TAG

Treatment Action Group

GONORRHEA, CHLAMYDIA, AND SYPHILIS

PIPELINE REPORT 2019

Dedication

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Pipeline for Gonorrhea, Chlamydia, and Syphilis

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Introduction

The current toolbox for addressing gonorrhea, chlamydia, and syphilis is inadequate. At a time where all three epidemics are dramatically expanding in locations all around the globe, including record-breaking rates of new infections in the United States, stakeholders must make do with old tools, inadequate systems for addressing sexual health, and a sparse research pipeline of new treatment, prevention, and diagnostic options. Lack of investment in sexual health research has left the field with inadequate prevention options, and limited access to infrastructure for testing and treatment have allowed sexually transmitted infections (STIs) to flourish.

The consequences of this underinvestment are large: according to the World Health Organization (WHO), in 2012 there were an estimated 357 million new infections (roughly 1 million per day) of the four curable STIs: gonorrhea, chlamydia, syphilis, and trichomoniasis.[1] In the United States, the three reportable STIs that are the focus of this report—gonorrhea, chlamydia, and syphilis—are growing at record paces. In 2017, a total of 30,644 cases of primary and secondary (P&S) syphilis—the most infectious stages of the disease—were reported in the United States. Since reaching a historic low in 2000 and 2001, the rate of P&S syphilis has increased almost every year, increasing 10.5% during 2016–2017. Also in 2017, 555,608 cases of gonorrhea were reported to the U.S. Centers for Disease Control and Prevention (CDC), an increase of 18.6% since 2016 and 75.2% since the historic low in 2009. A total of 1,708,569 reported cases of *Chlamydia betrigtrachomatis* infection in 2017 make it the most common notifiable condition in the United States.

Costs to the U.S. medical system are substantial for all three infections. In 2008, the CDC estimated that annual chlamydia costs were $517 million, gonorrhea costs were $163 million, and syphilis costs were $40 million.[2] However, these estimates are over a decade old; the recent dramatic increases as well as rising health care costs have likely substantially raised costs since then.

When these infections go undetected, the results can be dire. Syphilis remains the second leading cause of stillbirth and miscarriage worldwide.[3] Congenital syphilis cases are on the rise in the United States; in 2017, there were 918 reported cases of congenital syphilis, including 64 syphilitic stillbirths and 13 infant deaths.[4] Undetected gonorrhea and chlamydia carry an increased risk of blindness for babies.[5] With chlamydia, most of the infections (70–80%) in women are asymptomatic; however, an estimated 5 out of 1,000 will develop tubal factor infertility.[6]

These bacterial infections have long been known to be associated with an increased risk of acquiring and transmitting HIV.[7] A recent modeling study found that 10.4% of new HIV infections among men who have sex with men (MSM) could be attributed to chlamydia and gonorrhea infections.[8] The specter of possible STIs has also dramatically slowed the scale-up of essential innovations in the prevention of new HIV infections. Fears of "risk compensation"—the possibility that reducing the risk of transmitting or acquiring HIV will lead to a reduction in condom usage and an increase in sexual partners—have led health care providers to withhold access to preexposure prophylaxis (PrEP) for HIV, despite the fact that STIs began rising in MSM prior to the 2012 U.S. Food and Drug Administration (FDA) approval of PrEP. That same absurd rationale has historically led to rationing of alternative contraception methods for women, even though this practice has no discernable benefit on addressing STIs; it only ensures greater harm to patients. These paternalistic attitudes are almost certainly a factor in slow dissemination of "undetectable=untransmittable" (U=U) messaging: the scientific fact that an individual living with HIV who has achieved viral suppression cannot transmit the virus sexually.[9]

These highly stigmatized diseases also create untold psychological and relationship burdens. Individuals who find that condoms and behavior change do not work for them for whatever reason—including circumstances where condom negotiation is not an option with sexual partners—and acquire an STI are subjected to stigma from within their interpersonal networks, from health care providers, and from society at large, often in the form of shame- and fear-based messaging campaigns, such as the AIDS Healthcare Foundation's notorious "Trust Him?" billboards.[10]

Many traditional STI prevention approaches, including behavior change related to frequency/number of sexual partners and levels of condom use, appear to be largely inadequate from a public health perspective in curbing rising infections. Although advocacy for increased sexual health infrastructure and access to testing—including expedited partner therapy—and guideline-recommended treatment remain an essential cornerstone of any STI response, advocacy that maintains a narrow, singular focus on individual sexual behaviors as the sole means of addressing any morbidity related to sex is extremely shortsighted and ignores lessons learned from the HIV pandemic. For years, the benefits of behavioral interventions and condom usage plateaued and declined, forcing advocates to look at the structural and social factors fueling the epidemic and, ultimately, to push for research for better tools. Highly active antiretroviral therapy, PrEP, and U=U ushered in the most dramatic progress toward ending HIV as an epidemic in locations around the globe. Stakeholders in addressing STI epidemics must learn these same lessons to have hope of turning the tide.

For years, the STI research pipelines for treatment, prevention, and diagnostics/testing have been relatively dry. However, recent developments may provide hope for increasing movement in these fields of research.

By far, the greatest advancement in recent years has been in alternative treatments for gonorrhea. With signs of continued widespread resistance to quinolones and azithromycin and the emergence of decreased susceptibility to extended-spectrum cephalosporins, public health leaders have called for immediate investment in the development of new antimicrobials.[11] During 2014–2017, the percentage of isolates with elevated azithromycin minimum inhibitory concentrations (MICs) increased from 2.5% to 4.4% in the United States.[12] Although the percentage of isolates with elevated ceftriaxone MICs has remained low in the United States and was only 0.2% in 2017, these emerging signs of resistance have made replenishing the treatment pipeline a top public health priority. Sounding the alarm has generated significant progress, with three new molecules introduced to the pipeline in recent years, the most exciting of which, zoliflodacin, has shown efficacy in a phase II study.

Hopeful developments have also emerged in the area of prevention. In recent years, doxycycline has been investigated as a possible prophylaxis either pre- or post-exposure. Renewed investment by the U.S. National Institutes of Health (NIH) in vaccine research for all three STIs may help researchers expand upon previous advancements in the field, including the 2017 discovery that a meningococcal B vaccine led to a 31% reduction in new gonorrhea infections in New Zealand and elsewhere.[13] However, the initial $9 million NIH investment is a far cry from what will be needed to develop these essential tools, and advocates should make the case for increased investment now.[14]

This report will explore the STI biomedical research pipeline, primarily focusing on ongoing or recently completed studies listed on ClinicalTrials.gov. In line with other Pipeline Reports from Treatment Action Group for HIV, viral hepatitis, and tuberculosis (available at www.pipelinereport.org), the present analysis does not address advancements in behavioral research or pressing implementation/funding needs for scaling up existing tools. With so many gaps in the development of new tools, the report will also highlight a few areas where innovation is particularly needed, including background information on the history of vaccine research and the current gaps in rapid testing for all three diseases. As this report covers extensive ground for three different pathogens, many of these sections draw heavily from the work of other reviewers and summary articles to familiarize advocates and other readers with key arguments and resources.

Our hope is that this report will generate discussion on, and investment in, sustained research advocacy for STIs, to move beyond a singular focus on repackaging and rebranding of resource-intensive sexual behavior approaches with continually diminishing returns. Given that STI-related stigma also adversely impacts the efforts of HIV advocates working on the scale-up of PrEP and U=U messaging, our hope is that more of these community leaders will also see the development of better tools for STI prevention, diagnosis, and treatment as integrally linked to their own success in ending HIV.

Preventive Technologies for Gonorrhea, Chlamydia, and Syphilis

Humans need choices when it comes to maintaining and improving their sexual health. The following pipeline research seeks to provide additional modalities, beyond just condom use or limiting the number of partners, for the prevention of multiple bacterial STIs.

