Episode #11: The Global Fight Against Antimicrobial Resistance

SPEAKERS
Heather Howard, Dr. Martin Blaser, Ramanan Laxminarayan

Heather Howard 00:02
Hi, and welcome to the Princeton Pulse Podcast. I'm Heather Howard, professor at Princeton University and former New Jersey Commissioner of Health and Senior Services. On campus and beyond, I've dedicated my career to advancing public health. That's why I'm excited to host this podcast and shine a light on the valuable connections between health research and policy. Our show will bring together scholars, policymakers, and other leaders to discuss today's most pressing health policy issues, domestically and globally. We'll highlight novel research at Princeton, along with partnerships aimed at improving public health and reducing health disparities. I hope you'll listen in as we put our fingers on the pulse and examine the power and possibilities of evidence informed health policy.

Heather Howard 00:51
Today's episode takes on one of the top 10 global public health threats facing humanity, antimicrobial resistance, often called AMR. According to the World Health Organization, this concerning phenomenon directly, or indirectly claims more than 5 million lives each year. That means that antimicrobial resistant infections are more deadly than AIDS or malaria. But the human toll is only part of the story. AMR also endangers animals in the environment, along with food security, the economy, and equity within societies. It even diminishes our ability to fight future pandemics. AMR is a global challenge that requires a global solution, which is why the United Nations will convene a high level meeting to address the issue this fall. World leaders will gather to create a coordinated action plan that recognizes the intrinsic connection between human, animal, and environmental health.

Heather Howard 01:47
Here with me to discuss the drivers, impacts and potential solutions is Ramadan Laxminarayan, an environmental economist, epidemiologist, and lecturer here at Princeton, as well as the founder and president of One Health Trust, a public health research organization. Ramanan is joining us from across the world where he's actually at a planning meeting for the UN meeting focused on AMR. So we faced a few technical challenges, but we are going to have a great conversation and we wanted to give it a go because this is such an important issue. We're also joined by and delighted to welcome Dr. Martin Blaser, a physician, microbiologist, and professor at Rutgers University, where he directs the Center for Advanced Biotechnology and Medicine. He was the author 10 years ago of "Missing Microbes: How the Overuse of Antibiotics is Fueling Our Modern Plagues," which was made into a movie released last year, "The Invisible Extinction." Ramadan. Marty, welcome to the show.

Dr. Martin Blaser 02:46
Thank you.
Ramanan Laxminarayan 02:48
Thank you.

Heather Howard 02:49
Thank you. I want to start with Dr. Blaser. Marty, as I just mentioned, 10 years ago, you published "Missing Microbes" on the perils of inappropriate antimicrobial use. Can you tell us a little bit about how you came to this issue?

Dr. Martin Blaser 03:05
Well, it's a long story. And I want to see if I can abbreviate it for the podcast. But I was advising a student about obesity. And I said to the student, well, you know that farmers have been feeding antibiotics to their livestock for decades. Because it works. It fattens them up. And that's why they do it. It's so profitable. And then I thought, "Wow, I wonder if that's what we're doing to our kids." And that began almost a 20 year story now about how antibiotics are affecting the human body, not just acutely, but in the long term, driving such diseases as obesity and asthma, and food allergies and neurodevelopmental problems. The list goes on. And so I kind of I kind of stumbled onto a goldmine of really important issues that affect our future, our human future.

Heather Howard 04:11
So what's exciting about having the two of you on here is that you bring very different backgrounds, but you're both at the forefront of raising AMR as a public health crisis through your both your research and sustained policy engagement. So Ramanan, I'm going to you. You're an economist and an epidemiologist. How did you come to this issue?

