatory value than patient characteristics alone. Using a larger sample size, with data from multiple sources, could result in more robust estimates of the prevalence of resistance in different participant groups. This could help to ascertain whether this approach is feasible in practice. Using a larger dataset could also enable more in-depth stratified analysis, allowing the development of alternative algorithms for determining the best risk factors to include the model, without being limited by small numbers of individuals per stratum. This could facilitate the development of a model with less broad participant categories, with greater distinguishing power, and potentially more accurate predictions for individual susceptibility. In the future, this modelling approach could also be used in conjunction with bioinformatic data from WGS to predict antibiotic susceptibility from genetic information; this aims to link genome sequence data from the gonococcal isolate to predict their phenotypic susceptibility, but is not currently completely accurate at predicting susceptibility.[37 39 53] Molecular assays to detect genetic markers of resistance at the patient level are another available tool which could be combined with a modelling approach.[34 35] Use of a combination of data sources in the model to inform prescribing could result in more nuanced individualised decision-making.

Importantly, future research could explore testing the model in real-life circumstances, including culture and AMR testing of samples, to determine the applicability of the model to clinics in the UK as well as the compliance of clinicians with the predictions of the model, ensuing that any change to prescribing practice was fair and optimised patient treatment. Similar user-friendly tools to predict cancer risk and antibiotic resistance risk using patient characteristics have been acceptable to clinicians provided that the tool is easy to use, quick to complete for each patient and endorsed by clinical bodies.[26 54–56] Surveillance data used in a tool to guide prescribing would also need to be accurate and relevant for the patient population.[57] Further development work with clinicians could help to assess the acceptability of this prescribing approach, any barriers or facilitators to its use, and whether it could feasibly be integrated into clinical practice.

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Ethics approval Permission was obtained to access GRASP surveillance data stored and collected by Public Health England (PHE), under the Data Protection Act (1998) and the STI and HIV Data Sharing Policy. All individual-level data extracted from GRASP were pseudonymised and accessed from a secure PHE laptop and server and were not taken from PHE premises. The GRASP data were used to estimate model parameters which were not considered confidential (for example, the prevalence of antibiotic resistance). Ethical approval for the study was obtained from the University of Bristol Ethics Committee (ID: 87902).

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