

Emerging Antimicrobial Resistance in *Neisseria gonorrhoeae*: Urgent Need to Strengthen Prevention Strategies

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Prevention and control of gonorrhea is an important public health concern due to the high burden of disease, the recent increase in reported infection rates, and the reproductive and economic consequences of infection. Effective antibiotic treatment is one essential component of an integrated approach to gonorrhea control. Over the past 60 years, however, development of resistance in *Neisseria gonorrhoeae* to multiple antimicrobial classes challenges this component of gonorrhea control. An integrated, comprehensive prevention strategy should include enhancement of national and international surveillance systems to monitor antimicrobial resistance

and new strategies to maximize the benefit and prolong the utility of antimicrobials, including combination regimens, implementation of screening recommendations for individuals at high risk for infection, and the assurance of prompt and effective treatment for infected persons and their sexual partners. Progress in controlling the epidemic and avoiding a resurgence as treatment options wane will require careful attention to all components of a comprehensive prevention strategy.

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N*isseria gonorrhoeae* infection can cause cervicitis, urethritis, proctitis, pelvic inflammatory disease with long-term sequelae (infertility, ectopic pregnancy, chronic pelvic pain), adverse outcomes of pregnancy, and increased susceptibility to and transmission of HIV infection (1, 2). *Neisseria gonorrhoeae* infection is the second most common notifiable disease in the United States, with 358 366 cases reported in 2006 (3). However, reported cases probably represent an underestimate of the actual disease burden because of underdiagnosis and underreporting; it is estimated that there were approximately 718 000 incident gonorrhea cases in 2000 (4). After national implementation of gonorrhea control activities in the 1970s, the incidence of gonorrhea in the United States declined markedly, with a 74% reduction in rates from 1975 to 1997. Although rates have remained relatively stable over the past decade, in 2006 the national gonorrhea case rate (120.9 cases per 100 000 population) increased for the second consecutive year, particularly in the western United States (3, 5). Rates of gonorrhea remain high in the South and among African Americans, adolescents, young adults, and men who have sex with men. Recent reports have also documented high rates of gonorrhea among HIV-infected men who have sex with men (3). Because of increased infection rates, high burden of disease, and the reproductive and economic implications of gonorrhea infection, prevention and control of gonorrhea is an important public health concern (6, 7). As current therapeutic options become more limited, we describe the emergent challenges to

maintaining antimicrobial effectiveness and a comprehensive approach to gonorrhea control.

HISTORICAL PERSPECTIVE ON ANTIMICROBIAL RESISTANCE

An essential element in gonorrhea control is the availability and provision of appropriate, effective antimicrobial therapy. Effective treatment not only eradicates infection in the affected individual and prevents the development of complications, it also has an important public health benefit of shortening the duration of infection, thus decreasing transmission and eliminating reservoirs of infection. However, over the past 60 years *N. gonorrhoeae* has developed resistance to multiple classes of antimicrobials (**Appendix Figure**, available at www.annals.org). Sulfanilamides were used for gonococcal treatment after their introduction in 1936, but their efficacy was short-lived because of the rapid emergence of resistance by 1945 (8). Penicillin became the recommended antimicrobial regimen for the next 40 years. The progressive decline in susceptibility—initially associated with chromosomally mediated resistance (exhibited by a stepwise increase in resistance) and later by the acquisition and spread of plasmids containing genes for penicillinase production—required serial increases in the recommended dose of intramuscular procaine penicillin (with probenecid) from 50 000 units in 1945 to 4.8 million units by the early 1970s (9). In 1985, because of emerging penicillin resistance, ceftriaxone became a recommended regimen for the treatment of uncomplicated gonococcal infections (10). At the same time, tetracycline resistance (both plasmid and chromosomally mediated) was spreading to the extent that tetracycline was no longer a viable treatment option. By 1989, resistance to penicillin was sufficiently widespread that penicillin was no longer effective. Ceftriaxone then became the recommended regimen for gonorrhea therapy, with ciprofloxacin as an alternative treatment option (11). By 1993, on the basis of data re-

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garding high efficacy, safety, and convenience as single-dose therapies, oral fluoroquinolones (ciprofloxacin, ofloxacin) were recommended as oral regimens for gonorrhea treatment, as was the oral third-generation cephalosporin cefixime (12).

