Gemma Ware: When Alexander Fleming, the scientist who discovered Penicillin, received a Nobel Prize in 1945, he used his acceptance lecture to deliver a warning about the dangers of resistance to the very antibiotic that he'd discovered. Today that warning has become a deadly reality, with some now calling antibiotic resistance "a slow pandemic".

I'm Gemma Ware and this is The Conversation Weekly, the world explained by experts. In this episode, we speak with a Nigerian doctor working on the front lines against antibiotic resistance in hospitals, and a biochemist about the new scientific techniques including artificial intelligence being deployed to find new antibiotics.

I'm joined for this episode by Fron Jackson-Webb, the senior health editor at The Conversation in Australia. Welcome to the show, Fron.

Fron Jackson-Webb: Thanks, Gemma.

Gemma Ware: Fron, you're running a series of stories at the moment called ‘The Dangers of Antibiotic Resistance’ about this huge issue that's facing humanity. What got you interested in this problem?

Fron Jackson-Webb: I think it's the idea of what we would look like as a society without antibiotics. So you know, if you couldn't treat a urinary tract infection or if we really had to think twice about doing something like a hip replacement or having cancer treatment because of the risk of having an infection that just couldn't be treated by any antibiotics. And then alongside all of that, as a health journalist, I'm always getting press releases and you know, reading different journal articles about promising new antibiotics in the pipeline, and then they never seem to go anywhere. And so I wanted to, you know, just take a really deep dive into where exactly we're at with this situation, where all these antibiotics that are in the
pipeline are actually going, how we got into this big mess that we're in, and most importantly, how we can get out of it.

**Gemma Ware:** Because that's the key, the solutions to this because we're dealing with this problem but we need to find solutions. So, many listeners may be aware of the issue of antibiotic resistance, but can you give us a quick reminder of what it actually is?

**Fron Jackson-Webb:** Yes, so antibiotic resistance is not about your body becoming resistant to antibiotics. It happens when bacteria develop the ability to defeat the drugs designed to kill them. So, when bacteria are exposed to levels of antibiotics that don't immediately kill them, they develop these defenses that prevent the same antibiotic from harming them in the future, even if those antibiotics are given at higher doses. So they really cleverly replicate themselves very, very quickly, and these mutations slip in, and then this new and improved version of the bacteria then, you know, keeps replicating and it can actually be passed on to other people at that stage.

**Gemma Ware:** And how serious a problem is antibiotic resistance?

**Fron Jackson-Webb:** It's a really serious problem. So, the World Health Organization says that it's one of the top 10 global public health threats that we're facing. So, one of the last estimates from 2019 was that around five million people a year were losing their lives to anti-microbial resistant infections, and that's likely to more than double to 10 million people by 2050 without action.

**Gemma Ware:** Thanks Fron, for explaining all of that to us.

**Fron Jackson-Webb:** Thanks, Gemma.

**Gemma Ware:** So we're going to be talking to a scientist later in this episode about that search for solutions you were talking about. But first, we wanted to hear what it's like being a hospital doctor faced with antibiotic resistance. So I called up Nubwa Medugu. She's a clinical microbiologist based in Abuja, the capital of Nigeria. Nubwa started her career back in 2008, and she was working at that time in a pediatric unit at a hospital in Kano in northern Nigeria. She told me that what she saw there was deeply concerning.
Nubwa Medugu: A lot of these patients seemingly had typhoid, and had taken antibiotics. The antibiotics didn't work and then they had their intestines becoming perforated.

Gemma Ware: So these are children with typhoid?

Nubwa Medugu: Yes, exactly.

Gemma Ware: And they were given what multiple types of antibiotics and nothing was working?

Nubwa Medugu: So, unfortunately, the way they present is with perforation. That means the intestine bursts essentially. But they would have been having typhoid for probably weeks and tried several different antibiotics at smaller hospitals, at chemists, just not the regular healthcare system. And the first time they come into the real healthcare system, they just come in with perforation and there are lots and lots of children like that.

Gemma Ware: That must be devastating to be a doctor trying to help these children.

Nubwa Medugu: Oh very. Yeah. It is very. I think one of the most challenging things in practicing medicine is seeing children suffer when they really don't have to. The fact that a lot of patients have infections that are very difficult to treat. I didn't know it was just the tip of the iceberg then. And continuing in my practice, specializing in medical microbiology, the problem seems to have gotten worse.

