Maggie Fox
Hello and welcome to One World, One Health, with the latest ideas to improve the health of our planet and its people. I'm Maggie Fox. All of us on planet Earth are facing problems such as pollution, climate change, and new and reemerging infectious diseases, and they're all linked. This podcast is brought to you by the One Health Trust with bite-sized insights into ways to help.

Germs are everywhere, of course, and the world's become used to the sight of people washing their hands, wearing face masks, and disinfecting tabletops. But one place where people might not think to look for a dangerous infection is eyedrops. But the US Centers for Disease Control and Prevention warned against the use of certain brands of eye lubricants after dozens of people across the US became ill with an unusual strain of bacteria. Some even died.

A CDC investigation found the one thing most of these people had in common was the use of these eye drops. Some of the patients had eye infections, but the infections had spread to the rest of their bodies too. Worse, these infections were resistant to some of the drugs normally used to treat them. It's an example of how antimicrobial resistant organisms, sometimes called superbugs, are turning up in unexpected places. And it's an example of how an outbreak anywhere can become an outbreak everywhere.

Today, we're chatting with Dr. Maroya Walters, a CDC epidemiologist and commander in the US Public Health Service who led the investigation. Dr. Walters, thanks so much for joining us.

Maroya Walters
Thanks for having me.

Maggie Fox
This was a very unusual outbreak. How would a microbe like this ever even get into eyedrops in the first place?

Maroya Walters
Yeah, Maggie, you're right that this was really unusual because it's actually the first outbreak in the US where we've had a highly resistant *Pseudomonas* strain that's been linked to a manufactured product. And our investigation is still ongoing to really understand how these eye drops may have become contaminated and to understand really, if they even were contaminated during manufacturing, because we're still waiting on some results for testing of unopened product. But we know that the FDA did an inspection of the manufacturer and found gaps in their procedures for sterile processing and sterile manufacturing. And so we do suspect that something at the manufacturing plant led to contamination of the eyedrops.

Maggie Fox
This particular strain of bacteria, *Pseudomonas aeruginosa*, is what's called an extensively drug-resistant strain. Can you tell us what that means?

Maroya Walters

Yeah, so first, antibiotic resistance is what happens when bacteria are able to survive the effects of the drugs, the antibiotics, that are designed to kill them. And when a bacteria is extensively drug-resistant, it means that it is resistant, so it's able to withstand the effects of most available antibiotics to treat that organism. There's actually only one antibiotic that this strain was not resistant to, and that antibiotic is called cefiderocol. Cefiderocol is a new drug, it was actually first FDA-approved in late 2019. And so that's the only drug that we know can successfully treat these bacteria.

Maggie Fox
How does that happen in the first place? How did these germs develop resistance to so many different agents?

Maroya Walters
Bacteria can accumulate these resistance mechanisms. Resistance mechanisms are genetic changes that enable bacteria to withstand the effects of antibiotics. They can really accumulate those mechanisms over time and they can pass that resistance onto their progeny, to more bacteria when they divide.

Some resistance mechanisms can also be transferred between different bacterial strains, so bacteria are sharing the genetic code for antibiotic resistance with each other. It's actually that sort of sharing that really can help antibiotic resistance spread rapidly. What happens is that bacteria can accumulate these resistance mechanisms, and each resistance mechanism can actually confer resistance, not just to one type of antibiotic, but in some cases, to multiple different types of antibiotics. And so that is really the net effect, is that you have many different resistance mechanisms and one bacteria that is making it extensively drug-resistant.

Maggie Fox
This was such an odd one, how did the CDC even figure out what was happening? How did you discover that it was eye drops that were to blame, and then which particular ones?

Maroya Walters
This was a really challenging investigation. So it's important to recognize first that when we're talking about extensively drug-resistant *Pseudomonas*, you know, I mentioned that it's the first time we found this strain in a manufactured product. We usually find these strains in patients in healthcare settings and they're spreading patient-to-patient, through health care workers who maybe had forgotten to wash their hands, through contaminated medical equipment, or contaminating the healthcare environment. And so we typically see these facility outbreaks of patient-to-patient transmission. So this was very unusual.

