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Proceedings of the 2017 International Forum on Gonococcal Infections and Resistance in Shenzhen, China

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Abstract

The 2017 International Forum on Gonococcal Infections and Resistance (2017 IFGIR) was held at Shenzhen, China from September 17, 2017, to September 19, 2017. The key objectives of the conference were to review and analyze the epidemiological profiles of gonococcal infections and antimicrobial resistance (AMR) at global, regional, and national levels; to share and discuss findings from ongoing and completed research studies; and to identify research needs to respond to the spread of gonococcal infections and AMR. The following contents were presented at the conference: global estimates of infections with *Neisseria gonorrhoeae*; global, regional and country status of gonococcal AMR; molecular techniques for predicting gonococcal AMR and the use of these technologies to enhance gonococcal AMR surveillance and clinical management; and updates on therapeutic approaches to gonococcal AMR.

Gonorrhea, caused by *Neisseria gonorrhoeae* (NG), is a major public health priority globally because of high, in many settings, rising disease rates and increasing antimicrobial resistance (AMR). Many biological and behavioral factors have played an important role in driving the transmission and spread of gonococcal infections. The emergence and spread of AMR threatens disease prevention and control strategies. Gonococcal AMR is now widely recognized as one of most significant AMR threats to global health and is highlighted by recent reports from the World Health Organization (WHO),[1] the G20 summit[2] and the United Nations Assembly,[3] and also by many countries.[4,5] The rise in gonococcal AMR and

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the threat of untreatable gonococcal infection has called for developing innovative strategies to limit the spread of the resistant gonorrhea.[6,7] To update to the epidemiological profiles of gonococcal infections and AMR, share the findings from the currently ongoing and completed research projects, and identify new research needs to help address the spread of gonococcal infections and AMR, the Chinese Academy of Medical Sciences (CAMS) and Peking Union Medical College (PUMC) Institute of Dermatology, the National Center for STD Control and the Shenzhen Center for Chronic Disease Control in China jointly organized the 2017 International Forum on Gonococcal Infections and Resistance (2017 IFGIR) in Shenzhen, China from September 17, 2017, to September 19, 2017. Over 100 participants attended the forum, in which there were 21 presentations followed by extensive discussion. Key findings and outcomes from the scientific program of the conference together with relevant literature review are summarized in this report.

SESSION 1: OVERVIEW OF GONOCOCCAL INFECTION AND AMR

Regarding the global epidemic of gonococcal infection, the World Health Organization (WHO) estimated that there were 78 million new cases infected with gonorrhea among 15- to 49-year-olds worldwide in 2012.[8] Surveillance data in the US, Australia and European countries indicate an increasing rate of gonococcal infection among men who have sex with men (MSM) in recent years.[9–12] Several issues potentially related to the spread of gonococcal infection were highlighted in the conference. First, extragenital gonococcal infections are common, especially among MSM. Data from the Sexually Transmitted Disease Surveillance Network in the United States between 2010 and 2012 shows that 10.2% of MSM tested for NG were positive for rectal NG either at their most recent visit or in the 12 months prior, 7.9% tested positive for pharyngeal NG and 11.1% positive for urogenital NG. In total, extragenital NG infections made up 53% of all NG infections found among MSM.[13] Given that extragenital infections are usually asymptomatic, appropriate screening is critically important and should be based on a behavioral history that relates to anatomical sites of sexual exposure. It was noted that suboptimal screening for NG, particularly at extragenital sites among MSM, represents missed opportunities for effective control of the infection. Second, the impact of introducing human immunodeficiency virus (HIV) treatment as prevention or preexposure prophylaxis (PrEP) approach on compromising safe sexual behaviors, which consequently result in transmission of gonorrhea and other sexually transmitted infections (STIs), is a concern. In a study among a subset of 657 PrEP initiators enrolled for evaluation between 2012 and 2015, no new HIV infections were found but 15% and 28% were diagnosed with NG 6 and 12 months after PrEP use, respectively, and the rate of self-reported condom use decreased by 41% after 6 months of PrEP use.[14] It has been noted that STI rates in MSM, including NG, have been increasing for some time (for a variety of reasons including serosorting) in a health center in Chicago[15] and that PrEP may increase NG further among PrEP users through a recommendation of more frequent NG screening and “risk compensation” related to changes in sexual behaviors. Third, an increasing number of cases with *Neisseria meningitidis* (NM; an organism closely related to NG)-associated urethritis have been reported among people at risk for STIs. Because NM is a commensal bacteria present in the oropharyngeal flora that causes invasive infections, more cases with NM-associated urethritis were observed among