Ramanan Laxminarayan 04:31
So Heather, I'm actually an environmental economist. And microeconomics is a form of applied economics, focused very much on problems. A common feature of these problems is externalities, or public goods, where things that we do affect other people, and that we might not take into consideration. You can think of air pollution or water pollution or the fact that we're concerned about catching as much fish as we can. But we don't care about the effect on other people, generally. And oddly enough, antibiotic resistance falls squarely into that way of thinking. If you think about it, antibiotic effectiveness is a common resource. It's global; any of us can access it. But in accessing it, we're making sure that other people have less of it if we overuse or misuse antibiotics. So that's what makes antibiotic resistance a very different challenge than any other medical problem. And there is a lot for folks outside of just pure medicine to say about a problem like this. In the same way that there's a lot of room for people outside of atmospheric chemistry to say about climate change. Climate change is not just about atmospheric chemistry. It's about why people pollute, put out carbon. It's about economics. It's about sociology. It's about politics. And I think AMR falls into that same kind of frame and, therefore, it's familiar to other environmental problems.

Heather Howard 06:11
Marty, let's start with you. So we're talking about bringing different tools to bear, but can you help us understand the biology of this issue? You've called it the biological cost of anti microbials, right? People who work in public health know that antimicrobials have been revolutionary in modern medicine. But
can you talk about how you came to this conclusion, that there's a biological cost that we had been ignoring?

Dr. Martin Blaser 06:40
Well, what's funny is that not only is Ramadan an economist, but my first degree is in economics. So I've been very interested in that as well. In economics, we've learned that there are trade-offs in all directions. So something may be good, but it may have some costs somewhere else. Basically, we all know that antibiotics are wonderful medicines that have saved many lives. But doctors and health practitioners and farmers and others are using antibiotics more and more and more, and the global scale is just enormous. The problem is that antibiotics not only kill the organisms that they're designed to kill, but they have collateral effects. They affect the microbiome of people and animals. And the microbiome is all the microbes that normally live there. So in a person taking an antibiotic, that antibiotic is affecting their microbiome. And in a Darwinian sense, it is selecting for resistant organisms. But in addition, it is perturbing the microbiome, and that makes antibiotic resistant organisms more fit, more able to live. It's also having effects on human metabolism and human immunity. I made a model a few years ago. We're all concerned about the ecological effects of antibiotics. I consider an analogy; it's like an iceberg. The tip of the iceberg is antibiotic resistance. We've known about it for 80 years. But the body of the iceberg is what antibiotics are doing to the microbiome. Those effects are fueling AMR. But they are also selecting for conditions in which AMR organisms are or live better. And they're perturbing the microbiome, which is leading to changes in our metabolism and our immunity. And that's the unrecognized portion of the iceberg. It's under water. We don't see it. But it's at least as dangerous.

Heather Howard 08:59
Let's unpack that. Ramadan, you've done a lot of research on multi-drug resistant tuberculosis. Can you talk about that? Is that the part of the iceberg we're seeing? Can you describe what trends you're seeing with with TB?

Ramanan Laxminarayan 09:14
So tuberculosis is where drug resistance is really a big problem. It's also different from other bacterial infections simply because most other bacterial infections are what you would call acute. In other words, they last for a much shorter period of time. And if you don't get the antibiotic treatment correct, that patient could be dead in just 24 to 48 hours, especially if they're a small child with, say, sepsis. With tuberculosis, it's a much longer period of treatment and there is an opportunity to correct. That said, drug resistance has been emerging and spreading to tuberculosis for quite some time, to the point where our first line drugs don't work in five to 20% of the time, particularly in high-burden countries like India, South Africa, and Russia. That has been fueled largely by sales of antibiotics, not through a quality approved or government facility, but rather through the private sector. And this is a story you will hear again and again, which is that people take the wrong antibiotics. And then they develop drug resistance. So as much as drug resistance is a externality, which is what we do affects other people, it is also a direct consequence for ourselves. If we take antibiotics inappropriately, or we take the wrong ones, there's a greater chance that they won't work for us as well in the future. With tuberculosis, you see both kinds, the ones that are acquired resistance, as well as resistance that was engendered by misusing the antibiotics. Today, the second line antibiotics are probably about 10 or 15 times the cost of the first line antibiotics, which is completely unaffordable for many people, and which is why you see
that multi-drug resistant tuberculosis is now becoming an issue that more and more people talk about. In recent years, we also have extremely drug resistant tuberculosis or XDR TB, which is not responsible to first line drugs or the drugs that we use for MDR tuberculosis that was first observed in South Africa but is now worldwide. Fortunately, there is still a fairly small proportion of people with XDR TB, but it's extremely concerning because there's not a whole lot we can do for them, except for some highly toxic drugs.