Doxycycline as Pre- and Post-Exposure Prophylaxis

Doxycycline is a second-generation tetracycline, available worldwide for half a century. It is an inexpensive broad-spectrum antimicrobial agent largely used in the management of bacterial infections, as well as in the treatment of acne or for the prophylaxis of malaria.[15] Doxycycline remains an important CDC-recommended medication for nonpregnant individuals for the treatment of syphilis and urogenital and oropharyngeal chlamydial infections, as well as for those with a penicillin allergy who cannot take azithromycin.[16]

In recent years, doxycycline has been investigated as a possible bacterial STI prophylaxis either pre- or post-exposure. A small pilot study released in 2015 demonstrated that doxycycline provided as a preexposure prophylaxis (STI-PrEP) may be effective in reducing STI incidence.[17] The study was small, with only 30 gay men and transgender women, but it showed a statistically significant 70% decrease in STIs when half the participants were assigned doxycycline as STI-PrEP and half the participants were offered financial incentives to avoid infections. Absolute numbers of syphilis, gonorrhea, and chlamydia infections were all lower in the doxycycline arm; however, the study was too small to provide statistically significant reductions when infections were broken down by specific disease.

A 2018 substudy of Ipergay—a French study of oral HIV-PrEP users—showed that doxycycline provided as a post-exposure prophylaxis (STI-PEP) led to a 47% reduction in bacterial STIs, with a 70% drop in chlamydia and a 73% drop in syphilis, but no reduction in gonorrhea.[18] The study randomized 232 MSM from the French Ipergay HIV-PrEP study and provided half with doxycycline for STI-PEP; the other half received no STI prophylaxis. Those in the treatment arm were told to take a 200 mg pill up to 72 hours after each episode, though nearly every participant who took a pill did so within 24 hours. Participants were followed for 8.7 months, with 212 participants—106 in each arm—completing the study. STI percentages were extremely high in each arm, though the 38% annual STI incidence rate in the doxycycline arm was a significant improvement compared with 70% in the control arm.

Two new studies looking at doxycycline for STI prevention are being conducted by the British Columbia Centre for Disease Control. One is a smaller pilot study that will look at the feasibility and tolerability of using daily doxycycline for syphilis PrEP in a group of 50 HIV-negative MSM who are also taking tenofovir disoproxil fumarate / emtricitabine (TDF/FTC) as HIV-PrEP.[19] The second study is an early phase I study

to determine whether the daily use of doxycycline is an efficacious and acceptable intervention for syphilis prevention in a group of 288 HIV-positive MSM.[20] The study focusing on HIV-negative men was almost fully enrolled at the time of publication, with preliminary findings expected to be available in the next year. The study of HIV-positive men is set to run through May 2020.

Another study evaluating doxycycline as STI-PrEP, conducted at the Kirby Institute in Australia, is a nonrandomized observational cohort trial using a before-and-after comparison to evaluate whether taking 100 mg doxycycline daily would help gay and bisexual men at high risk of infection to reduce the possibility of acquiring gonorrhea, syphilis, and chlamydia. The study is currently recruiting to reach its target of 125 participants, with an estimated study completion date of December 2021.[21]

Concerns over the development of antibiotic resistance will be one of the factors in determining the future of doxycycline as STI-PrEP or STI-PEP, specifically in the case of gonorrhea. The threat of development of resistance has been cited as a concern around giving doxycycline as prophylaxis, as there are so few new antibiotics in the treatment pipeline for gonorrhea. However, as doxycycline has not been recommended as treatment for gonorrhea for years, there is new progress in the treatment of gonorrhea, and there are no plans to reintroduce doxycycline as a recommended treatment, stakeholders likely need to take a much closer look at opportunities to prevent new syphilis and chlamydia infections with doxycycline. The benefits likely far outweigh the risks.

RFA-AI-18-005: New NIH Funding for Chlamydia, Gonorrhea, and Syphilis

A highly effective, scalable, easily administered vaccine is in many ways the holy grail in the prevention of any infectious disease. Stakeholders may be surprised to find that biological plausibility for vaccination to prevent all three bacterial infections has been previously established, and, in some cases, there have been significant recent advancements in this field of research. Often, it may appear that the reason better interventions don't exist is because of some scientific barrier, yet in the case of STI vaccine research, it is likely a question of investment.

In 2018, the NIH made a significant new investment in vaccine research for gonorrhea, chlamydia, and syphilis. RFA-AI-18-005 will invest $9 million in FY 2019 to fund three to five awards. The funding opportunity solicited applications for the Sexually Transmitted Infections Cooperative Research Centers, which will facilitate multidisciplinary, synergistic collaborations to support the development of vaccines to control and prevent STIs caused by the three major reportable bacterial infections.[22]

Meaningful discussion on the development of vaccines for syphilis, gonorrhea, and chlamydia has advanced in recent years. A 2013 WHO meeting on the development of vaccines for STIs outlined a number of targets and objectives in order to address common sexually transmitted bacterial pathogens.[23] There was agreement that standard required qualities from a production standpoint will include a vaccine that (1) requires only standard operating procedures and equipment for generation of a high-quality vaccine product, (2) can be easily produced and manufactured on large scale to meet supply demand, and (3) exhibits no or minimal batch-to-batch variability and has optimal stability regardless of storage conditions. The biologic considerations that were discussed and found important to achieving vaccine efficacy included (1) racial and gender differences and the impact of genetic differences and hormones; (2) different clinical (tissue) sites of infection; (3) ancillary microbial flora (e.g., microbiome); and (d) genotypic and phenotypic strain variations.

From a public heath perspective, a vaccine should (1) use a routine route of administration; (2) be inexpensively produced to appeal to industry partners and public health officials and ensure the vaccine reaches target groups; (3) achieve sufficient protection with a reasonable number of immunizations and a convenient immunization schedule to help achieve vaccinee return-visit compliance; (4) be administered safely with no adverse health consequences post-vaccination; and (5) provide long-lasting protection against infection, irrespective of age, gender, or type of sexual activity.

The new investment from NIH is an exciting shift toward achieving these aspirational goals for future vaccines; however, $9 million is not likely to be enough of an investment. Development will require significant funding, and commercial vaccine producers are unlikely to commit themselves unless there is some certainty that the vaccine would have minimal side effects and an established market in order to deliver a reasonable return on their investment.

While this report is primarily concerned with interventions that have already gone through preclinical development, we will briefly review some of the previously conducted research that makes this new influx of NIH funding so exciting. In particular, recent efforts to map the proteins produced by each pathogen have led to the development of potential targets for vaccination for all three diseases. Hopefully, more advocates will be inspired to press for ongoing investment in vaccines that will be effective, easy to use, accessible, and affordable. Stakeholders may also be inspired to make the case for a market for newly developed vaccines by conducting additional research to establish the demand for these highly needed interventions.

Gonorrhea Vaccine

Gonorrhea vaccine research dates back more than a century. Four candidate vaccines have been evaluated in clinical trials; none of them managed to provide any protection. Limited in vivo studies of the pilus vaccine and in vitro studies of the Por vaccines had shown efficacy; however, three gonococcal vaccine trials (whole cell, pilus, and Por) conducted since 1970 were unsuccessful in protecting participants from either natural or experimental infection.

A few years ago, surprising results from the study of a meningococcal vaccine renewed hope for successful vaccine development. Researchers in 2017 reported that a group B meningococcal vaccine custom-made for an epidemic of that disease in New Zealand may also prevent gonorrhea infection in a third of vaccinated individuals.[25] The retrospective case-control study examined records from almost 15,000 young-adult patients at 11 sexual health clinics in New Zealand who were eligible to receive the outer membrane vesicle meningococcal B vaccine (MeNZB) between 2004 and 2008 and were diagnosed with either gonorrhea or chlamydia, or both. Patients who received MeNZB were substantially less likely to have been diagnosed with gonorrhea than chlamydia, and the researchers estimated the vaccine was 31% effective against the former.[26] Although 31% protection is modest—and lower than that achieved with most approved vaccines—modeling published in 2015 suggested that a vaccine against gonorrhea with such efficacy could decrease prevalence of the STI by more than 30% within 15 years.[27]

The same team also presented results in 2017 from a cohort study of more than 600,000 individuals in New Zealand.[28] Those who were vaccinated with MeNZB were less likely to be diagnosed with gonorrhea than those who did not receive the vaccine, which appeared to be 45% effective against the STI in this group. MeNZB, which is no longer available, was composed of purified protein components from buds on the cell surface of a strain of meningococcal B.

