

Refocusing Research on Sexually Transmitted Infections

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This article highlights biomedical research goals for the development of critical tools, including innovative diagnostics, safe and effective vaccines, and new and improved therapeutics, necessary to achieve an end to the global epidemic of sexually transmitted infections. The incidence of sexually transmitted infections (STIs), including gonorrhea, syphilis, chlamydia, and trichomoniasis, is increasing by over 1 million new cases daily and represents a global public health crisis. There is an alarming increase of gonorrhea and syphilis among men who have sex with men and bisexual men, 2 key populations also at high risk for human immunodeficiency virus. A refocused, dedicated, and intensive biomedical research program is needed targeting development of innovative diagnostics, safe and effective vaccines, and new and improved therapeutics. This article highlights biomedical research goals providing critical tools necessary to achieve an end to the global STIs epidemic.

Keywords. sexually transmitted infections; refocusing biomedical research.

Sexually transmitted infections (STIs) represent a major public health crisis worldwide and in the United States, with the incidence of gonorrhea, syphilis, chlamydia, and trichomoniasis increasing by over 1 million new, curable cases daily [1]. The World Health Organization (WHO) estimates that in 2016 among women and men 15–49 years of age, there were 86.9 million people newly infected with *Neisseria gonorrhoeae*, 6.3 million people newly infected with *Treponema pallidum*, 127.2 million people newly infected with *Chlamydia trachomatis*, and 156.0 million people newly infected with *Trichomonas vaginalis* [1]. In 2017, the Centers for Disease Control and Prevention reported a total of 2.3 million new cases of STIs in the United States, including 600 000 cases of gonorrhea, 30 000 cases of primary and secondary syphilis, and 1.7 million cases of chlamydia, representing an increase since 2013 of 67%, 76%, and 22%, respectively.

An alarming increase in both gonorrhea and syphilis has been reported among men who have sex with men (MSM) and bisexual men [2]. Superimposed on this increasing incidence of STIs is the urgent threat of the increasing global incidence of drug-resistant gonorrhea that is likely to also become a major future health problem in the United States [2].

While these STIs are effectively treatable with a variety of antibiotic regimens, serious short- and long-term complications can result if STIs are left undiagnosed and untreated. Additionally, an untreated individual with an STI poses a threat of transmitting the infection to others—further expanding the STI epidemic. Gonorrhea and chlamydia can cause pelvic inflammatory disease, resulting in tubal scarring and infertility, life-threatening ectopic pregnancy, and chronic pelvic pain. Disseminated gonorrhea can cause infectious arthritis and other serious morbidities. Both STIs can be transmitted to a newborn during pregnancy and delivery resulting in blindness or serious life-threatening infections. Syphilis, if untreated, can cause serious cardiovascular, neurological, and dermatological disease in adults and can be transmitted during pregnancy. Congenital syphilis can result in premature delivery, stillbirth, neonatal death, as well as severe health complications

in newborns. The social impact of STIs include stigma, discrimination, shame, and, in some cases, can lead to gender-based violence, all of which serve as barriers to access of STI prevention, testing, and treatment services [1]. Clearly, STIs are a formidable global and domestic public health problem. Unfortunately, the overall response to this problem has been unsatisfactory and not commensurate with its public health impact, including in the arena of biomedical research and private sector investments. In this regard, there is an urgent need for a renewed focus on STI research in both the public and private sector and on the development of improved and innovative strategies for prevention, diagnosis, and treatment. In order to achieve the WHO Sustainable Development Goal of ending STI epidemics as major public health threats by 2030, there is a critical need for rapid, point-of-care (POC) diagnostics, new and repurposed treatments and treatment regimens, and vaccines [3].

DIAGNOSTICS

Improved and innovative diagnostics that are rapid, accurate, easy to use, low-cost, multiplex, POC, and even home-based allowing for self-testing will be critical components of the refocused efforts to rapidly and accurately diagnose and determine antibiotic susceptibility of STIs.

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The identification of asymptomatic infections will permit linkage to treatment and care and decrease the risk of transmission to others. Low-cost antigen- and antibody-detection POC gonorrhea [4] and chlamydia [5] diagnostic assay systems are easy to use, but insufficiently sensitive for screening purposes [6]. While the GeneXpert platform recommended by WHO is capable of detecting gonorrhea and chlamydia with acceptable sensitivity and specificity, it requires multiple steps, takes 90 minutes to perform, and requires a source of electricity, thus limiting its utility in low-resources settings [7]. Rapid POC treponeme-based diagnostics that identify syphilis infections also are needed, because current assays demonstrate varied sensitivity and a high probability of false positives in both laboratory and field testing [8]. Research and development of new STI diagnostics must be refocused to incorporate new technologies, including microfluidics, lateral flow, nanoparticles/nanodots, and miniaturization techniques, with the ultimate goal of POC detection of STIs using minimal biosamples [6].

