**RECENT PUBLICATIONS**

**Reviews and Commentary**

Unemo M, Del Rio C, Shafer WM.

**Abstract**
*Neisseria gonorrhoeae* is a strictly human pathogen that is typically transmitted by sexual contact. The associated disease gonorrhea has plagued humankind for thousands of years, with a current estimated incidence of 78 million cases per year. Advances in antimicrobial discovery in the 1920s and 1930s leading to the discovery of sulfonamides and penicillin begun the era of effective antimicrobial treatment of gonorrhea. Unfortunately, the gonococcus developed decreased susceptibility or even resistance to these initially employed antibiotics, a trend that continued over subsequent decades with each new antibiotic that was brought into clinical practice. As this pattern of resistance has continued into the 21st century, there is now reason for great concern, especially in an era when few new antibiotics have prospects for use as treatment of gonorrhea. Here, we review the history of gonorrhea treatment regimens and gonococcal resistance to antibiotics, the mechanisms of resistance, resistance monitoring schemes that exist in different international settings, global responses to the challenge of resistance, and prospects for future treatment regimens in the 21st century.

*Includes table of main antimicrobial resistance determinants in Neisseria gonorrhoeae for previously and currently recommended antimicrobials for treatment of gonorrhea.*

*Antimicrobial Resistance Surveillance for Neisseria gonorrhoeae—What Do We Really Need to Know to Guide Public Health Interventions?*
Lewis DA.

**Recommended strategies**
The most important strategies we can put in place today must focus on (i) addressing stigma and legal barriers to care, (ii) encouraging behavior change including ongoing condom promotion, (iii) ensuring appropriate therapy is always provided based on timely antimicrobial resistance surveillance data, (iv) designing novel molecular assays to determine susceptibility to antimicrobial agents, in particular cephalosporins, as part of integrated diagnostic algorithms (v) developing and evaluating of new antimicrobial agents, and (vi) funding research aimed at developing an effective gonococcal vaccine.

**Epidemiology**

*Failure of Dual Antimicrobial Therapy in Treatment of Gonorrhea.*
Fifer H, Natarajan U, Jones L, Alexander S, Hughes G, Golparian D, Unemo M.

**Summary**
Describes treatment failure with dual therapy in a patient with gonorrhea.

Global surveillance programs
*Drifting towards ceftriaxone treatment failure in gonorrhoea: risk factor analysis of data from the Gonococcal Resistance to Antimicrobials Surveillance Programme in England and Wales.*
Town K, Obi C, Quaye N, Chisholm S, Hughes G; GRASP Collaborative Group.

**Summary**
Analysis of data from the Gonococcal Resistance to Antimicrobials Surveillance Programme (GRASP) in England and Wales to identify groups most at risk of reduced susceptibility to the currently recommended first-line therapy, ceftriaxone.

METHODS: Data from GRASP between 2007 and 2013 on ceftriaxone susceptibility and strain types were analysed. Risk factors associated with isolates exhibiting a ceftriaxone minimum inhibitory concentration (MIC) of ≥0.015 mg/L (CTR ≥0.015 mg/L) were identified using logistic regression.

RESULTS: One third of isolates from men who have sex with men (MSM) (1279/4203) and 9.9% from heterosexuals (458/4626) exhibited CTR ≥0.015 mg/L. Between 2007 and 2013, the modal MIC for isolates remained at 0.004 mg/L for MSM but increased from 0.002 to 0.004 mg/L for heterosexuals. Among MSM, CTR ≥0.015 mg/L was associated with Asian ethnicity (crude OR: 1.42; 95% CI 1.07 to 1.88) and previous gonorrhoea (1.34; 1.16 to 1.54). Among heterosexuals, CTR ≥0.015 mg/L was associated with older age (35+ years: 4.31; 3.34 to 5.55), ≥6 sexual partners (1.58; 1.01 to 2.44) and sex abroad (2.23; 1.71 to 2.91). CTR ≥0.015 mg/L was associated with older age (35+ years: 4.31; 3.34 to 5.55), ≥6 sexual partners (1.58; 1.01 to 2.44) and sex abroad (2.23; 1.71 to 2.91). CTR ≥0.015 mg/L was less likely in isolates from heterosexuals of black Caribbean or African ethnicity (0.29; 0.20 to 0.41, 0.66; 0.43 to 0.99), with a concurrent chlamydial infection (0.25; 0.19 to 0.34) or women (0.57; 0.46 to 0.71). Over 600 isolates (CTR ≥0.015 mg/L) were typed; the majority were in Genogroup 1407, containing sequence type 1407.