Adding to these unexpected findings out of New Zealand, researchers are also making real progress on narrowing down targets for a potential gonorrhea vaccine. Oregon State University has recently completed proteomic profiling on all the proteins produced by 15 gonorrhea strains. Among the isolates in the study were WHO-maintained reference strains that show all known profiles of gonococcal antimicrobial resistance.[29,30] For each strain, researchers divided the proteins into those found on the cell envelope and those in the cytoplasm. More than 1,600 proteins—904 from the cell envelopes and 723 from the cytoplasm—were found to be common among the strains, and from those, nine new potential vaccine candidates were identified. Researchers also found six new proteins that were expressed in all of the strains, suggesting they might be effective targets for new antimicrobials.

These promising discoveries, in addition to the significant concerns posed by increasing antimicrobial resistance, make this an ideal time for stakeholders to push for increased investment in vaccine research for gonorrhea. In 2013, the WHO and NIH organized a

technical consultation to evaluate how to advance STI vaccine development.[31] Several key recommendations were made to improve ongoing research for a gonorrhea vaccine. Currently, the only small laboratory animal model for gonorrhea is experimental infection of female mice. Both collaboration and the pace of vaccine development could be enhanced by broader access to in vitro assays, reagents, and animal models with the goal of harmonizing selected protocols across laboratories, ensuring that the members of the research community are striving to achieve the same goals.

The use of experimental infection in male volunteers to evaluate vaccine candidates was discussed at the same WHO/NIH meeting. Experimental infection of male volunteers reproduces the clinical features of naturally acquired gonococcal urethritis. The ethical concerns are obvious; however, several advantages were noted. A paper published after a 2016 National Institute of Allergy and Infectious Diseases (NIAID) meeting on gonorrhea vaccinology encouraged ongoing efforts to refine existing animal models to better mimic human infection. It also recommended that dialogue should continue on the potential and feasibility of leveraging the experimental human male infection model for phase I/II clinical trials to test candidate vaccines and/or define correlates of protection.[32]

Chlamydia Vaccine

A 2017 review of the field of chlamydia vaccine research summarizes evidence, which support greater investment.[33] The plausibility of a mechanism for an effective chlamydia vaccine has long been established. Attempts to find a vaccine for chlamydia initiated more than 100 years ago, long before it was recognized as a form of sexually transmitted infection, due to its role in the development of trachoma, which remains a significant cause of preventable blindness in many parts of the world. In these early experiments using whole organisms, protective responses were obtained; however, upon exposure to chlamydia, disease exacerbation developed in some immunized individuals.[34]

Genital chlamydial infections are more frequent in young sexually active individuals, between the ages of 15 to 20, than in older persons. This finding has been interpreted as evidence of naturally induced immunity. Some clinical and experimental evidence supports this suggestion. For example, in sex workers, resistance to infection correlates with duration of sex work, independently of age, indicating development of acquired immunity.[35] A 2013 study also showed that natural immunity occurs in females with a *C. trachomatis* genital tract infection.[36] Treatment with antibiotics can lessen this immunity.

Natural immunity to chlamydial infection does not provide complete or long-term protection, but human clinical data show that young women who spontaneously cleared chlamydial genital infections subsequently were resistant to re-infections.[37] Thus, natural immunity can elicit partial protection from chlamydial re-infection, providing evidence that it may indeed be possible to design an efficacious vaccine.

But in addition to efficacy, safety is paramount. STIs like chlamydia and gonorrhea cause significant morbidity but not mortality, and are often treatable, so the first priority a

vaccine is safety. Based on the findings observed during the vaccine trachoma trials, delayed-type hypersensitivity reactions, increased susceptibility to infection, and any other negative effects need to be avoided.

However, current technological advances in chlamydial genetics and proteomics, as well as novel and improved adjuvants and delivery systems, provide new hope that the elusive chlamydial vaccine is an imminent and realistic goal.[38] Researchers from McMaster University recently demonstrated that a novel chlamydial antigen known as BD584 is a potential vaccine candidate for chlamydia.[39] Administering BD584 through the nose was able to reduce chlamydial shedding by 95%.

A report that tissue-resident memory T cells contributed long-lived vaccine-induced protection against chlamydial infection is also a significant advance for the design of an effective chlamydial vaccine,[40] and current candidate vaccines aimed at eliciting this type of response are in various stages of development. A chlamydia vaccine using the oral Vaxonella platform is currently being tested in animal models for its immunogenicity and efficacy in the prevention of chlamydia infection.[41] Recently, Imperial College Research in the United Kingdom conducted a phase I double-blind, parallel, and placebo-controlled trial of the Statens Serum Institut's chlamydia vaccine CTH522, using two different adjuvants: CAF01 and Al(OH)3.[42]

Syphilis Vaccine

The most compelling evidence in support of the feasibility of syphilis vaccine development is the protection against infection achieved in experiments by Dr. James Miller in 1973.[43] In his study, Miller used an extended immunization regimen in rabbits, the optimal animal model for syphilis investigations, with 60 intravenous injections of γ-irradiated *T. pallidum* over 37 weeks, followed by intradermal challenge with the homologous *T. pallidum* strain. Immunized rabbits displayed complete protection against infectious challenge that persisted for at least one year, as demonstrated by lack of chancre development at challenge sites and the absence of infectious bacteria in lymph nodes from the challenged immunized rabbits. This groundbreaking study demonstrates that syphilis vaccine development may be possible and highlights the importance of treponemal surface proteins in generating protective immunity.

Given Miller's promising results and the fact that the supply chain for benzathine penicillin G (BPG), the recommended treatment for syphilis, is frequently unpredictable in several locations worldwide,[44] an investment in syphilis vaccine development is absolutely worthwhile. In the United States alone, more than $966 million in direct and indirect costs is spent each year as a result of syphilis, including cost of care associated with infectious syphilis ($185.5 million), congenital syphilis ($28.5 million), and HIV attributable to syphilis ($752.2 million).[45] Recent mathematical modeling studies predicted that development of a vaccine with 80% efficacy would eliminate or markedly reduce congenital/infectious syphilis cases, a prediction that remained consistent regardless of whether the model used a mass vaccination or targeted high-risk vaccination strategy.[46]

As with gonorrhea and chlamydia, recent efforts to map all proteins produced by syphilis and identify unique targets for vaccination have dramatically improved the outlook for the development of a vaccine. University of Connecticut researchers have identified outer membrane proteins that vary the least across strains and are now collaborating with researchers at the University of North Carolina to enroll patients in Guangzhou, China, and Lilongwe, Malawi, to determine whether the syphilis strains they have been studying are similar to strains in those countries, as well.[47]

Future investigations will require determination of the immune correlates associated with protection from disease and selection of adjuvants to achieve these immune correlates.[48] Additionally, a recent review of syphilis vaccine development listed a number of requirements for potential vaccines, including the following: (1) safe for use in pregnant women at any stage of gestation to combat the deadly consequences of congenital infections; (2) efficacious at preventing all stages of infection to avoid the potential for disease transmission in primary syphilis, the establishment of latency in an infected individual, as well as the symptoms of secondary and tertiary syphilis; efficient at inducing cross-strain protection, which is required to protect against re-infection due to the numerous *T. pallidum* strains circulating globally, the well-documented lack of cross-protection induced by syphilis infection, and the propensity for individuals to be infected multiple times; and (4) effective when administered to HIV-positive individuals, including those taking antiretroviral therapy, due to the high prevalence of HIV/syphilis coinfections and the altered immunity in coinfected individuals.[49]

Additional Prevention Interventions for Gonorrhea, Chlamydia, and Syphilis

The pipeline for novel prevention options is growing but remains sparse for gonorrhea, chlamydia, and syphilis. Although doxycycline as PrEP or PEP has shown efficacy in preventing chlamydia, and new NIH funding is breathing new life into vaccine research, here we are able to review only one more novel prevention choice in development that is listed on ClinicalTrials.gov: Amphora gel for prevention of chlamydia and gonorrhea in women.

