

IUSTI–E Scientific Advisory Council

Topic Report 2016 **Gonorrhoea**

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Advances in the field 2015-6

The worrying antimicrobial resistance situation in *Neisseria gonorrhoeae* continues to be the main focus in Europe¹, as well as all over the world. Dual antimicrobial therapy (ceftriaxone plus azithromycin) appears to be very effective, however, the evidence base for this treatment remains weak and its possibilities to prevent resistance emergence have been discussed². Furthermore, an ongoing outbreak of high-level azithromycin resistant *N. gonorrhoeae* in England causes concern regarding future use of the dual therapy³. Moreover, additional ceftriaxone- and multidrug-resistant *N. gonorrhoeae* strains were identified⁴. Several molecular assays for prediction of antimicrobial resistance have been published in 2015⁵⁻⁷, however, no commercial assay is currently available.

The search for new treatments for gonorrhoea continues, and current and possible future antimicrobial treatment of gonorrhoea was thoroughly reviewed.⁸ The two new orally administered antimicrobials solithromycin and zoliflodacin (also known as AZD0914 or ETX0914) are the ones closest to clinical use. The Phase 2 trial for solithromycin was published in 2015⁹. Zoliflodacin was reviewed comprehensively¹⁰ and a European surveillance study proved the high susceptibility of this drug in contemporary clinical *N. gonorrhoeae* isolates from 21 European countries¹¹. However, the only sustainable solution to manage gonorrhoea might be with an appropriate vaccine, and the potential impact of vaccination on the prevalence of gonorrhoea was modelled¹².

Whole genome sequencing of *N. gonorrhoeae* has also become more commonly used¹³⁻¹⁴. In the near future, whole genome sequencing will most likely revolutionize the surveillance of *N. gonorrhoeae* (gonorrhoea), diagnostics, antimicrobial resistance testing, and more.

5 Most Important Recent Publications

1. Chisholm SA, Wilson J, Alexander S, Tripodo F, Al-Shahib A, Schaefer U, Lythgow K, Fifer H. An outbreak of high-level azithromycin resistant *Neisseria gonorrhoeae* in England. *Sex Transm Infect.* 2015 Nov 24. pii: sextrans-2015-052312.
2. Hook EW 3rd, Golden M, Jamieson BD, Dixon PB, Harbison HS, Lowens S, Fernandes P. A Phase 2 trial of oral solithromycin 1200 mg or 1000 mg as single-dose oral therapy for uncomplicated gonorrhea. *Clin Infect Dis.* 2015;61(7):1043-8.
3. Basarab GS, Kern GH, McNulty J, Mueller JP, Lawrence K, Vishwanathan K, Alm RA, Barvian K, Doig P, Galullo V, Gardner H, Gowravaram M, Huband M, Kimzey A, Morningstar M, Kutschke A, Lahiri SD, Perros M, Singh R, Schuck VJ, Tommasi R, Walkup G, Newman JV. Responding to the challenge of untreatable gonorrhea: ETX0914, a first-in-class agent with a distinct mechanism-of-action against bacterial Type II topoisomerases. *Sci Rep.* 2015;5:11827.
4. Ezewudo MN, Joseph SJ, Castillo-Ramirez S, Dean D, Del Rio C, Didelot X, Dillon JA, Selden RF, Shafer WM, Turingan RS, Unemo M, Read TD. Population structure of

Mulvey MR. Whole-genome phylogenomic heterogeneity of *Neisseria gonorrhoeae* isolates with decreased cephalosporin susceptibility collected in Canada between 1989 and 2013. J Clin Microbiol. 2015;53(1):191-200.

Potential Speakers

Gianfranco Spiteri, ECDC, Sweden on European epidemiology

Michelle Cole, PHE, UK on Antimicrobial resistance surveillance in Europe

Helen Fifer, PHE, UK on Treatment

Yonatan Grad, Harvard, USA or Simon Harris, Sanger, UK on Genomics of *Neisseria gonorrhoeae*

Christian Althaus, University of Bern, Switzerland on Mathematical modelling on infection and resistance spread

Magnus Unemo, WHO CC, Sweden

Questions to be answered by future Research

Evidence base for efficacy, including prevention of resistance emergence, of dual antimicrobial therapy (ceftriaxone plus azithromycin)?

Efficacy of antimicrobials at different anatomical sites, focus on pharynx?

New treatment for gonorrhoea?

How widespread is ceftriaxone and azithromycin resistance, in Europe and globally?

Molecular methods for resistance prediction: i) which methods, and ii) when and how to use in surveillance and clinical routine?

Vaccine only sustainable solution for future management of gonorrhoea?