men attending sexual health clinics and MSM in communities in the United States although the cases were less common than the infections caused by NG.[16,17] However, recent outbreaks of NM infection in the United States have also occurred in heterosexuals.[18,19]

Most recent data from the WHO Gonococcal Antimicrobial Surveillance Programme (GASP) shows that among the countries participating in the program (most countries used either the interpretative criteria of the European Committee on Antimicrobial Susceptibility Testing or the Clinical Laboratory and Standards Institute), 66% (51/77) reported decreased susceptibility to cefixime or ceftriaxone, 81% (47/58) reported resistance to azithromycin, and 97% (70/72) reported resistance to ciprofloxacin in 2014.[20] Of 12 countries reporting surveillance data to the GASP in the WHO Western Pacific in 2016, 5 (42%) reported more than 5% isolates resistant to azithromycin and/or more than 5% isolates less susceptible to ceftriaxone. Data from the national surveillance programs in high-income countries, including Gonococcal Isolates Surveillance Project in the United States,[21] the Gonococcal Resistance to Antimicrobials Surveillance Programme in England and Wales[22] and Australian Gonococcal Surveillance Programme,[23] indicate a relatively low prevalence of isolates with an elevated minimum inhibitory concentration (MIC) of ceftriaxone (≥ 0.125 mg/L) or elevated MIC of azithromycin (≥ 2.0 mg/L). In 2016, Gonococcal Isolates Surveillance Project showed 0.27% of isolates had elevated MICs of ceftriaxone (≥ 0.125 mg/L) and 3.6% had elevated MICs of azithromycin (≥ 2.0 mg/L). Isolates with both elevated MICs of ceftriaxone and azithromycin represented 0.08% of all isolates, all of these 4 isolates were from Hawaii and were successfully treated with 250 mg ceftriaxone and 1 g azithromycin. Quality programs and data of gonococcal AMR at national level in lowor middle-income countries are limited. In India, an increase from 2.4% in 2002–2006 to 4.2% in 2007–2012 for decreased susceptibility to ceftriaxone (MIC ≥ 0.06 mg/L) and from 0.8% to 1.5% for azithromycin resistance (MIC ≥ 1.0 mg/L) was observed but the sample sizes in these surveys are generally small. The Gonococcal Resistance Surveillance Programme in China shows a high prevalence of isolates resistant to azithromycin (MIC ≥ 1.0 mg/L, ~20%) or less susceptible to ceftriaxone (MIC ≥ 0.125 mg/L, ~10%) in 2016, and an increasing proportion simultaneously resistant to azithromycin and less susceptible to ceftriaxone, reaching at more than 3% in 2016.[24]

SESSION 2: IMPROVEMENT OF AMR SURVEILLANCE PROGRAMS IN *Neisseria gonorrhoeae*

Current culture-based AMR surveillance is challenged by increasing use of nucleic acid amplification test (NAAT)-based diagnostic test for gonorrhea in well-resource settings[25,26] and lack of capacity in bacterial culture in poor-resource settings. In this conference, research updates on strategies to enhance current AMR surveillance by the use of molecular technologies were reviewed and discussed. Molecular technologies that allow for testing of AMR determinants in NG can be primarily categorized into molecular epidemiological genotyping methods including NG multiantigen sequence typing (NG-MAST) and multilocus sequence typing (MLST)[27] to determine sequence types for predicting AMR with varying sensitivity and specificity, and whole-genome sequencing (WGS) or next-generation sequencing (NGS)[28,29] to detect AMR determinants as well as phylogeny of strains. The