**Heather Howard** 11:38
So that's TB. Ramanan, you also recently co-authored a paper looking at why newborns and children are particularly high-risk. Can you talk about those findings?

**Ramanan Laxminarayan** 11:49
Newborns, typically children in the first 30 days of life, are prone to infections. Either they're born in places where there are infections around them, or bacteria around them, where they then get infected. Also, their immunity tends to be weak, because they still depending on immunity through maternal antibodies, what they get from their mother, particularly directly through breast milk. So they are prone to infections. And when you get bloodstream infections, even when the antibiotics work, there's a high chance of mortality, especially in low and middle income countries. But it's true in high income countries as well. In most studies, you can see rates upwards of 50%, which is another way of saying that more than half the babies who have newborn sepsis are likely to die. Having an infection that does not respond to antibiotics is now something that is far more common. In fact, there was a paper that came out just two days ago from a massive study that was funded by the Gates Foundation, called "Champs." And what "Champs" does is look at newborns who have died and see why they died. It's like an autopsy. What they find is shocking. About one in four of these sepsis infections are caused by Klebsiella pneumonia, one pathogen for which treatments are very hard to come by. So we're seeing this newborn sepsis burden increasing, and in fact, if we keep going on this trajectory, we are unlikely to meet the sustainable development goals that the United Nations has set out for itself to be able to reduce newborn infant mortality as well as "under five" mortality. So it's very urgent that we tackle AMR as a way of reaching our sustainable development goals.

**Dr. Martin Blaser** 13:36
I want to comment on this because newborn sepsis, as Ramadan mentions, is a terrible disease with high mortality. But in fact, most infections in childhood are mild and do not require antibiotics. They're not even bacterial, in which antibiotics wouldn't even be valuable. So there's tremendous overtreatment with antibiotics. And that is having the effect that Ramanan talked about, the tragedy of the commons by this massive overuse for minimal conditions. We are making it worse. For those babies who have life threatening conditions, the overuse is a huge, huge issue.

**Heather Howard** 14:26
Marty, I want to explore further your analogy of the iceberg. I think you've written about how this is making it more difficult for us to prepare for pandemics. Can you talk about that... our pandemic preparedness and response?
"Missing Microbes" was published in 2014. That's before COVID. But I was concerned about pathogens arising out of nowhere, that could sweep across the earth and not just stay in the river valleys, but spread out onto the floodplains. And that's actually exactly what we found. And unfortunately, COVID-19, or SARS-CoV-2, is not the last pathogen that we’re going to see. It's not the last one in the world, and I'm worried about an antibiotic resistant bacteria emerging in which, because of how we've misused antibiotics, we just won't have tools available to treat it. I call that scenario "antibiotic winter." In fact, I wanted to entitle the whole book "Antibiotic Winter," but the publisher thought it was too scary.

So, is there an updated edition coming out with that title?

No, but I'm working on the sequel.

So Ramonan, Marty has painted this bleak picture for human health. But we know that this global crisis isn't just about human health, right? It has economic implications. It has implications for animal and plant health, and food, safety and security. Can you paint an even broader picture of the implications.