At first, we had three separate outbreaks in different types of healthcare facilities, including very different types of healthcare facilities: an outpatient eye clinic, and then these long-term care facilities with different infection types. And so those just seem to be sort of fairly typical outbreaks of this organism with the exception of the eye clinic, which was definitely atypical because we'd actually never seen eye infections with this organism before.

But it was really through whole genome sequencing for these outbreaks, and then comparing across the outbreaks that we were able to first identify, hey, these three outbreaks in different strains with different types of infections, and really, in very, very different healthcare settings, are actually the same strain of bacteria. And it's a strain of bacteria we had never seen before, it had a very unique combination of genetic features.

So the first thing you think, because of how they spread is, well, maybe there's a patient in each of these states, you know, who traveled, who had health care in another state and brought this in. But we didn't find those sort of more typical explanations for this phenomenon, so we really quickly came to the conclusion that this seemed to be a contaminated product that was used across the patients in the different health care facilities.

There are a couple of challenges there. So first, these were healthcare facility clusters, and so we had to really figure out or keep in mind that in these clusters, many patients could have gotten the same contaminated product, or just a few of those patients could have gotten the product. And then we would have our more usual routes of patient-to-patient transmission to explain the other cases.

We also know that *Pseudomonas* can colonize the body, meaning it stays on or in the body for a long period of time for many months before ever causing an infection. So there's not a typical incubation period like you might have with a foodborne outbreak. And so we really had to think, what is the exposure period, what's a reasonable exposure period to look at, keeping in mind that we were seeing lots of different types of infection, and we're actually seeing patients who didn't have infections, but just had this bug in their digestive tract.

Also, just because of the different patient presentations and different types of healthcare settings, we really had to think that this was a universe of products we were initially considering. It could have been a medicine, it could have been something like a bathing wipe. It even could have been like a cleaner used in the facility.

What we did was we worked with our health departments to narrow in on what potential products might have been used. Initially, we really didn't find anything in common. So we did a case-control study, which is where you compare the products and medicines that patients with the bug got to what products patients without the bug got. And that was our breakthrough. That was when we realized that artificial tears were the signal, and we had to dig deeper to figure out what the brand was.

Maggie Fox
And this is a really complex type of investigation that CDC does, in conjunction, I know, with the state health departments. You go to people's houses, right, and look at the stuff they've got?

Maroya Walters

Well, that can happen, particularly in a community outbreak. In this case, what we did was we went to the healthcare facilities, the health departments went to the healthcare facilities with clusters. They actually did that long before we knew this was a what we call a multi-state outbreak, [with] the same strain in multiple states. And so what we did for this case-control was with a health department, CDC went on-site, and we worked with that healthcare facility to look at the patient records, and also just to look at facility practices. It was in doing that, that we were able to figure out that artificial tears signal.

Maggie Fox
Because you must have at first suspected that the people were picking the germ up in the health facility because that's normally where people are catching *Pseudomonas*.

Maroya Walters
That absolutely was one of the complicating factors in this outbreak, was who got this from the product, and who got it just from patient-to-patient transmission? And so it was actually quite surprising that a case-control study really worked for this. But we were cautiously optimistic in this healthcare facility where we did the case-control, because their infection control practices were really quite good. We knew that they were continuing to see cases of this resistant organism, but they weren't seeing cases of other similar resistant organisms that maybe they had just a single case of that was introduced to the facility and then it didn't spread. That really made us think that this was a good place to do that study, and ultimately, that that did pan out.

Maggie Fox
Pseudomonas is actually not terribly uncommon. But I think this is an example of an infection people are not necessarily aware of. Why aren't people more aware of the risks of these kinds of infections and especially *Pseudomonas*?

Maroya Walters
Pseudomonas aeruginosa infections are common, especially when we're thinking about susceptible infections and even for multidrug-resistant infections.

We know that in 2017, CDC estimated that there were more than 32,000 multidrug-resistant *Pseudomonas* infections in hospitalized patients in the US. So, this is something that is happening every day.

