Challenges in Forecasting Antimicrobial Resistance

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

[Sarah Gregory] Hello, I'm Sarah Gregory, and today I'm talking with Dr. Sen Pei, an assistant professor at the Mailman School of Public Health at Columbia University. We'll be discussing challenges in forecasting antimicrobial resistance.

Welcome, Dr. Pei.

[Sen Pei] Hello, everyone. Glad to be here. Thank you for inviting me.

[Sarah Gregory] Happy to have you here. How does antimicrobial resistance happen?

[Sen Pei] Antimicrobial resistance occurs when pathogens evolve in a way that allows them to survive exposure to antimicrobial drugs that would normally kill them or inhibit their growth. The overuse and misuse of antibiotics are the major drivers of antimicrobial resistance. So when pathogens are exposed to the drugs more frequently, some may develop mutations that allow them to survive treatment, so you can see if it's really a combination of the mutation of the pathogens and the selection pressure that gave rise to antimicrobial resistance.

[Sarah Gregory] How big a problem is it? Do people die from it?

[Sen Pei] Yes, of course. AMR is a big problem, certainly. And AMR is an urgent global public health problem. In a global burden study, researchers estimated that in 2019 alone, over one million deaths were directly caused by AMR bacterial infection, and about 5 million deaths were related to bacterial AMR. So it's really an urgent and big problem.

[Sarah Gregory] Are there certain microbes that are more likely to become resistant than others?

[Sen Pei] Yes. So the likelihood of resistance developing depends on several factors, which includes other features of the microbe, the type of drug used, and the frequency and duration of drug exposure. For example, bacteria such as *Staph aureus*, *E. coli*, *Klebsiella*, and *Pseudomonas* are known to develop resistance to antibiotics relatively quickly. So those are some of the high-priority AMR bacteria in healthcare settings.

[Sarah Gregory] If a microbe becomes resistant to a certain treatment, can't we just use a different treatment or antibiotic or something?

[Sen Pei] In theory, yes, it is possible to develop new treatments for infections caused by those resistant microbes. However, developing new antimicrobial drugs is a complex and very challenging process that can take many years and require significant investment. And additionally, even when new treatments are developed, resistance can still emerge over time because it's an arm race between drugs and resistance. So...and also because over the last few decades, there are a lot of antibiotic drugs. Therefore, it's becoming increasingly difficult to develop new treatments for those antimicrobial-resistant pathogens.

[Sarah Gregory] Does AMR only affect people? Or does it affect animal health as well? And do they affect each other?

[Sen Pei] Yeah. AMR affects both people and animal health. So AMR pathogens causing infections in people can also infect animals, and vice versa. So those two are interconnected, so we really need to take a One Health perspective to control AMR. The use of antibiotics in animal agriculture is a significant contributor to the development of AMR. So the use of antibiotics in

animals can lead to development of resistant bacteria in animal populations, which can then spread to humans through the food chain, direct contact with those animals, or environmental contamination. So it affects both people and animals.

[Sarah Gregory] Are there certain populations or places, such as community levels versus, say, hospital settings, that are more at risk for AMR?

[Sen Pei] Yes. Definitely certain populations or places may be at higher risk—for instance, in healthcare settings, long-term care facilities, and communities with high antibiotic use and communities with a high prevalence of infectious disease. In those places, typically, for instance, in hospital settings and long-term care facilities, people living there are relatively vulnerable to AMR infections. If they were to get infected, the outcome would be very severe. And then in communities and also in those places, the use of antibiotics is really high. So it could be the places where resistance can emerge and spread to the broader community. So those places with a higher use of antibiotics may be at more risk for AMR.

[Sarah Gregory] Help me understand this a little bit. This is sort of a wide-spread community thing, and are people who have a history of taking a lot of antibiotics more at risk than people who, say, only take one once or twice a year or maybe haven't had one in a long time?

[Sen Pei] Yes, of course. There are several risk factors associated with increased AMR infections. And the frequent use of antibiotics is one of those. If people take antibiotics regularly or frequently, there's a higher risk of those people getting infected by AMR pathogens.

[Sarah Gregory] I see, okay. Are there specific countries where AMR is more of an issue?

[Sen Pei] Different pathogens have different prevalence. It really depends on what kind of pathogens we are talking about. For instance, for *Staph aureus* (a type of bacteria), resistance was generally highest in countries in north Africa or the Middle East. For multi-drug resistant TB (another pathogen, another bacteria), resistance was highest in east Europe. So it just really depends on what kind of pathogen we are talking about. Also, countries with weaker healthcare systems and infrastructure may have heavier burdens due to a lack of resources for infection control and tracking and also treatment. Basically, it's a global problem, but the issue could be more severe in certain countries depending on the pathogens we are talking about.

[Sarah Gregory] What has been done or can be done to slow AMR spread?

[Sen Pei] So the major driver of AMR is antibiotic misuse or overuse. So the most important measure to slow down AMR spread is to reduce overuse or misuse of antibiotics. Many countries have implemented antibiotic stewardship programs. Antibiotics and other drugs should only be used when necessary, and healthcare providers should prescribe them appropriately. So for instance, when you get a flu infection, usually you will not...the antibiotics are not effective because it's treating a bacteria, but a flu is a virus. A lot of people, they take antibiotics when they get flu infections, which is not appropriate. Those are the kind of misuse of antibiotics.

