

Gonorrhea

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Abstract

Purpose of Review Gonorrhea is a sexually transmitted disease caused by the bacteria *Neisseria gonorrhoeae*. In this review, we summarize recent updates in gonorrhea epidemiology, laboratory diagnosis, antimicrobial resistance, treatment, and prevention and control approaches.

Recent Findings Gonorrhea rates are increasing in the USA, driven primarily by increases among men—and likely among men who have sex with men. Continued emergence of antimicrobial resistance, declining antimicrobial options, and changes in sexual behavior further challenge current treatment, prevention, and control efforts. Investigations of novel antimicrobial agents and molecular assays for drug susceptibility and renewed interest in vaccine development are promising.

Summary Efforts to reduce gonorrhea incidence and address antimicrobial resistance face substantial challenges. Research

areas of the greatest need and of the greatest potential impact include development of new antimicrobials and rapid tests for resistance, identification of highly effective public health prevention and control approaches, and development of a gonorrhea vaccine.

Keywords Gonorrhea · *Neisseria gonorrhoeae* · Epidemiology · Resistance · Susceptibility · Treatment · STD

Introduction

Gonorrhea is a sexually transmitted disease caused by the bacteria *Neisseria gonorrhoeae*. Gonorrhea case rates have increased across the USA over the past 7 years, although they remain significantly lower than peak rates observed in the late 1970s [1]. Gonorrhea rates declined during the 1980s and 1990s, due in part to changing sexual behaviors related to HIV/AIDS awareness as well as to the advent of a National Gonorrhea Control Program [2]. Today, gonorrhea remains at the forefront of national interest due to the continued emergence of antimicrobial resistance and the potential for “untreatable” gonorrhea [3].

This review describes the basic epidemiology and clinical aspects of gonorrhea with an emphasis on new findings from the past decade. The report highlights current diagnostic technology—including antimicrobial susceptibility testing methods—and changing treatment recommendations that attempt to keep pace with our understanding of antimicrobial susceptibility. We also describe current gonorrhea prevention and control efforts and conclude with a discussion of future directions for research and gonorrhea prevention and control.

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Epidemiology

N. gonorrhoeae is a strictly human pathogen whose primary route of transmission is through sexual contact. Mother-to-child transmission during vaginal delivery can occur [4].

In 2015, 395,216 cases of gonorrhea were reported to the Centers for Disease Control and Prevention (CDC), making it the second most common reportable disease in the USA [1•]. Given that much of the disease is asymptomatic, under-diagnosis is likely. CDC estimates that about 820,000 new infections actually occur per year [5•]. Globally, there are 78 million new gonococcal infections each year [6].

Due in large part to changing demography, sexual mores, and the advancement of test technology permitting better diagnosis of *N. gonorrhoeae*, rates of gonorrhea rose sharply in the late 1960s and 1970s, reaching a peak in 1975 (464.1 cases per 100,000 persons) (Fig. 1) [1•]. Following the introduction of a National Gonorrhea Control Program in 1972 that enhanced screening and partner notification efforts as well as likely changes in sexual behavior that accompanied recognition of the HIV/AIDS epidemic, gonorrhea rates declined through the 1990s, reaching a historic low in 2009 (98.1 cases per 100,000 persons). However, during 2009–2015, the rate of gonorrhea increased 26% to 123.9 cases per 100,000 persons [1•], an increase primarily observed among men. Data from the STD Surveillance Network (SSuN) suggest that recent increases among men reflect increasing rates among gay, bisexual, and other men who have sex with men (MSM) (personal communication, Mark Stenger 2016). These increases may be due to increased screening of extra-genital anatomic sites (i.e., the pharynx and rectum), increasing incidence of infection in this population, or a combination of the two.

Rates among non-Hispanic blacks declined during 2014–2015, but marked racial/ethnic disparities persist. In 2015, the rate of gonorrhea among blacks was 9.6 times the rate among non-Hispanic whites (424.9 vs. 44.2 cases per 100,000

persons, respectively) [1•]. Observed racial/ethnic disparities persist after controlling for socioeconomic status and may reflect differences in sexual mixing patterns, residential segregation, and access to healthcare [7–9]; disparities are not simply a function of differences in individual risk behaviors across races/ethnicities [10–12].