But the difference here is that these particular strains, like what caused the outbreak, had these really fairly unusual, currently unusual, genetic markers in the United States, these resistance mechanisms that allow them to share their resistance with other bacteria. We call these carbapenemases.

These carbapenemases are incredibly rare in the US. Among carbapenem-resistant *Pseudomonas*, so a kind of resistant *Pseudomonas*, only about one or two percent of US resistant *Pseudomonas* are going to *harbor* these carbapenemases. And so I think there's just

not a high suspicion that when a resistant Pseudomonas is found, that it's going to have one of these carbapenemases.

In the US, we see that carbapenemases and *Pseudomonas* are more common in other parts of the world. For these resistant organisms, we've always known that we're connected by travel, right, we always think of healthcare outside of the US as being a risk factor for acquiring unusual resistance. But I think what this really reinforces is that we're also connected by trade, and that resistance, perhaps in the environment, or growing resistance rates outside of the US don't just affect us because of travel, but they also can affect us through products, through the global network of trade.

Maggie Fox
If this particular strain of bacteria and others resist so many different drugs, what are some of the other alternatives for treating these infections?

Maroya Walters
So I think it's the fact that this was susceptible to cefiderocol, which is a new antibiotic, and [it] reinforces that we do need to continue to innovate, we do need new antibiotics. Antibiotics alone, new antibiotics, we're not going to invent our way out of the resistance problem.

And we need to be thinking of other approaches. Those can be treatments. For example, there are two groups in the US that have identified bacteriophages that are active against this strain of Pseudomonas. Bacteriophages are viruses that infect and can destroy certain strains of bacteria. So that is promising, although bacteriophage therapy is not widely used in the United States.

It also reinforces that we need other approaches to fight resistance, including better detection. We talked about how this bug isn't really on the radar of a lot of clinicians and maybe even laboratorians. So maybe one positive outcome of this really awful outbreak is that clinicians and laboratorians may be more likely to report this unusual resistance or consider that these unusual resistance mechanisms are present.

We also need to work on infection control in our healthcare facilities. Because right now, what we're trying to do, we think we've addressed the source through removing the artificial tears product from the market, but we now know that we have patients who are colonized with this organism, and we want to prevent that organisms from spreading to other patients through the more usual routes of person-to-person transmission.

Maggie Fox
And when you're colonized, that means that this bacteria is living in your body, but not necessarily causing any kind of symptoms.

Maroya Walters

That's exactly right. And the risks of colonization are two-part. One is that patients who are colonized with an organism are more likely to get an infection with the organism than someone who is not colonized. And then colonized patients really serve as a reservoir. They can transmit to other individuals. And so that's actually why, in this outbreak, we saw that a number of patients actually didn't have an infection, we said that they were colonized.

What happens with these organisms is that they are so unusual in in our country, that when we identify even just a single case, because we know that that single clinical case is simply the tip of the iceberg, potentially, for the patients that have this organism because so many are colonized, we do screening. CDC recommends screening, and we have our health departments that are able to implement that screening in collaboration with our public health laboratories. So they actually go test patients in a facility where the organism has been identified.

It was really through those actions that we were able to detect many of the cases in this outbreak and, I hope, prevent spread to other patients because we then knew who had this and could use appropriate infection control measures to prevent them from transmitting to others.

Maggie Fox
What else is the CDC advising people to do?

Maroya Walters
This is a product that people may have in their homes, that they may have purchased from major retailers, and so really, we would advise people to check to see if you have this product in your home. And if you do have it, just throw it away. We know that most patients who use these products probably didn't develop any infection. But if you have been using this product and you think you have an infection, whether it's in your eyes or at another site, we would advise that you tell your physician that you have been using this product when you seek care.

Maggie Fox
Dr. Walters, thanks so much for your time.

Maroya Walters
Thank you for having me, Maggie.

Maggie Fox
If you liked this podcast, which is brought to you by the One Health Trust, please share it by email or on social media, and let us know what else you'd like to hear about at owoh@onehealthtrust.org. Thanks for listening.

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