Analysis of the potential impact of a point-of-care test to distinguish gonorrhoea cases caused by antimicrobial-resistant and susceptible strains of *Neisseria gonorrhoeae*

Katy ME Turner (1), Hannah Christensen (1), Elisabeth Adams (2), David McAdams (3), Helen Fifer (4), Anthony McDonnell (5), Neil Woodford (4,5)

(1) University of Bristol, (2) Aquarius Population Health, (3) Duke University, (4) Bacteriology Reference Department, National Infection Service, Public Health England, London NW9 5EQ (5) The O'Neill Review on Antimicrobial Resistance, Wellcome Trust, London

Background/rationale

The 70-year history of antibiotics has been marked by the continual and seemingly inevitable rise of antibiotic resistance. Gonorrhoea, a sexually-transmitted bacterial infection, illustrates very well our constant 'battle' to overcome resistant bacteria and so treat drug-resistant infections. Because of the public health importance placed on limiting spread of this infection, a single dose of effective antibiotics should be prescribed empirically and administered at the time patients first present rather than waiting until the results of antibiotic susceptibility tests become available. This first-line prescribing follows national gonorrhoea treatment recommendations, which should be reviewed regularly against surveillance data and changed whenever more than 5% of strains of the causative bacterium, *Neisseria gonorrhoeae* or 'the gonococcus', exhibit resistance to the recommended antibiotic. In consequence, many antibiotics, including penicillin, at ever increasing doses, then tetracycline, ciprofloxacin and cefixime, have been recommended over the past 70 years as effective first-line gonorrhoea treatments, only for them each to be sequentially abandoned and replaced whenever resistant strains of gonococci arose and proliferated to exceed the critical 5% threshold.

We rely on agreed, empirically-prescribed first-line antibiotics, since treatment is usually given prior to the results of susceptibility testing [1]. Currently the recommendation is for 'last resort' dual therapy with injectable ceftriaxone and oral azithromycin, and gonorrhoea is considered internationally to be an urgent priority because resistance to one or both of these agents heralds potentially untreatable infections. Some antibiotics are being developed as future treatments for gonorrhoea, but with no guarantee that they will be licensed. We therefore need also to consider new strategies that will maintain the effectiveness of the ceftriaxone / azithromycin combination.

One such strategy would be to diversify the antibiotic regimens used to treat gonorrhoea and, by so doing, reduce the narrowly-focussed selective pressures for resistance to which gonococci have been repeatedly exposed. This could be achieved either (i) by having several equally-effective antibiotics in use for reliable empiric treatment, rather than a single recommended regimen, or (ii) by tailoring treatment of individuals to the susceptibility of the strain(s) causing their infection. This second option requires access to innovative, rapid point-of-care diagnostic tests, which don't currently exist, but which would potentially allow abandoned first-line treatments to be re-introduced for those patients with infections that are susceptible to these drugs. For instance, 70% of gonorrhoea cases in the United Kingdom in 2013 were treatable with oral ciprofloxacin (based on susceptibility testing of the causal strains) and over 80% with classical penicillin. However, we lack the diagnostic tests to recognise such susceptible strains at the time of presentation, and we must avoid undertreating the 20-30% of patients who have infections resistant to one or both of ciprofloxacin or penicillin, and so all patients are prescribed the ceftriaxone plus

azithromycin combination; this is a poor strategy in terms of antibiotic stewardship, but is unavoidable with currently available tools. If doctors had access to a test to detect resistance to ciprofloxacin or to penicillin, 70-80% of patients who currently receive azithromycin and ceftriaxone could instead be treated with one of these former first-line drugs, improving patient welfare and substantially reducing the selective pressure favoring the emergence of gonococci resistant to azithromycin and ceftriaxone ([2]Woodford (2015), “The gonorrhea urgency,” Longitude Prize blog).