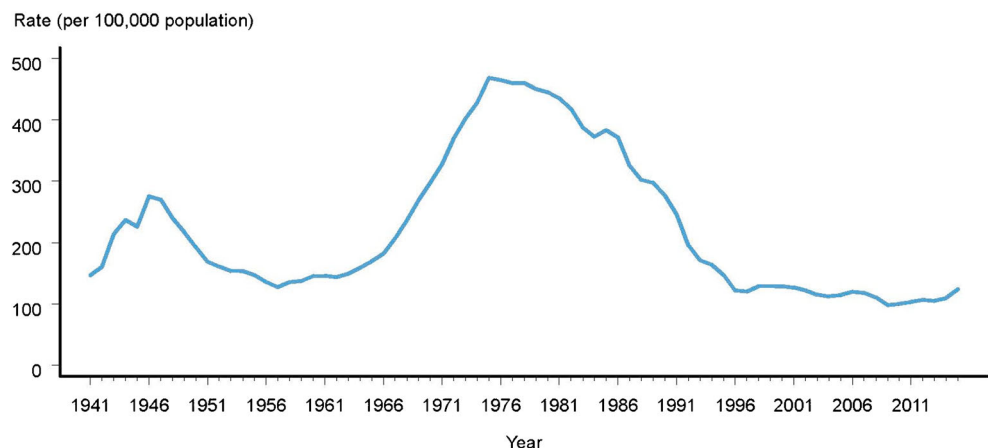
The modern epidemic of gonorrhea in the USA occurs among two primary populations defined by geography, race, and sexual behavior [13]. In the South, where overall rates are highest, gonorrhea disproportionately affects black, heterosexual young adults and adolescents; in the West, where rates have seen the most striking increase in recent years, gonorrhea disproportionately affects older, white MSM. Continued increases among MSM may alter this pattern.

Pathogenesis

Unlike other *Neisseria* species, *N. gonorrhoeae* is always considered pathogenic. *N. gonorrhoeae* derives its pathogenicity from the hair-like pili that coat its outer membrane, degrading IgA and facilitating attachment at mucosal membrane sites [4, 14]. These pili also mediate its attachment to spermatozoa [15], allowing *N. gonorrhoeae* to ascend upward into the female reproductive tract or peritoneal cavity [14].

Following attachment, *N. gonorrhoeae* induces a pyogenic infection. Spontaneous resolution of gonorrhea may occur through a reparative process known as fibrosis, or the laying down of fibrous bands of connective tissue, leaving the involved membranes scarred. Duration of asymptomatic gonococcal infection is difficult to study; however, the duration of asymptomatic infection among MSM (before spontaneous resolution) is estimated to range from 114 to 138 days at the pharynx to 346 days at the rectum [16]. Duration of infection for asymptomatic cervical infections in women is less well understood.

Fig. 1 Rates of Reported Gonorrhea Cases by Year, United States, 1941–2015. Source: Centers for Disease Control and Prevention. *Sexually Transmitted Disease Surveillance 2015*. Atlanta: U.S. Department of Health and Human Services; 2016



Clinical Presentation and Sequelae

Gonorrhea is primarily a localized infection, detected in the anatomic sites associated with sexual exposure, including the urethra, vagina, endocervix, rectum, and pharynx. Classically, gonorrhea causes purulent discharge at the site of infection, a result of the acute inflammatory reaction triggered by *N. gonorrhoeae*.

Aside from discharge, the most commonly reported symptoms of gonococcal infection in the lower reproductive tract include dysuria and, in women, abnormal uterine bleeding and lower abdominal pain. However, 50–60% of all female urogenital infections are asymptomatic, detected only through screening or partner diagnosis. The ascension of *N. gonorrhoeae* from the vagina or cervix into the upper reproductive tract is especially problematic as it is more difficult to detect and treat once it has ascended. Upper reproductive tract gonococcal infections can lead to severe reproductive complications, such as pelvic inflammatory disease (PID) or ectopic pregnancy and infertility. Older studies indicate that 10–20% of acute gonococcal infections will progress to PID [17].

