Deciphering the impact of bystander selection for antibiotic resistance in Neisseria gonorrhoeae

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The challenges facing clinical and public health management of gonorrhea are mounting [1].

The number of gonorrhea cases in the US increased 18% from 2016 to 2017, and rising antimicrobial resistance (AMR) imperils current therapies and threatens widespread treatment failures [2, 3]. In a multifaceted strategy to meet these challenges, including the development of rapid point-of-care diagnostics that enable the use of antibiotics previously abandoned for empiric treatment, work on vaccines to limit acquisition and transmission, and campaigns to promote safe sex practices, new antibiotics are urgently needed [1]. However, just as with each previous antibiotic, we can expect that gonococcal resistance to new antibiotics will emerge [4].

To maximize and prolong the effectiveness of antibiotics, new and old, we need to understand the factors that drive resistance and determine the extent to which modulating those factors could contribute to slowing or controlling AMR.

Recent studies have suggested that "bystander selection", when \textit{N. gonorrhoeae} is exposed to antibiotics because the patient is being treated for a condition other than gonorrhea, may play a key role in driving resistance. Because \textit{N. gonorrhoeae} carriage is often asymptomatic, and because antibiotic use is so common [5], it may be that "bystander selection" plays a more important role in selecting for resistance in \textit{N. gonorrhoeae} than "direct selection", that is, those instances when \textit{N. gonorrhoeae} is exposed to antibiotics as part of a patient’s treatment for gonorrhea [6]. If bystander selection contributes significantly to antibiotic resistance in gonococcus, then modifying the methods of antibiotic treatment for gonorrhea will not affect a primary driver of gonococcal resistance. Instead, efforts to slow and control the emergence and spread of resistant gonorrhea would also need to take into account the antibiotics used by the population of asymptomatic carriers.
To determine the role of bystander selection in gonococcal AMR, multiple studies have analyzed antibiotic use and resistance in the gonococcus at individual and population levels. The results have been mixed. A study of macrolide use and resistance in a Dutch clinic found that recent azithromycin use was associated with higher gonococcal azithromycin MICs [7], suggesting that direct selection plays the dominant role in determining azithromycin resistance. In contrast, a study in United Kingdom sexual health clinics that used several STI diagnoses as a proxy for azithromycin exposure, found no association between previous azithromycin exposure and subsequent resistance [8], suggesting that direct selection does not play an important role. Ecological studies have detected signals compatible with bystander selection, though results here, too, have been mixed. An analysis of cephalosporins, azithromycin, and quinolones using data from 35 countries suggested the presence of at least a small effect for each of the antibiotics [9], and a study in the US using monthly data that leveraged the large variation in seasonal prescribing of azithromycin—far in excess of what is observed in year-to-year variations in the US—supported the presence of an azithromycin bystander effect in the gonococcus [10]. In contrast, an ecological analysis in the United States based on annual prescribing data and MIC results found no support for a relationship between antibiotic consumption and gonococcal resistance [11], although the study may have been underpowered [10].

In an article in this issue of the *Journal of Infectious Diseases*, Kenyon et al. complement these prior studies by comparing population-wide antibiotic use of three drug classes with gonococcal resistance to each of those classes across 24 European countries. Kenyon et al. used antimicrobial consumption data from IQVIA MIDAS, a proprietary pharmacy sales database, finding large variations in consumption of cephalosporins, macrolides, and quinolones between
countries. Their analyses showed associations between population-level antibiotic use and gonococcal resistance for cephalosporins and quinolones. They did not observe this relationship for azithromycin. An important technical advance is the study’s consideration of multiple measures of resistance—the proportion resistant, mean MIC, and mean MIC among susceptible isolates—which aid in efforts to understand the kinds of selection that are driving gonococcal resistance. These results support the observation that bystander selection may be at play, though the size of the effect is uncertain.

The results presented by Kenyon et al. expand on previous studies, but we still lack a clear measure of the relative impact of direct versus bystander selection on gonococcal AMR. One possible approach to achieve a definitive result would be an analysis that directly compares the two types of selection via a model that predicts an individual’s risk for resistant gonorrhea from two sources. The first predictor, measuring direct selection, is that individual’s number of antibiotic treatments for gonorrhea or the time since treatment. The second predictor, measuring bystander selection, is the antibiotic use in the surrounding population. Such a study would have three main challenges. First, population-level antibiotic consumption is a proxy for the exposure of the pathogen to the antibiotic among asymptomatic carriers, for which there is no other obvious measure. Second, the definition of “surrounding population” is uncertain, particularly given the dynamic nature of resistance prevalence and of sexual networks. Finally, such a study would require individual-level antibiotic use and resistance data, with details on who got what antibiotic for which reason and when that reason was gonococcal infection.