Gemma Ware: Today, Nubwa works at Nigeria's National Hospital in Abuja, where she specializes in infectious diseases and antibiotic resistance. She also teaches microbiology and immunology in Abuja's Nile University.

Nubwa Medugu: Because I'm a clinical microbiologist, I straddle two things. So I work in the lab and I also work with the patients, meaning that when there's a patient with an infection, especially one that is difficult to treat, physicians and surgeons ask for my input. So when I go to the clinic or to the ward, usually, to see this critically ill patient, I do what physicians do. But with my extra training, I'm able to find peculiarities within the patient and use that information to run for that test in the lab or give more in-depth suggestions into how best to treat the patient.
Gemma Ware: Nubwa’s team also looks at the results of all the infections in the hospital, even if they don't see the actual patients.

Nubwa Medugu: What we're seeing increasingly is the rate of anti-microbial resistance, like it's really, really high. So when you go through lab results to review on a day-to-day basis, it's actually difficult to find a sample or a bacteria isolated that’s not resistant to at least one antibiotic.

Gemma Ware: Antibiotic resistance is a global health threat, but it hits regions of the world such as Africa particularly hard. According to the World Health Organization, antibiotic-resistant bacteria are estimated to cause over 700,000 excess deaths every year across the African continent, and those living in poorer regions of Africa are even more vulnerable. To get a sense of just how serious antibiotic resistance is in Nigeria, in 2022 Nubwa and her colleagues looked at cases of E. coli in her hospital in Abuja. They isolated 107 different specimens of E. coli and did a genetic analysis on them. The results were shocking.

Nubwa Medugu: Out of the 107 bacteria that we had, 102 were resistant to at least three antibiotics.

Gemma Ware: Five of these 107 bacteria samples were resistant to all antibiotics, and another 15 were resistant to 90% of antibiotics.

As you walk around the hospital and you're seeing these patients, are there any similarities in infection? Are we talking literally every type of infection, like kind of lung infections, skin infections, or are there some that are more resistant to others?

Nubwa Medugu: So whether you have a blood infection, or a chest infection, or a urinary tract infection, in general, the resistance rates for the bacteria causing them, seem to be the same. However, there are some bacteria that are particularly troublesome for us around where we are, and they include E. coli and Klebsiella.

Gemma Ware: Klebsiella is a bacteria that's found in the environment and in the gastrointestinal tracts of humans and other animals. It can cause conditions including urinary tract infections, pneumonia, and bloodstream infections, particularly in people with weakened immune systems or underlying health conditions.
Nubwa Medugu: Resistance rates, especially for Klebsiella, are way above 90% for a lot of antibiotics. So when we see Klebsiella, like we're scared, you start having palpitations because you know that antibiotics are going to be a problem in this case.

Gemma Ware: Nubwa says that antibiotic-resistant Klebsiella infections are particularly concerning for newborn babies.

Nubwa Medugu: So you are in the newborn unit and you have a lot of patients that have Klebsiella. And it spreads really fast. Like it affects one baby, it can spread quickly to another baby. So of course that is where infection control measures come in and the mortality rates are pretty high.

Gemma Ware: So you're a doctor and you do a test and you see this baby a couple of weeks old, a couple of days old maybe, got Klebsiella, 90% resistant. What do you do? I mean, is the outlook just that, that baby is quite likely to die?

Nubwa Medugu: So it's a number of things. I would say that the mortality rate depends on the hospital. So where you have a good support system, you have oxygen, you have ventilators, they are likely to pull through. But in other centers where I have worked, then when you see Klebsiella in a newborn, especially in other states like Sokoto, Kano, then you know that the chances are high that the baby is not going to make it, unfortunately. Infection prevention and control plays a key role really. And for our hospital, once we identify there's one Klebsiella, now what we do is immediate deployment of infection prevention and control, remove the patient, make sure everybody is gowned and things like that. This helps to prevent the spread of the infection.

Gemma Ware: In another study published in June this year, Nubwa and her team analyzed lab data from six hospitals across northern Nigeria. They wanted to understand what bacteria are most prevalent and determine which antibiotics might still be effective in the region. They analyzed 49 bacteria samples from children, mainly those with blood and urinary tract infections that had been resistant to more than one drug. These samples included blood, urine and sputum, a bodily fluid produced in the lungs.