Unlike the frequently asymptomatic female urogenital infection, 80–90% of men will experience some form of mild urethritis within 2 to 5 days following urogenital infection [17]. Pharyngeal and rectal gonococcal infections are almost always asymptomatic or present with non-specific signs and symptoms. Pharyngeal symptoms, when present, include acute pharyngitis, tonsillitis, fever, or cervical lymphadenopathy. Rectal symptoms range from mild anal pruritus to severe proctitis with pain, tenesmus, and constipation [18]. Having a lifetime history of gonorrhea is associated with a 20% increase in the risk of prostate cancer [19].

Infrequently, *N. gonorrhoeae* disseminates into the blood stream, leading to cardiac and joint infections. Disseminated gonococcal infection (DGI) may occur in 0.3 to 5.0% of cases that begin as urethritis or cervicitis, although recent estimates are not available [20]. In very rare instances, *N. gonorrhoeae* has invaded the meninges, leading to a classic presentation of meningitis that is difficult to distinguish from meningococcal meningitis.

N. gonorrhoeae can be transmitted during delivery from an infected mother to her infant, resulting in a gonococcal infection of the eye, known as ophthalmia neonatorum or neonatal conjunctivitis. Neonatal infection is typically identified 1 to 4 days after birth based on swelling, redness, and discharge from the eyelids and conjunctiva. Without quick treatment, this can lead to corneal perforation and blindness. In 2015, rates of reported gonococcal conjunctivitis (among infants <1 year of age) were lower than rates of reported chlamydial conjunctivitis (0.25 vs. 1.53 cases per 100,000 live births, respectively) [21].

Diagnosis

The primary methods for diagnosing *N. gonorrhoeae* include Gram stain, culture, and nucleic acid amplification tests (NAATs) [22•]. The choice of test depends on the rationale for testing and the setting in which specimens will be collected.

Gram Stain

The Gram stain technique remains an excellent point-of-care test for symptomatic urethral gonorrhea, detecting infection with $\geq 95\%$ sensitivity and $\geq 99\%$ specificity [22•]. Observing polymorphonuclear leukocytes with Gram-negative, intracellular diplococci on microscopic examination of a smear of urethral discharge is considered diagnostic in symptomatic men [22•]. Gram stain lacks sensitivity in urethral specimens from asymptomatic men, and the presence of nonpathogenic Gram-negative diplococci in the cervix, rectum, and pharynx renders specimens from these sites unreliable [22•]. The primary advantage of diagnosing gonorrhea by Gram stain is the ability to offer same-day diagnosis and treatment for symptomatic males. The primary disadvantage is the need for a skilled microscopist and an on-site laboratory. Although a Gram stain performed on urethral discharge is quite sensitive for *N. gonorrhoeae*, other *Neisseria* species can be difficult to distinguish. Recent increases in urethritis caused by *Neisseria meningitidis* were reported in 2 Midwestern cities [23]; the cases were identified as likely *N. meningitidis* when nucleic acid testing was negative for gonorrhea despite initial Gram stain and culture results that appeared consistent with gonorrhea.

Culture

Isolation of *N. gonorrhoeae* on antimicrobial-containing selective media (e.g., modified Thayer-Martin) can be performed on specimens from any anatomic site [22•]. However, sensitivity of culture varies by anatomic site (80–90% sensitive for cervical specimens; 67–72% sensitive for rectal specimens; 50–60% sensitive for oropharyngeal specimens) and is dependent on appropriate specimen collection technique and specimen handling [17, 24, 25]. *N. gonorrhoeae* is not viable for long outside the human body and should be streaked immediately onto selective media and incubated in a CO₂-enriched environment. Some non-nutritive transport media can be used to extend gonococcal viability up to 48 h to facilitate culturing [22•]. In addition to basic growth, colonies must demonstrate typical colony morphology consistent with *N. gonorrhoeae* and have a positive oxidase reaction and typical Gram-negative morphology [22•]. The primary advantages of diagnosing gonorrhea by culture are the range of specimen types that can be tested and the ability to conduct antimicrobial susceptibility testing. The primary disadvantages arise from the technical demands

of the test, which requires a trained biologist to distinguish colony morphologies, as well as limitations imposed by the gonococcus, which includes stringent collection and transport requirements to maintain viability and the time needed to conduct and interpret the test, which may take 24–48 h once plated due to the life cycle of *N. gonorrhoeae*. With the widespread adoption of nucleic acid testing, use of culture has declined dramatically in the USA [26, 27].

