combination's safety and the effect on mortality should be considered early in its development.

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Neisseria gonorrhoeae — Rising Infection Rates, Dwindling Treatment Options

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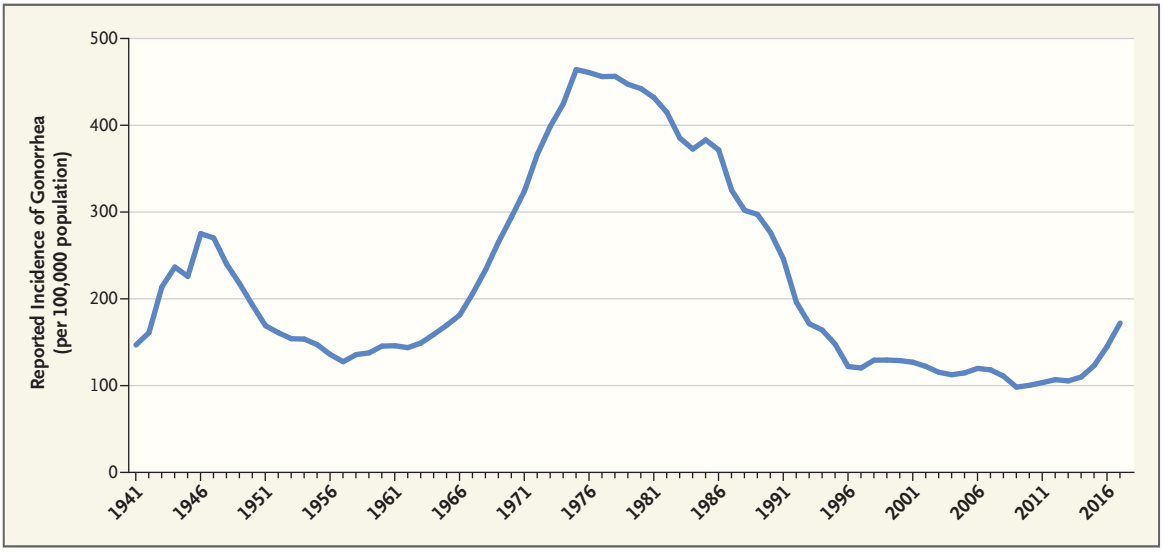
Related article, page 1835

Gonorrhea infection is the second most commonly reported notifiable condition in the United States, and case rates have been increasing since 2009. In 2017, a total of 555,608 cases of gonorrhea were reported nationally, the largest number since 1991 and an 18.6% increase over 2016 (see graph).[1]

In 2015, the Obama administration deemed *Clostridium difficile*, carbapenem-resistant Enterobacteriaceae, and *Neisseria gonorrhoeae* the most urgent infectious public health threats to national security, given the accelerating emergence of antibiotic resistance in these organisms.[2] Though gonorrhea ranked third on this list, the number of cases of gonorrhea dwarfs those of the other two infections. Worldwide, gonorrhea cases have persistently affected young adults. Without a concerted global effort to mitigate antibiotic resistance, infected persons (primarily, sexually active young adults, who tend to be otherwise healthy) may require extended hospital stays and additional follow-up visits for an infection that can currently be managed on an outpatient basis. Such a shift could impose a serious burden on health care systems and societal productivity internationally. In the United States, this concern is compounded by the fact that for decades, gonorrhea infections have disproportionately affected black Americans, American In-



Rates of Reported Cases of Gonorrhea, United States, 1941–2017.
Data are from the CDC, Sexually Transmitted Disease Surveillance, 2017.

dians and Alaska Natives, Native Hawaiians and other Pacific Islanders, and Hispanic Americans.

Untreated gonorrhea infection can have serious health consequences. It is transmitted from an infected person to a partner during sex or from an infected woman to her baby at delivery. Infections are frequently asymptomatic, but they can lead to serious sequelae such as pelvic inflammatory disease, ectopic pregnancy, infertility, destructive arthritis, disseminated infection, and blindness in neonates born through an infected birth canal. In addition, the mucosal inflammation caused by *N. gonorrhoeae* may facilitate the transmission of HIV between sex partners.

The Centers for Disease Control and Prevention (CDC) estimates that the annual domestic cost of treating these acute infections and their sequelae is $182.2 million (in 2017 dollars). This estimate excludes the cost of gonorrhea-attributable HIV infections and adverse pregnancy outcomes.[3]

Controlling gonorrhea in a population requires many connected activities. It requires access to screening, routine assessment of patients' sexual practices to guide the identification of anatomical sites requiring specimen collection, laboratory capacity to perform testing, diagnostic technology that can characterize the organism and its antibiotic susceptibility, systems for gathering that information to guide treatment recommendations, and above all, effective and simple antibiotic therapy.

N. gonorrhoeae is prone to the development of antibiotic resistance, and our ability to monitor antibiotic susceptibility is limited. The advent and increasing adoption of nucleic acid amplification tests (NAATs) has enabled molecular screening of urine as well as of swabs from the vagina, rectum, and oropharynx. These tests for diagnosing gonorrhea are more reliable and convenient than bacterial cultures and have largely supplanted the use of cultures. However, NAAT technology for *N. gonorrhoeae* currently does not provide antibiotic-susceptibility information. Culture is required for that purpose, but since it is impractical to perform for every patient, many practices have ceased to stock the correct culture medium for such testing.

