Expert Interviews

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Antimicrobial Resistance in Neisseria Gonorrhoeae: Past, Present, and Future

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CDC and the World Health Organization consider *Neisseria gonorrhoeae* an urgent antibiotic-resistant threat because it continuously develops resistance. Microbiologist and Associate Professor at the University of Washington Dr. Olusegun Soge provides a historical overview of past efforts, an update on the current situation, why global surveillance is so important, and a potential new treatment for uncomplicated gonorrhea.

Topics:

- antimicrobial
- Gonorrhea
- ceftriaxone
- zoliflodacin

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Disclosures

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Transcript

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introduction**[00:00] Introduction**

Dr. Ramchandani

Hello, everyone. My name is Meena Ramchandani. I'm an infectious disease physician at the University of Washington in Seattle. This podcast is dedicated to an STI [sexually transmitted infection] review for health care professionals who are interested in remaining up to date on the diagnosis, management, and prevention of STIs.

We are delighted to have Dr. Olusegun Soge, who also goes by S.O., join us for this episode. Dr. Soge is a microbiologist with expertise in molecular diagnostics and antimicrobial resistance of sexually transmitted pathogens, as well as other clinically important pathogenic bacteria. He's an associate professor in the departments of Global Health, Medicine, and Laboratory Medicine and Pathology at the University of Washington. He collaborates with the Centers for Disease Control and Prevention (CDC), the [WA] State Department of Health, STD/HIV, and their public health laboratories in five different states to monitor trends in gonococcal antimicrobial resistance and provide data to guide evidence-based selection of effective treatment regimens for gonorrhea. Welcome, S.O. Thank you for being on this episode.

Dr. Soge

Well, thank you. Thank you so much for having me. I'm honored to be here to talk about my favorite bacteria, the *gonococcus*.

Dr. Ramchandani

We are very excited.

antimicrobial-resistance**[01:19] Antimicrobial Resistance**

So, first, some background for our audience. Tell us a little bit more about antimicrobial resistance for *Neisseria gonorrhoeae*.

Dr. Soge

So, when we talk about antimicrobial resistance, *Neisseria gonorrhoeae*, first we need to understand what is *Neisseria gonorrhoeae.* I know the audience I'm talking to probably know what *Neisseria gonorrhoeae* is because they know what gonorrhea is. So, *Neisseria gonorrhoeae* that I always will call *gonococcus* is a bacterium that causes gonorrhea, and gonorrhea is the second most commonly reported bacterial STI in the United States. The *gonococcus*, or *Neisseria gonorrhoeae*, is a very fascinating bacterium, and why is it so fascinating? It’s because it has an impressive history of rapidly and sequentially developing resistance to all antibiotics that have been recommended for treatment.

Over the years, there has been successive acquisition of antimicrobial resistance in *Neisseria gonorrhoeae* to previously recommended, as well as currently recommended therapies for gonorrhea. And as this has happened, it has limited the options that are available for treatment of gonorrhea. Currently, CDC

recommend only one effective antibiotic for gonorrhea treatment, and this is injectable ceftriaxone. However, in the United States, we are very happy that the number of ceftriaxone-resistant *Neisseria gonorrhoeae* are so few. Actually, there have been only a few cases that have been reported in the United States.

However, it's a completely different story in other parts of the world. For instance, in Vietnam, in Cambodia, in Thailand, they've seen high percentages of ceftriaxone-resistant *Neisseria gonorrhoeae*. We're down to only one effective treatment, ceftriaxone. There are only two drugs that are actually in development that are very promising for gonorrhea. The dire need of alternative gonorrhea treatment is concerning because there could be a time when gonorrhea will become untreatable, maybe not in the U.S. but it's going to start in other parts of the world. Eventually it's going to get to the U.S. and that's why it's a very, very serious global health issue.

Dr. Ramchandani

Thank you. That's a fantastic summary. It makes it very challenging as a provider taking care of patients, especially when ceftriaxone might not be an option.

antimicrobial-resistance-timeline**[04:05] Antimicrobial Resistance Timeline**

Dr. Ramchandani

Tell us a little bit more about when did antimicrobial resistance for *Neisseria gonorrhoeae* become such a significant public health issue?