Nucleic Acid Amplification Tests

NAATs are a culture-independent diagnostic platform that detects *N. gonorrhoeae*-specific nucleic acid sequences. NAATs detect gonococcal infection with $\geq 90\%$ sensitivity and $\geq 99\%$ specificity [22•, 28•]. NAATs have been cleared by the Food and Drug Administration (FDA) for detection of urogenital gonorrhea in men and women [22•]. Appropriate specimens include endocervical swabs, vaginal swabs (self-collected or provider-collected), first-catch urine specimens, and urethral swabs from men. CDC also recommends NAATs for detection of pharyngeal and rectal gonorrhea. Although testing of extragenital specimens has not been cleared by the FDA, several large commercial laboratories have met Clinical Laboratory Improvement Amendments (CLIA) regulatory requirements for testing these specimens [22•, 28•]. The primary advantages of NAATs include the automated testing platform which reduces time to results, the ability to use non-invasive specimen types such as urine, and the relative ease of specimen handling, all of which have facilitated expanded screening in non-traditional healthcare settings. The primary disadvantage is that current commercially available NAATs do not allow for antimicrobial susceptibility testing.

Antimicrobial Susceptibility Testing

Antimicrobial susceptibility testing (AST) for *N. gonorrhoeae* currently requires isolation of live organisms by culture and is conducted using one of three quantitative methodologies—agar dilution, disc diffusion, or Etest (BioMérieux, Durham, NC). These AST methods all use graduated concentrations of gonorrhea antimicrobials to determine a minimum concentration of drug required to inhibit the growth of *N. gonorrhoeae*.

In the USA, AST is rarely used to guide patient therapy; this is due in part to the decline of culture as a diagnostic tool and also to the fact that test results often take ≥ 72 h to obtain given the life cycle of the gonococcus. The utility of “personalized medicine” for gonorrhea treatment is questionable; national antimicrobial resistance patterns are monitored through the CDC Gonococcal Isolate Surveillance Project (GISP) and treatment guidelines are modified based on surveillance findings. However, assessing gonococcal resistance in real time may expand the number of available treatment options in the

USA. AST is necessary to evaluate possible treatment failures and identify resistant infections.

The widespread use of NAATs for gonorrhea diagnosis has prompted promising research into molecular assays to detect genetic markers of resistance in *N. gonorrhoeae* [29–31]. New polymerase chain reaction (PCR) assays for resistance do not require live organism and may be combined with diagnostic NAATs. The development of a non-culture-based AST option may expand treatment options available to clinicians. Identification of appropriate genetic markers is being facilitated by whole genome sequencing analyses [32]. Because novel resistance mutations will continue to develop, phenotypic susceptibility testing for surveillance remains necessary and can inform changes in PCR assay targets as *N. gonorrhoeae* mutates.

Treatment

Prompt and effective therapy can prevent the sequelae of gonococcal infection for the patient as well as transmission to sex partners, making patient and partner treatment the cornerstone of gonorrhea prevention and control.

In the USA, gonorrhea is treated based on established treatment guidelines, such as the CDC STD Treatment Guidelines, which change regularly in response to antimicrobial susceptibility surveillance data. These guidelines do not rely on the availability of patient-specific antimicrobial susceptibility results; rather, they make general treatment recommendations for different presentations of gonococcal infection [28•]. Currently, CDC recommends that uncomplicated urogenital, rectal, and pharyngeal gonorrhea be treated with dual therapy consisting of a single intramuscular dose (250 mg) of ceftriaxone and a single oral dose (1 g) of azithromycin [28•]. Azithromycin should be administered at the same time as ceftriaxone regardless of the presence or absence of *Chlamydia trachomatis*. The rationale for dual therapy hinges upon the theoretical basis that using 2 antimicrobial agents with different molecular mechanisms of action will lessen the possibility of treatment failure due to resistance to 1 of the drugs and possibly slow the emergence and spread of resistance [28•].

The European Centre for Disease Prevention and Control (ECDC), the World Health Organization (WHO), and several other countries have released updated treatment guidelines recommending dual therapy with ceftriaxone and azithromycin, although recommended doses of ceftriaxone and azithromycin vary across international guidelines [33–36]. Japan recommends monotherapy but with a high dose (1 g) of ceftriaxone [37].