In healthcare settings, many hospitals use a 'search and destroy' policy, which typically involves screening of patients, isolation of the patients who tested positive, and the decontamination of the environment. So those kinds of measures can slow down the spread of AMR pathogens within healthcare facilities and settings, which is also helpful to reduce the mortality and morbidity associated with AMR infection.

[Sarah Gregory] Your article is about challenges in AMR forecasting. What is forecasting and are there different kinds and tell us about them.

[Sen Pei] Forecasting is the process of making predictions or estimates about future events or conditions or trends based on existing data as well as other factors. So we are very familiar with weather forecasts. For infectious disease, we aim to estimate future incidence or burden of a disease. Forecasting...there are different types of forecasting, depending on how we classify them. Depending on the forecast horizon, forecasting can be short-term or long-term. We can predict the infection in the next couple weeks, or we can talk about forecasting a disease burden in the next few decades (that's a long-term forecasting). And depending on the methods we use, forecasting could be generated using statistical models, which really captures historical trends or patterns in those disease data, or we can use process-based models, which relies on our understanding of the physical or biological process that produced the data. So there are different types of techniques we can use in forecasting.

[Sarah Gregory] How is AMR forecasted?

[Sen Pei] Yeah, as we mentioned in the paper, currently AMR forecasting methods are very limited. Because the process related to AMR is so complex, most methods can only use statistical methods trained on historical data to look at what happened in the past, and to use those methods (those information) to predict what will happen in the future. For instance, people have used some series methods linking antibiotic consumption to the prevalence of AMR in society. So those models were mostly used within specific facilities (within a hospital), given they have access to those data to make those predictions. So it has not been widely used operationally in real time. We heard a lot about forecasting COVID-19, which is open to the public, but that kind of application is very limited for AMR right now.

[Sarah Gregory] What about forecasting on population-level versus facility-level scales? What's the same forecasting methods that are applied? Are they different or the same for each?

[Sen Pei] Yeah, forecasting for AMR at population-level and facility-level...they have different targets and utility. For the population level, you really want to look at the prevalence and the trends of AMR in the general population, like what the percentage of those bacteria become resistant. And it can support our situational awareness of AMR or what's happening—is AMR going up or going down? But at the facility level, when we make predictions in a specific hospital, we are usually focused on clinical infections with symptoms (like infected people). It can help us to control AMR transmission within those healthcare settings and to improve treatment of patients. So they have different purposes and utilities at different levels. And theoretically, we can use the same mathematical or statistical method to generate forecasts. However, the data sources, the populations, and the processes are very different at the population and facility levels, so we usually treat them as separate forecasting questions and look at them differently.

[Sarah Gregory] So far, infectious disease forecasting apparently has been mostly focused on viral infections and not bacterial AMR. Is there a reason for this?

[Sen Pei] Actually, there are a couple of reasons for this. The first one is, the surveillance and data availability of viral infections are much better than bacterial AMR. So in general, we have a much better understanding of viral infection disease burdens. For instance, when you get a cold, you can easily get a test to confirm whether it's caused by influenza or RSV or other different

viruses. For AMR, it's kind of more...it's difficult to do that because many of the bacteria are commensal within our human body. So people can carry those bacteria without any symptoms, and it's very hard to link the symptoms (the infection) with a specific bacteria causing the symptoms. So it's difficult to quantify the burden of AMR.

And then, secondly, the timescales of outbreaks and their impact on society are different. So viral infections can spread rapidly and disrupt society when a large number of people get infected at the same time. So think about COVID-19 and other pandemics in the past. So maybe there's, maybe...the whole population in the world will be infected within a couple of months. And in contrast, AMR is a very...it's more like a slow-burning issue that quietly kills millions of people each year. It is an important question, but the disruption on society is less noticeable because it mostly affects vulnerable people, like old people. And lastly, our understanding on AMR emergence and spread is still very limited. It is hard to design process-based models to forecast AMR in the future, while for some viral infections, models have been developed a few hundred years ago, and people have been working on those models for centuries. So we have a much better understanding of how viral infections transmit from person to person, but very limited understanding for AMR.

[Sarah Gregory] With these limitations, what are the public health benefits of forecasting AMR?

[Sen Pei] Yeah. So if we have a better understanding of what will happen in the future about AMR, certainly it can improve our situational awareness of this issue—we need to know whether *Staph aureus* has developed a new type of resistance; do we need to change our treatment? It can inform the trend of AMR and support public health policy making, such as how do you prescribe antibiotics? Do you need to implement stewardship programs here? And projections based on...there are some other questions we can answer using AMR forecasting. For instance, we can make projections of AMR based on some control scenarios using models so we can know if some control will be more effective than others to make the decision on whether we are on the ticket or not. So those kinds of forecasting work to inform policy making and to reduce...help to reduce the emergence and the spread of AMR in the future.

[Sarah Gregory] Are there any suggestions as to how the public health and scientific communities can overcome these challenges you've mentioned?