We need to understand better the potential impact of rapid diagnostic tests for gonorrhoea that provide information on antibiotic susceptibility, and how gonococci might evolve in response to the changes in treatment strategies made possible by such diagnostic tests [3]. Here, we examine the implications of point-of-care resistance diagnosis (or, more simply, “resistance diagnosis”) for the treatment and control of gonorrhoea.

Rationale

The aim is to reduce the use of ceftriaxone for treating gonorrhoea by reserving it for infections caused by strains of *N. gonorrhoeae* with resistance to alternative antimicrobial agents, thus decreasing the selective pressure for emergence of resistance to ceftriaxone and extending the lifespan of ceftriaxone as a treatment option.

Objectives

To develop a simple spreadsheet model of testing and treatment of *N. gonorrhoeae.*
To assess the incremental effect of introducing a point-of-care test (POCT) for gonorrhoea with the ability to discriminate between antimicrobial resistant/susceptible infections compared with current off-site, laboratory-based testing practice from the perspective of the health care system in the UK.

Method

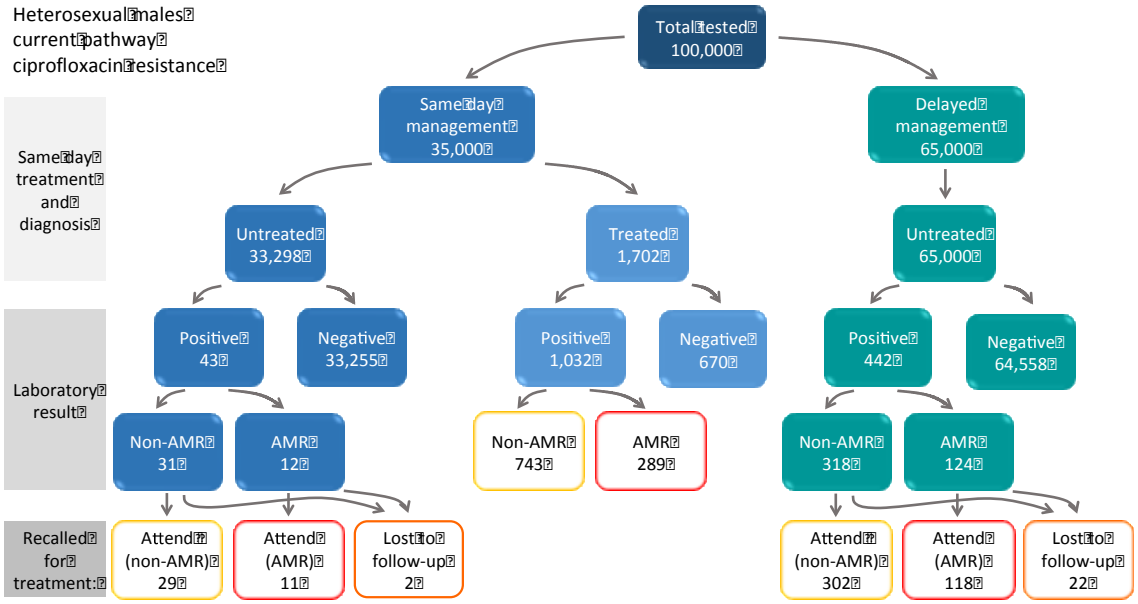
A new spreadsheet model was developed, by adapting an existing pathway model. The previous model had been used to investigate the impact of introducing point-of-care dual diagnostic tests for gonorrhoea and chlamydia in a genitourinary medicine clinic setting (economic perspective: GUM clinic). [4,5]

The new model was simplified compared with that previously published and did not consider onward transmission of gonorrhoea or partner notification, but only the impact of new test technology on testing, diagnosis and treatment of gonorrhoea. New components were added to differentiate susceptible and resistant isolates within the pathway framework. Parameter values were selected based on current levels of resistance to previous first-line therapies (penicillin or ciprofloxacin). These agents could potentially be re-used, for example ciprofloxacin to treat ciprofloxacin-susceptible infections, in place of ceftriaxone in combination with azithromycin (**Figure 1)**.