Following treatment, all persons diagnosed with gonorrhea should be re-screened in 3 months, and clinicians should strive to ensure that recent sex partners of persons diagnosed with gonorrhea be referred for evaluation, testing, and presumptive treatment [28•].

Ongoing assessment of clinician adherence to gonorrhea treatment recommendations and targeted provider education efforts based on those data are important for preventing and controlling gonorrhea and stemming the tide of antimicrobial resistance. Estimated provider compliance with recommended treatment regimens is high (87.9% in 2015) [38], although compliance varies by provider type [39]. Providers adapt treatment practices relatively quickly following the release of new treatment guidelines [40, 41•].

Antimicrobial Resistance

Monitoring of *N. gonorrhoeae* resistance in the USA is conducted through GISP, a CDC-supported sentinel surveillance system that has operated continuously since 1987, allowing for long-term trend data to inform treatment guidelines [42•].

N. gonorrhoeae has successively developed resistance to nearly all antimicrobials used for its treatment. The bacteria's accumulation of penicillin resistance mutations over 30 years led to continued escalations in recommended penicillin doses [43]. By the late 1970s, penicillinase-producing *N. gonorrhoeae* appeared on the West Coast of the USA, likely imported from East Asia, before spreading eastward [44]. This pattern repeated itself with the emergence of fluoroquinolone resistance in the early 2000s and reduced cephalosporin susceptibility during 2006–2010 [42•, 45, 46]. Resistance tends to emerge initially in the West and the prevalence of resistance often remains highest there. Interestingly, prevalence of resistance tends to be lowest in the South, the region that consistently has the highest rates of gonorrhea [1•, 42•].

Treatment guidelines are regularly updated with the aim of limiting the use of agents that have demonstrated reduced susceptibility. However, continuing emergence of resistance and the declining number of new antimicrobial agents have resulted in only a single recommended regimen in the current CDC treatment guidelines [28•]. The spread of *N. gonorrhoeae* strains with reduced susceptibility to cephalosporins has threatened the effectiveness of gonorrhea treatment [3]. Recent developments have cast doubt on the long-term viability of the currently recommended regimen. In 2014, a man in the UK was found to have a persistent infection despite therapy with ceftriaxone and azithromycin [47]. That same year, the prevalence of isolates with reduced susceptibility to azithromycin increased sharply in the USA [42•]. In 2016, Hawaii observed a cluster of 7 gonorrhea cases, all of which had high-level azithromycin resistance and several of which exhibited reduced ceftriaxone susceptibility [48].

Fortunately, a few promising compounds are under investigation. Solithromycin, a fluoroketolide, appeared highly effective during a Phase 2 trial, and a Phase 3 trial is ongoing [49]. ETX0914, a spiropyrimidinetrione and novel DNA gyrase/topoisomerase inhibitor, has demonstrated potent in vitro activity

and robust clinical efficacy in a recent Phase 2 trial [50, 51]. A third compound, GSK2140944, a novel type II topoisomerase inhibitor, is currently under investigation in a Phase 2 trial (NCT02294682). Although encouraging, new agents may still be years away from reaching the commercial market.

N. gonorrhoeae susceptibility breakpoints have been established for most antimicrobials, distinguishing susceptible *N. gonorrhoeae* from reduced susceptibility and resistant variants. Breakpoints may not always correlate well with clinical information like treatment outcome. New studies that correlate pre-treatment MICs and clinical outcomes may help refine existing breakpoints and may help inform the establishment of new breakpoints.

Prevention and Control Programs

Efforts to prevent and control the spread of gonorrhea can be classified as either primary or secondary prevention. Primary efforts aim to prevent gonococcal infection before it occurs; secondary efforts aim to prevent sequelae in an infected person as well as the prevention of onward transmission.

Primary Prevention

Behaviors such as abstinence, condom use, and a decrease in the number of sex partners can reduce the likelihood of acquiring or transmitting gonorrhea. Changes in these primary prevention behaviors may have far-reaching effects on gonorrhea incidence when other factors—such as the underlying risk network—remain unchanged.