NG-MAST is the best assay for short-term molecular epidemiological surveillance, whereas MLST is more conservative and more suitable for long-term surveillance in a large scope in geographic area. Whole-genome sequencing is the most promising method for future surveillance of gonococcal AMR (particularly if it becomes more affordable) because it has the highest resolution and can also simultaneously provide all the established NG-MAST, MLST, and NG-STAR genotyping information. The Gonorrhoea Resistance Assessment via Nucleic Acid Detection Project in Australia reported their studies comparing results of 8 NG AMR PCR assays with the routine culture-based surveillance data, indicating that molecular methods can enhance NG AMR surveillance for a range of antimicrobial drugs, particularly in remote areas where bacterial culture is impractical or not possible.[30] In addition, their study further confirmed that the GyrA S91 locus is highly predictive of ciprofloxacin susceptibility with a sensitivity of 99.0% and a specificity of 99.4%.[31]A novel technology which can simultaneously detect numerous targets in a single test, the Agena MassARRAY has been designed for use in genotyping of gonococcal isolates in Australia, but further validation of the technology in more settings may be needed.[32]In addition, it is suggested that the molecular results could be linked to the enhanced epidemiological, behavioral, and clinical data collected from the routine surveillance program for improving our understanding of spread of NG AMR within a sexual network or in an outbreak. It is generally agreed that culture-based antibiotic susceptibility testing is still a central part of gonococcal AMR surveillance. Although several molecular methodologies have been successfully developed, showing promising results in predicting AMR to different classes of antimicrobials, none of these methods has been routinely applied to the national surveillance programs for gonococcal AMR at the time of the conference.

SESSION 3: THERAPEUTIC APPROACHES TO AMR

To respond to the increasing threat of gonococcal AMR, a series of therapeutic approaches have been proposed or developed. One of the approaches is to introduce the dual therapy combining ceftriaxone and azithromycin, which has been recommended as national treatment guidelines in many countries.[33,34]In this conference, the progress on development and application of the drugs in a pipeline for treatment of gonorrhea was reviewed, and the updated findings from the researches toward development of efflux pump inhibitor and immunotherapeutic therapy were reported.

Development of new drugs has been listed as a high priority by the WHO, the National Institute of Allergy and Infectious Diseases and additional organizations such as the Global Antibiotic Research and Development Partnership. A number of drugs or drug candidates for NG are in different stages of the development pipeline: (1) those at a preliminary research stage include 5 arenicin compounds (antibiotics against Gram-negative bacteria), deoxynybomycin (novel fluoroquinolone), and dalbavancin (lipoglycopeptide); (2) those at a translational research stage include JNJ-Q2 (novel fluoroquinolone), cethromycin (ketolide), and modithromycin (macrolide), and (3) those at a clinical evaluation stage include zoliflodacin (DNA gyrase inhibitor), gepotidacin (topoisomerase II inhibitor), and solithromycin (fluoroketolide). Zoliflodacin (formerly ETX0914 and AZD0914; Entasis Therapeutics) is a novel oral spiropyrimidinetrione antimicrobial with dual DNA topoisomerase II inhibitory activity targeting GyrB and ParE and is expected to be used for