In 1986, concerns about emerging gonococcal antimicrobial resistance lead to the development of the Gonococcal Isolate Surveillance Project (GISP), a national sentinel surveillance system that monitors antimicrobial susceptibility in the United States. Each year, approximately 6000 urethral gonococcal isolates from men attending 25 to 30 sexually transmitted disease (STD) clinics throughout the country are collected and analyzed to provide national data that help guide treatment recommendations. The GISP findings of notable importance include the continued high prevalence of penicillin and tetracycline resistance, which has remained greater than 15%; the increasing prevalence of isolates with decreased susceptibility to macrolides; the appearance of a limited number of multidrug-resistant isolates with decreased susceptibility to cefixime (3); and most important, the dramatic spread of quinolone-resistant *N. gonorrhoeae*.

Based in part on data from GISP, the emergence of quinolone-resistant *N. gonorrhoeae* was first identified in Hawaii in 1991, at about same time that it was recognized as a problem in Asia (13). Thereafter, sporadic occurrences of quinolone-resistant *N. gonorrhoeae* were noted in the United States throughout the 1990s. By 2000, quinolone-resistant *N. gonorrhoeae* was increasingly observed in persons who became infected in Asia, the Pacific Islands (including Hawaii), or California. As a result, fluoroquinolones were no longer recommended for treating gonorrhea acquired in those locales (14, 15). Over the next several years, GISP identified increased rates of quinolone-resistant *N. gonorrhoeae* among men who have sex with men. This finding prompted an advisory in 2004 that fluoroquinolones were no longer recommended for treating gonorrhea in men who have sex with men, regardless of locale (16). Most recently, data from GISP indicate that quinolone-resistant *N. gonorrhoeae* is widely dispersed in the United States and that in 2006 the infection accounted for 39% of gonococcal isolates in men who have sex with men and 7% in heterosexual men. On the basis of these cumulative data, the Centers for Disease Control and Prevention (CDC) announced that fluoroquinolones are no longer recommended for treating gonococcal infections and associated conditions, such as pelvic inflammatory disease or epididymitis, in any population in the United States (17).

The antimicrobial resistance data from GISP have provided a rational basis for recommended gonococcal treatment regimens. However, data from this sentinel surveillance system have limitations. The GISP data may not be representative of the total population with gonorrhea in the United States, because the current national surveillance system oversamples West Coast locations (where new resistant strains have been first detected), evaluates only male

urethral isolates obtained from STD clinics, and samples only a minority of reported gonococcal infections. Dramatic differences in quinolone-resistant *N. gonorrhoeae* prevalence by geographic location and sexual orientation illustrate the challenge of achieving accurate representation (18). The rapid spread throughout the United States of quinolone-resistant *N. gonorrhoeae* in heterosexual men, as well as among men who have sex with men, makes defining remaining pockets of continued susceptibility of *N. gonorrhoeae* problematic. These limitations highlight the difficulty of defining an appropriate sentinel population and a frequency of sampling with sufficient representation to assure susceptibility in a particular locale. Thus, there is a need to monitor antimicrobial resistance at the local level, which would provide a more in-depth understanding of resistance trends and contribute to decisions that affect treatment recommendations in various locations (19, 20).

EVOLUTION OF CRITERIA FOR GONORRHEA TREATMENT RECOMMENDATIONS

The epidemiology of antimicrobial resistance guides decisions about gonococcal treatment recommendations. As discussed, data from GISP are critical when evaluated along with other relevant data, such as those provided by the Gonococcal Antimicrobial Surveillance Program of the Western Pacific Regional Office of the World Health Organization (WHO) in Southeast Asia and the Pacific region. The CDC and the WHO have recommended a change in the treatment regimen when the prevalence of antimicrobial resistance exceeds 5% for a specific antibiotic, while taking into account the prevalence of gonorrhea in the community, the cost of diagnostic and treatment regimens, and the availability of antimicrobial susceptibility data (21–23).

An accepted definition of gonococcal treatment efficacy requires a cure rate of over 95% with a lower bound of the 95% CI of at least 90% (24). At the time this criterion was proposed, many antimicrobial regimens met this standard, but in an attempt to reduce the risk for therapeutic failure and development of antimicrobial resistance, more stringent criteria were proposed by Moran and colleagues (25). Their criteria specified that efficacy exceed 95% in summed clinical trials, but required that the lower bound of the 95% CI also be at least 95%. In addition to efficacy data, decisions regarding treatment recommendations involve consideration of other factors. These include administration of at least twice the minimum dose to ensure therapeutic reserve, documentation that susceptibility is not lower among organisms recovered after treatment, and evidence that the serum or plasma concentration with the recommended dose is at least 4 times the minimum inhibitory concentration required to inhibit 90% of strains (MIC_{90}) for 10 hours after the concentration peak (25). These stringent clinical efficacy criteria (95% efficacy with 95% CI) were used to determine the gonorrhea treatment

regimens recommended in the CDC STD Treatment Guidelines since 1993.

