

Antimicrobial Drug Resistance and Gonorrhea

[Announcer] This program is presented by the Centers for Disease Control and Prevention.

[Sarah Gregory] Today, I'm talking with Dr. Robert Kirkcaldy, a medical officer at CDC, about his article on antimicrobial resistance and gonorrhea. Welcome, Dr. Kirkcaldy.

[Robert Kirkcaldy] Thank you for inviting me. I'm happy to be here.

[Sarah Gregory] So tell me, why did you decide to do this study?

[Robert Kirkcaldy] *Neisseria gonorrhoeae* is a bacterium that causes gonorrhea and it can infect the cervix, urethra, throat, and rectum during sex. If untreated, gonorrhea can cause severe reproductive health complications, including pelvic inflammatory disease and infertility, may facilitate HIV transmission, and can infrequently cause dangerous bloodstream infections. Since the introduction of antibiotics in the first half of the 20th century, *Neisseria gonorrhoeae* has successively developed resistance to each antibiotic recommended for gonorrhea treatment. Meanwhile, fewer and fewer new antibiotics are being developed. Currently, there is only a single treatment regimen left that is recommended by CDC for gonorrhea treatment, a combination of two drugs—ceftriaxone and azithromycin. And many experts are growing increasingly concerned that resistance to these drugs might be emerging. For example, a report was just published in EID describing a ceftriaxone-resistant infection in Canada.

In order to effectively monitor and perhaps slow the development of resistance, it's important to understand what's causing it. Based on our surveillance data, we think that resistant strains first appear in the United States largely because they're imported from other countries. And this is a pattern we've seen repeat itself over time. We hear a lot about how use of antibiotics in the United States can cause resistance in other bacteria, but we don't know whether this is the case with *Neisseria gonorrhoeae*. So we set out to try to figure that out.

[Sarah Gregory] You used an ecological approach to conducting your study. Tell us what that means.

[Robert Kirkcaldy] Sure. An ecological study is a type of epidemiological study. But instead of using data from individual people, an ecological study uses data about populations or groups. It's a useful approach when information is not available about each individual person. In our case, we used data at a county level. We investigated whether there was an association between annual antibiotic prescribing rates in each county and the antibiotic susceptibility of *Neisseria gonorrhoeae*. If local antibiotic use *does* lead to gonococcal resistance, then you would expect to find that counties with higher prescribing rates would also have more resistance.

[Sarah Gregory] What time period does your study cover and what methods did you use?

[Robert Kirkcaldy] We used data from 2005 through 2013. And we combined antibiotic susceptibility data from CDC's long-standing surveillance system called the Gonococcal Isolate Surveillance Project, or GISP, with antibiotic prescribing data from IMS Health for each county that corresponded to GISP sites. We performed linear regression analyses, which is a type of analysis that tries to see if there's a linear relationship between two things. For example, if one thing goes up does another thing also go up and by how much? We measured antibiotic susceptibility, using a special kind of average called a geometric mean, of the antibiotic

susceptibility test results, and those results are given in something called minimum inhibitory concentrations, or MICs, which are the lowest concentration of antibiotic that inhibits bacterial growth in the lab. So basically, lower MICs mean the bacteria get killed when exposed to only a little bit of antibiotic, which is good, and higher MICs mean the bacteria can survive despite being exposed to more and more antibiotics, which is bad, and can move the bacteria toward resistance. So essentially, we used a linear regression to ask if antibiotic prescribing goes up do MICs also go up the following year. We looked at two currently recommended antibiotics, ceftriaxone and azithromycin, an antibiotic that's similar to ceftriaxone, called cefixime, and an antibiotic that was previously recommended for gonorrhea, called ciprofloxacin.

[Sarah Gregory] You constructed mixed models for measuring three potential confounders. What were they and why those?

[Robert Kirkcaldy] So based on data from GISP, we know there are differences in resistance patterns among different populations in the United States. For example, gonorrhea resistance tends to be highest in the Western United States and lowest in the South. And among men, infections among men who have sex with men tend to be more resistant than infections among men who report sex only with women. And there are racial differences as well, with more resistance among white men than men of other racial/ethnic groups. So we anticipated that antibiotic use might also differ among these groups, so we wanted to boost the chances that any relationship we found was because of the influence of antibiotics on resistance itself and not caused by, or what we call "confounded" by, other factors.

[Sarah Gregory] How many sites for measuring were included and why did you choose those sites?

[Robert Kirkcaldy] During the time period that we studied, 33 different counties or cities participated in GISP. However, only 23 of those participated continuously. Because we wanted to look at changes over time in each place, we decided to include only those sites for which we had data over the entire time period.

[Sarah Gregory] The study has very interesting findings since we hear more and more about over prescribing of antibiotics. Tell us about what you found.

[Robert Kirkcaldy] Surprisingly, we did not actually find an association between population-level outpatient prescribing rates and *Neisseria gonorrhoeae* antibiotic susceptibility for the four antibiotics that we looked at. We found that prescribing rates were actually highest in the South, where the prevalence of resistance has tended to be the lowest, and prescribing rates were lowest in the West, where resistance has often been the highest.

[Sarah Gregory] What are some of the possible reasons for this?

[Robert Kirkcaldy] One possibility is that antibiotic prescribing in the United States does not actually play a large role in the emergence or persistence of *Neisseria gonorrhoeae* resistance in the U.S. We know that resistant strains spread worldwide, so perhaps other factors, such as importation of resistant strains from other countries, might play more important roles. As an example, people might become infected when traveling overseas and bring a resistant strain with them back to the U.S.

Alternatively, it's possible that the data we used or our analytic approach did not allow us to detect a relationship between prescribing and resistance that actually does exist. For example, it's possible that prescribing rates in each county do not reflect the prescribing rates of people actually with gonorrhea in each county. So we may have missed a relationship that does exist.

[Sarah Gregory] Ultimately, what do your findings suggest about prescribing antimicrobial drugs?

[Robert Kirkcaldy] Antibiotics are powerful drugs that save lives, but each time an antibiotic is used, it can increase the risk that a future bacterial infection will be resistant to antibiotics. So improving antibiotic use is very important. But there may be significant differences in how antibiotic use contributes to resistance among different bacteria. And we hope this paper encourages other researchers to study the causes of gonorrhea resistance.

And I'd like to make one last point, as well. Although our study didn't address it, it is really important for healthcare providers to make sure that people with gonorrhea are treated with the CDC-recommended treatment. The recommended treatment is still highly effective and will help prevent the severe complications of gonorrhea and prevent spread to partners.

[Sarah Gregory] Dr. Kirkcaldy, care to tell us a little bit about your job at CDC?

[Robert Kirkcaldy] Sure. I'm currently the team lead for the epidemiology research team, in the Division of STD Prevention at CDC. And the team focuses on conducting epidemiological research on a range of STDs, including gonorrhea, syphilis, and chlamydia. The focus of my own research has been on gonorrhea, gonorrhea resistance, and treatment.

[Sarah Gregory] Thank you so much for taking the time to talk with me today, Dr. Kirkcaldy. Listeners can read the entire October 2017 article, Antimicrobial Drug Prescription and *Neisseria gonorrhoeae* Susceptibility, United States, 2005–2013, online at cdc.gov/eid.

I'm Sarah Gregory for *Emerging Infectious Diseases*.

[Announcer] For the most accurate health information, visit cdc.gov or call 1-800-CDC-INFO.