The CDC Gonococcal Isolate Surveillance Program (GISP) has monitored population-level antibiotic susceptibility and resistance patterns from selected sites throughout the United States since the 1980s and has used these data to inform its national treatment recommendations. Since 2015, funds from the national initiative to Combat Antibiotic Resistant Bacteria (CARB) have been used to expand surveillance and laboratory capacity for detecting *N. gonorrhoeae* and to monitor antibiotic susceptibilities, as well as to respond to any significant changes.[2] Previous national monitoring efforts revealed high rates of resistance to penicillin and tetracycline, and these drugs are no longer recommended for gonorrhea. In 2007, with the emergence of fluoroquinolone-resistant gonorrhea, the CDC stopped recommending the use of that class of drug as well. Thereafter, increasing minimum inhibitory concentrations (MICs) of cefixime identified by GISP, combined with reports of treatment failures with cefixime and other oral cephalosporins, led the CDC to cease recommending the use of cefixime regimens as first-line treatment in the United States. Ceftriaxone is now the only reliably effective antibiotic, and the CDC recommends one dual regimen for treating gonorrhea: intramuscular ceftriaxone with oral azithromycin.[4] The two drugs have different mechanisms of action, which will theoretically slow the emergence and spread of gonorrhea resistance to cephalosporins.

In the past several years, GISP data have shown increases in the number of specimens with elevated azithromycin MICs, but almost no increase in the number of specimens with elevated ceftriaxone MICs or in the extent of elevation of those MICs.[1] Certain regions of the world have reported gonorrhea cases with resistance to third-generation cephalosporins and macrolides, the mainstays of treatment. It is unclear how to treat such cases, and if they spread more widely, treating gonorrhea will become substantially more difficult. Fortunately, in the United States in 2017, all isolates with elevated azithromycin MICs were susceptible to ceftriaxone, and no treatment failures were reported; these findings suggest that the threat of untreatable gonorrhea in this country has been curtailed for now.

Nevertheless, as the history of this organism has proven, progression of resistance of *N. gonorrhoeae* is an ever-present concern, and we are facing the real danger of multidrug-resistant, nearly untreatable gonorrhea. There is still no effective preventive vaccine against this organism to assist us with disease control. To avoid untreatable cases of this high-incidence infection, we need to advance diagnostic technology and

develop treatments with different mechanisms of action. Development of new and effective treatments is also an urgent matter of health equity, given that minority racial or ethnic groups are overrepresented among patients with gonorrhea in the United States and that men who have sex with men and young people are also at the leading edge of increased gonorrhea incidence.

Studies like the one reported on by Taylor et al. in this issue (pages 1835–45) are a step forward in the quest to identify new antimicrobial options for gonorrhea treatment. Given the challenges in clinical follow-up in this patient population, the single-dose regimen is promising. Though the study was small, the efficacy shown is encouraging, and zoliflodacin has the potential to be an effective antibiotic for treating gonorrhea, though the limited activity observed in key anatomical sites of infection such as the pharynx will need to be better defined.

In parallel with ongoing work to develop and approve new drugs, we need to develop point-of-care molecular diagnostics that permit rapid diagnosis of gonorrhea with real-time assessment of antimicrobial susceptibility in order to allow targeted therapy rather than empirical treatment that may be inadequate in the context of increasing antibiotic resistance.

With more dedicated research on sexually transmitted infections to advance biomedical innovation and develop better diagnostics, therapeutics, and even vaccines, we may be able to avoid the advent of gonorrhea that is either treatable only with expensive intravenous or intramuscular agents or entirely untreatable. Meanwhile, additional support for the public health infrastructure required for the surveillance, prevention, and treatment of sexually transmitted infections will be critical.

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Terra Nova

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A few months before I started my surgical residency, I became obsessed with tales of polar exploration. I devoured accounts of early 20th-century Englishmen attacking the problem of the great unknown, seeking the extreme reaches of the earth for the benefit of science and the glory of their country (see photo). In expectation of my own impending journey, I was enthralled by the idea of explorers bidding farewell to their wives and children and setting out in flimsy wooden boats, knowing that they might not return, compelled by a deeply felt duty to see, to know, to map. Equally seductive was the sheer act of enduring: slogging forward in gale-force winds; dutifully documenting their expeditions in temperatures well below zero; eating "hoosh" — a foul-sounding sludge made from hot water, beef tallow, dried meat, and oats — all in pursuit of a technicality. Being the first person to stand on a particular bit of earth in the middle of an icy hell made all manner of discomfort and suffering worthwhile. The whole undertaking seemed mad, and yet the idea of undergoing true physical hardship for a greater goal, the path and price unknown, was not so foreign.

Bound by our menial status, my fellow surgical interns and I quickly became a close-knit crew. Our year comprised 12 rotations lasting 4 weeks each, and "You can do anything for a month" became the mantra we repeated to each other when the enormous scope of the job overtook us. We set our alarms for 4 in the morning 6 days a week, gritted our teeth through the inevitable humiliating "beats" from our chiefs, took responsibility for dozens of