the treatment of uncomplicated gonorrhea. An open-label phase 2 trial demonstrated high microbiological cure rates at 6 ± 2 days of zoliflodacin in comparison with ceftriaxone (98% of 49 patients receiving single dose of 2 g and 100% of 47 patients receiving a single dose of 3 g vs 100% of 21 patients receiving single intramuscular 500 mg of ceftriaxone). Entasis has partnered with the Global Antibiotic Research and Development Partnership to codevelop formulation and design of phase 3 trial. Gepotidacin (GSK2140944; GlaxoSmithKline) is a novel oral triazaacenaphthylene antimicrobial with DNA topoisomerase II inhibitory activity targeting the GyrA and ParC. A phase 2 trial demonstrated that 29 of the 30 patients receiving 1.5 g of oral gepotidacin achieved microbiological cure of urogenital NG at the test-of-cure visit and 37 of the 39 patients receiving a 3.0-g dose achieved microbiological cure. Isolates from 2 patients developed resistance between baseline and test-of-cure (D86N in ParC and A92T in GyrA).[35,36]Basic studies on the first "superbug" H041,[37] which has high level resistance to ESCs and most other antimicrobials show that a single nucleotide deletion in the *mtrR* promoter results in overexpression of the MtrCDE efflux pump in H041. This promoter mutation results in loss of production of MtrR which is the transcriptional repressor of the MtrCDE efflux pump. By experimentally expressing a wild-type MtrR from a second site on the H041 chromosome, the MtrCDE efflux pump was dampened and gonococcal susceptibility to penicillin was greatly increased. In vivo experiments also show that increased efflux pump gene expression can significantly impact clinical efficacy of antibiotics in a mouse model. By decreasing the level of MtrCDE through use of an efflux pump inhibitor, adjunctive therapy with an efflux pump inhibitor may allow for return of penicillin or other previously used antimicrobials for effective treatment of gonorrhea.

Given that lipooligosaccharide (LOS) is the most abundant molecule on the gonococcal surface and plays a key role in pathogenesis, several immunotherapeutic approaches against NG that target LOS sialylation are under investigation. The first approach is based on fusing the region in the complement inhibitor factor H (FH) that binds to gonococci to the Fc region of IgG to create a FH/Fc fusion molecule. Factor H/Fc can bind to sialylated gonococci and activate complement; complement activation consequently kills gonococci by membrane attack complex and/or through phagocytosis. In vitro studies indicate that FH/Fc given intravaginally decrease the duration of colonization and bacterial burden of multidrug resistant (MDR) isolate H041, both in wild-type and human FH/C4BP transgenic mice, suggesting that FH/Fc could be a useful agent against gonorrhea. The second is based on 2 CMP sugars of sialic acid analogs, that is, a 9-azido derivative of CMP-Neu5Ac called CMP-Neu5Ac9Az and a diacetyl legionaminic acid (Leg) derivate called CMP-Leg5Ac7Ac. Studies have shown that Leg5Ac7Ac or Neu5Ac9Az incorporation into gonococcal LOS prevents serum resistance mediated by physiologic Neu5Ac, and reduces the burden of MDR NG in the mouse model. Based on efficacy, safety, and stability, CMP-Leg5Ac7Ac is thought to be the lead molecule for potential use for immunotherapy. In addition, a study of female partners of NG infected men in Nanjing indicated significantly higher levels of antibodies directed against a LOS epitope defined by binding of a monoclonal antibody (mAb) called 2C7 (the "2C7 epitope") in women exposed to and infected with NG than women exposed to but not infected with NG or control women who were not exposed to NG but rather were exposed to chlamydia. Mice inoculated with NG strain FA1090 and

passively immunized with mAb 2C7 or control IgG3 antibody showed that the mAb 2C7 treated animals had significantly shorter time to clearance of NG, lower bacteria colonization loads and less bacterial burdens consolidated over time (area under the curve [$\log_{10}$ CFU] analysis) than IgG3 (control)-treated animals.[38]Further studies have also shown that a human IgG1 chimeric mAb derivative of mAb 2C7 is efficacious in wild type and human FH/C4BP transgenic mice, suggesting possible utility of mAbs to treat AMR gonorrhea. Results from a preliminary study in humans infected with NG suggest that expression of gonococcal AMR genes may not only be programmed genotypically but also be driven by site-specific environments and that distinct NG gene expression signatures are detected during genital infection in men and women and are related, in part, to clinical outcomes. These findings may imply that therapeutic strategies could target gender-specific differences in expression of AMR genes.