Dr. Soge

Wow, thank you. That's a very excellent question. I think there is a difference between when it became such a significant public health issue and when a surveillance program was established in recognition of its public health significance. Following the introduction of sulfonamide for treatment of gonorrhea in the 1930s, the *gonococcus*quickly developed resistance. And by the 1940s, sulfonamide resistance became predominant. Isn't that a public health issue? Yes, it is. But there wasn't any surveillance program established to monitor antimicrobial susceptibilities in *Neisseria gonorrhoeae* in the 1940s, probably because there wasn't an investment or there wasn't any financial investment in terms of public health to monitor resistance.

Dr. Ramchandani

Did they have the tools to do resistance assays back then?

Dr. Soge

To my knowledge, there was nothing in the U.S. until when the Gonococcal Isolate Surveillance Program was established in 1986, so there was no monitoring. It doesn't mean there were no tools to do susceptibility testing like Kirby-Bauer disk diffusion testing and all this antimicrobial susceptibility testing methods. They've been around for quite a long time. So, it takes finance, it takes funds, it takes money to do that, and it takes recognition of the importance of the problem for Congress to actually appropriate funding to do kind of monitoring. So, it's not like the tools are not there, but I think there were no recognition of the importance of monitoring such resistance in STI. And, as you are aware, that the leaders in the field of STI did a lot to get STI to be recognized, and to be given the proper attention to be monitored, and also to do all necessary intervention as well as prevention, as well as control. So, I think that was the reason.

There wasn't any monitoring of antimicrobial resistance in the 1930s and the 1940s, then penicillin was introduced, and penicillin was effective for some time, and then they used higher doses of penicillin. But during the 1980s, penicillin and tetracycline resistance became so widespread in the U.S., then the experts came together and realized that it's important to actually establish a surveillance to monitor antimicrobial resistance in *Neisseria gonorrhoeae*, and that was what made CDC to establish the Gonococcal Isolate

Surveillance Project (GISP) in 1986. So, to me, that was when the recognition was actually backed up with monitoring so that we actually know what is going on other than just few labs doing susceptibility testing, then there was systematic monitoring of antimicrobial susceptibility of *Neisseria gonorrhoeae*. Then the data that is generated from that program is used to inform treatment guidelines. So, they're using that data to revise treatment guidelines, to suggest changes to treatment guidelines, and that is still ongoing until today.

past-90-years-the-us**[07:50] Past 90 Years in the U.S.**

Dr. Ramchandani

Tell us a little bit more about antimicrobial resistance changing over time in the U.S.

Dr. Soge

Well, antimicrobial resistance has changed. Not just in the U.S. It's changed globally, and I think there's no way we can talk about the changes of antimicrobial resistance in the U.S. without looking at the global picture or the parts of the country. And what has been shown is that antimicrobial resistance in *Neisseria gonorrhoeae* do not usually develop in the U.S. It's going to develop in other parts of the world, especially Southeast Asia, then it gets imported into the U.S. The first identification of such resistance is in Hawaii, and then it comes to the West Coast, and then it spreads to other parts of the United States.

Since the introduction of sulfonamide to treatment, we have actually seen in the 1930s to 1940s, sulfonamide was introduced in the 1930s and it was effective, but by mid-1940s, sulfonamide resistance has become widespread. But we're so lucky that fortunately we had the miracle new drug, which is penicillin, that was discovered by Alexander Fleming. Penicillin was very effective for gonorrhea treatment in the 1940s until there was development of chromosomally mediated resistance. And when I say chromosomally mediated resistance, those are resistance that the MICs [minimum inhibitory concentrations] are not very high, the MICs are, you know, 1 or 2, they're not like 64 or 128.

In the 1970s to 1980s, there was the identification of the new strain of *Neisseria gonorrhoeae*, which is called the penicillinase-producing *Neisseria gonorrhoeae*, and this is plasmid-mediated. It has the beta-lactamase plasmid, and that plasmid confer high-level resistance to penicillin because the enzyme, the beta-lactamase enzyme, degrades or breaks down the beta-lactam rings of the penicillin and just makes penicillin useless.

