O05.6 DISTINCT GROWTH AND GENOME PROFILES ARE PRESENT IN CLINICAL ISOLATES FROM WOMEN WHO FAIL TO RESOLVE GENITAL CHLAMYDIA INFECTION AFTER AZITHROMYCIN TREATMENT

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Introduction Treatment failure to be appears to occurring in women with genital *Chlamydia trachomatis* after azithromycin treatment. This study aimed to characterise the molecular basis of treatment failure by characterising clinical isolates from these women who failed to resolve the infection.

Methods A selection of 6 clinical isolates were cultured and whole genome sequence examined. Cultures were conducted in variety of cell lines, and in the presence of a novel anti-chlamydial drug to examine differences in growth and drug responses between isolates from treatment failure cases and treatment resolved cases.

Results The clinical isolates showed distinct growth profiles in different cell lines, with variation in infectious progeny yield and kinetics. Cervical, endometrial, gastrointestinal and fibroblast cell lines were compared and distinctions in growth were observed. There were no genome mutations in the ribosome loci in any isolate that would confer a direct resistance to azithromycin. However, there was less susceptibility to a novel anti-chlamydia drug by a clinical isolate from a treatment failure case as well as higher growth yield in the absence of the drug.

Conclusion Distinct phenotypic growth traits were observed in clinical treatment failure isolates of *C. trachomatis* that could underlie the mechanism of azithromycin treatment failure clinically.

Disclosure of interest statement This study was funded by the NHMRC.

O06 - STI therapy: new and old

O06.1 THE EFFICACY OF PRISTINAMYCIN FOR *MYCOPLASMA GENITALIUM* – AN INCREASING MULTIDRUG RESISTANT PATHOGEN

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Introduction To determine the efficacy of pristinamycin-based regimens for *M. genitalium*-infections failing prior regimens and to examine the presence of 23S rRNA and ribosomal protein gene mutations and their association with treatment failure.

Methods In 2013 *M. genitalium*-infected men and women attending Melbourne Sexual Health Centre who failed azithromycin and moxifloxacin were treated with pristinamycin 1g qid for 10 days with a test-of-cure (TOC) 3–4 weeks post-pristinamycin. From December 2014 pristinamycin was prescribed 1g bid for 10 days second-line following azithromycin failure. Pre- and post-treatment samples were stored and sequenced to detect 23S rRNA and ribosomal protein gene mutations, as potential markers of pristinamycin resistance.

Results By March 2015 37 *M. genitalium*-infected patients had received pristinamycin: 32 males (10 rectal; 22 urine samples) and 5 females (1 rectal; 3 urine; 1 cervical). TOC data are available on 25 patients at abstract submission: 20 were cured (80%; 95% CI 61–92%) and 5 (20%; 8–39%) failed pristinamycin. Failure rates in the 16 patients treated with 1g qid 10 days were 12% (n = 2), and 33% (n = 3) in the 9 treated with 1g bd 10 days, p = 0.23. Of the 5 pristinamycin failures; 2 were cured with moxifloxacin, 3 failed moxifloxacin and are awaiting TOCs following solithromycin or combined doxycycline/pristinamycin. Mutations in 23S rRNA and ribosomal protein genes were associated with failure of pristinamycin.

Conclusion Increasing reports of azithromycin and moxifloxacin failure for *M. genitalium*-infections necessitates evaluation of new agents. We present some of the earliest data on the use of pristinamycin for *M. genitalium*. Treatment failure occurred when delivered as monotherapy following failure of prior regimens. Current data on use of combined pristinamycin and doxycycline as a second line regimen after azithromycin failure will be available for presentation. Resistance mutations in the 23S rRNA and ribosomal protein genes are associated with pristinamycin failure.

Disclosure of interest statement No pharmaceutical grants were received in the development of this study.

O06.2 HIGH *IN VITRO* SUSCEPTIBILITY TO THE NOVEL SPIROPYRIMIDINETRIONE AZD0914 AMONG 873 CONTEMPORARY CLINICAL *NEISSERIA GONORRHOEAE* ISOLATES IN 21 EUROPEAN COUNTRIES DURING 2012–2014

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Introduction Resistance in *Neisseria gonorrhoeae* has emerged to all antimicrobials available for treatment of gonorrhoea. The first gonococcal strains with high-level resistance to ceftriaxone, the last option for first-line empirical antimicrobial monotherapy, were recently described. Consequently, new treatment options are essential. In this study, the *in vitro* activity of the novel spiropyrimidinetrione AZD0914, a DNA topoisomerase II inhibitor, among contemporary consecutive clinical *N. gonorrhoeae* isolates obtained in 21 European countries was investigated and compared to the activities of antimicrobials currently or previously recommended for treatment.

Methods Consecutive clinical *N. gonorrhoeae* isolates (n = 873) cultured in 21 European countries during 2012–2014 were examined for their susceptibility to AZD0914. The MICs of AZD0914 were determined using agar dilution method. For comparison, the MICs of ceftriaxone, cefixime, azithromycin

and ciprofloxacin were determined using Etest or agar dilution method.

