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Gonorrhoea: tackling the global epidemic in the era of rising antimicrobial resistance

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Gonorrhoea: tackling the global epidemic in the era of rising antimicrobial resistance

Neisseria gonorrhoeae (NG), a sexually transmitted infection, remains a major global public health concern, estimated to have caused 87 million infections among 14-49 year olds in 2016 worldwide(1), with rising rates particularly among men who have sex with men (MSM).(2) Since the advent of effective antibiotic use in the 1930s, this pathogen has acquired resistance to most antibiotic classes used against it, and with the threat of increasingly resistant NG and dwindling treatment options, we are facing the very real possibility of untreatable NG.(3, 4) If not appropriately managed, gonorrhoea can result in severe sequelae such as pelvic inflammatory disease, infertility adverse pregnancy outcomes and newborn infections causing significant morbidity.(5) Gonorrhoea can also facilitate further transmission and increased risk of HIV.(6) To address this rising threat of gonorrhoea, we commissioned this Special Issue to summarize the latest updates on the burden of NG and inform strategies to control gonorrhoea in this era of rising antimicrobial resistance (AMR). It contains important reviews from global leaders in gonorrhoea and original research to better understand NG epidemics and patterns of resistance, gonorrhoea prevention, diagnosis and treatment including appropriate drug use for antibiotic stewardship (including the role of molecular diagnostics), and to provide an update on novel innovations. The Special Issue highlights the urgent need to invest in accelerating new antimicrobials against NG, point-of-care tests and promising vaccines. We thank the World Health Organization (WHO) for their generous sponsorship to make this Special Issue open-access.

Understanding the burden of NG and NG-AMR

Kirkcaldy and colleagues, provides a global epidemiologic overview of the growing international threat of gonorrhoea, emphasizing the disproportionate burden among men who have sex with men (MSM), transgender individuals, racial/ethnic minorities and indigenous populations, sex workers and international travellers. There is a need to improve STI surveillance including collecting more data among key populations especially from transgender and adolescents as well as the burden of extragenital gonorrhoea. Unemo and colleagues, describes the critical work of the WHO Gonococcal Antimicrobial Surveillance Programme, a network of reference laboratories, established in 1990. The 'real-world' value of such a program is demonstrated by the data from 2015/16 of the susceptibility to ceftriaxone/cefixime, azithromycin and ciprofloxacin, and confirmed treatment failures with ceftriaxone with/without azithromycin or doxycycline. Further strengthening this program will be essential to provide the most up-to-date quality-assured surveillance data to ensure ongoing global surveillance of NG-AMR.

Callander and colleagues underscores the importance of reporting anatomical site-specific gonorrhoea diagnoses. The authors showed that the rise in gonorrhoea incidence among MSM attending Australian sexual health services, were disproportionate from rectal and oropharyngeal gonorrhoea.(7) This was not accounted for by use of diagnostic technology (nucleic acid amplification test (NAAT) vs. culture) and frequency of testing. Kohli and colleagues explore the role of Chemsex (using substances during sex to intensify and extend sexual sessions) in gonorrhoea diagnoses in the United Kingdom. They report that the use of crystal metamphetamine and gamma-hydroxybutyric acid (GHB) among MSM in the past

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year was associated with twice the risk of gonorrhoea, and nearly four times the risk if men used all three chemsex drugs (+ mephedrone), compared to men reporting no use. To better understand the rise of NG in heterosexuals, Philipps and colleagues' study examines a decade of data (2007-2017) from Melbourne, Australia to explore the risk factors associated with NG detection among heterosexual males. They report an 80% increase in urethral gonorrhoea diagnosis among high-risk and symptomatic heterosexual males between 2007 and 2017 and highlight the need to better characterize the rise of NG in heterosexual networks and inform public health campaigns.

Understanding NG case management

Loo and colleagues uncover suboptimal management of gonorrhoea in a hospital network in Australia, reminding us of the need for a concerted, broad public health response involving multiple stakeholders including hospital systems, if we are to control this epidemic. They examined five parameters of care - eliciting a sexual and travel history, culture of specimens for antimicrobial susceptibility testing, consideration of HIV testing, contact tracing to identify and treat other potential cases, and notification to health authorities for ongoing surveillance. These parameters provide a useful benchmark to evaluate the quality of NG case management in other settings.

Novel thinking is needed

To effectively control NG, new thinking is needed in several areas: prevention, diagnostics and management, particularly in the era of NG-AMR.

Novel primary prevention methods

Non-antibiotic interventions and vaccinations are needed to stem the global rise of NG.(8) Gottlieb and colleagues review the data for gonorrhoea vaccination and efforts to advance viable gonococcal vaccine development, in light of a proof-of principle study demonstrating the cross-protection from the group B meningococcal outer membrane vesicle (OMV) vaccine to confer protection against NG.(9) The authors review promising vaccine candidates and describe the important activities of the Global STI Vaccine Roadmap.