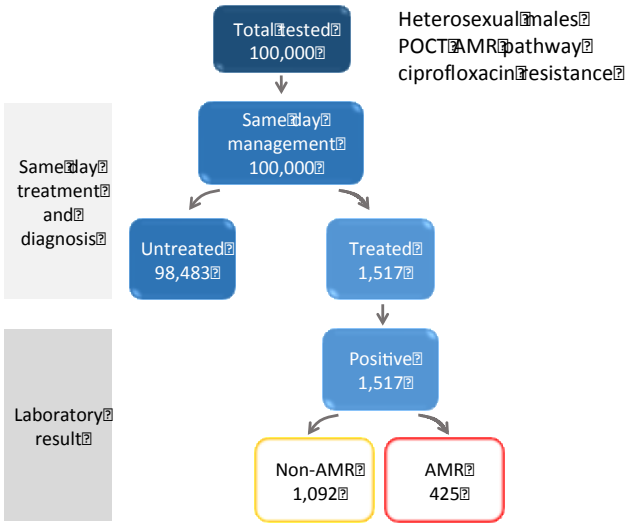
The primary outcome measures of interest were 1) the number of doses of ceftriaxone saved and 2) the mean time to appropriate treatment. In addition we calculated the average number of visits per person and per infected person, the total cost of testing and the number of patients lost to follow up. In each case we compared the incremental benefit of a point-of-care AMR test (POCT AMR) with current testing practice.

Figure 1 Pathway diagram with illustration of flow for heterosexual males under a) current care, b) point of care (AMR) test, using example of current levels of ciprofloxacin resistance.

a)



b)



Model parameters and assumptions

Model parameter values were updated to reflect recent data from Public Health England on tests and diagnoses of gonorrhoea (PHE GUMCAD data 2014, [6]). In the base case we assumed that all infections are treated with ceftriaxone (since there is >5% resistance to alternative regimens, resulting in 100% of infections treated as if resistant to other antibiotics such as ciprofloxacin). We analysed alternative scenarios based on prevalence of resistance to ciprofloxacin and penicillin reported in GRASP [7], provided in Appendix Table A1.

The economic perspective is that of the health system and therefore the cost of attendance was taken from the latest payment by results tariff for GUM attendance [8]. A full list of model parameters and definitions is given in the Appendix (Table A2).

List of scenarios

- **Base case:** 100% treatment with ceftriaxone, no knowledge of resistance profile at point of treatment (current care)
- **Scenario 1:** POCT AMR that can identify infections that could be treated with an alternative regimen, additional test cost £50. Assuming current **ciprofloxacin** resistance prevalence (GRASP 2014)
- **Scenario 2:** POCT AMR as scenario 1, additional test cost £50 but assuming current **penicillin** resistance prevalence (GRASP 2014).

We assume for simplicity that the cost of a POCT AMR adds £50 to the current tariff cost, however in reality other current activities could be reduced/discontinued such as testing, microscopy, culture and physical exams or re-attendances as well as reduced costs associated with re-using cheaper oral antibiotics. This can therefore be considered a conservative scenario. New DNA-based point of care test technologies can be combined or updated relatively easily to produce multiplex test, which may be more economically viable than separate specific AMR tests.

Results

Under current treatment guidelines, all gonorrhoea infections are treated as if they are resistant to ciprofloxacin i.e. using ceftriaxone as first-line therapy in combination with azithromycin. A total of 33,431 ceftriaxone treatments are estimated to be administered annually and a small number of infections remain untreated due to loss to follow-up. We considered three different scenarios possible with a point-of-care AMR test (such that ceftriaxone is only used if needed). Scenario 1) explored the situation with current levels of resistance to ciprofloxacin (overall 37% of infections in 2014 [3]). A POCT for ciprofloxacin resistance could prevent a total of 22,054 treatments of ceftriaxone annually (66% reduction). Similarly a POCT AMR for penicillin resistance (Scenario 2) could prevent 33,431 ceftriaxone treatments. Table 1 summarises the main outcomes of interest, based comparing scenario 1) to the base case.