However, it was recently suggested that these criteria be modified, given the propensity of *N. gonorrhoeae* to develop antimicrobial resistance to a wide variety of antibiotics, the paucity of novel antimicrobial agents being developed, and the decreased number of highly effective and available treatment regimens (22). Antimicrobials would now be recommended as “alternative treatment regimens” if their clinical efficacy is greater than 95% and the lower bound of the 95% CI is at least 90%; the more stringent criteria would be maintained as required criteria for the primary recommended gonorrhea treatment regimens.

CURRENT TREATMENT RECOMMENDATIONS

Because of the emergence of quinolone-resistant *N. gonorrhoeae* in the United States, the current recommended gonorrhea treatment options are from a single class of antimicrobials—cephalosporins. Ceftriaxone, available only as an injection (125 mg intramuscularly), is the recommended regimen for uncomplicated urogenital and anorectal infection. Several other parenteral cephalosporins (ceftizoxime, cefoxitin, cefotaxime) are efficacious in treating gonorrhea but do not offer any substantial advantages over ceftriaxone. Cefixime, 400 mg, is the only oral regimen recommended for gonorrhea treatment. Single-dose oral regimens have potential benefits of convenience and reduced risk for needlestick injury in health care workers. However, as a result of the decision by the manufacturer to discontinue U.S. production, cefixime tablets have not been available in the United States since October 2002 (26). In 2004, Lupin (Mumbai, India) received approval from the U.S. Food and Drug Administration (FDA) to manufacture generic cefixime, currently available as a suspension (200 mg/5 mL), with approval of a tablet formulation anticipated in 2008. Several oral regimens for uncomplicated urogenital and anorectal gonococcal infections may be considered as alternative gonococcal therapies using the less stringent efficacy criterion (that is, lower bound of 95% CI \geq 90%). Some evidence suggests that cefpodoxime, 400 mg, may be effective for treating urogenital and anorectal gonorrhea (22, 27). Cefuroxime axetil, 1 g, also meets the less stringent efficacy criteria, but it has poor pharmacodynamic characteristics that may select for stepwise increases in resistance, as has occurred with penicillin (28).

Because cephalosporins are the only currently recommended class of antimicrobials, it is critical that susceptibility to these drugs be actively monitored. Data from GISP indicate that the MIC₉₀ distribution for ceftriaxone has remained relatively stable: Only 4 isolates identified since 1987 have had decreased susceptibility to ceftriaxone, and no resistant isolates have been identified (29). Cefixime susceptibility testing through GISP has demonstrated 48 isolates with decreased susceptibility since 1992 (29), with several isolates having possible epidemiologic

links to Asia (30). Recent reports from Japan and several other countries in the WHO Western Pacific Region (Australia; Brunei; China; and Papua, New Guinea) suggest decreased susceptibility to cephalosporins, with the reported mechanism of resistance being alterations in *penA* genes (30–33). Some *N. gonorrhoeae* strains demonstrating reduced cephalosporin susceptibility also have reduced susceptibility to multiple drug classes, including quinolones, macrolides, penicillins, and tetracyclines (30, 32). The emergence and dissemination of such strains is of particular concern.

Management of Cephalosporin Allergy

Allergy to antibiotics is another barrier to successful treatment. Many regard a history of penicillin allergy as a relative contraindication to cephalosporin administration (34). Allergic reactions to cephalosporin occur in approximately 5% to 10% of persons with a history of penicillin allergy. However, immediate (30 to 60 minutes after administration) and accelerated (1 to 12 hours after administration) IgE-mediated anaphylactic or urticarial reactions to cephalosporins are rare, relative to reactions associated with penicillin (34, 35). Although a cross-reactivity rate of 10% has been reported, this estimate is based on retrospective studies in which penicillin allergy was not routinely confirmed by skin testing. However, some of the reactions may have not been immune-mediated (35). Available data suggest an increased risk for cephalosporin reactions among persons with positive results on penicillin skin tests (34). Skin testing (major and minor penicillin determinants) is warranted for individuals who require cephalosporin treatment and have a history of penicillin allergy that is consistent with an IgE-mediated mechanism (36). However, skin testing is not feasible in many settings because benzylpenicilloyl polylysine is not currently available; a companion major and minor determinant mixture is anticipated in the future. Cephalosporin desensitization may also be considered in the management of persons who have had documented severe allergic reactions to a cephalosporin or to penicillin, but this is impractical in most clinical settings.