In the absence of such a definitive analysis, we must do our best to interpret ecological and clinic- and individual-level studies, which are subject to numerous study design and technical
challenges. As Kenyon et al. point out, the emergence and spread of resistant gonorrhea results from a large number of interacting factors and controlling for all of these factors will limit efforts to disentangle the selective pressures driving resistance. First, the time scale for these studies is not clear. It is standard practice in ecological studies to correlate antibiotic use in one year with resistance in the following year, but conclusions may well be confounded if use and resistance are correlated across years [12]. For antibiotics that have large seasonal variations in use, seasonal variations in resistance may be more informative than mean annual data [10, 13, 14]. Second, what is the optimal statistical model for inference? Kenyon et al. used a mixed model, with country as a random intercept, meaning that differences between countries’ resistance prevalence are not attributed to differences in antibiotic use. This approach avoids confounding due to everything that differs between countries, but it also means that the differences in antibiotic use between countries are not used to predict the differences in resistance between countries, potentially discarding the most important contrasts in antibiotic use. Third, what metric or set of metrics are most informative and comparable across datasets and models? Kenyon et al. use mean MIC, percentage resistance, and mean MIC among susceptible isolates in their study. Should future studies adopt similar metrics, another metric, or some combination? Fourth, what datasets should be used? Studies using proprietary datasets like IQVIA MIDAS benefit from their size, but the cost to access them hampers replicability. As efforts to curb resistance rely on antibiotic use data, public datasets should be favored over proprietary datasets. In the US, legislative and other efforts should aim to overcome obstacles to public health data availability, especially those imposed by the 2016 Gobeille v. Liberty Mutual Insurance Company Supreme Court decision (REF?).
A final, technical challenge in interpreting previous reports is in comparing those reports to one another. For example, Kenyon et al. measure associations between antibiotic use and resistance using mixed linear regressions models predicting the square of percentage points resistant from “standard units” of antibiotic use per 1,000 people per year across countries [9]. Other studies reported differences in resistance per 10% difference in antibiotic use [10, 11]. How can these results, reported using different metrics, be compared? At a minimum, studies should include confidence intervals as a way to convey uncertainty about the conclusions. If a correlation has $p > 0.05$, it does not follow that no relationship exists, as the analytical method employed or the particular dataset under investigation may not have had the statistical power to detect a relationship.

The policy implications of the relative contributions to AMR of direct and bystander selection underscore the importance of unraveling these technical tangles. If direct selection is the main contributor to resistance, then we must continue to focus on strategies to optimize gonorrhea treatment and slow resistance. The use of azithromycin and ceftriaxone dual therapy was proposed with this idea in mind, but multiple factors may have conspired to undermine this strategy [15]. For example, if a patient is diagnosed with gonorrhea, treated with azithromycin, and then re-infected within a few days, azithromycin’s long half-life may result in sub-inhibitory single-drug pressure on re-infection pathogen. Optimizing antibiotic treatment for gonorrhea would require considering issues like which therapies are most effective at eradicating infection in different infected body sites and finding ways to determine which infecting strains are most likely to acquire or retain resistance.
On the other hand, if bystander selection is a major contributor to resistance, the policy ramifications are much more complex. In this case, efforts to combat resistance would include ensuring that asymptotically infected people are minimally exposed to the antibiotics used to treat symptomatic cases. We foresee three main paths: reduce population-wide use of drugs that are also used to treat gonorrhea, treat gonorrhea with antibiotics that are rarely used by the population of asymptomatic carriers, or reduce transmission from asymptomatic cases. Each path has its own difficulties. For example, increased screening could detect more of the asymptomatic cases, but preventing onward transmission by treating those individuals might not reduce resistance but instead only tip the scales from bystander selection toward direct selection and increase resistance [16].

The study by Kenyon et al. is an important contribution to solving a pressing problem in public health. However, even if bystander selection is definitively identified as a key driver of AMR, we still have a long road ahead of us in our efforts to control gonococcal resistance.

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