VACCINES

Safe and effective vaccines would potentially transform efforts to contain the epidemics of STIs. The STI vaccine pipeline has had very few candidates over the last century and there are no licensed vaccines currently available to prevent syphilis, gonorrhea, or chlamydia. An observational study demonstrated that receipt of a meningitis vaccine comprised of the outer membrane proteins of *Neisseria meningitidis* also offered a degree of protection against gonorrhea [9]. This finding suggested that an efficacious gonorrhea vaccine may be achievable and, even if only modestly efficacious (40%), could decrease rates of gonorrhea by about 80% within 20 years [10]. A recent mathematical modeling study predicted that a syphilis vaccine with 80% efficacy would eliminate or markedly decrease the incidence of syphilis, including congenital syphilis, if a targeted

high-risk or mass vaccination approach was implemented [11]. New, sophisticated technologies, including quantitative proteomics, immunoproteomics, reverse vaccinology, structure-based vaccine design, and a diverse array of vaccine platforms, are beginning to lead to the development of a number of STI vaccine candidates [12]. For example, the first large-scale proteomic profiling of 15 gonococcal strains, including the 2016 WHO reference strains, led to the recent identification of 9 novel gonococcal vaccine candidates [13]. Similar types of ongoing studies are developing candidate vaccines against chlamydia and syphilis. To respond to the urgent need for STI vaccines, the National Institute of Allergy and Infectious Diseases (NIAID) of the National Institutes of Health (NIH) has refocused its STI vaccine portfolio by launching an initiative involving 6 new STI Cooperative Research Centers. These Centers will accelerate the development and testing of potential vaccines against gonorrhea, syphilis, and chlamydia utilizing innovative, multidisciplinary, and synergistic approaches based on structural biology of key bacterial surface proteins, protein antigen diversity, targeting bacterial systems, and immune system responses to these pathogens [14].

THERAPEUTICS

The increasing incidence of antimicrobial resistance (AMR), limited treatment options, and supply-chain shortages of certain commonly used antibiotics, for example, benzathine penicillin for syphilis, underscore the urgent need for new classes of drugs and antimicrobial strategies to treat STIs. Challenges with regard to therapeutics for STIs also include adherence to multidose regimens, drug toxicities and side effects, drug resistance, and drug-drug interactions. Currently, ceftriaxone is the single reliable drug option available in the United States to treat gonorrhea due to evolving resistance [2]. Recent results from a phase 2 clinical trial with zoliflodacin, a new oral

antibiotic that inhibits DNA synthesis, showed promise for the treatment of gonorrhea. In this study, a single oral dose of zoliflodacin successfully treated uncomplicated urogenital and rectal gonococcal infections [15]. The application of proteomics, structural and molecular biology, and other state-of-the-art techniques may result in the identification of markers for AMR, proteomic biosignatures [13], and novel microbial targets that can lead to the development of urgently needed antimicrobials.

Another approach warranting further investigation is the use of antibiotics for either preexposure prophylaxis (PrEP) or postexposure prophylaxis (PEP) [16]. Recent studies have demonstrated that a single dose of doxycycline as PEP significantly reduced chlamydia (70%) and syphilis (73%) infections in MSM who had condomless anal sexual intercourse [17]. A small clinical trial has demonstrated that daily doxycycline used as PrEP in HIV-infected MSM at high risk for STIs resulted in decreased incidence of gonorrhea, chlamydia, and syphilis infections [18]. A large, randomized clinical trial (NCT03980223), sponsored by the NIAID/NIH, is assessing the effectiveness of doxycycline PEP on STI incidence among users of PrEP for HIV and among MSM with HIV.

STIs AND HIV

Because gonorrhea, chlamydia, and syphilis are associated with increased risk for HIV transmission and acquisition [3], their increasing incidence may also serve as an obstacle to the new Health and Human Services plan for ending the HIV epidemic in the United States within 10 years [19]. Increased use of PrEP by individuals at risk for HIV as well as prompt treatment of persons with HIV, as called for in this new initiative, need to be accompanied by a parallel increase in STI testing and treatment among PrEP users [16] and persons with HIV who are receiving antiretroviral therapy and are practicing high-risk behaviors.

CONCLUSIONS

A refocused and enhanced research portfolio directed at the development of innovative diagnostics, therapeutics, and vaccines for STIs will be needed to adequately address the global STIs epidemic. In order to optimally utilize the fruits of these research efforts, partnerships among local, regional, and state health departments and community health care providers and clinics must be formed to effectively implement state of the art evidence-based STIs prevention, diagnosis, and treatment strategies. Such an approach will be critical for successfully ending the current STIs epidemic.

Notes

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