Alternative Treatment Options

Spectinomycin is another therapeutic option for persons with gonococcal urogenital infection who cannot tolerate cephalosporins. Of note, spectinomycin has limited effectiveness for the treatment of pharyngeal infection, limiting its utility in populations in which such infections are common, such as men who have sex with men. However, spectinomycin is not currently commercially available for gonococcal treatment but is expected to be available in the United States during 2008. Updated information regarding the availability of spectinomycin is available at www.cdc.gov/std/gonorrhea/arg (37). However, even if spectinomycin were available, it would probably remain an alternative treatment rather than a recommended one, be-

cause high levels of resistance developed when this antimicrobial was widely used in the mid-1980s (38).

Azithromycin, 2 g, taken orally is effective against uncomplicated gonococcal infection and is another option for persons who are allergic to cephalosporins. However, concerns about the development of antimicrobial resistance to macrolides with widespread use restrict current treatment recommendations to limited circumstances. Macrolide antibiotics, such as azithromycin and erythromycin, have been associated with the multiple transferable resistance efflux system (39, 40). Gonococcal isolates with reduced susceptibility or resistance to azithromycin have been documented in the United States and many other countries (29, 33). Of additional concern, the 2-g dose has been associated with adverse gastrointestinal effects, such as nausea, diarrhea, and vomiting, possibly due to the drug's effect on motilin receptors, as demonstrated with other macrolides (41). However, a recently developed extended-release microsphere formulation delivers 2 g of azithromycin in a single tablet. This has improved tolerability owing to release in the lower gastrointestinal tract and bypass of the motilin receptors in the upper tract (42).

A test of cure is not required after appropriate treatment for uncomplicated urogenital gonorrhea with any of the recommended or alternative regimens (43), but local jurisdictions may elect to perform such testing. Persons whose symptoms persist after a recommended regimen should be evaluated by culture and antimicrobial susceptibility testing; such cases should be reported to the local health department.

NEW DIRECTIONS IN GONORRHEA TREATMENT

Given the possible emergence of cephalosporin resistance, other effective therapeutic regimens and new agents for gonorrhea treatment are urgently needed. Although aminoglycosides (kanamycin, gentamicin) have been widely used for syndromic treatment for urethral discharge in some settings (44), additional information is needed before such drugs can be considered. For example, data are limited on the prevalence of gonococcal resistance to aminoglycosides because there is no standard MIC that defines antimicrobial resistance. Furthermore, correlations between laboratory data and clinical outcome have not been established, aminoglycosides are administered only by injection, and resistance has developed with widespread use (44). Another drug that may be considered is rifampicin, which is widely available in many countries; however, resistance develops rapidly, and recent data from Indonesia suggest that resistance is prevalent (45). Other antimicrobials, including co-trimoxazole, chloramphenicol, and erapenem, have been investigated to a limited extent. Concerns about emergence of resistance, cost, efficacy, and safety of each of these alternative regimens remain (22, 46).

New strategies are needed to maximize the benefit and prolong the utility of antimicrobials. Some have suggested

that use of a limited number of treatment regimens may accelerate emergence or spread of antimicrobial resistance and should be avoided (47), but recent data have not supported this view (48). Use of combination therapy may reduce the selective pressure that monotherapy exerts on drug resistance; using different antimicrobial classes or combination regimens is analogous to the therapeutic approaches to tuberculosis and HIV infection. Macrolides combined with either aminoglycosides or rifampin are possible treatment options. For example, some have suggested that routine co-treatment for chlamydia with azithromycin may hinder the development of antimicrobial-resistant *N. gonorrhoeae* (43). Clinical and laboratory evaluation of the pharmacokinetics and pharmacodynamics of such combinations will help to identify efficacious regimens that deter antimicrobial resistance.