Nubwa Medugu: We found that antibiotic resistance rates were high. For the antibiotics, we used the most. For instance, we had over 80% resistance of
ceftriaxone. Once you enter a hospital, one of the first things that's prescribed is ceftriaxone.

**Gemma Ware:** 65% of the bacteria were also resistant to the antibiotics of last resort. These are antibiotics reserved for treating the most difficult infections such as tuberculosis, malaria, and typhoid.

**Nubwa Medugu:** We have a lot of typhoid in Nigeria. Now, typhoid, some of the best treatments have always been fluoroquinolones. So because typhoid is endemic, it means that once you have a fever, they think of malaria and then typhoid. And therefore give a lot of fluoroquinolones. So if you have fluoroquinolone resistance, then it is likely that drugs, the top-line drugs like meropenem are also unlikely to work. So essentially, it's a marker of overall resistance in some sense.

**Gemma Ware:** There was also a lot of resistance to another set of antibiotics of last resort called carbapenems.

**Nubwa Medugu:** Now, if nothing works, the carbapenems usually work. But in this case, we also had over 60% resistance to the carbapenems.

**Gemma Ware:** There was some good news from the study though. Two antibiotics called tigecycline and fosfomycin remained very active, even against highly resistant strains of bacteria. These antibiotics are expensive though, and they aren't readily available in many Nigerian hospitals or in Africa more generally.

Why do you think Africa is particularly hard hit by this problem, which is not just an African problem but why is Africa having the heaviest burden?

**Nubwa Medugu:** I think it's a reflection of the health care system in general. Vaccination levels are low. When vaccination levels are low then infection rates are high and of course, antibiotic use is high.

**Gemma Ware:** Nubwa says that in countries such as Nigeria, antibiotics are a cheap and quick way of dealing with illness especially when sick people lack access to good health care.

**Nubwa Medugu:** So if you want to see a doctor you would have to travel a long distance. You would have to pay so meaning you have to have transport money, you have to afford hospital fees, the lines are long, the staff at the hospital are few. So if
you want to see a doctor you would typically leave your house around 6 a.m. and it will take you some six, eight, 10 maybe more hours to see a doctor. Now given that stress, a lot of people use the easy one which is just walk to the nearby chemist and get antibiotics.

**Gemma Ware:** But she says that the people who work in pharmacies in the country aren't always qualified or knowledgeable about the drugs that they sell.

**Nubwa Medugu:** So if you go to the chemist what they would do is pick five different antibiotics of different colors and give you to take for three days. They don't even know what the names are in a lot of instances. In fact, you can be like walking to the hawker that has a lot of antibiotics. So it's commonly called mix me. So you tell the hawker please give me mix me. Mix me means oh he's going to put ciprofloxacin, ampicillin, like different antibiotics and you're just going to take all of that, hoping that one of them will work.

**Gemma Ware:** Even when the right medication is available it's often very expensive.

**Nubwa Medugu:** The good ones are expensive. means that you go to a pharmacy and they tell you there's a let's say one pound antibiotic and probably 200 pound antibiotic, good versus bad, but then you don't have the money. So you say okay I know this brand is all good, but I don't have the money to get the good one, so I'm going to get the cheap one. Then they will use some standard antibiotics.

**Gemma Ware:** For those patients who do get to see a doctor, a lack of laboratory tests makes it hard to determine which bacteria are causing an infection. This leaves doctors trying to make an assessment without much information about which antibiotics would work best.

**Nubwa Medugu:** For instance, when I'm seeing patients and they come and see me, I have a cough and I've taken three antibiotics and it hasn’t gone. Doctor, give me something so that the cough would go. So my next line, of course, is do a sputum MCS. So you put sputum and then you go to the lab for tests. So that tells me what organism it is and what antibiotic would work. But then the patient says, oh, doctor, I don’t have money for tests. I can spare a little to buy an antibiotic, but certainly not enough for any test. You are left to either pay ing for the tests or looking for the best antibiotic based on your best guess.
**Gemma Ware:** This is called empirical therapy, and it means that doctors decide what course of action to take based on their clinical judgment and the patient's symptoms rather than a laboratory test.

**Nubwa Medugu:** So you look at the age, the sex, the occupation, and other risk factors of the patient and decide what is the most likely organism and what antibiotic is likely going to work the best.