A phase IIb/III study being conducted by Evofem, Inc., in collaboration with Clinical Research Management, Inc., is evaluating the efficacy and acceptability of Amphora gel for the prevention of acquisition of urogenital *Chlamydia trachomatis* infection. As a secondary outcome, the study will also evaluate its potential preventive benefits for gonorrhea. Amphora is a pH-buffering, acidity-maintaining gel (pH 3.5) containing three active compounds: lactic acid, citric acid, and potassium bitartrate. Participants will be instructed to apply five 5 g of Amphora® gel intravaginally at least one hour prior to vaginal intercourse. Members of the control arm will instead apply 5 g of an isotonic, nonbuffering gel, pH adjusted to 4.5, containing 2.7% hydroxyethylcellulose, sorbic acid, sodium hydroxide, sodium chloride, and purified water. The researchers planned to enroll 844 participants into the double-blind, placebo-controlled study; results are expected in May 2019.[50]

Preventive Technologies Pipeline: doxycycline and Amphora gel				
Pathogen	**Agent**	**Delivery**	**Manufacturer/Research Institutions**	**Status**
Chlamydia, gonorrhea, syphilis	doxycycline	PrEP, 100 mg daily	Kirby Institute British Columbia Centre for Disease Control	NCT03709459 (Kirby) Early Phase I NCT02864550 (BCCDC)
Chlamydia, gonorrhea, syphilis	doxycycline	PEP, 200 mg up to 72 hours following possible exposure	Ipergay	Completed
Urogenital chlamydia	Amphora gel (lactic acid, citric acid, potassium bitartrate)	5 g applied intravaginally one hour prior to vaginal intercourse	Evofem, Inc., and Clinical Research Management, Inc.	Phase IIb/III

Gonorrhea and Chlamydia Treatment Pipelines

Treatment				
Pathogen	Antimicrobial	Delivery	Manufacturer/Research Institution	Status
Anorectal chlamydia	doxycycline	Oral, 100 mg twice daily	University Hospital in Bordeaux (in women) NIAID (in MSM)	Phase IV NCT03532464 (Bordeaux) NCT03608774 (NIAID)
Chlamydia	azithromycin	Oral, 1 g single dose	Ain Shams Maternity Hospital	Phase IV NCT03233880
Gonorrhea	zoliflodacin	Oral, 2 g, 3 g, and 4 g being evaluated	NIAID (cardiac evaluation) Drugs for Neglected Diseases (evaluation with or without food)	Phase I NCT03613649 (cardiac) Phase I NCT03718806
Gonorrhea	gepotidacin		GlaxoSmithKline	Phase II NCT02294682 (completed)
Gonorrhea	solithromycin	Oral, 1,000 mg single dose	Cempra, Inc., NIAID	Phase III NCT02210325 (completed)

Treatment for Gonorrhea and Chlamydia

Almost all antibiotic classes used against gonorrhea have lost their efficacy because of resistance.[51] Sulfonamides, penicillins, early-generation cephalosporins, tetracyclines, macrolides, and fluoroquinolones can no longer be relied upon. The extended-spectrum cephalosporins (ESCs, e.g., cefixime and ceftriaxone) are also under threat, with resistance reported worldwide. The WHO Gonococcal Antimicrobial Surveillance Programme (GASP) found that resistance to ESCs is spreading especially in Asia, North America, Europe, Latin America and the Caribbean, and Australia, with large data gaps in Africa and Central Asia. Reports of treatment failures with ESC are on the rise, and the first case of treatment failure with a dual therapy has recently been reported.[52]

Effective treatment of pharyngeal infections (regardless of resistance) is more difficult than treatment of urogenital infections; the average cure rate for urogenital infection is 96% but only 79–84% (males and females) for oropharyngeal infections.[53] This may relate to insufficient drug exposure in the latter site. Worryingly, these infections most likely act as a reservoir, and persistence of pathogens at these sites jeopardizes global efforts to slow the spread of resistant gonorrhea.

A 2017 review outlined the urgency of replenishing the antibiotic drug discovery pipeline.[54] In the meantime, for gonorrhea, there is a need to advance, prioritize, and evaluate the three new molecules (solithromycin, zoliflodacin, gepotidacin) in the clinical pipeline, investigate new antimicrobial combinations, and reconsider the use of existing antibiotics. Moreover, for both new and existing drugs, there is a lack of clinical efficacy data on oropharyngeal infections.

Of note, a recently wrapped phase III trial of a fourth new molecule, delafloxacin, looked at a single oral dose of 900 mg but was unable to prove noninferiority compared with 250 mg of intramuscular (IM) ceftriaxone.[55] Although other dosing options could potentially be explored in the future, it appears that delafloxacin is unlikely to advance further.

The following gives a brief overview of ongoing research and evaluation of several new and existing antimicrobials for gonorrhea treatment. Although resistance concerns are not nearly as pressing, a few studies evaluating the treatment of chlamydia are also listed on ClinicalTrials.gov, and we will begin with a brief review of that research.

New Research on Treating Chlamydia

Although the vast majority of current treatment research is dedicated to finding new options for gonorrhea, there are two studies on ClinicalTrials.gov comparing doxycycline to azithromycin for the treatment of anorectal chlamydia. The first study, conducted at University Hospital in Bordeaux, France, will involve 460 women with positive vaginal and anorectal chlamydia swabs. One randomized group will be treated with doxycycline twice daily for seven days, with one tablet of 100 mg of doxycycline in the morning and evening, while a second randomized group will be treated with four tablets of 250 mg of azithromycin in one intake. Researchers are particularly concerned that

azithromycin may be less effective for anorectal infections, increasing the potential for autoinoculation and re-infection of the vagina, given the close proximity to the anus. The study is projected to complete by the end of 2019.[56]

Similarly, NIAID has initiated a study comparing azithromycin to doxycycline for the treatment of anorectal chlamydia infections in MSM. Subjects will be males over 18 years old with a microbiologically confirmed diagnosis of rectal chlamydia and at least one male sex partner in the past 12 months. The trial will be conducted at two sites in the United States and will enroll up to 550 total subjects to achieve 442 subjects for the primary analysis. The effect of lymphogranuloma venereum (LGV) infection on microbiologic cure in MSM with rectal chlamydia will also be assessed. Arm 1 will include subjects receiving 1 g of azithromycin (four capsules of 250 mg) orally as a single dose and doxycycline placebo (one capsule) orally twice daily for seven days. Arm 2 will include subjects receiving 100 mg of doxycycline (one capsule) administered orally twice daily for seven days and azithromycin placebo (four capsules) administered orally as a single dose. The study is listed as recruiting, with results expected by the end of 2019.[57]

Finally, a study from Ain Shams Maternity Hospital in Cairo seeks to assess the impact of chlamydia treatment on rates of preeclampsia in pregnant women. The randomized controlled trial gave 1,200 pregnant women either 1 g of azithromycin or placebo between 16 and 20 weeks of pregnancy, during routine antenatal care between July 2016 and September 2017. The study was set to finish in August 2018; at the time of this publication, no results were available.[58]

Novel Antimicrobials for Gonorrhea Treatment

Zoliflodacin

An investigational oral antibiotic called zoliflodacin was well tolerated and successfully cured most cases of uncomplicated gonorrhea when tested in a phase II multicenter clinical trial.[59] Zoliflodacin (formerly known as ETX0914 and AZD0914), developed by Entasis Therapeutics based in Waltham, Massachusetts, represents a new type of oral antibiotic that inhibits DNA synthesis in a different way than currently approved antibiotics. The trial, conducted at the Louisiana State University Health Sciences Center in New Orleans between 2014 and 2015, enrolled 179 participants (167 men and12 nonpregnant women) aged 18 to 55 years with either symptoms of uncomplicated urogenital gonorrhea, untreated urogenital gonorrhea, or sexual contact with someone with gonorrhea within 14 days before enrollment. Participants were randomly selected to receive either a single 2 g or 3 g dose of oral zoliflodacin or a 500-mg dose of injectable ceftriaxone. Among the 117 per-protocol participants who were evaluated six days after treatment, 98% (48 of 49 participants) of those who received the 2 g zoliflodacin dose, 100% (47 of 47 participants) of those who received the 3 g dose, and all (21 of 21) of the participants in the ceftriaxone group were considered cured of their urogenital gonorrhea based on culture results.