Antimicrobial treatment alone is inadequate in addressing emerging gonococcal antimicrobial resistance. Gonococcal resistance has emerged and spread from countries in which disease is highly prevalent, syndromic treatment algorithms (urethritis, cervicitis) are widely used, the capacity to identify asymptomatic reservoirs is lacking, and surveillance and prevention program activities are limited (46). The discovery of novel agents or a combination of antimicrobials is only one component of an integrated, global approach to gonorrhea prevention.

GONORRHEA PREVENTION AND CONTROL

Prevention and control programs for STDs have been critical in achieving the substantial reduction in rates of gonorrhea infection in the United States over the past 30 years (6). Continuing progress in controlling this important STD requires a comprehensive approach to confront the considerable challenges presented by the high global burden of disease, an adaptable organism, emerging antimicrobial resistance, and sparse treatment options. A comprehensive prevention strategy must enhance global surveillance systems that monitor antimicrobial resistance, adapt screening recommendations for individuals at high risk for infection, and assure prompt and effective treatment for infected persons and their sexual partners (Table).

Surveillance for Resistance

Effective antimicrobial treatment is the foundation of our national gonorrhea prevention program; vigilant surveillance to identify emerging antimicrobial resistance is essential if treatment is to remain highly effective. The national sentinel gonococcal surveillance system (with close monitoring of cephalosporin MICs) must be strengthened, and collaboration with international partners must be enhanced to monitor emerging resistance globally. In addition, we must expand geographic information systems to track infections at the local level, evaluate risk factors associated with antimicrobial resistance, and heighten surveillance of treatment failures to identify emerging cephalosporin resistance. We must increase local capacity to monitor

Table. Gonorrhea Prevention and Control*

Issues	What Is Known	What We Need
Surveillance for resistance	Antimicrobial resistance monitored in male urethral gonococcal isolates from STD clinics in the United States (GISP)	Strengthen national sentinel surveillance system to monitor emerging resistance to recommended gonorrhea treatment regimens Expand geographic information systems to track infections locally; investigate appropriate sentinel populations and sampling frequency to determine susceptibility Maintain capacity to monitor for antimicrobial resistance at the local level with gonorrhea culture and susceptibility testing
	Development of gonococcal resistance is a global issue: Countries with greatest burden of disease and limited prevention activities are likely to be the source of new patterns of resistance	Implement global approach: Enhance collaboration with international partners to monitor global resistance patterns; strengthen surveillance monitored by the GASP of the Western Pacific Regional Office of the WHO in Southeast Asia, the Pacific Region, and elsewhere
Primary screening	Surveillance data on antimicrobial resistance provides rational basis for recommended gonococcal treatment regimens	Evaluate risk factors associated with antimicrobial resistance
	Gonorrhea screening recommendations in sexually active women at risk for infection (USPSTF Guidelines)	Implement screening guidelines for women at risk for infection: Screen women age <25 y, or those with previous gonorrhea, other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, drug use
Secondary screening	STD screening recommendations in sexually active men who have sex with men, including those with HIV infection (CDC STD Treatment Guidelines)	Perform annual STD screening for men who have sex with men: Screen more frequently (every 3–6 mo) in men who have sex with multiple or anonymous partners, sex with drugs, use of methamphetamine, partners who participate in these activities
	Asymptomatic infection is common at the pharyngeal and rectal sites in men who have sex with men	Screen annually for gonorrhea/chlamydia (urethral or urine); test for pharyngeal gonorrhea infection (orogenital exposure); test for gonorrhea/chlamydia rectal infection (receptive anal intercourse); HIV and syphilis serology
Gonorrhea treatment	High incidence of gonococcal reinfection	Repeat testing for gonorrhea at 3–4 mo after treatment for initial infection, ideally at all exposed anatomical sites
	Prompt evaluation of sexual partners is necessary to prevent reinfection and disrupt transmission	Evaluate and treat sexual partners whose last sexual contact was within the past 60 d before symptom onset or diagnosis of gonorrhea/chlamydia Expedited partner therapy is an option in heterosexual men or women with gonorrhea
	Treatment options are limited to a single antimicrobial class	New strategies are needed to maximize benefit and prolong the utility of antimicrobials; clinical and laboratory evaluation of combination therapy Provider, public health, and industry collaboration to ensure development and clinical evaluation of new antimicrobials and the continued availability of drugs of proven benefit Provide legislative and regulatory incentives for drug discovery

* CDC = Centers for Disease Control and Prevention; GASP = Gonococcal Antimicrobial Surveillance Project; GISP = Gonococcal Isolate Surveillance Project; STD = sexually transmitted disease; USPSTF = U.S. Preventive Services Task Force; WHO = World Health Organization.

antimicrobial susceptibility, which requires the technical capacity to culture gonococci. However, the ability to perform a gonococcal culture and susceptibility testing is affected by the expansion of nucleic acid amplification testing for diagnosis of infection (20). The CDC has encouraged state and local health departments to maintain a capacity to perform culture and antimicrobial susceptibility testing or develop partnerships with experienced laboratories that can perform such testing (17).