CONCLUSIONS: The emergence and spread of gonorrhoea with reduced susceptibility to ceftriaxone seems a realistic prospect, most likely in those involved in 'rapid-transmission' or bridging sexual networks.


Results
A total of 5,093 isolates were collected in 2014. Of these, 25.3% were resistant to tetracycline, 19.2% to ciprofloxacin, and 16.2% to penicillin (plasmid-based, chromosomal, or both). Reduced azithromycin susceptibility (Azi-RS) (defined as minimum inhibitory concentration [MIC] ≥2.0 µg/mL) increased from 0.6% in 2013 to 2.5% in 2014. The increase occurred in all geographic regions, and was greatest in the Midwest, and among all categories of sex of sex partners (men who have sex with men [MSM], men who have sex with men and women [MSMW], and men who have sex with women [MSW]). No Azi-RS isolates exhibited reduced cefixime or ceftriaxone susceptibility (Cfx-RS and Cro-RS, respectively). The prevalence of Cfx-RS (MIC ≥0.25 µg/mL) increased from 0.1% in 2006 to 1.4% in both 2010 and 2011, decreased to 0.4% in 2013, and increased to 0.8% in 2014. Cro-RS (MIC ≥0.125 µg/mL) increased following a similar pattern but at lesser percentages (increased from 0.1% in 2008 to 0.4% in 2011 and decreased to 0.1% in 2013 and 2014). The percentage of isolates resistant to tetracycline, ciprofloxacin, penicillin, or all three antimicrobials, was greater in isolates from MSM than from MSW.

Grad YH, Harris SR, Kirkcaldy RD, Green AG, Marks DS, Bentley SD, Trees D, Lipsitch M.

Summary
We define the prevalence and dynamics of resistance markers to extended-spectrum cephalosporins, macrolides, and fluoroquinolones in 1102 resistant and susceptible clinical Neisseria gonorrhoeae isolates collected from 2000 to 2013 via the Centers for Disease Control and Prevention's Gonococcal Isolate Surveillance Project. Reduced extended-spectrum cephalosporin susceptibility is predominantly clonal and associated with the mosaic penA XXXIV allele and derivatives (sensitivity 98% for cefixime and 91% for ceftriaxone), but alternative resistance mechanisms have sporadically emerged. Reduced azithromycin susceptibility has arisen through multiple mechanisms and shows limited clonal spread; the basis for resistance in 36% of isolates with reduced azithromycin susceptibility is unclear. Quinolone-resistant Neisseria gonorrhoeae has arisen multiple times, with extensive clonal spread.

Trends in antimicrobial susceptibility for azithromycin and ceftriaxone in Neisseria gonorrhoeae isolates in Amsterdam, the Netherlands, between 2012 and 2015.
Wind CM, Schim van der Loeff MF, van Dam AP, de Vries HJ, van der Helm JJ.

Results
Between 2012 and 2015 azithromycin resistance (MIC > 0.5 mg/L) was around 1.2%, the percentage of isolates with intermediate MICs (> 0.25 and ≤ 0.5 mg/L) increased from 3.7% in 2012, to 8.6% in 2015. Although no ceftriaxone resistance (MIC > 0.125 mg/L) was observed during the study period, the proportion of isolates with decreased ceftriaxone susceptibility increased from 3.6% in 2012, to 8.4% in 2015.

Lahra MM, Enriquez RP; National Neisseria Network.

Summary
The Australian Gonococcal Surveillance Programme (AGSP) has continuously monitored antimicrobial resistance in clinical isolates of Neisseria gonorrhoeae from all Australian states and territories since 1981. Among 5,411 isolates decreased susceptibility to ceftriaxone (minimum inhibitory concentration or MIC value 0.06-0.125 mg/L) was found nationally in 1.8% of isolates, which was lower than that reported in the AGSP annual report 2014 (5.4%). The highest proportions were reported from South Australia and New South Wales (3.6% and 2.7% respectively). High level resistance to azithromycin (MIC value ≥ 256 mg/L) was again reported in 2015, with 1 strain in each of New South Wales and urban Western Australia. There was no reported Azithromycin resistance in the Australian Capital Territory, the Northern Territory, or remote Western Australia. The proportion of strains resistant to penicillin in urban and rural Australia ranged from 8.7% in Tasmania to 33% in the Australian Capital Territory. In rural and remote Northern Territory, penicillin resistance rates remain low (2.2%). In remote Western Australia relatively low numbers of strains are available for testing, however there is now widespread molecular testing for penicillin resistance in Western Australia to monitor resistance and inform guidelines and these data are included in the AGSP annual report. Quinolone resistance ranged from 11% in the urban and rural areas of the Northern Territory, to 41% in South Australia. Quinolone resistance rates remain comparatively low in remote areas of the Northern Territory (3.3%) and remote areas of Western Australia (3.4%). There was no reported quinolone resistance in Tasmania, but the number of isolates tested was relatively low. Azithromycin resistance ranged from 1.8% in Victoria to 5.8% in Queensland.