Zoliflodacin cured all rectal gonorrheal infections (four of four participants who received the 2 g dose and six of six participants who received the 3 g dose) as did ceftriaxone (three of three participants). However, the investigational drug did not fare as well in treating patients with gonorrhea infections of the throat (pharyngeal): 67% of volunteers who received the 2 g dose (four of six participants) and 78% of those who received the 3 g dose (seven of nine participants) were cured. All of the participants in the ceftriaxone group (four of four) achieved a cure.

The investigational antibiotic was well tolerated, with transient gastrointestinal upset the most commonly reported adverse effect. Microbiological evaluation of post-treatment clinical isolates did not demonstrate resistance to zoliflodacin. In March 2018, NIAID completed a study to evaluate zoliflodacin's pharmacokinetics, safety, and tolerability as a single oral dose to serve as a bridge from the phase II clinical trial formulation to the final formulation for phase III testing.[60] Results from that study have not yet been made public. Additionally, in September 2018, NIAID launched a phase I study to evaluate the investigational drug's cardiac effects, a standard safety test for many new drugs. The study recently concluded, with results forthcoming. Additionally, another phase I study listed on ClinicalTrials.gov and being run by Drugs for Neglected Diseases and Quotient Sciences appears to be looking at the effects of food intake on 3 g and 4 g oral suspensions of zoliflodacin. The study recently completed, with results forthcoming.[62]

Zoliflodacin has been awarded fast-track status by the FDA for development as an oral treatment for gonococcal infections. It is expected to begin phase III testing in the Netherlands, South Africa, Thailand, and the United States next year.

Gepotidacin

A phase II study with results published in 2018 evaluated the efficacy and safety of oral gepotidacin, a novel triazaacenaphthylene bacterial type II topoisomerase inhibitor, for the treatment of uncomplicated urogenital gonorrhea. Pretreatment and post-treatment urogenital swabs were collected for gonorrhea culture and susceptibility testing. Pharyngeal and rectal swab specimens were collected if there were known exposures. Participants were stratified by gender and randomized 1:1 to receive a 1,500-mg or 3,000-mg single oral dose of gepotidacin. Ultimately, 69 participants were available for final evaluation, with gonorrhea isolated from 69 (100%) urogenital, two (3%) pharyngeal, and three (4%) rectal specimens. Microbiological eradication was achieved by 97%, 95%, and 96% of participants (lower one-sided exact 95% confidence interval [CI] bound 85.1%, 84.7%, and 89.1%, respectively) for the 1,500-mg, 3,000-mg, and combined dose groups, respectively. Microbiological cure was achieved in 66 of 69 (96%) urogenital infections. All three failures were isolates that demonstrated the highest observed gepotidacin MIC of 1 µg/mL and a common gene mutation. At the pharyngeal and rectal sites, one of two and three of three gonorrhea isolates, respectively, demonstrated microbiological cure. There were no treatment-limiting adverse events for either dose.[63]

The same study looked at the microbiological correlates for the successful treatment of gonorrhea.[64] Culture, susceptibility testing, genotypic characterization, and frequency of resistance determination were performed for selected isolates. All three isolates from microbiological failures were ciprofloxacin resistant, had a baseline gepotidacin MIC of 1 µg/mL, and carried a preexisting *parC* D86N mutation, which is in a location critical for gepotidacin binding. In a test-of-cure analysis, the resistance to gepotidacin emerged in two isolates (MICs increased ≥32-fold) with additional *gyrA* A92T mutations, also implicated in gepotidacin binding.

The manufacturer of gepotidacin, GlaxoSmithKline, has indicated that they intend to proceed to phase III trials by the fourth quarter of this year.[65]

Solithromycin

Solithromycin, developed originally by Cempra, Inc., is an oral fluoroketolide with activity against gonorrhea, mycoplasma genitalium, and chlamydia.[66] It has also been evaluated in phase III trials for the treatment of community-acquired bacterial pneumonia.[67] It showed good efficacy in a phase II study, with a 100% efficacy for gonorrhea in genital, oral, and rectal sites of infection in men and women. However, concerns for drug-induced liver injury and infusion-site reactions have placed its regulatory future in doubt.

A phase III study of solithromycin for the treatment of gonorrhea—co-funded by NIAID—has shown unimpressive results.[68] Preliminary data presented at the June 2017 American Society for Microbiology meeting showed 80.5% of patients (99 of 123) in the solithromycin group were cured, versus 84.5% (109 of 129) of patients in the ceftriaxone/azithromycin group.[69] Although the data established the noninferiority of solithromycin to standard treatment, the authors speculated that a higher dose of solithromycin might be needed to effect a 100% cure rate and reportedly planned to recruit additional participants. However, at present, no additional publications from the phase III trials were available via a Google Scholar search or on ClinicalTrials.gov, and there seems to be little future for solithromycin in the treatment of gonorrhea. Cempra merged with Melinta Therapeutics in the second half of 2017;[70] Melinta currently has solithromycin listed as a noncore asset in its pipeline.[71]

Existing Antimicrobials Under Evaluation for Gonorrhea Treatment

Antimicrobial	Delivery	Research Institution	Status
ertapenem	1,000 mg IM	Public Health Service of Amsterdam	Phase III NCT03294395
fosfomycin	6 g oral suspension	Public Health Service of Amsterdam	Phase III NCT03294395
gentamicin	5 mg/kg IM (maximum 400 mg in two doses)	Public Health Service of Amsterdam	Phase III NCT03294395
gentamicin (for pharyngeal infections)	360 mg IM	University of Washington	Phase II/III NCT03632109

Existing Antimicrobials Under Evaluation for Gonorrhea Treatment

Ertapenem

A study published in 2017 sought to determine the in vitro activity of nine alternative currently licensed and late-development antimicrobials with the potential to treat gonococcal infections against 112 clinical isolates of *Neisseria gonorrhoeae* resistant to one or multiple antimicrobials.[72] The study found that ertapenem had comparable activity to cefixime and ceftriaxone.

An ongoing double-blind phase III study comparing three older antibiotics to ceftriaxone for the treatment of uncomplicated anogenital gonorrhea—including 1,000 mg of ertapenem—is currently being conducted by the Public Health Service of Amsterdam in partnership with the Universiteit van Amsterdam. Researchers plan to enroll 548 participants who will be randomly assigned to one of four treatment arms receiving either 1,000 mg IM ertapenem, fosfomycin 6 g oral suspension supplemented with an IM placebo, gentamicin 5 mg/kg IM with a maximum of 400 mg (in two doses) supplemented with an oral placebo, or ceftriaxone 500 mg IM. The study is presently recruiting, with results expected by the end of 2019.[73]

A 2018 review of the evidence for ertapenem for gonorrhea treatment underscores the importance of weighing the benefits of its use against unintended resistance in other microorganisms. The implications of a shift to a carbapenem such as ertapenem as first-line empirical therapy for gonorrhea are manifold. Most carbapenem prescribing starts in inpatient settings, where patients are often older with more comorbidities, and a shift toward administration of these drugs in healthier individuals could cause greater selection pressure on nontarget pathogen microbial flora within people in the community. The authors urge that the potential effect of selection of antibiotic resistance across all exposed organisms must be considered, or gonorrhea might indirectly pave the way for the emergence of other untreatable infections.[74]

Fosfomycin

Fosfomycin is an old antibiotic that shows potent bactericidal activities against common organisms and is an appealing choice for the management of gonococcal infections because of its single and oral formulation (3 g), low toxicity, and very high peak concentration levels in different body sites.

Fosfomycin is one of the three older antibiotics being studied in the above-described Public Health Service of Amsterdam trial.

A recent study evaluated the in vitro activity of fosfomycin alone and in combination with ciprofloxacin or azithromycin against a collection of both susceptible and highly resistant multiple-drug resistant (MDR) strains of gonorrhea, comparing the efficacies of these treatments to those of the current standard therapeutic options.[75] Fosfomycin was active against gonorrhea in vitro and might also be effective in vivo for treatment. However, for other Gram-negative pathogens (e.g., *Escherichia coli*), fosfomycin can

rapidly lead to resistance when used as monotherapy. To overcome this problem, the drug has been used in combination therapy.