Condoms are more than 90% effective at preventing *N. gonorrhoeae* transmission when used consistently and correctly during all sex acts [52, 53]. Inconsistent condom use with non-monogamous partners and errors in condom use (e.g., late application, early removal, slippage during sex, and reuse of condoms) are associated with decreased condom effectiveness and an increased risk of gonococcal infection [54].

Over the past 15 years, the proportion of men reporting condom use “some of the time” and “every time” for sex acts in the prior 4 weeks has increased (from 6.1% in 2002 to 10.6% in 2011–2013 and from 22.5% in 2002 to 24.7% in 2011–2013, respectively) [55]. This positive trend for condom use among men may mask differences by sex of sex partner. Although not a parallel measure, among MSM, reports of condomless anal sex at least once in the past year increased from 48% in 2005 to 57% in 2011 [56]; increases continued through 2014 [57]. Condom use should continue to be monitored closely as new biomedical interventions to prevent HIV, such as pre-exposure prophylaxis (PrEP), are fully implemented [58].

Age at first sexual intercourse is strongly associated with the total number of sex partners that an individual will have in his lifetime. Changes in age at first intercourse may have

consequences for STD risk. The proportion of never-married females aged 15–19 who have ever had sexual intercourse decreased from 51% in 1988 to 44% in 2011–2013 [59]. Sexual activity among adolescent boys is slightly different—with 60% reporting sexual intercourse in 1988, 42% in 2006–2010, rebounding to 47% in 2011–2013. Efforts to collect data documenting changes in sexual behaviors, including sexual debut, among lesbian, gay, and bisexual adolescents began in 2015, but results are not currently available [60].

Health communication and social marketing campaigns are often used to modify STD-related behaviors. STD-related behavior change often exhibits a dose-response relationship that is dependent upon the amount of exposure individuals receive to the health campaign [61]. A 15-year review of social marketing and health communication campaigns found 16 STD-related campaigns with evaluation information; only 6 of these were focused on primary prevention behaviors like increasing condom use and decreasing one's number of sex partners. Behavior change was often not significantly different at the implementing unit level (e.g., city or county) but among those *exposed* to the campaign, increases in self-reported condom use were often significant relative to non-exposed persons. Campaign effects persisted for 3 to 18 months.

The threat of antimicrobial resistance has reinvigorated interest in the development of another primary prevention strategy, the gonococcal vaccine, which may reduce incidence of infection and adverse reproductive outcomes like infertility [62, 63, 64•, 65]. The development of an effective vaccine has been challenging [62]. Because *N. gonorrhoeae* is an obligate human pathogen, animal models are limited; however, several infection models have been developed to study disease pathology and immune response [63]. “Humanized” murine models (e.g., estradiol-treated or transgenic mice) provide a proxy for human genital mucosa and have allowed testing of candidate vaccines and investigation of antigen-specific immune responses [63, 64•]. Potential vaccine targets include immunogenic proteins with high levels of antigenic conservation and stable expression within and between *N. gonorrhoeae* strains (i.e., TbpAB, 2C7 epitope of LOS, AniA, transferrin-binding) and outer membrane vesicles combined with other proteins (i.e., fHBP, NHBA, and NadA) that were used in serogroup B meningococcal vaccines [63, 66]. Animal models are limited in their ability to mimic all gonococcal-host interactions, including anatomical and physiological differences between humans and mice and differences between male urethral and female cervical mucosal infections [67].

Microbicides, or topical antimicrobials applied to vaginal or rectal mucosa, are another biomedical intervention of interest [68]. However, no marketed microbicides are currently available for the prevention of gonorrhea. Several candidate microbicides were explored in randomized controlled trials, but none has demonstrated any protective effect against *N. gonorrhoeae* [69–71].

Male circumcision is not currently used as a gonorrhea prevention strategy in the USA, but it bears mention given the attention it received as a biomedical intervention for HIV. Male circumcision has demonstrated effectiveness at reducing HIV acquisition and transmission, and has shown some benefit for other sexually transmitted pathogens like Herpes Simplex Virus (HSV) and those causing ulcerative disease. Observational studies initially indicated that male circumcision may also have benefit for *N. gonorrhoeae* and *C. trachomatis*, but later randomized controlled trials did not confirm any protective effect [72, 73].