**Gemma Ware:** Inequality and poverty are a big part of the problem here. If people aren't able to access vaccinations, diagnostic testing, medical advice, and the right drugs if they're infected, this can exacerbate antibiotic resistance. But even in a world where everybody has the access to the healthcare that they need, bacteria would still become resistant to antibiotics. And so as the problem deepens, the hunt continues for new antibiotics. One of the microbiologists doing that searching is André Hudson. He's dean of the College of Science at the Rochester Institute of Technology in New York State in the US, and in his research, André spends his time searching for new antibiotics. I asked him how scientists traditionally do this.

**André O. Hudson:** The traditional way involves a process called bioprospecting. So, basically, we go out to the natural world and we find organisms that, through evolution, has evolved pathways to synthesize compounds that kind of be used as medicines, you know, so you think about in the soil, for example, right? It's like a turf war, no pun intended, where you have organisms that are all fighting over the same space, the same resources, etc. So, evolution has designed pathways for one fungi to make the compounds to wean off or kill another fungi or other bacteria.

**Gemma Ware:** Much of this bioprospecting is done using plants.

**André O. Hudson:** If they get infected, they can just move away. So, they have actually designed what we call secondary metabolites. So, these metabolites are these compounds not necessarily used for survival of the organism itself, in terms of growth and development, but they're great to have when there's infections and then the plant needs to fight off those infections.

**Gemma Ware:** André says that around 90% of all drugs that we use today are modeled after plant compounds.

**André O. Hudson:** So, aspirin, for example, is salicylic acid, right? It's from the bark of willow and there's tons and tons of drugs that are actually modeled after plant compounds.
Gemma Ware: So, that's the traditional method to find antibiotics and the one that you use in your lab. But it takes a lot of time and there are now new techniques being used to speed up that discovery process. One of them is artificial intelligence. Can you tell us how that's being used in this battle against resistance?

André O. Hudson: Artificial intelligence affords, in my opinion, basically two things. It affords speed because, the way we traditionally do it, right? That means I have to go search and do tons and tons of downstream experiments, so forth and so on. By using a computational approach, I could basically provide the computer with an enzyme that I know is essential, which means that if the enzyme is inhibited, then the bacteria cannot survive. So I could input the three-dimensional model of the enzyme into the computer, and basically what I'm asking the computers to do is to find some location on the protein or the enzyme where something would bind and it will stop the enzyme from working.

Gemma Ware: The second part of the process that AI could help with is to actually design that very new molecule that could stop the enzyme from working.

André O. Hudson: Something that I can't even fathom. I don't even know, exists. So we could say design basically a fake key for me that will fit into the lock but won't open the door. And so the computer could do that in a much, much more facile fashion. And it also could do many iterations of it.

Gemma Ware: Once scientists find this potential molecule, they can go about trying to create it. They do this either by synthesizing it from scratch in the lab or trying to find a natural compound that can be modified to make it into a drug.

André O. Hudson: So with artificial intelligence, I think it just allows it to go faster and actually it provides us with things that we cannot even think about or we don't even know how to do yet in the lab.

Gemma Ware: So it's essentially designing molecules that may or may not exist that it thinks will be antibiotics that won't be resistant to anything that we know of yet.

André O. Hudson: Right.

Gemma Ware: AI is already being used to find new potential antibiotics. In May this year, scientists in Canada and the US said they'd used this approach to identify
an experimental antibiotic that could kill a dangerous superbug. During the COVID-19 pandemic, scientists have also relied on AI to predict new mutations of the virus and to test and simulate potential drugs.

One of the issues slowing down the traditional search for antibiotics, that's the bioprospecting that André talked about earlier, is that 99% of microorganisms on Earth are actually unculturable. That means if you find them and bring them into the lab, there's no way of actually growing them to test whether they could become the antibiotics of the future.

One new method trying to get around this problem is called metagenomics. This involves studying genetic material recovered directly from environmental samples such as soil, water, or even the microbiome in the human gut.

**André O. Hudson:** A metagenomic approach is to basically go directly to the source of those organisms and we sequence the entire community. So that rather than cherry-picking a particular bacteria, I go to the soil, I extract DNA directly from the soil. So not from a bacteria per se, but everything, all nucleic acids, all DNA that is present in the soil, and sequence the entire community.

**Gemma Ware:** When two bacteria inhabit the same community of organisms, chances are that both develop ways to protect themselves from each other.

**André O. Hudson:** The propensity for antibiotic production goes way up just by the presence of its foe, for example. If I know that you're going to attack me, if you're not next to me, then I really don't care. But as soon as I see you, then I'm going to start arming myself just in case you want to attack.