According to the study, fosfomycin may be a potential substitute of azithromycin to be given with ciprofloxacin. The high oral bioavailability, excellent safety, and good track record of fosfomycin in the treatment of urinary tract infections further support this. However, the authors recommend additional studies to prepare for the potential future implementation of fosfomycin in the treatment of gonorrhea: (1) testing of activity in vitro against a wider variety of gonorrhea strains representing the current clones in circulation worldwide, (2) characterization of mechanisms of fosfomycin resistance in gonorrhea, (3) provision of pharmacokinetic and pharmacodynamic data for the tissues involved in gonococcal infections, and finally, (4) randomized controlled clinical trials in patients with genital and extragenital (especially pharyngeal) gonorrhea while evaluating optimal dosing and efficacy.

Gentamicin

Gentamicin, an old and inexpensive antibiotic, is recommended in combination with azithromycin for gonorrhea treatment failure as per the latest CDC STI treatment guidelines.[46] The guidelines also recommend dual treatment with gentamicin plus azithromycin in individuals with cephalosporin allergy.

An ongoing phase II/III study at the University of Washington is currently evaluating the efficacy of a single dose for treatment of pharyngeal gonorrhea. Researchers chose to focus on pharyngeal gonorrhea because of the frequency of these infections, the key role they play in fostering gonococcal resistance, and the difficulty in treating infections of the pharynx. Researchers hypothesize that although gentamicin is 91% efficacious for genital gonorrhea, its efficacy at the pharynx may be less since streptomycin, another aminoglycoside previously used to treat gonorrhea, was not effective for pharyngeal infections. It is unknown whether streptomycin's poor efficacy is indicative of the limitations of aminoglycosides as a class. The demonstration study will enroll 60 MSM to test the efficacy of 360 mg of gentamicin given IM. At time of publication, the study was recruiting, with results expected over the summer of 2019.[77]

As with ertapenem and fosfomycin, gentamicin is under study for the treatment of uncomplicated anogenital gonorrhea currently being conducted by the Public Health Service of Amsterdam.

A recent study was carried out to evaluate the in vitro synergy of gentamicin in combination with azithromycin and five other antimicrobials. Maximum efficacy of gentamicin was observed in combination with ertapenem, followed by cefixime. There was no antagonism for both these combinations. However, antagonism was demonstrated in 5.3%, 8%, 8%, and 10.7% of strains when gentamicin was paired with spectinomycin, ceftriaxone, azithromycin, and moxifloxacin, respectively. The findings suggest that gentamicin significantly enhances the in vitro therapeutic potency of ertapenem and cefixime, which will be potentially effective to control the spread

of MDR and extensively drug resistant (XDR) gonorrhea. The study warrants more in vitro studies and clinical trials for gentamicin plus azithromycin and the other three combinations because of considerable antagonism.[78]

Another recent study indicates the continued susceptibility of gonorrhea to gentamicin, but with 71% of the isolates demonstrating an MIC of 8 µg/mL and two% of the isolates demonstrating an MIC of 16 µg/mL. The increase in the proportion of intermediate susceptible isolates between 2015 and 2016 points to the possibility that susceptibility to gentamicin might be decreasing; continued surveillance of gentamicin susceptibility is needed.[79]

Spectinomycin

The aminocyclitol spectinomycin was commercialized in the 1960s as a specific treatment for gonorrhea. Resistance rapidly emerged in some settings, and spectinomycin use was discontinued. But resistance is currently rare worldwide, and spectinomycin retains excellent activity against most gonococcal isolates. It is used in some European countries, China, and South Korea, but its availability in other regions is limited.[80]

In a recent study, aminomethyl spectinomycins, a new class of semisynthetic analogs of spectinomycin, were developed on the basis of a computational analysis of the spectinomycin binding site of the bacterial 30S ribosome and structure-guided synthesis. The compounds display particular potency against common respiratory tract pathogens as well as the sexually transmitted pathogens that cause gonorrhea and chlamydia.

In the study, the compounds displayed higher potencies against gonorrhea compared to that of spectinomycin and, significantly, demonstrated activity against chlamydia that is not observed with spectinomycin. Efficacies of the compounds were compared to those of spectinomycin and gentamicin in a mouse model of infection caused by ceftriaxone/azithromycin-resistant gonorrhea; the aminomethyl spectinomycins significantly reduced the colonization load and were as potent as the comparator compounds. The study supported aminomethyl spectinomycins as a promising replacement for spectinomycin and antibiotics such as ceftriaxone for treating drug-resistant gonorrhea, with the added benefit of treating chlamydial coinfections.

Comparing Existing Antimicrobials Individually or in Combination for Gonorrhea Treatment

A few recent publications have compared the efficacy of existing antimicrobials either individually or in combination for the treatment of gonorrhea. In a 2018 PLoS One article, the potential utility of 21 combinations of existing antimicrobials was investigated against 95 gonorrhea strains in vitro, including 79 MDR strains and one XDR strain collected from March 2013 to July 2017.[82] These 21 combinations

comprised two currently recommended by WHO (cefixime + azithromycin, ceftriaxone + azithromycin); two recommended by WHO in treatment-failure cases (azithromycin + gentamicin, spectinomycin + azithromycin), and 17 other combinations.

The WHO-recommended cefixime + azithromycin and ceftriaxone + azithromycin combinations showed no antagonism, indicating their continued clinical utility. Highest antagonism without any synergistic effect for the WHO-recommended spectinomycin + azithromycin in treatment-failure cases suggests that this combination should be evaluated further both in vitro and in vivo. The highest synergistic or additive effects without any antagonistic effects of five novel combinations (gentamicin + ertapenem, moxifloxacin + ertapenem, spectinomycin + ertapenem, azithromycin + moxifloxacin, cefixime + gentamicin) suggest that these may be recommended for treatment in the future.

The above-mentioned 2017 study that found ertapenem to have comparable activity to cefixime and ceftriaxone also sought to determine the in vitro activity of other currently licensed and late-development antimicrobials.[83] The MICs of conventional antigonococcal antimicrobials (penicillin, ceftriaxone, cefixime, azithromycin, ciprofloxacin, tetracycline, and spectinomycin) and alternative antimicrobials (ertapenem, gentamicin, netilmicin, tigecycline, eravacycline, fosfomycin, linezolid, ceftazidime/avibactam, and ceftaroline) were determined by agar dilution. Among potentially therapeutically useful alternative agents, the aminoglycosides (gentamicin and netilmicin), eravacycline, tigecycline, and fosfomycin had good in vitro activity.

Ciprofloxacin Susceptibility Testing

Another way to potentially expand the use of available medications and potentially slow the development of drug resistance is to develop tools that pinpoint the best gonorrheal treatment option for each individual. In a new trial, scientists will employ a rapid molecular assay using swabbed samples from participants' infection sites to determine whether they are infected with gonorrhea of a specific genetic profile (genotype), *gyrA* serine 91. Participants with that strain who agree to take part in the study will receive one dose of oral ciprofloxacin (500 mg) and will return for clinical and laboratory assessments within five to nine days to determine if they are cured. Participants who remain infected will be referred for standard treatment. Researchers intend to treat 381 participants with ciprofloxacin.[84,85]

If the *gyrA* serine 91 genotype proves to be a reliable marker of vulnerability to ciprofloxacin, health care providers may be able to reintroduce ciprofloxacin as a viable treatment for gonorrhea in some cases. The study is being funded by NIAID and led by principal investigator Jeffrey D. Klausner, with the David Geffen School of Medicine and Jonathan and Karin Fielding School of Public Health at the University of California, Los Angeles (UCLA). At present the study is listed as still recruiting, although the project was estimated to be completed in January of this year.

Developing Point-of-Care Tests for Gonorrhea, Chlamydia, and Syphilis

Timely and accurate testing and treatment is the bedrock of all efforts to eliminate infectious disease. Rapid point-of-care (POC) tests or 'near-patient' tests are of significant interest for stakeholders looking to improve early diagnosis.

This section will provide an overview of the need for new development in the area of rapid testing. Full coverage of the rapid POC diagnostics pipeline for gonorrhea, chlamydia, and syphilis is beyond the scope of this present report; however, this section will briefly review some of the major priorities for novel diagnostics.