But the good thing is tetracycline was available and then tetracycline was being used for gonorrhea treatment. And guess what happened? As tetracycline is being used, *Neisseria gonorrhoeae* will always do what it loves to do, what it is really an expert in doing, just finding ways to develop resistance. And what happened was the chromosomally mediated resistance was emerged in *Neisseria gonorrhoeae* and the chromosomally mediated resistance also will confer low-level resistance. MIC will be 1 or 2. And what is being shown is a mutation in the rpsJ that actually confer the chromosomally mediated resistance. When you are still seeing that low-level resistance, the world has not come to an end, but the moment the plasmid gets there, it's going to confer high-level resistance and that will be the end of the drug. And that was exactly what happened.

The first tet(M)-mediated isolate was reported in the U.S. in 1985. By late 1980s, tetracycline was withdrawn completely for gonorrhea treatment in the U.S. The reason is because the tet(M), which is plasmid-mediated, confer high-level resistance, the MIC will be greater than or equal to 16. And when you have the tet(M) isolate in a patient, the chances that they're going to fail treatment is just—it's very high. And so, tetracycline was withdrawn.

Fortunately, we have the ciprofloxacin, which is a fluoroquinolone, and for some time, from 1990s to 2000s, we were able to treat gonorrhea using ciprofloxacin. However, as we actually having a lot of success treating gonorrhea with ciprofloxacin in Southeast Asia, cipro resistance, fluoroquinolone resistance emerged and it was spreading, and then eventually got to Hawaii, got to the West Coast. By 2000s, Seattle was doing its own

thing in terms of treatment. They stopped treating with fluoroquinolone, they moved to cefixime, cefpodoxime, so you have different treatment in the U.S., depending on the prevalence of fluoroquinolone resistance.

Finally, by 2007, CDC no longer recommend fluoroquinolone for gonorrhea treatment. And guess what? After that, then we tried oral cephalosporins. Cefixime was recommended, and when there were shortages of cefixime, then we used cefpodoxime. And you know, cefpodoxime is not a good oral drug, then in time, CDC no longer recommend oral cephalosporins for treatment. And then we're like, "How are we going to continue to be successful in treating gonorrhea?" And said, "Well, we have to use combination therapy. We have to use two drugs. And we didn't have data. So, we are going to do dual therapy, azithromycin and ceftriaxone."

And that was introduced, and guess what happened? With dual therapy, using combination of azithromycin and ceftriaxone, we didn't have a lot of azithromycin resistance. And with time, azithromycin resistance increased such that even in Seattle was greater than 10%. And eventually, CDC withdrew azithromycin combination therapy with ceftriaxone. Now we are down to only one effective treatment, injectable ceftriaxone, and they increased the dose to 500 milligrams. So, as you can see, *Neisseria gonorrhoeae*, it's been the master troublemaker that is just continuously developing resistance, and also keep us just running on our feet to see what we can do to make sure that gonorrhea remains a treatable infection.

Dr. Ramchandani

It really just shows how this organism gained resistance over time to almost every single oral antimicrobial. It also speaks to the importance of antimicrobial stewardship because it can really affect gonorrhea resistance to different oral antibiotics.

global-health-problem**[14:13] Global Health Problem**

Dr. Ramchandani

So, tell us a little bit about the concern for antimicrobial resistance, globally. You know, you mentioned different parts of Asia, what about parts of Europe? Is antimicrobial resistance and *Neisseria gonorrhoeae* a global health problem?

Dr. Soge

Yes, thank you. That's a very good question and you are very correct. *Neisseria gonorrhoeae* antimicrobial resistance is not just a problem in the U.S. It's a global health problem. It's a problem globally. And just let's start from the U.S. In 2013, CDC actually designated *Neisseria gonorrhoeae* antimicrobial resistance as an urgent antibiotic-resistant threat. And then they published another report in 2019. And guess what? *Neisseria gonorrhoeae* is still on that list as an urgent antibiotic-resistant threat, and the reason is because we don't have various treatment options for *Neisseria gonorrhoeae.* We are down to only one effective treatment option. And the concern is if *Neisseria gonorrhoeae* were to develop resistance to this, our last-line effective treatment option, then we don't have a way to manage *Neisseria gonorrhoeae*. So, that was a concern.