The primary effect is on human health. But we have to remember that of all of the mammals on the planet, 30% of the mammalian biomass is humans, and 60% of the mammalian biomass is animals that humans eat primarily -- the cattle and pigs. Over the last 20 years, drug resistance in infections that animals encounter has gotten a lot worse. Now, many animals in developed countries particularly, but also in developing countries, get antibiotics every day as part of the food just as a prophylaxis -- with the objective, as Marty mentioned earlier, of fattening that just increases the weight gain. Oddly enough, it works the same way for children, which causes obesity. For animals, it's an economic input. Therefore, it is hard, but not impossible, to get farmers to stop that practice. But it does harm the animals. And it will create a food security issue down the road. We're not quite there yet, where we have a lot of animals dying because of bacterial infections. But we have seen examples of diseases that completely wipe out animal populations. We see this with bird flu periodically. We saw it with chickens in Southeast Asia a couple of years ago. African swine fever wiped out something like 60 or 70% of all the pigs in China. That's a huge number. So I know we're focused on pandemics that affect us, but the pandemics that affect animals can be absolutely devastating. They can harm, obviously, the animals, the farmers, and a lot of the farming communities that raise animals, which are not wealthy but quite poor. A family might own one or two cows. It's like a bank account for them. It's really their main source of wealth. And when those get wiped out because of diseases, and particularly of infections that are not treatable, then it sets the whole family back. So dealing with these issues, through better animal health, through better use of antibiotics, through vaccines, is going to be an important way in which we tackle poverty itself.
Dr. Martin Blaser 18:34
Can I follow up on what Ramanan said, because he raised some really important points. If I'm worried about an antibiotic resistant bacteria spreading across the globe, chances are it's going to originate on the farm, from all the antibiotic use of the farm, the sub-therapeutic use to fatten up farm animals. We've already seen some emergence, but that would be something that's quite predictable.

Heather Howard 19:00
Marty, you mentioned that pathogens don't respect borders. So this is a global crisis. But are we seeing equitable distribution of the crisis? Ramanan, you just mentioned people living in poverty, in low resource settings. Is the burden equally distributed here, or are poverty and inequality exacerbating it?

Dr. Martin Blaser 19:27
Well, inequality exacerbates everything. So that wouldn't be surprising. What's remarkable is this growth promotion of antibiotics is happening all over the world, in every country. In fact, China produces a huge amount of antibiotics, not just for people in China or animals in China, but for export. China exports about 10 times the antibiotics that are produced in the United States, each year, to farmers all over the world so that they can use it for growth promotion.

Heather Howard 20:03
Ramadan, how is AMR interconnected with other planetary crises, such as climate change and global conflict?

Ramanan Laxminarayan 20:14
Starting with conflict first... there are many situations of global conflict, Ukraine being the most recent example, where drug resistance is a major issue. It's an issue for populations that are under attack. It's an issue on military battlefields. We saw that in Iraq. We're seeing this now in Ukraine, in a big way. Any place where you have health systems break down and you have new infections, then you're more dependent on antibiotics. And when the antibiotics stop working, we're in trouble. Now, climate change is an important issue that relates to AMR in the following ways. First of all, we, for reasons that we don't fully understand, tend to see more of these pathogens called Gram-negative bacteria, for which we have fewer antibiotics. They're increasing in places where there are higher temperatures. Second, there is evidence associating, although we don't yet have good causal evidence, which links antibiotic resistance to increases in temperature and humidity. Again, we don't fully understand why, but the evidence is building up. So I'm sure you've heard of things like the the melting of the Arctic permafrost in Siberia, and so forth, which then may uncover bacteria that we have not encountered in a very, very long time simply because they were hidden. Again, this potentially is related to increases in infection. So far, we're only seeing these in reindeer or animals that are in those areas. We haven't yet seen them in humans, but, you know, we're playing this big experiment with climate, and we don't know how this is going to unfold. A major reason why farmers, particularly in low and middle income countries, give antibiotics to animals, is just as a way of keeping them alive when there are other variabilities in the production system, of which temperature was a very important one. So when they're facing mortality from other things, like not having sufficient water, drought, or flooding, which causes infections and certainly temperature variability, we will probably see antibiotic consumption in the animals go up...
as a coping mechanism, which then leads to higher resistance for the humans and, as Marty said, in animals.

**Heather Howard 22:38**
And the cycle continues, right? You're both painting this dire picture, but you're both researchers who are deeply engaged in policy on this issue. So Marty, I'd love to explore some of the solutions in the trade-offs. Can you start by talking about antibiotic stewardship, and what role that plays in addressing the problem?