**Gemma Ware:** A metagenomic approach allows researchers to study a whole community of organisms and how they interact and fight against infection. In September, a group of scientists in Germany, the Netherlands, and the US published a paper announcing that they discovered a new antibiotic using this method. Called Clovibactin, it was isolated from uncultured soil bacteria. Now there's a big difference to announcing experimental results like this and actually producing drugs that will go through all the necessary clinical trials before making it onto a doctor's prescription.

**André O. Hudson:** I think to get it from the lab in order to a clinical setting, that's the hard part because it takes a lot of time and effort.
**Gemma Ware:** Part of the problem, says André, is a lack of economic incentive for drug companies to bring new antibiotics to market. The infections and superbugs that these antibiotics treat aren't chronic diseases, and so the drugs are unlikely to yield a lot of ongoing profits for pharmaceutical companies. Efforts are underway in the US, at least, to try and tackle this issue through a proposed new piece of legislation called the Pasteur Act.

**André O. Hudson:** You have a collaboration between academia, pharma, and the government, so let's come up with a new model to say let's fast-track it.

**Gemma Ware:** The goal of the Pasteur Act is to bring together the public and private sectors to encourage and fund antibiotic development. This would target the most threatening infections and ensure the availability of new antibiotics when they're needed. Alongside this hunt for new antibiotics, André says let's not forget about actually slowing down resistance from developing in the first place.

**André O. Hudson:** The overabuse of antibiotics, I think, has exacerbated the problem. Because it's a natural phenomenon, it will happen over time, but it's just sped up more by just the overuse of antibiotics, not only in medicine but in agriculture, which is a huge problem.

**Gemma Ware:** He stresses the importance of what's called antibiotic stewardship, coordinated efforts by hospitals, doctors, and pharmacies to prevent the overuse of antibiotics. One approach is to make sure people aren't repeatedly given the same drugs.

**André O. Hudson:** If you have to take antibiotics, depending on what the infection is, right, and you can treat it, it would probably be best for you not to take the same antibiotic over and over again. So let's say you get infected with bacteria A. We know that antibiotic B is effective against bacteria A. Okay, so you get antibiotic B, you get cured. You get reinfected. I would say you should get another antibiotic, not the same antibiotic that you were before. And the reason is, is because this kind of diversity of compounds, so to speak, makes it very hard to predict what's going to come next, or you're not tuning or training the infections in order to become resistant.

**Gemma Ware:** For Nubwa Medugu, working on the front lines against antibiotic resistance in Nigeria, it's this kind of stewardship which offers the most hope for the future, rather than an endless pipeline of new antibiotics.
**Nubwa Medugu:** You can develop as many new antibiotics as you like. The bacteria will definitely get resistant to those new antibiotics. So it's more of looking at how to manage better the antibiotics that we have currently. Otherwise, the problem just continues. You don't turn your antibiotics into the market and then give them two years. We're back to being resistant to antibiotics.

**Gemma Ware:** Nubwa says that at her hospital in Abuja, the doctors are careful about which antibiotics they recommend.

**Nubwa Medugu:** I would choose the one that is the cheapest and the one that is least likely to give side effects and the one that is likely to work the fastest for the patient. So when I'm releasing my results, I wouldn't send out the one that would knock out all good bacteria in the patient, right? So that's part of the stewardship. So stewardship is key in the hospital. Physicians don't like it, right? Because it looks like you want to control them. They want to prescribe this antibiotic, but you're only giving them this antibiotic, but it's a balanced really.

**Gemma Ware:** That's it for this week's episode. Thanks to our colleagues Wale Fatade in Nigeria, Vivian Lam in the US, and Fron Jackson-Webb in Australia. We'll put a link to some articles that Nubwa Medugu and André Hudson wrote for The Conversation, and to Fron’s series the dangers of antibiotic resistance, in our show notes. We also recently asked seven experts around the world, including André Hudson, whether they thought we'd still have antibiotics in 50 years’ time. We'll put a link to that story in our show notes too.

This episode of the Conversation Weekly was written and produced by Mend Mariwany and me, Gemma Ware with assistance from Katie Flood. I'm also the show's executive producer. Sound design was by Eloise Stevens, and our theme music is by Neeta Sarl. Stephen Khan is our global executive editor. Alice Mason runs our social media, and Soraya Nandy does our transcripts.

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