Secondary Prevention

Current secondary prevention or “control” efforts for gonorrhea in the USA rely on screening, prompt and effective treatment of infected individuals, and treatment of those individuals' sex partners. The United States Preventive Services Task Force (USPSTF) and CDC currently recommend annual gonorrhea screening for women ≤ 24 years old and older women at increased risk for infection, including those with a history of gonococcal infections, diagnoses of other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use [28•, 74•]. CDC also recommends gonorrhea screening at first prenatal visit for pregnant women that meet these same criteria. Although the USPSTF currently has no recommendations for men, CDC recommends at least annual screening of sexually active MSM at anatomic sites of exposure [28•]. High-risk venues such as jails and prisons have a high burden of prevalent STDs; as such, CDC recommends gonorrhea screening at intake for women ≤ 35 and men < 30 years entering juvenile and adult correctional facilities [28•].

Prompt and effective antimicrobial therapy can prevent complications of gonorrhea in the infected patient and prevent transmission to sex partners. “Partner services” refers to a variety of tools that are designed to increase the number of infected sex partners brought to treatment and to disrupt transmission networks; these responsibilities may be carried out by the case-patient, the diagnosing provider, or the public health department. In the latter two methods, recent sex partners are elicited and referred for evaluation and treatment. For heterosexual patients whose sex partners are unwilling to present for care, expedited partner therapy (EPT) can be considered. EPT is the clinical practice of treating recent sex partners of gonorrhea case-patients by providing medications or prescriptions to the case-patient, without having examined the partner [28•].

In recent studies, EPT was associated with the treatment of more sex partners and fewer index patient reinfections compared with traditional partner referral practices [75–77, 78•], although the data do not conclusively support population-level reductions in gonorrhea with this partner treatment practice [79•]. Use of EPT remains relatively low [80]. CDC does not currently recommend EPT for MSM because efficacy data

do not exist for this sub-population and missed opportunities to diagnose other co-infections, like HIV, may be higher [28•].

Unlike other communicable diseases (e.g., HIV and tuberculosis), whole genome sequencing of *N. gonorrhoeae* isolates is not routinely used to identify sexual networks and to engage interventions to interrupt gonococcal transmission. This is due in part to the volume of cases reported each year and the slower advancement of molecular sequencing for *N. gonorrhoeae* relative to other pathogens. Whole genome sequencing may prove useful for outbreak identification and response in the future [38].

Future Research Directions

Taken together, these observations establish the need for progress in the following areas: (1) molecular assays to identify antimicrobial resistance, allowing for the expansion of treatment options in the face of emerging resistance; (2) correlation between in vitro susceptibility results and clinical outcome; (3) new antimicrobial agents to treat gonorrhea; (4) development of a gonorrhea vaccine; and (5) identification of effective population-level prevention strategies, perhaps informed by novel laboratory techniques such as whole genome sequencing.

Conclusions

Though gonorrhea case rates remain well below the 1975 peak, gonorrhea remains positioned at the forefront of US public health concerns because of increasing incidence, particularly among men (and most likely MSM), and the continued threat of antimicrobial resistance. The past decade has seen the promise of new test technologies and treatment recommendations in response to evidence of reduced antimicrobial susceptibility. However, it remains difficult to obtain antimicrobial susceptibility results in real time and susceptibility “findings” are not well correlated with treatment outcomes. In the absence of highly effective biomedical interventions to prevent gonorrhea acquisition and transmission, gonorrhea prevention and control rely heavily on individual-level disease interruption in the form of partner services—a practice that has substantial benefit for individuals but disputed benefit at the population level. These findings suggest a way forward for gonorrhea research and programming that includes renewed investment in vaccines and new antimicrobial agents as well as the identification of interventions that can impact gonorrhea at the population level.

Compliance with Ethical Standards

Conflict of Interest Virginia Bowen, Shacara Johnson, Emily Weston, Kyle Bernstein, and Robert Kirkcaldy declare that they have no conflicts of interest.

Human and Animal Rights and Informed Consent All reported studies/experiments with human or animal subjects performed by the authors have been previously published and complied with all applicable ethical standards (including the Helsinki declaration and its amendments, institutional/national research committee standards, and international/national/institutional guidelines).

Disclaimer The findings and conclusions in this report are those of the authors and do not necessarily represent the official position of the Centers for Disease Control and Prevention (CDC).

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