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Holistic actions are essential to combat the global public health burden of non-viral sexually transmitted infections: challenges and future perspectives

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Sexually transmitted infections (STIs) represent a significant international public health burden. These infections result in substantial morbidity, mortality and economic costs globally, and require more attention and resources internationally. This special focus issue of *Expert Review of Anti Infective Therapy* invited key opinion leaders to review and discuss the challenges associated with the diagnosis and treatment of non-viral STIs. The issue also elucidates the future perspectives, ways forward and holistic actions imperative to effectively combat these STIs.

Sexually transmitted infections (STIs) represent a significant global public health burden. In 2008, the WHO estimated 499 million new cases of four curable STIs among adults, that is, trichomoniasis (276 million cases), gonorrhea (106 million cases), *Chlamydia trachomatis* infections (106 million cases) and syphilis (11 million cases) [1]. In total, this represented an 11% increase from the number of cases in 2005. These STIs, including their severe complications such as infertility, ectopic pregnancy, stillbirth, preterm birth, neonatal death, tertiary syphilis and enhanced HIV transmission, result in significant morbidity, mortality and economic costs globally. These infections and additional STIs, including the challenges and future perspectives of their management, are discussed by key opinion leaders in this special focus issue of *Expert Review of Anti Infective Therapy*.

More incident cases of trichomoniasis are annually estimated than the combined burden of gonorrhea, chlamydia and syphilis globally [1]. Despite this fact and the substantially enhanced HIV transmission by the infection, trichomoniasis has not received significant attention internationally. In this issue, Sena *et al.* [2] review the characteristics, epidemiology, treatment and management of persistent and recurrent trichomoniasis. The knowledge regarding the health and economic impact of trichomoniasis needs to be enhanced, and the control, diagnostics and treatment of trichomoniasis should be improved. For resourced and, particularly, less-resourced settings, which suffer from the highest burden of trichomoniasis, sensitive, specific and cost-effective nucleic acid amplification tests (NAATs) or point-of-care (POC) tests would be exceedingly valuable. Furthermore, novel effective antibiotics for treatment of metronidazole- and tinidazole-resistant cases are crucial and several non-nitroimidazole drugs have demonstrated acceptable *in vitro* activity. However, randomized clinical trials are crucial to evaluate their clinical efficacy [2]. The lack of new therapeutic antibiotics is a severe problem that affects the management of many non-viral STIs. For gonorrhea, due to the emergence of resistance to the last treatment option, that is, ceftriaxone novel antimicrobials are urgently needed [3]. Unemo *et al.* [4] discuss the challenges and strongly emphasize on taking holistic action to combat this most worrying

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situation, including implementing action/response plans; considering the use of dual antimicrobial regimens (mainly ceftriaxone plus azithromycin); enhancing surveillance of gonorrhea, gonococcal antimicrobial resistance, treatment failures and antimicrobial use/misuse; improving prevention, early diagnosis, contact tracing and treatment; developing and evaluating appropriate use of molecular antimicrobial resistance testing, ideally POC and with simultaneous detection of gonococci, to supplement culture-based methods and ideally guide tailored treatment; and, most importantly, conducting an intensified research to develop novel antimicrobials. Furthermore, for *Mycoplasma genitalium* infections, clinical resistance to the recommended treatment (azithromycin) is widespread and the first resistant cases with moxifloxacin, the last remaining option for monotherapy, are now verified. Taylor-Robinson [5] reviews the detection of *M. genitalium* (NAATs are the only feasible methods), antimicrobial resistance, and previous, current and possible future treatment options. As for gonorrhea, if no new therapeutic antimicrobials are timely available, combination therapy might be the only solution for *M. genitalium* infections also.

Nevertheless, lack of resistance to recommended therapeutic antimicrobials alone is not sufficient in the combat against non-viral STIs and, accordingly, improved prevention and management, in general, is frequently imperative. For example, despite the fact that diagnostic tests for syphilis have been available since the early 1900s and effective treatment (penicillin) has been widely available since the 1940s, 11 million new syphilis infections are estimated annually among adults worldwide [1]. Trope *et al.* [6] discuss the devastating disease, congenital syphilis. Since 2007, the WHO has been leading a global initiative to eliminate mother-to-child transmission of syphilis, with an elimination target of 50 cases per 100,000 live births. However, in some settings, for example, in many countries in Africa, to achieve this target, the prevalence of syphilis in pregnant women needs to decrease and, for this, interventions targeting people other than pregnant women are crucial to decrease the prevalence in the general population also. Ways forward include an increased awareness, consistent case definition of congenital syphilis, improved access and quality of antenatal care services (diagnostic tests, testing and accessibility to penicillin), and case reporting. Furthermore, an increased focus on STI prevention, testing, and treatment in the general population, with a special focus on key populations (non-pregnant women and high-risk populations), is crucial [6].