**Dr. Martin Blaser 23:00**
I'm very happy to because I think that is the major thing, the most important thing, that we have to do. We've been using antibiotics with abandon, both in the clinic and on the farm, as if there was only benefit and no costs. Ramanan and I have talked now about a lot of the costs of which AMR is the tip of the iceberg. So we have to educate providers about the use of antibiotics, and when to use them and when not. I was struck that after the U.S. published data on antibiotic use (the CDC publishes), a group in Sweden published their use, and Swedish doctors are using 40% of the antibiotics per capita that U.S. doctors do. That's at every age and is a stable finding. So somehow, they are utilizing their antibiotic armamentarium much more efficiently than we are. And there is no epidemic in Sweden of childhood deafness, or sepsis. They're just taking better histories and doing better physical exams and understanding their patients much better than the U.S. With the limited period of time our doctors have with patients, they spend most of their time typing and not really examining patients. So a patient has a cough or a fever, give him an antibiotic. We have to change that dramatically.

**Heather Howard 24:30**
Okay, so that's one avenue. What about the research and treatment pipeline? Marty? What should we be doing?

**Dr. Martin Blaser 24:40**
There are two things that we need to do. One, because of the AMR crisis, we have to develop new antibiotics that will give us the backstop that we need for very serious emergent infections. But I think even more importantly, we have to develop new classes of antibiotics. We need to develop narrow spectrum antibiotics, antibiotics that are just focused on the one organism that somebody has, and will not have so much collateral damage. The collateral damage is what is largely fueling AMR. We need to develop those antibiotics, and we need to develop diagnostics that support them. This requires massive investment at the governmental scale. Just like when we want to build a new interstate highway, we don't build it ourselves. That's what we use tax dollars for, something for the public.

**Heather Howard 25:33**
Ramanan, I'm going to go to you on that. As an environmental economist, you've written about the the common resource problem. How do we get more government investment? And how do we get more research into these new treatments?
Ramanan Laxminarayan  25:48
New treatments have always been typically developed in the antibiotic space by private companies. It has not typically been developed by governments. That is changing. Now, with massive investments in this area from BARDA, which is an agency of the U.S. government and the Department of Health and Human Services, and investments in other mechanisms and the drugs for neglected diseases initiative, the paradigm is changing. It's changing to help these pharmaceutical companies in the antibiotics space survive, by providing them with funding, but then also to be able to bring down the costs of development. Today, the average new antibiotic costs anywhere between a billion and $2 billion to develop. A private company is required to make a return of seven or $8 billion dollars in revenues in order to justify that kind of investment. Otherwise, their investors are not going to be agreeable. There is not $8 billion available to be able to pay for these drugs because most of the people with infections that are drug resistant are in poor countries, and they simply cannot afford antibiotics that are going to cost 10 to $20,000, which is what most antibiotics cost today. So we're going to have to change the entire paradigm of how drugs are developed. For starters, we have to start making drugs, which are, the cost of development is much lower than what it is right now. And it's not, it's not impossible. Most malaria drugs, in fact, all the malaria drugs until about 15 years ago, were developed by one entity in the world, in a country that has had very little malaria. And this is the Walter Reed Army Institute in Bethesda in the United States, which was doing it primarily to protect U.S. service men and women outside the country. The cost of those developments was much lower than what the pharmaceutical industry would do on its own. They did partner with pharma, but they were in the lead there. And I suspect that the model for new antibiotics will have to go that route. Because we have seen a spate of bankruptcies amongst biotechs engaging in the pharmaceuticals, in the new antibiotic space. Simply there's not enough money to be made, and there's not enough public support to then compensate them to make the antibiotics. The starting point is to make the drug for cheaper. Then we can find a way to get it out. There’s no member of Congress that's willing to step up and write that big check, particularly the farmer in this day and age. It's like a political third rail to do that. So I think we need to be pragmatic and think of ways to bring new drugs to market. And I'd like to emphasize the point that Marty made, which is that it's not just about developing new antibiotics. It's about developing new antibiotics that have either a feature of novel mechanisms of action, which means they are different, or that they are uniquely narrow spectrum. So they're not like these bombs that go off and kill all the other organisms as well. They're very specifically targeted just to the organisms that we're trying to attack. And a lot more work needs to be done in this direction.

Heather Howard  29:25
That's a good segue to talk about the UN meeting that is planned for this fall, a high level meeting. I think it's the second high level meeting that the UN hosted. The last one was in 2016. Marty, what would be your hopes for that meeting?