The POCT reduced the average time to receiving treatment by just over 2 days and increased the proportion of positive cases treated on the same day as the test to 100% (Table 1a). Note that these outcomes could be achieved by using generic point of care tests, as previously considered [5], however only a discriminatory POCT AMR test enables improved *choice* of antimicrobial treatment (Table 1b).

Table 1a Summary of main outcomes: number of ceftriaxone treatments, proportion treated on day of test, mean time to treatment and number lost to follow-up (Scenario 1)

	Heterosexual male	MSM	Female	Total
Annual ceftriaxone treatments				
Current	7690	17691	8050	33431
POCT AMR	2188	7933	1257	11378
Difference	5502	9759	6793	22054
Proportion treated same day				
Current	68%	63%	21%	54%
POCT AMR	100%	100%	100%	100%
Difference	32%	56%	80%	57%
Mean time to treatment				
Current	1.5	1.8	3.9	2.3
POCT	0	0	0	0
Difference	-1.5	-1.8	-3.9	-2.3
Number lost to follow up (untreated)				
Current	125	338	329	792
POCT	0	0	0	0
Difference	-125	-338	-329	-729

Table 1b Summary of main outcomes: number of ceftriaxone treatments
(all other outcomes same as in Table 1a) (Scenario 2)

	Heterosexual male	MSM	Female	Total
Annual ceftriaxone treatments				
Current	7690	17691	8050	33431
POCT AMR	1407	4688	838	6932
Difference	6283	13004	7212	26499

Note all other outcomes identical to Scenario 1, given in Table 1a

Table 2 Summary of costs implications of more expensive test (Scenario 1 and 3)

	Heterosexual male	MSM	Female	Total
Baseline	£69,784,517	£20,358,694	£105,826,467	£195,969,677
Scenario 1 (test £50)	£95,292,390	£26,984,655	£144,130,725	£266,407,770
Change in cost compared with baseline				
Scenario 1 – baseline	£25,507,873	£6,625,961	£38,304,258	£70,438,093

Assume that additional cost of POCT AMR test is simply added to the cost of attendance, and is not offset by reductions in treatment costs or costs of other tests which could be potentially reduced or discontinued (such as microscopy or culture of all swabs).

Discussion

The major benefit of POCTs for gonorrhoea in general is increasing the proportion of patients treated appropriately on the same day as the test, which is likely to improve outcomes by reducing infectious duration, reducing loss to follow-up and potentially improving partner notification efficacy. In our example, the mean time to treatment (for those who receive treatment) is reduced by on average 2.3 days. A definitive diagnosis on the day of first presentation also prevents unnecessary of those not infected with gonorrhoea.

The additional benefit of a POCT which can discriminate between sensitive and resistant infections is in enabling the re-introduction of abandoned first-line therapies. If ciprofloxacin could be used in place of ceftriaxone in the 63% of individuals with ciprofloxacin-susceptible infections, this could save over 22,000 doses of ceftriaxone annually. Reducing the use of antibiotics, especially of last-line therapies is a key aim of the UK national strategy on antimicrobial resistance.

Although new POCTs are likely to be more expensive than existing tests this is to some extent offset by the reduction in further attendances and in the ability to re-use older, cheaper drugs. However given the low prevalence of gonorrhoea, the cost of treatment and re-attendances is small in comparison with the cost of attendances for testing and diagnosis.

If a new discriminatory test were prohibitively expensive for routine use, a combination of a standard point of care NAAT (e.g. chlamydia/gonorrhoea) test could be considered in conjunction with a more specialised gonorrhoea AMR test, although the time implications of this for patients and clinicians would have to be carefully considered.