Gonorrhea and Chlamydia Rapid POC Diagnostics

POC testing already exists for both gonorrhea and chlamydia; however, current platforms lack sufficient sensitivity to be of any real use. One near-patient test performs well but requires 90 minutes, which can hardly be called rapid in most patient situations.

A 2017 review of POC gonorrhea diagnostics platforms looked at six tests: five were immunochromatographic tests (ICTs) or optical immunoassays (OIAs) based on antigen detection with five to seven steps and results in 25–40 minutes, and one (GeneXpert CT/NG) was a near-patient test based on nucleic acid amplification technique (NAAT) with three steps, electricity required, and results in 90 min. When compared with laboratory-based NAATs as the reference tests, the sensitivities of the ICT and OIA-based POC tests ranged from 12.5% to 70% when cervical/vaginal swabs were tested, whereas the specificities ranged from 89% to 99.8%. GeneXpert CT/NG had sensitivities of >95% and specificities of >99.8% consistently across all specimen types (urine, cervical swabs, and vaginal swabs). Authors concluded that antigen-detection POC tests for gonorrhea lacked sufficient sensitivity to be used for screening. Although GeneXpert CT/NG had acceptable performance and only involved a few steps, it has several drawbacks, as the platform needs electricity and a temperature-controlled environment and has a 90-min run time.

Another 2017 paper looked at two previous systematic reviews of chlamydia POC tests.[87] The paper described the evaluation of nine brands of antigen-detection POC tests and one NAAT (again, GeneXpert CT/NG) that can be labeled as near patient. Although these antigen-detection rapid POC tests exhibited high specificity across all specimen types (range 97–100%), the pooled sensitivity was 37% for vaginal swabs (95% CI 22.9% to 52.9%; range 17.1–74.2%), 53% for endocervical swabs (95% CI 34.7% to 70.8%; range 22.7–87%), and 63% for urine (95% CI 43.2% to 78.5%; range 49.7–88.2%).
The aQcare Chlamydia TRF kit was the best-performing antigen-detection POC test, with sensitivities and specificities comparable to that of GeneXpert.

The best-performing test overall again was the GeneXpert CT/NG. The sensitivity showed no significant difference between self-collected vaginal swabs (98.7%), cervical swabs (97.4%), female urine specimens (97.6%), and male urine specimens (97.5%) with specificities ranging from 99.4% to 99.9%. The sensitivity and specificity of this assay for rectal swabs were 86.0% and 99.2%, respectively.

As with gonorrhea, the systematic reviews showed that antigen-detection POC tests for chlamydia, although easy to use, lacked sufficient sensitivity to be recommended as screening tests. GeneXpert again showed acceptable performance as a screening or diagnostic test, but the authors once again noted that it requires electricity, takes 90 min, and is costly.

Beyond diagnosis, for gonorrhea there is also a need to address antimicrobial resistance by developing new rapid methods to determine susceptibility to relevant antibiotics without resorting to culture. As part of two WHO gatherings in 2014 and 2015 on the topic of POC tests for STIs, participants recommended the identification of genetic markers to predict gonococcal resistance/susceptibility, including nucleic acid targets, against recommended therapeutic agents for gonorrhea.[88] The previously mentioned current NIAID-funded study of markers of ciprofloxacin susceptibility is one component of this.

Syphilis Rapid POC Diagnostics

Testing guidelines from the CDC highlight the challenges of timely, accurate diagnosis of a syphilis infection. Darkfield examinations and tests to detect syphilis directly from lesions or tissue are the definitive methods for diagnosing early syphilis.[89] Although no syphilis detection tests are commercially available, some laboratories provide locally developed and validated PCR tests for the detection of *T. pallidum* DNA.

For syphilis, biomarkers to easily and rapidly distinguish acute infection from prior infections are lacking, both in adults and infants.[90] A presumptive diagnosis of syphilis requires use of two tests: a nontreponemal test (i.e., Venereal Disease Research Laboratory or rapid plasma reagin [RPR]) and a treponemal test (i.e., fluorescent treponemal antibody absorbed tests, the *T. pallidum* passive particle agglutination assay, various enzyme immunoassays, chemiluminescence immunoassays, immunoblots, or rapid treponemal assays).[91] Use of only one type of serologic test is insufficient for diagnosis and can result in false-negative results in persons tested during primary syphilis and false-positive results in persons without syphilis.

A U.S. Preventive Services Task Force (USPSTF) 2016 review of syphilis screening of MSM found that testing every three months has greater benefits for early detection of new infections compared with 6- or 12-month intervals.[92] Four non-U.S. studies indicated higher rates of detection with screening every three months versus six or 12 months for early syphilis in HIV-positive men or MSM. For example, there was a higher proportion of asymptomatic, higher-risk MSM in Australia (N = 6789 consultations) receiving a diagnosis of early syphilis when tested every 3 months versus annually (53% vs 16%, P = .001), but no difference among low-risk MSM.

There is a need for improved rapid testing for syphilis, particularly if testing among MSM is ever to scale up to the degree recommended by the USPSTF. Quick, accurate diagnosis with rapid testing alleviates the possibility of an individual falling out of contact and not receiving results, allowing for early treatment and reducing the risk of onward transmission. Many rapid tests have been under development or in use outside the United States as single treponemal antibody tests or as treponemal antibody tests combined with HIV or hepatitis C virus rapid tests.[93] These rapid tests have targeted a global market in recent years and have sought WHO prequalification approval, including Chembio DPP HIV-Syphilis (a dual treponemal and HIV test; Chembio, Medford, New York); SD DUO (a treponemal and HIV test) made by Standard Diagnostics, which is now Alere (SD Bioline, Gyeonggi-do, Korea); and Multiplo (a treponemal and HIV test; Medmira, Halifax, Nova Scotia, Canada). Furthermore, Chembio is currently seeking FDA clearance for DPP Syphilis Screen and Confirm, which has both treponemal and nontreponemal tests in one cartridge (SD Bioline). In December 2014, Diagnostics Direct received a Clinical Laboratory Improvement Amendments (CLIA) waiver for their previously FDA-approved rapid immunochromatographic test called the Syphilis Health Check (SHC).[94] Similar to other immunoassays, the SHC uses a nitrocellulose strip loaded with *T. pallidum* antigen designed to capture passing antibodies. It is presently the only CLIA-waived option available in the United States.

With some rapid POC tests on the market, the need for new diagnostics may seem less of a priority. However, the possibility of false-positive diagnoses with current diagnostic platforms can be quite high. A recent review of syphilis screening for pregnant women conducted for the USPSTF found varying sensitivity and a high probability of false positives.[95] Some recent reviews of the field performance of rapid tests have also shown poor sensitivity for existing tests.[96] A 2017 meta-analysis looked at studies that evaluated the operational characteristics of dual HIV/syphilis rapid tests. All diagnostic accuracy evaluation studies showed a very high sensitivity and specificity for

HIV. For syphilis diagnosis, reported sensitivities ranged from 93% to 100% in laboratory settings, whereas for field settings, they ranged from 47% to 96%. Diagnostic accuracy for syphilis varied with manufacturer, with the SD BIOLINE HIV/Syphilis Duo Test being the most accurate.

A 2016 Morbidity and Mortality Weekly Report coming out of Florida also found that the potential for false positives was quite high with the CLIA-waived SHC. Results from the testing of 202 patients indicated a high proportion of reactive SHC tests were not confirmed by reference treponemal testing (16 of 26, 61.5%). This relatively low positive predictive value suggests that reactive SHC results should be interpreted with caution. Furthermore, 4 of 14 specimens that tested positive on the reference treponemal test tested negative on the SHC, including one from a patient with primary syphilis.[97]

In another recent study, the field performance of the INSTI Multiplex HIV-1/HIV-2/Syphilis Antibody Test (Multiplex) was evaluated in Los Angeles and New York.[98] The sensitivity of the Multiplex for detection of HIV was high at 98.8% (95% CI 93.4% to 100%), and the specificity was 100% (95% CI 98.1% to 100%). However, the sensitivity for detection of syphilis antibodies was only 56.8% (95% CI 44.7% to 68.2%), and the specificity was 98.5% (95% CI 95.7% to 99.7%).