The epidemiology of non-viral STIs also fluctuates over time and in different geographic areas. For example, the invasive etiological agent of lymphogranuloma venereum (LGV), *C. trachomatis* genovars L1–L3, was earlier mainly observed in tropical regions, such as parts of Africa, southeast Asia, Latin America and the Caribbean. However, this changed in 2003 when the first endemically acquired LGV cases were reported in Rotterdam, the Netherlands, predominantly among HIV-positive men-who-have-sex-with-men, which was followed by cases reported from several countries in western Europe, North America and Australia. de Vrieze and de Vries [7] elaborate on the epidemiology, clinical presentation, diagnosis, treatment and current knowledge of LGV. Worryingly, LGV is now reported as asymptomatic in 5–27% of cases and shows an increasing trend in several European countries. It is crucial to have an increased awareness, improved prevention, early diagnosis and directed screening in high-prevalent settings (all men-who-have-sex-with-men who report having receptive anal sexual practices in the previous 6 months); commercialize sensitive, specific and cost-effective LGV NAATs; and use only appropriate treatment (extended doxycycline regimen) for patients and traced sexual contacts. It would be valuable to have an antibiotic regimen with a shorter duration to improve patient compliance and enhance the knowledge regarding the biology of the disease, exact modes and risks of transmission, and pathogenic and/or host mechanisms causing the invasive nature of the LGV genovars [7].

Interestingly, chancroid (soft chancre, ulcus molle), whose etiological agent is *Haemophilus ducreyi*, is now likely to be close to extinction in many settings where it was previously endemic, such as resource-poor countries of Africa, Asia, Latin America and the Caribbean. Lewis [8] reviews the epidemiology, clinical features, diagnosis and treatment of chancroid. The widespread implementation of syndromic management for genital ulcer disease, including effective antimicrobials to treat the mostly symptomatic chancroid, the sexual behavioral changes observed within communities and key/risk populations, the roll out of male circumcision in sub-Saharan Africa and a rise in socioeconomic circumstances in some countries have certainly led to the demise of chancroid. However, the inaccuracy of clinical diagnosis, lack of laboratory specimens as a result of the STI syndromic approach, the difficulty to detect *H. ducreyi* in most laboratories and the absence of NAAT-based etiological surveillance for genital ulcer diseases in many countries have resulted in limited recent prevalence data for chancroid. This might be the time to call for public health investment and to determine exactly where and at what prevalence chancroid exists globally. This would highlight those countries where efforts should be focused in order to possibly achieve the worldwide eradication of chancroid as the first STI [8].

Undoubtedly, early, sensitive, specific and cost-effective diagnoses would be invaluable to combat the non-viral STIs. Appropriate rapid POC tests would be ideal for this, that is, patients can receive immediate diagnoses and treatment, which prevents onward transmission, offers the opportunity for counseling messages and to avoid a loss of follow-up and, accordingly, would significantly affect the STI public health burden locally, nationally and internationally. Gaydos and Hardick [9] provide an up-to-date review of the current POC tests for STIs and discuss future perspectives and advances of rapid POC diagnostics of STIs. Appropriate POC tests exist for HIV and syphilis (the newest ones also detecting non-treponemal antibodies), and notable advances have been made in *Trichomonas vaginalis* POC tests (i.e., the OSOM Trichomonas Rapid test). Unfortunately, sufficiently sensitive POC tests for, for example, *Neisseria gonorrhoeae*, *C. trachomatis* and

M. genitalium, are lacking. Nevertheless, particularly in less-resourced settings and for high-risk populations, modeling studies have indicated that even less-sensitive POC tests can result in additional patients being treated [10,11]. Furthermore, if a POC test could simultaneously detect determinants for resistance (or susceptibility), it would be invaluable for immediately guiding a tailored antimicrobial therapy. For bacterial STIs such as gonorrhea and chlamydia, investment in terms of funding, time and research effort is required to develop appropriate POC tests. New technologies including isothermal amplification and low-cost, low-complexity microfluidic paper-based platforms assure that major advancements for POC tests can be expected in the near future [9].

In the next few years, novel genetic and phenotypic technologies will likely revolutionize the STI diagnostics; molecular antimicrobial resistance testing; drug discovery and design; our understanding regarding emergence, evolution and prediction of antimicrobial resistance; and possibly the STI vaccine field. Presently, holistic actions are essential to combat the persistent STI public health burden, including an improved generalized and targeted prevention (increased awareness, sexual behavioral changes, improved condom use, testing, contact tracing), diagnostics (early testing and access to appropriate tests, particularly validated NAATs or effective POC tests), treatment (early treatment, access to effective antimicrobials, detecting and combating antimicrobial resistance), of patients and traced sexual contacts, case reporting and epidemiological surveillance.

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