Epidemiology studies using whole genome sequencing
Whole-genome sequencing to determine transmission of Neisseria gonorrhoeae: an observational study.

Summary
This study used whole-genome sequencing to study transmission and track resistance in N gonorrhoeae isolates among isolates from samples collected from patients attending sexual health services in Brighton, UK, between Jan 1, 2011, and March 9, 2015 and some isolates from the UK. Cefixime susceptibility testing was done in selected isolates by agar incorporation, and we used sequence data to determine multi-antigen sequence types and penA genotypes. We derived a transmission nomogram to determine the plausibility of direct or indirect transmission between any two cases depending on the time between samples: estimated mutation rates, plus diversity noted within patients across anatomical sites and probable transmission pairs, were used to fit a coalescent model to determine the number of single nucleotide polymorphisms expected.

FINDINGS: 1407 (98%) of 1437 Brighton isolates between Jan 1, 2011, and March 9, 2015 were successfully sequenced. We identified 1061 infections from 907 patients. 281 (26%) of these infections were indistinguishable (ie, differed by zero single nucleotide polymorphisms) from one or more previous cases, and 786 (74%) had evidence of a sampled direct or indirect Brighton source. We observed multiple related samples across geographical locations. Of 1273 infections in Brighton (including historical data), 225 (18%) were linked to another case elsewhere in the UK, and 115 (9%) to a case in the USA. Four lineages initially identified in Brighton could be linked to 70 USA sequences, including 61 from a lineage carrying the mosaic penA XXXIV allele, which is associated with reduced cefixime susceptibility.

INTERPRETATION: We present a whole-genome-sequencing-based tool for genomic contact tracing of N. gonorrhoeae and demonstrate local, national, and international transmission. Whole-genome sequencing can be applied across geographical boundaries to investigate gonorrhoea transmission and to track antimicrobial resistance.

Use of whole-genome sequencing data to analyze 23S rRNA-mediated azithromycin resistance.
Johnson SR, Grad Y, Abrams AJ, Pettus K, Trees DL.
Abstract
The whole-genome sequences of 24 isolates of Neisseria gonorrhoeae with elevated minimum inhibitory concentrations (MICs) to azithromycin (≥2.0 µg/mL) were analyzed against a modified sequence derived from the whole-genome sequence of N. gonorrhoeae FA1090 to determine, by signal ratio, the number of mutant copies of the 23S rRNA gene and the copy number effect on 50S ribosome-mediated azithromycin resistance. Isolates that were predicted to contain four mutated copies were accurately identified compared with the results of direct sequencing. Fewer than four mutated copies gave less accurate results but were consistent with elevated MICs.

Novel methods of detection and monitoring of AMR
WGS to predict antibiotic MICs for Neisseria gonorrhoeae.

Summary
We investigate whether WGS and simultaneous analysis of multiple resistance determinants can be used to predict antimicrobial susceptibilities to the level of MICs in N. gonorrhoeae using 681 N. gonorrhoeae isolates, from England, the USA and Canada, with phenotypes for cefixime, penicillin, azithromycin, ciprofloxacin and tetracycline determined as part of national surveillance programmes. Multivariate linear regression models were used to identify genetic predictors of MIC. Model performance was assessed using leave-one-out cross-validation. Overall 1785/3380 (53%) MIC values were predicted to the nearest doubling dilution and 3147 (93%) within ±1 doubling dilution and 3314 (98%) within ±2 doubling dilutions. MIC prediction performance was similar across the five antimicrobials tested. Prediction models included the majority of previously reported resistance determinants. Applying EUCAST breakpoints to MIC predictions, the overall very major error (VME; phenotypically resistant, WGS-prediction susceptible) rate was 21/1577 (1.3%, 95% CI 0.8%-2.0%) and the major error (ME; phenotypically susceptible, WGS-prediction resistant) rate was 20/1186 (1.7%, 1.0%-2.6%). VME rates met regulatory thresholds for all antimicrobials except cefixime and ME rates for all antimicrobials except tetracycline. Country of testing was a strongly significant predictor of MIC for all five antimicrobials.