And then what also happened in 2016, the World Health Organization (WHO), in recognition of the global problem of antimicrobial resistance in *Neisseria gonorrhoeae,* actually designated *Neisseria gonorrhoeae* as one of the top priority list of antibiotic-resistant bacteria, which warrant urgent discovery and development of a new drug called zoliflodacin for treatment of uncomplicated gonorrhea. And this study was conducted in 16 clinical sites including Seattle, Washington was one of the sites (our sexual health clinic), and there were clinical sites in Netherlands, in South Africa, in Thailand.

And the good news is that the study is now completed, and as of 2023, showed very promising result that zoliflodacin is noninferior to combination therapy of ceftriaxone and azithromycin.

global-surveillance**[16:38] Global Surveillance**

Dr. Ramchandani

How would you describe MIC?

Dr. Soge

The way we describe minimum inhibitory concentration is the lowest concentration of the antibiotic that will prevent the growth of the bacteria, and you have to be able to prevent the growth of 90% of that population. Ideally, you don't see growth at that minimum concentration. Elevated MICs, that would prompt some public health action because the CLSI [Clinical & Laboratory Standards Institute] has not established a breakpoint for ceftriaxone, resistance breakpoint, they have susceptible breakpoint. So, the MIC I'm talking about is MIC greater than or equal to 0.125. What we're seeing in the U.S. right now is less than 0.1%. The drug that we're using for treatment, that's for ceftriaxone; azithromycin is no longer recommended for treatment.

In places like Cambodia, Vietnam, and China, what they're seeing in terms of resistance to ceftriaxone is 10% to 38%. A lot! And these isolates are not just resistance to ceftriaxone, they are resistance to other antibiotics that have been previously recommended for treatment, and so they call them multidrug-resistant or extensively drug resistant *Neisseria gonorrhoeae*. So, those are circulating, they're widespread in Asia, they're widespread in other parts of the world, even though right now we're not seeing them. So, it's a global problem. And in Europe there have been cases of ceftriaxone-resistant *Neisseria gonorrhoeae* in some parts of Europe, but they're not seeing high percentages like it's been seen in Vietnam, Cambodia, and China.

Dr. Soge

So, this is a global health problem. This is a problem that really calls for coordinated surveillance, not just what we're doing in the U.S. alone, but working with WHO to expand surveillance of *Neisseria gonorrhoeae* antimicrobial resistance to African countries, to countries where they do not have systematic surveillance of antimicrobial resistance. And this is what the WHO has tried to do with working in collaboration with CDC through the Enhanced Gonococcal Antimicrobial Resistance Surveillance: to expand the surveillance of antimicrobial resistance in *Neisseria gonorrhoeae*to countries that do not have any infrastructure to do it. And with that support, that's how they were able to establish surveillance in Cambodia. They were able to establish it in Vietnam, in Thailand, and they also established it in Zimbabwe, which my lab was providing some support, as well as Côte d'Ivoire, as well as other countries. But, currently, right now, those activities have been paused, and it's unsure to what extent the WHO will continue those activity. But in the U.S., the surveillance continues, is robust through various programs.

Dr. Ramchandani

That data is really important because we are one true world. And so, as we see with most infectious diseases, those infectious diseases don't stay within a particular country. They get spread. And so, even though we don't see it maybe in the U.S. now to that same degree, at some point, we potentially might. Is that correct?

Dr. Soge

I totally agree with you. That's very correct. And, that was the rationale behind CDC supporting WHO to expand surveillance to other countries where you actually find those resistance. And that's why we're able to get the data from Cambodia that the resistance to ceftriaxone in 2022, I think, was about 38%, a lot, and then in 2023, was still at 31%. And, this is in recognition of the fact that even though we're not seeing the resistance in the U.S. right now, those resistance are actually in some other places, and we can promptly identify them. We can at least do some interventions to try and mitigate the spread of those resistance to other parts of the world, especially to the U.S.

Dr. Ramchandani

Thank you, S.O. I know our audience is going to enjoy this episode in learning more about antimicrobial-resistant *Neisseria gonorrhoeae.* Thank you for your time.

Dr. Soge

Thank you so much for having me.

credits**[21:11] Credits**

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past-present-future