A growing body of work has arisen that demonstrates the importance of oropharyngeal transmission of gonorrhoea in the epidemic.(10) The oropharynx is an important environment where AMR strains may evolve. Therefore, using a mouthwash has been proposed as a novel method for gonorrhoea prevention(11) and we await the results from a randomised controlled trial (Oral Mouthwash use to Eradicate GonorrhoeaA, OMEGA trial) that examines whether daily mouthwash use could prevent incident gonorrhoea.(12) Philipps and colleagues explored the current practice of mouthwash use among MSM and its association with oral sex practices, and show that currently there is no association between frequent mouthwash use and oral sex practices,(13) suggesting a need for public education if mouthwash is shown to be effective in preventing gonorrhoea. Chow and colleagues' timely review addresses the practical question of what are the evidence gaps in implementing mouthwash use as a public health campaign.(14) The authors also raise practical questions that remain e.g. which mouthwash works (out of all the products available), optimal frequency, time, volume, how to use it (gargle), and timing (post-sex,

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daily).

Novel diagnostics using molecular tests

AMR to the first-line NG treatment of ceftriaxone plus azithromycin has now been reported. A diagnostic-based antibiotic stewardship strategy is urgently needed to 1) identify the etiologic agent through a rapid easy to use point-of-care test (e.g. differentiate CT/NG) to ensure immediate treatment with the right antibiotic that may reduce over-treatment, follow-up and onward transmission; and 2) identify susceptible strains through a near patient AMR diagnostic (e.g. for ciprofloxacin susceptibility) to conserve current regimen and future treatment. Currently there are several well-characterised molecular AMR determinants that can be used for effective prediction of AMR in NG, particularly for ciprofloxacin, but less adequately for azithromycin, cefixime and ceftriaxone. Hall and colleagues' timely and important review describes the resistance-associated genotype markers with phenotypic resistance to fluoroquinolones and macrolides. They found that the S91 and D95 mutations in the GyrA protein had high sensitivity (98.6%, 95% CI: 98.0-99%) and specificity (91.4%, 95% CI: 88.6-93.7) for ciprofloxacin resistance. Cefixime, a third-generation extended-spectrum cephalosporin, is one of few antibiotics that NG is susceptible to. Deng and colleagues' systematic review describes the molecular characteristics and potential mechanisms for gonococcal resistance to cefixime, gives critical information for optimal targets for molecular assays seeking to predict cefixime susceptibility. Together, these data are helpful in assessing potential accuracy of these markers for AMR diagnostic platforms.

Diagnostics are critical in characterizing NG strains that fail treatment. Buckley and colleagues highlight the importance of strengthening methods to verify gonorrhoea treatment failures. They reinvestigated the two Australian cases associated with treatment failure with ceftriaxone, using whole genome sequencing (WGS) to provide better discrimination between strains rather than traditional Sanger sequencing (which examines two highly variable regions). Whilst WGS offers faster and better prediction, and the ability to compare with similar cases elsewhere, the cost-effectiveness of WGS would need to be further explored, particularly in light of decreasing prices over time of this technology.

Novel management

Most countries use ceftriaxone or cefixime plus azithromycin in their empiric treatment of NG. There are now debates on the use of azithromycin as dual therapy for gonorrhoea, as well as treatment of chlamydial infection due to increasing resistance to NG, as well as *Mycoplasma genitalium*. Mensforth and colleagues' review tackles the practical issue of how to wisely use azithromycin for gonorrhoea management: reviewing evidence for its use as monotherapy, dual therapy and its impact on other STIs. They challenge the use of 1 g Azithromycin as part of dual therapy. With very little second-line options available, Lewis reviews the search for new agents to manage NG and find that the pipeline is disappointingly sparse. The authors discuss the latest evidence for ertapenem, modern fluoroquinolones (gemifloxacin, sitafloxacin, delafloxacin), solithromycin, gepotidacin, and zoliflodacin, though none obviously emerge as a clear winning candidate.

To tackle an "old foe", there is a pressing need for new thinking in how we approach the foundations for controlling an STI: better primary prevention methods (through vaccination,

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mouthwash and smarter condom promotion), earlier detection (of the index case and their partners) and appropriate antimicrobial treatment (through improved diagnostic capabilities, antimicrobial stewardship and search for new antimicrobials) and a stronger inter-connected global surveillance systems to better inform public health guidelines and policies. We hope that the articles within this Special Issue provides you with an overview of the latest thinking and novel approaches for the control of NG and spurs new ideas to tackle the global epidemic of gonorrhoea.

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