Primary Screening

Another essential and well-established component of gonorrhea control is the screening of populations at risk for infection. Because gonococcal infections among women frequently are asymptomatic, screening of women at high risk is essential to detect reservoirs of infection. The U.S. Preventive Services Task Force recommends screening sexually active women (including pregnant women) and women at increased risk for infection. Risk factors include

age younger than 25 years, previous gonorrhea infection or other STDs, new or multiple sex partners, inconsistent condom use, commercial sex work, and drug use (49). Screening low-risk women and men is not recommended.

Routine screening for gonorrhea and other common STDs is also recommended for sexually active men who have sex with men, including those with HIV infection (43). Specific screening recommendations include annual tests for gonorrhea and chlamydia on urethral or urine specimens, a test for gonococcal pharyngeal infection in men with orogenital exposure, and a test for gonorrhea and chlamydia rectal infection in men who have had receptive anal intercourse during the past year (43). More frequent screening (at 3- to 6-month intervals) may be indicated for men who have sex with men, who have multiple or anonymous partners, who have sex in conjunction with illicit drug use, who use methamphetamines, or whose partners participate in these activities. Adherence to these screening

recommendations is an important strategy for gonorrhea control in sexually active men who have sex with men, because asymptomatic infection at pharyngeal and rectal sites is common and gonorrhea can be easily transmitted with insertive or receptive rectal intercourse and fellatio (3, 50–52). Screening for pharyngeal infection among men who have sex with men is also important because this infection is more difficult to treat than urogenital or anorectal infection. Few antimicrobial regimens, including ceftriaxone, can eradicate more than 90% of gonococcal pharyngeal infections (22, 53, 54). Culture is the preferred method for detection of *N. gonorrhoeae* at the pharyngeal and rectal sites (43) because the FDA has not approved nucleic acid amplification tests for use at those sites. However, such tests have been used at the pharyngeal and rectal sites after local validation tests were done to meet Clinical Laboratory Improvement Amendment requirements (50, 51). In addition, all persons tested for gonorrhea should be evaluated for other STDs, including syphilis, chlamydia, and HIV infection (43).

Secondary Screening and Management of Sex Partners

Persons who have had gonorrhea and received appropriate treatment in the past several months have a high incidence of repeated infection (55–57). Most of these infections result from reinfection rather than treatment failure, which indicates the importance of prevention counseling and partner referral. As a result, retesting—ideally at all exposed anatomical sites—is recommended 3 to 4 months after treatment for initial infection (43, 57). Prompt and effective evaluation and treatment of sexual partners is necessary to prevent reinfection and disrupt routes of transmission; therefore, partners whose last sexual contact was within 60 days before symptom onset or diagnosis of infection should be evaluated and treated for both gonorrhea and chlamydia (43). If medical evaluation, counseling, and treatment of partners are not possible, expedited partner therapy, in which partners of infected persons are treated without medical evaluation or prevention counseling, is a reasonable alternative for partners of heterosexual men or women (58). There is no documented experience with expedited partner therapy for gonorrhea or chlamydia infection among men who have sex with men.

Dependence on Commercial Interest in Drug Development

Despite the manifest need for additional antimicrobial agents with the recommended treatment options now limited to a single antimicrobial class, financial incentives for novel drug discovery and clinical evaluation of existing agents have not stimulated ongoing research by industry. The current problem with gonorrhea treatment regimens is part of a larger pattern of declining investment in antimicrobials. Many consider this trend to be a looming public health crisis and have proposed legislative and regulatory incentives to spur development of new therapies (59). Clinicians and public health officials must collaborate with

the pharmaceutical industry to ensure the discovery and clinical development of new antimicrobials. Limited availability of drugs of proven benefit (cefixime and spectinomycin) for infections for which few other options exist is a serious threat to public health.