Dr. Martin Blaser  29:42
I think the goal is to bring this to the world's attention, to put this right on the front burner instead of the back burner, because, as was said, it's a crisis that's very analogous to climate change. I learned about climate when I was a high school student 50 years ago. It was there then, but nobody was paying attention. Now, not surprisingly, it's a lot worse. And this one is going to get worse unless we pay attention to it. We have to start to develop agreements that will enable the development of new drugs,
that will strengthen stewardship. I want to just keep mentioning stewardship. Ramanan mentioned malaria. Great drugs were developed for malaria. But over time, the organisms became resistant to those drugs. Darwin was right there; there is survival of the fittest. The bugs are always going to win. So we can't just try to obliterate them, because we can't.

**Heather Howard** 30:52

Ramanan, what about you? What would you hope for this UN meeting?

**Ramanan Laxminarayan** 30:57

The first time we had a UN meeting, it was primarily about bringing attention to the problem. This time, the hope is that we would have targets. UN language doesn't help unless the actual targets that are set for the world take the 1.5 degree increase in temperature that the climate targets. We need something equivalent for humans for drug resistance. In fact, I'm in a meeting in Malta today, with stakeholders from various countries talking about what that the UN resolution is going to look like. In fact, Malta is one of the two countries that is charged with shepherding this document through the UN General Assembly. And what we're looking for are targets we call 10, 20, 30, or 10% reduction in antibiotic resistance burden, that's mortality and morbidity; a 20% reduction in inappropriate use in humans; and a 30% reduction in inappropriate antibiotic use in animals, same stuff and stewardship that Marty was talking about. And we want to do all of those by 2030, compared to a baseline of 2019. We think that these targets are feasible and achievable. Using mechanisms and tools we already have, one of the things we didn't discuss was how can we actually lower resistance. And the tools to lower resistance are vaccination, water and sanitation, infection prevention and control. Everything that we do to reduce the number of infections also effectively reduces the number of drug resistant infections. And these are all tools that are both well understood and well known, but also well funded, globally. And so we need to focus on these to get the world to focus on targets. Then along with the targets, we also need governance mechanisms and accountability. So we're calling for an independent panel. Just like the IPCC, the Intergovernmental Panel on Climate Change, which is independent and neutral, where scientists were able to provide feedback on progress, to bring new data to the table. We need to address it in a similar way to climate, but my hope would be in a slightly more successful way than we've done with climate.

**Heather Howard** 33:07

Before we wrap, any lessons from your deep engagement in using research to shape the policy debate? Any lessons for future work on global health crises? Marty, I'll start with you.

**Dr. Martin Blaser** 33:23

Actually, Ramadan raised a very interesting point, which is worth emphasizing, and that is the role of vaccines in preventing or minimizing AMR. If somebody comes to the doctor with a fever, in some percentage of cases, the doctor will give them an antibiotic. Now, if those fevers were due to influenza or COVID, they'll be giving the antibiotic in vain, but that is what's happening. If the vaccinations can prevent some of these illnesses, it will decrease the pressure on AMR. So vaccines against viruses are an important tool for AMR reduction.
As so often happens in public health, it comes back to prevention. Very interesting. Ramadan, any final thoughts? Maybe you could just comment on the role of "one health." Are you seeing them take a "one health" focused lens?

"One health" recognizes the connectedness between humans, animals, and the environment. I think, in some sense, this is such a well understood paradigm by everyone. But somehow we need this new definition to go back to remembering this kind of idea. Because it's a relatively new way of thinking, it can also confuse people, and so we're trying not to be too labelistic about it. For some countries, "one health" is seen as a western approach to, in some way penalize less developed countries for the way in which animals are raised, even if that might not be the intent. So it is still developing as a concept. I think everyone is aligned that we need to take into account humans, animals and the environment, whether we use the "one health" tag, per se, or not. I think it's going to evolve over time. Because like I said, it's a tag that still means different things to different people because it's only 15 years old. I think, over time, we will understand it better.

Well, I want to thank my guests for helping to eliminate one of the greatest public health challenges today, and for also giving us a roadmap for progress, and giving us some hope with some really concrete suggestions. Thank you both.

Thank you.

Thank you for having us on your show.

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