Although reflexive confirmatory testing is an obvious recommendation for all rapid testing, this may not be an ideal solution in settings where loss to follow-up is highly possible. Reactive rapid tests may have benefits in terms of helping individuals to avoid onward transmission with sexual partners and increasing presumptive treatment, but there are also several potential costs if test results are not interpreted with caution and appropriately communicated to patients. False positives may create challenges for individuals in relationships and create stress, matters that should not be taken lightly with implementation of rapid testing. Ultimately, there is a need for better options for rapid POC tests, including single tests that can provide both treponemal and nontreponemal results.

The Syphilis Treatment Pipeline

Treatment			
Antimicrobial	**Delivery**	**Research Institution**	**Status**
BPG for early syphilis	Single injected dose of BPG 2.4 MU (compared to three successive weekly doses)	NIAID Peking Union Medical College	Phase IV NCT03637660 (NIAID) NCT02857959 (PUMC)
Cefixime	Oral, 400 mg capsule	UCLA and AIDS Health-care Foundation	Phase II NCT03660488

Treatment

Perhaps due to the ongoing challenges in accessing reliable, high-quality stocks of BPG,[99] in addition to the ongoing needs of individuals with a penicillin allergy, a few studies that could support conservation of stocks of BPG are currently underway. Two studies are looking at the use of one dose of BPG compared to three doses for treatment of early syphilis. Current CDC guidelines already note that no additional value has been observed for three-dose versus single-dose treatment of early syphilis; these trials appear to be providing additional evidence for the standard of care. NIAID is conducting a phase IV, randomized, open-label, multicenter trial to evaluate the efficacy of a single injected dose of BPG 2.4 million units (MU; arm 1) compared with three successive weekly injected doses of BPG 2.4 MU (arm 2) for treatment of early syphilis in HIV-infected and HIV-uninfected subjects. The study will enroll 560 adults (to achieve 420 evaluable subjects) aged 18 to 55 years with untreated early syphilis (primary, secondary, or early latent). The primary objective is to compare the serological response to therapy in subjects with early (primary, secondary, or early latent) syphilis treated with BPG) 2.4 MU once or weekly for three successive weeks. The secondary objectives are (1) to determine if the difference in response to therapy between treatment arms by month 6 differs among subjects with or without HIV infection; (2) to determine the impact of multiple BPG injected doses on subject adherence to scheduled follow-up visits; (3) to determine the incidence and manifestations of the Jarisch-Herxheimer reaction among subjects treated for early syphilis with BPG; (4) to collect prospective data up to month 12 on the serological response to therapy in subjects treated for early syphilis with either BPG regimen; and (5) to compare epidemiological characteristics of early syphilis among subjects with or without HIV infection. Results are expected in March 2022.[100]

A second study out of Peking Union Medical College Hospital appears to be researching the same question, though fewer details are available on the ClinicalTrials.gov site. The study intends to observe the serological response to one or three weekly doses of BPG in patients with early syphilis. It is currently enrolling 150 participants, with an estimated study completion in August 2020.[101]

A phase II study conducted by UCLA in partnership with the AIDS Healthcare Foundation is evaluating the efficacy of oral cefixime as an alternative treatment for syphilis infection. One hundred adult patients with syphilis infection will be recruited. Participants will be randomized (1:1) to receive either the standard of care BPG or cefixime. Participants of the cefixime group will be required to visit the clinic 14 days after treatment initiation. In each visit, participants will be asked about current symptoms and do laboratory tests for syphilis (RPR). A fourfold decrease in RPR titers from baseline at six months will be considered a positive treatment response. The study is currently recruiting with results expected in October 2020.[102]

Towards Earlier Detection of Neurosyphilis

Lumbar Puncture in the Management of Ocular Syphilis

A University of Washington study sponsored by the National Institute of Neurological Disorders and Stroke is evaluating the role of lumbar puncture in detecting possible neurosyphilis. T. pallidum invades the central nervous system in about 40% of patients with syphilis, which happens early after infection. Patients with neuroinvasion are at risk of developing serious neurological complications, including vision or hearing loss, stroke, and dementia. Because neuroinvasion can happen without symptoms, the only way to identify it is by performing a lumbar puncture to examine cerebrospinal fluid (CSF). The overall hypothesis to be tested in this study is that a strategy of immediate lumbar puncture, followed by therapy based on CSF evaluation, results in better serological and functional outcomes in patients with syphilis who are at high risk for neuroinvasion. The study is currently recruiting 280 participants and is estimated to complete in June of 2021, although the primary completion date is set for the middle of this year.[103]

Conclusions and Recommendations

Some notable progress has emerged in the research pipelines for the treatment and prevention of gonorrhea, chlamydia, and syphilis. Efforts to develop novel treatment options for gonorrhea have been particularly productive; there is also some movement in prevention research with promising findings for doxycycline as PrEP and PEP for chlamydia and syphilis, as well as increased funding for vaccine research across all three diseases. Additionally, our glimpse into some promising developments in the area of rapid POC diagnostics may assist with better detection and early treatment of bacterial STIs.

Based upon this review, TAG makes the following recommendations for community advocates and other key stakeholders in the worsening gonorrhea, chlamydia, and syphilis epidemics:

- **Advocacy to fight STIs must be more than repackaging condoms and behavioral interventions.** Promoting condoms and behavior change will never be enough to make sustained, meaningful progress in the control and elimination of the three major reportable bacterial STIs in America. Additionally, the ethical implications of monitoring and altering the sexual behaviors of marginalized communities, particularly through fear- and shame-based campaigns, should be questioned. Advocates must learn from the field of HIV prevention and focus much more aggressively on the structural, social, financial, and research barriers that undermine our ability to successfully utilize existing tools and develop essential new tools.

- **HIV PrEP and U=U activists must understand that their success is integrally linked to STI advocacy.** Not only are bacterial STIs drivers of new HIV infections, fears of 'risk compensation' will continually undermine scale-up of PrEP and U=U messaging, particularly when STI epidemics are breaking records.

- **Substantially more investment in new prevention modalities—particularly vaccine research—will be necessary.** The biological plausibility of vaccination against all three STIs has been established, and $9 million in new NIH funding shows increased investment in these essential tools. Advocates must continue to push for increased government expenditure on vaccine research as well as other biomedical primary prevention options. Additionally, advocates must make the case for a 'market' for STI vaccines in order to attract the kind of pharmaceutical company investment necessary to fully develop and implement these essential tools.

- **Doxycycline should be seriously considered for scale-up as a PrEP and/or PEP for syphilis and chlamydia.** Doxycycline is regularly prescribed for treatment of acne, yet health care providers remain concerned about prescribing it for STIs. Thus, the question remains as to whether the concern has to do with increased use of an antimicrobial in general or with how little we value sexual health in comparison to one's facial attractiveness. Given the relatively high efficacy (over 70%) of doxycycline in averting syphilis and chlamydia infections as PrEP and PEP, this must be considered in partnership with affected communities as a serious option for addressing rapid increases in STI rates.

- **Discussions on accessing zoliflodacin for treatment of MDR and XDR gonorrhea should begin now.** Although phase III trials are just beginning, the promising findings for zoliflodacin indicate that advocates should already be paving the way for rapid access. The medication has already been awarded fast-track status by the FDA, but much more work needs to be done, including rapid integration of zoliflodacin into STI treatment guidelines and broad provider and community education on its uses. Most

importantly, zoliflodacin must be priced in a way that ensures rapid and broad access while also providing a reasonable return on investment for Entasis Therapeutics.

- **Reliable, easy-to-use, CLIA-waived rapid tests for chlamydia, gonorrhea, and syphilis should be developed and made widely available.**

- **Infrastructure for the delivery of sexual health services remains highly underfunded in the United States, and declining funding for sexual health clinics must be addressed.** Although this recommendation is a bit beyond the scope of this report, existing and future tools for ending gonorrhea, chlamydia, and syphilis cannot be effectively implemented without increased investment in sexual health clinics in the United States, provider education, and appropriate curricula for providers-in-training.

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