CONCLUSION

Although there have been great successes in gonorrhea control in the United States, gonococcal infection remains an important public health problem, disproportionately affecting such populations as African Americans, adolescents and young adults, and men who have sex with men. The provision of effective antimicrobial treatment not only eradicates infection in the affected individual, it prevents transmission, thus reducing disease rates. However, effective antimicrobial treatment should be seen as only one essential component of an integrated approach to gonococcal control. Further progress in controlling the epidemic, and avoiding a resurgence as treatment options wane, will require careful attention to all components of a comprehensive prevention strategy.

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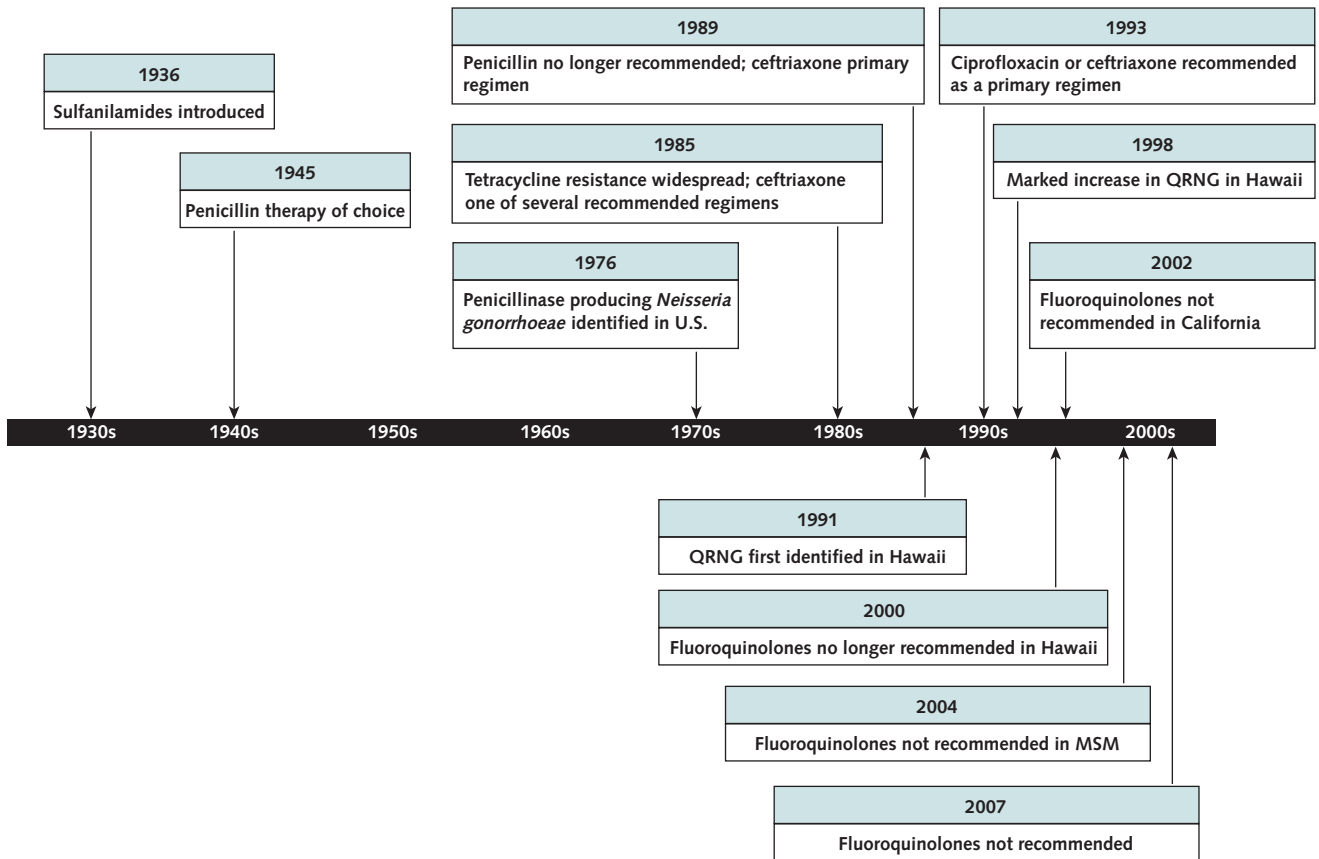
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Appendix Figure. Historical perspective on antimicrobial resistance in the United States.



QRNG = quinolone-resistant *Neisseria gonorrhoeae*; MSM = men who have sex with men.