[Sen Pei] Yeah. So there are a couple of things we can do right now. First, I think there should be better communication between different stakeholders, such as public health officials, academia, healthcare providers, and the general public. Sometimes communication can identify key scientific questions and the data needed to answer these questions. And secondly, we need to improve our surveillance and data collection for AMR because we have to get a better understanding of the disease burden, and data are critical to understand those questions. And also, we need to think about how to better use existing data to study scientific questions we can do right now. So mostly, right now, most of the data are siloed within each hospital system because you cannot share those data with other people, with other communities (there's some privacy issues). But there may be some ways we can think about how to combine those data to answer questions that can otherwise cannot be answered.

And lastly, I think there's a need to form a community to start thinking about how to implement AMR forecasting and to address some initial practical questions on forecasting design. For instance, when we think about forecasting, what variables should we include in those models? What is an appropriate forecasting horizon—should we make forecasts for the next couple of

months or the next couple of years or decades? And last, how should the forecast skill be evaluated in real time? Those are some critical practical questions we can start thinking about. I think those efforts we can start working on to address those challenges to forecast AMR.

[Sarah Gregory] What about further research and studies? Are there anything in particular you think should be done?

[Sen Pei] Yeah, I think the most important research is to study the basics on the mechanisms of AMR emergence and spread. There are a lot of people working on this and if we have a better understanding of how AMR emerged and how it spread across populations, it can help us to formulate some more specific process-based models to inform forecasting for AMR. And the second area I think we need to do research is to use models to guide data collection. But for now, most existing datasets were passively collected. When people get infected, people order a test, and they collect data for those people. But I think if we want to do some forecasting, we need to collect data more proactively to see which kind of data are the necessary data to answer scientific questions we need to answer, instead of just passively collecting data. And then I think it's important to try to implement those methods and challenge those methods in real-world settings.

There's examples of forecasting for influenza—the CDC has organized the flu forecasting challenge since 2013. So they ask people from different groups, generating real-time forecasting and put them online and archive them, and then they will do the evaluation after the season to see what method works best. So this stimulated the development of flu forecasting in the last decade. I think this kind of work should also be done for AMR, and I think overall, those kinds of research, spanning both scientific understanding and data collection and more applied applications of AMR, can help to improve and advance this field.

[Sarah Gregory] Well, Dr. Pei, tell us about your job and how you became interested in forecasting infectious diseases.

[Sen Pei] I'm an applied mathematician working on infectious disease and public health. I mostly study the environmental, social and ecological determinants of infectious diseases. And currently, I mostly work on respiratory diseases such as influenza and COVID-19, and also antimicrobial resistance in healthcare settings. I have an interdisciplinary background in mathematics, complex systems, and infectious disease. So thinking about how I got into this area...so when I was in my undergraduate in mathematics, I became interested in dynamical systems, which is a branch of mathematics that studies how systems...how things evolve over time following a set of rules or equations. So it has broad applications in the real world. And infectious disease is one of the typical dynamical systems, but also with a significant impact on our lives. It became very interesting to me when I started my post-doc, I started working on public health and infectious disease...I found out, "Okay, I can apply what I learned in math to solve real-world problems, generate real-time predictions". And also, it's very interesting for forecasting because it's very fascinating because you can test it in the real world. So you can use your model, you can generate forecasting and you can see whether the model actually works or not. And I think this is a fascinating topic that attracted me to work on this for the last couple of years.

[Sarah Gregory] Well, with all that mathematical knowledge, can you apply it to this question—thinking about all the emerging infectious diseases and possible ones, is there something that worries you the most?

[Sen Pei] Yeah. I think there are a couple of things that are really pressing for global public health. The first one is, as we've talked a lot about, is the next pandemic. We are still within the COVID-19 pandemic (although it's just becoming endemic). But the emergence of novel pathogens has been increasingly frequent in the last few decades. We have seen so many new viruses jumping from animals to humans and causing spillover events and causing human-to-human transmission. So those are the biggest concerns right now. I think most of the people working in public health would agree.

And then, the other area (the other threat) I can think about is AMR, which is the topic we are talking about here today. So AMR is a slow-burning problem. It's not causing such a large disturbance on society, but it kills millions of people each year and it's projected the number of deaths because of AMR will reach about 10 million in 2050. So that's a huge problem, because we are starting to run out of treatment options for some of those resistant bacteria. If we don't have any treatment, then you can think about the number of deaths because of AMR could be huge. And actually, I think climate change is also an important threat that changes a lot of things in our life, including public health and infectious disease, because the change of temperature, precipitation, and other climate factors will change the distribution and the problems of many infectious diseases, especially in those middle and low-income countries, which will be disproportionally affected by climate change. So I think overall, the pandemic, AMR, and climate change are the three major worries I have right now for our global health.

[Sarah Gregory] Well, on that somewhat not happy thought, I want to thank you for taking the time to talk with me today, Dr. Pei.

[Sen Pei] Thank you so much for having me today. It's really exciting.

[Sarah Gregory] And thanks for joining me out there. You can read the April 2023 article, Challenges in Forecasting Antimicrobial Resistance, 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.