Conclusions
We demonstrate a WGS-based MIC prediction approach that allows reliable MIC prediction for five gonorrhoea antimicrobials. Our approach should allow reasonably precise prediction of MICs for a range of bacterial species.

Implementation of a Rapid Genotypic Assay to Promote Targeted Ciprofloxacin Therapy of Neisseria gonorrhoeae in a Large Health System.

Abstract
Multidrug-resistant Neisseria gonorrhoeae is a top threat to public health. In November 2015, UCLA Health introduced a rapid gyrase A (gyrA) genotypic assay for prediction of Neisseria gonorrhoeae susceptibility to ciprofloxacin. We found a significant reduction in ceftriaxone use with a concomitant increase in targeted therapy

Treatment guidelines and policy
A systematic review and appraisal of the quality of practice guidelines for the management of Neisseria gonorrhoeae infections.
Dickson C, Arnason T, Friedman DS, Metz G, Grimshaw JM.
Results
We identified 10 guidelines meeting the inclusion criteria. The quality of the gonorrhoea treatment guidelines varied. Most scored poorly on Rigour of Development; information on the evidence review process and methods for formulating recommendations was often missing. The WHO Guidelines for the Treatment of Neisseria gonorrhoeae and UK National Guideline for the Management of Gonorrhoea in Adults scored the highest on Rigour of Development. Methods to address conflicts of interest were often not described in the materials reviewed. Implementation of recommendations was often not addressed.
**First line dual therapy for gonorrhoea to limit the spread of antimicrobial resistance.**

Mohammed H, Sile B, Furegato M, Woodhall S, Fifer H, Hughes G.


**Summary**

The national treatment guideline recommends first line dual therapy of 500 mg ceftriaxone (intramuscularly) and 1 g of azithromycin (orally) to extend the useful life of cephalosporins. Over 90% of cases treated at sexual health clinics receive the recommended first line therapy, compared with only 9% of cases treated by GPs.

**Mechanisms of resistance and antibacterial activity**

Control of gdhR Expression in Neisseria gonorrhoeae via Autoregulation and a Master Repressor (MtrR) of a Drug Efflux Pump Operon.

Rouquette-Loughlin CE, Zalucki YM, Dhulipala VL, Balthazar JT, Doyle RG, Nicholas RA, Begum AA, Raterman EL, Jerse AE, Shafer WM.


**Abstract**

The MtrCDE efflux pump of Neisseria gonorrhoeae contributes to gonococcal resistance to a number of antibiotics used previously or currently in treatment of gonorrhea, as well as to host-derived antimicrobials that participate in innate defense. Overexpression of the MtrCDE efflux pump increases gonococcal survival and fitness during experimental lower genital tract infection of female mice. Transcription of mtrCDE can be repressed by the DNA-binding protein MtrR, which also acts as a global regulator of genes involved in important metabolic, physiologic, or regulatory processes. Here, we investigated whether a gene downstream of mtrCDE, previously annotated gdhR in Neisseria meningitidis, is a target for regulation by MtrR. In meningococci, GdhR serves as a regulator of genes involved in glucose catabolism, amino acid transport, and biosynthesis, including gdhA, which encodes an l-glutamate dehydrogenase and is located next to gdhR but is transcriptionally divergent. We report here that in N. gonorrhoeae, expression of gdhR is subject to autoregulation by GdhR and direct repression by MtrR. Importantly, loss of GdhR significantly increased gonococcal fitness compared to a complemented mutant strain during experimental murine infection. Interestingly, loss of GdhR did not influence expression of gdhA, as reported for meningococci. This variance is most likely due to differences in promoter localization and utilization between gonococci and meningococci. We propose that transcriptional control of gonococcal genes through the action of MtrR and GdhR contributes to fitness of N. gonorrhoeae during infection.

Whole-Genome Sequencing of a Large Panel of Contemporary Neisseria gonorrhoeae Clinical Isolates Indicates that a Wild-Type mtrA Gene Is Common: Implications for Inducible Antimicrobial Resistance.

Vidyaprakash E, Abrams AJ, Shafer WM, Trees DL.


**Findings**

The presence of the wild-type mtrA is common among gonococci, and the majority of strains likely have the capacity to display inducible antimicrobial resistance through the MtrCDE efflux pump.

**Novel antibiotics and vaccines**

Gentamicin versus ceftriaxone for the treatment of gonorrhoea (G-TOG trial): study protocol for a randomised trial.


**Trial objective**

This trial aims to determine whether gentamicin is not clinically worse than ceftriaxone in the treatment of gonorrhoea.