Results For AZD0914, the MIC range, modal MIC, MIC_{50} and MIC_{90} was ≤0.002–0.25 mg/L, 0.125 mg/L, 0.064 mg/L and 0.125 mg/L, respectively. The MIC values were substantially lower than those of the fluoroquinolone ciprofloxacin and most other antimicrobials examined. No cross-resistance with any other examined antimicrobial was observed.

Conclusion The *in vitro* susceptibility to the novel spiropyrimidinetrione AZD0914 among 873 contemporary clinical isolates from 21 European countries was high and no cross-resistance to antimicrobials currently or previously used for gonorrhoea treatment was indicated. Additional studies investigating the *in vitro* and *in vivo* induction and mechanisms of AZD0914 resistance in gonococci, pharmacokinetics/pharmacodynamics in modelling/simulations and in humans, and performance in randomised controlled gonorrhoea treatment trials, are essential.

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006.3 HOST-DIRECTED THERAPEUTICS AS ADJUNCTIVE THERAPY FOR ANTIBIOTIC-RESISTANT *NEISSERIA GONORRHOEAE*

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Background Due to the emergence of antibiotic resistance, novel therapies such as host-directed therapeutics (HDT) are being explored as adjunctive therapies against *Neisseria gonorrhoeae* (Gc). Inhibitors of histone deacetylases (HDACi) are HDTs that restore the balance between host histone acetylases and HDAC, the latter of which are induced by pathogens to enhance infection. We recently reported that sulforaphane (SFN), a natural HDACi, induced effectors with anti-Gc activity in tissue culture cells and reduced colonisation of female mice. Here we tested SFN against the multidrug-resistant strain HO41 and its potential to increase the susceptibility of this strain to antibiotics.

Methods ME180 cervical epithelial cells were treated with 40 or 80 μM SFN or no SFN for 24 h. Cell culture supernatants were then incubated with HO41; in some experiments, sub-lethal concentrations of ciprofloxacin (CIP) or cefixime (CFX) were added to the supernatants. The number of viable Gc recovered after a 4-hour incubation was determined by quantitative culture.

Results Supernatants from cervical cells treated with 40 or 80 μM SFN reduced the survival of strain H041 to 53% and 20%, respectively, relative to recovery from supernatants from untreated cells. Addition of sub-inhibitory concentrations of CIP or CFX to supernatants from SFN-treated (40 μM) cells resulted in a dose-dependent reduction in survival, with 4 μg/ml CIP resulting in 27% survival. Two and 4 μg/ml doses of CFX resulted in 13% and 7% survival, respectively. Addition of 1, 2 and 4 μg/ml of CFX to supernatants from cells treated with 80 uM SFN reduced survival to 15%, 8% and 1%, respectively.

Conclusion The susceptibility of strain HO41 to CIP or CFX is enhanced when tested in tissue culture media containing SFN-induced host effectors. These findings suggest that a combination of HDACi and antibiotics may be an effective adjunct therapy against antibiotic-resistant Gc.

Disclosure of interest statement This project was funded by grant RO1 AI43053 from the US NIH. No pharmaceutical grants were received in the development of this study.

006.4 AZITHROMYCIN VERSUS DOXYCYCLINE FOR UROGENITAL CHLAMYDIA: A RANDOMISED CLINICAL TRIAL IN FEMALES AND MALES IN YOUTH CORRECTIONAL FACILITIES

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Background Urogenital *Chlamydia trachomatis* infection ("chlamydia") remains highly prevalent and causes significant reproductive morbidity. Earlier randomised chlamydia treatment trials comparing azithromycin 1g versus a 7-day regimen of doxycycline 100mg twice daily reported high cure rates, but used less sensitive diagnostics and results may have been confounded by chlamydia re-exposure or doxycycline nonadherence. Recent studies have raised concern about azithromycin efficacy for chlamydia.

Methods We conducted a randomised trial comparing azithromycin versus doxycycline for chlamydia in males and females in youth correctional facilities (YCFs) to evaluate for noninferiority of azithromycin compared to doxycycline. Treatment was directly observed and participants had no furloughs from the YCF throughout the study. The primary endpoint was treatment failure at 28 days after treatment initiation, determined by nucleic acid amplification test results, sexual history, and *C. trachomatis* OmpA genotyping.

Results Of 567 participants enrolled, 284 were randomised to azithromycin and 283 to doxycycline. There were 155 participants in each treatment arm comprising the per protocol population: 65% male and 35% female. No treatment failures occurred in the doxycycline arm. In the azithromycin arm, five treatment failures occurred (3.2%; 95% CI: 0.4–7.4%): four were males (3.9%; 95% CI: 1.1–9.7%) and one female (1.9%; 95% CI: 0.0–10.1%). The observed failure rate difference in the treatments was 3.2%, with a 90% upper CI of 5.9%, exceeding the predetermined 5% cutoff for establishing azithromycin noninferiority.

Conclusion Doxycycline had a 100% cure rate for chlamydia. Noninferiority of azithromycin to doxycycline was not established in this study, although azithromycin treatment failures occurred infrequently and the high azithromycin cure rate was consistent with earlier chlamydia treatment trials. Because of possible chlamydia treatment failures when azithromycin is used, further surveillance is needed and doxycycline might be considered for persons with suspected chlamydia treatment failure following azithromycin treatment.

Disclosure of interest statement Nothing to Declare.