For heterosexual men and MSM a relatively large proportion of infections are already treated on the same day as testing, based on epidemiological, clinical or microbiological evidence (microscopy). However this proportion is lower for women due to the higher percentage of asymptomatic infections. There is also a degree of unnecessary treatment of uninfected individuals although this is relatively small for gonorrhoea compared with epidemiological treatment for chlamydia.

The model did not capture the indirect effects of reduced transmission to partners or progression to complications, such as pelvic inflammatory disease and epididymitis. It also

did not consider the longer term effects of changing treatment strategy on the evolution of drug resistance over time in gonorrhoea infections.

This estimation of the potential reduction in ceftriaxone use is the first step towards evaluating what the long term effects of such a reduction translate into, e.g. if ceftriaxone use is reduced by 50%, what effect does that have on the useful lifespan of ceftriaxone as a therapy for gonorrhoea? In the context of the slow, expensive new drug pipeline, what is each additional year of ceftriaxone availability worth?

References

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2) Woodford (2015), "The gonorrhea urgency," Longitude Prize blog
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6) PHE STI annual report 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/436723/2014_Table_2_STI_diagnoses___rates_by_gender__sexual_risk___age_group.xls
7) GRASP annual report 2014 https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/476582/GRASP_2014_report_final_111115.pdf
8) PBR tariff costs https://www.gov.uk/government/uploads/system/uploads/attachment_data/file/300547/2014-15_National_Tariff_Payment_System_-Revised_26_Feb_14.pdf

Appendix

Table A1 Current prevalence of antimicrobial resistance to potential treatments for gonorrhoea

Drug	Class	Prevalence of resistance in GRASP 2014 isolates [4]		
		MSM (Men who have sex with men)	Heterosexual men	Women
Ceftriaxone	Cephalosporin (3rd generation)	0	0	0
Penicillin	□-lactam	26%	18%	10%
Ciprofloxacin	Fluoroquinolone	44%	28%	15%
Azithromycin	Macrolide	1.4%	0.0%	0.5%

Current first line (and last-line) therapy is i.m. ceftriaxone with azithromycin 1g orally. It may be possible to re-introduce older, abandoned first-line therapies in place of ceftriaxone, in combination with azithromycin.

Table A2 List of model parameters (base case values)

Baseline model parameters	Current			POCT AMR baseline		
	MSW	MSM	Women	MSW	MSM	Women
Initial population size[a]	515,094	145,863	779,085	515,094	145,863	779,085
Proportion entering same day management pathway*	35.0%	33.0%	48.0%	100.0%	100.0%	100.0%
Proportion infected with gonorrhoea (of total tested)[a]	1.5%	12.4%	1.1%	1.5%	12.4%	1.1%
Proportion of those in same day pathway infected with gonorrhoea	3.1%	26.0%	1.0%	1.5%	12.4%	1.1%
Proportion of delayed management infected with gonorrhoea	0.7%	5.6%	1.2%			
Relative risk infection gonorrhoea in same day vs delayed pathway	4.52	4.63	0.82			
Proportion in same day pathway who are infected & treated on same day	96%	90%	50%	100%	100%	100%
Proportion of same day pathway treated presumptively for gonorrhoea	5%	25%	2%	1.5%	12.4%	1.1%
Proportion who attend for treatment after lab test result	95%	95%	95%	100%	100%	100%
Proportion treated with last line therapy[b]	100%	100%	100%	28%	44%	15%
Cost of first attendance	£135	£135	£135	£135	£135	£135
Cost of follow-up attendance	£104	£104	£104	£104	£104	£104
Cost of POCT AMR (Scenario 1)	50	50	50	50	50	50

MSW – Men who have sex with women, MSM – Men who have sex with men
a) PHE STI annual report 2014
b) GRASP annual report 2014 (reported resistance to ciprofloxacin used to determine values for POCT AMR baseline)