SESSION 4: THE WAY FORWARD

The NG has been included in the Global Antimicrobial Resistance Surveillance System as one of the priority pathogens for AMR surveillance of routine clinical samples, and specific approaches are also under development for monitoring gonococcal AMR to align with the Global Antimicrobial Resistance Surveillance System objectives.[20] To address the gonococcal AMR, more advocacy will be needed to increase awareness of the threat from gonococcal AMR and the recognition that gonococcal AMR is not only an issue related to patient care but also to the social and economic impacts resulting from untreatable gonorrhea and its sequelae. In addition, stewardship of antimicrobials and improved gonococcal AMR surveillance must be incorporated into the national AMR action plans. It is important to further strengthen national-, regional- and global-level surveillance programs by increasing coverage, representativeness and quality in which WHO-GASP and its collaborators in each of WHO regions should take an important role in coordination, capacity-building, technical supports, quality assurance, and data analysis through the WHO global network. It is also critical for each surveillance program to ensure that gonococcal AMR surveys are implemented in a consistent, high-quality, standardized, and timely manner. In addition, collecting sufficient demographic, behavioral, and/or clinical data in the surveys is critical for enabling appropriate interpretation of the AMR results.

With regard to research priority, basic science studies, designed to explore gonococcal pathogenesis and mechanisms of gonococcal AMR, identify and characterize novel therapeutic or vaccination targets, discover new antimicrobial agents and develop simple and rapid point-of-care (POC) diagnostics are needed. Development and introduction of NAAT-based rapid POC diagnostics for gonorrhea has been listed as a high priority by the WHO; some products have been approved by the US Food and Drug Administration and more are in the pipeline. Given that NAAT-based assays for diagnosis of gonorrhea have been increasingly applied in clinical practice but the current molecular assays have limitations for use to predict gonococcal AMR, more studies on development, validation, and introduction of novel technologies, such as WGS- and NGS-based assays, for efficiently, rapidly, and accurately identifying gonococcal AMR and determining MIC values should be prioritized. These methods could be used to detect both known and novel mutations associated with NG AMR and to generate genotyping information, supporting AMR and epidemiological

surveillance in the absence of culture.[29,39] Given the proven ability of POC tests to increase the efficiency of health care, ideally both NAAT-based and WGS-based POC assays will eventually be available to clinicians for rapid diagnosis and precision treatment of gonococcal infections. Another research priority area is the need to facilitate studies on optimizing current treatments and validating new therapeutics. In addition to development of new antigonorrhea agents, ideally, currently available drugs could continue to be used in combined (dual) therapies to help preserve them, and real-time sequencing technologies could be used for individualized therapy to enable recycling of older antimicrobials. Although discussion on vaccine was very briefly,[40] the participants agreed that development of a gonococcal vaccine should be a research priority because the vaccine might be the only sustainable solution for gonorrhea control.

In the conference, a “ROADMAP” plan to address the research needs on NG AMR in China was proposed. The approach includes that Resistance surveillance of gonorrhea should be strengthened to provide an early detection and warning system for the emergence of AMR; Outcome impacts from emergence and spread of resistant gonococcal strains should be evaluated to estimate the epidemiological and socioeconomic consequences; Application behaviors of antimicrobial use by medical professionals and patients or for animal growth should be investigated to understand the selection pressures driving AMR; Diagnostic tools for efficient and timely detection of NG infection and AMR should be developed to guide targeted interventions; Mechanisms of gonococcal AMR should be explored to identify the potential targets for interventions; Antimicrobial efficacy evaluation of post-marketed antibiotics to treat gonorrhea and novel therapies to address gonococcal AMR should be conducted to provide evidence for updating the treatment recommendations; and Population pharmacokinetics and pharmacodynamics of the recommended antimicrobials for gonorrhea should be monitored to evaluate dose-concentration-response relationships in the patients with gonorrhea, particularly those immunocompromised by coinfection with HIV. In China, a ROADMAP-structured work team has been established by working towards a common goal and integrating the different sources all navigating the same directions.

CONCLUSIONS

In conclusion, the IFGIR in 2017 was very informative, interactive and successful. Participants of the conference agreed to the necessity of more collaborative projects to provide better evidence regarding prevention and control of gonococcal infections and AMR. Also, the participants agreed that although still at an early stage the Forum has the potential to be a high-quality and sustainable conference for scientists around world to debate the recent advances, to validate the available evidence, to prioritize the research needs, and to promote new areas for collaborative projects. It is planned to organize the next conference in 2019.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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