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1. Cole MJ, Spiteri G, Jacobsson S, Pitt R, Grigorjev V, Unemo M; Euro-GASP Network. Is the tide turning again for cephalosporin resistance in *Neisseria gonorrhoeae* in Europe? Results from the 2013 European surveillance. *BMC Infect Dis*. 2015;15:321.
2. Rice LB. Will use of combination cephalosporin/azithromycin therapy forestall resistance to cephalosporins in *Neisseria gonorrhoeae*? *Sex Transm Infect*. 2015;91(4):238-40.
3. Chisholm SA, Wilson J, Alexander S, Tripodo F, Al-Shahib A, Schaefer U, Lythgow K, Fifer H. An outbreak of high-level azithromycin resistant *Neisseria gonorrhoeae* in England. *Sex Transm Infect*. 2015 Nov 24. pii: sextrans-2015-052312.
4. Lahra MM, Ryder N, Whiley DM. A New Multidrug-Resistant Strain of *Neisseria gonorrhoeae* in Australia. *N Engl J Med*. 2015;373(10):982.
5. Buckley C, Trembizki E, Donovan B, Chen M, Freeman K, Guy R, Kundu R, Lahra MM, Regan DG, Smith H, Whiley DM; GRAND Study Investigators. A real-time PCR assay for direct characterization of the *Neisseria gonorrhoeae* GyrA 91 locus associated with ciprofloxacin susceptibility. *J Antimicrob Chemother*. 2016;71(2):353-6.
6. Trembizki E, Buckley C, Donovan B, Chen M, Guy R, Kaldor J, Lahra MM, Regan DG, Smith H, Ward J, Whiley DM. Direct real-time PCR-based detection of *Neisseria gonorrhoeae* 23S rRNA mutations associated with azithromycin resistance. *J Antimicrob Chemother*. 2015;70(12):3244-9.
7. Peterson SW, Martin I, Demczuk W, Bharat A, Hoang L, Wylie J, Allen V, Lefebvre B, Tyrrell G, Horsman G, Haldane D, Garceau R, Wong T, Mulvey MR. Molecular assay for detection of genetic markers associated with decreased susceptibility to cephalosporins in *Neisseria gonorrhoeae*. *J Clin Microbiol*. 2015;53(7):2042-8.
8. Unemo M. Current and future antimicrobial treatment of gonorrhoea - the rapidly evolving *Neisseria gonorrhoeae* continues to challenge. *BMC Infect Dis*. 2015;15:364.
9. Hook EW 3rd, Golden M, Jamieson BD, Dixon PB, Harbison HS, Lowens S, Fernandes P. A Phase 2 trial of oral solithromycin 1200 mg or 1000 mg as single-dose oral therapy for uncomplicated gonorrhea. *Clin Infect Dis*. 2015;61(7):1043-8.
10. Basarab GS, Kern GH, McNulty J, Mueller JP, Lawrence K, Vishwanathan K, Alm RA, Barvian K, Doig P, Galullo V, Gardner H, Gowravaram M, Huband M, Kimzey A, Morningstar M, Kutschke A, Lahiri SD, Perros M, Singh R, Schuck VJ, Tommasi R, Walkup G, Newman JV. Responding to the challenge of untreatable gonorrhea: ETX0914, a first-in-class agent with a distinct mechanism-of-action against bacterial Type II topoisomerases. *Sci Rep*. 2015;5:11827.
11. Unemo M, Ringlander J, Wiggins C, Fredlund H, Jacobsson S, Cole M. High in vitro susceptibility to the novel spiropyrimidinetrione ETX0914 (AZD0914) among 873 contemporary clinical *Neisseria gonorrhoeae* isolates from 21 European countries from 2012 to 2014. *Antimicrob Agents Chemother*. 2015;59(9):5220-5.
12. Craig AP, Gray RT, Edwards JL, Apicella MA, Jennings MP, Wilson DP, Seib KL. The potential impact of vaccination on the prevalence of gonorrhea. *Vaccine*. 2015;33(36):4520-5.
13. Ezewudo MN, Joseph SJ, Castillo-Ramirez S, Dean D, Del Rio C, Didelot X, Dillon JA, Selden RF, Shafer WM, Turingan RS, Unemo M, Read TD. Population structure of *Neisseria gonorrhoeae* based on whole genome data and its relationship with antibiotic resistance. *PeerJ*. 2015;3:e806.
14. Demczuk W, Lynch T, Martin I, Van Domselaar G, Graham M, Bharat A, Allen V, Hoang L, Lefebvre B, Tyrrell G, Horsman G, Haldane D, Garceau R, Wylie J, Wong T, Mulvey MR. Whole-genome phylogenomic heterogeneity of *Neisseria gonorrhoeae* isolates with decreased cephalosporin susceptibility collected in Canada between 1989 and 2013. *J Clin Microbiol*. 2015;53(1):191-200.