

Multidrug-Resistant MRSA, Rio de Janeiro

[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. Paul Planet. He's an assistant professor of Pediatrics at the Perelman School of Medicine at the University of Pennsylvania and at Children's Hospital Philadelphia, as well as a senior researcher at the Sackler Institute for Comparative Genomics at the American Museum of Natural History in New York. We'll be discussing multidrug-resistant MRSA in Rio de Janeiro, Brazil.

Welcome, Dr. Planet.

[Paul Planet] Hi. Thanks for having me.

[Sarah Gregory] MRSA is fairly well-known by now. We even see warnings about it on posters, on bus stops and in airports, but what is it?

[Paul Planet] MRSA is an acronym for methicillin-resistant *Staph aureus*, and basically what that means is that this kind of *Staph aureus* has acquired resistance to the antibiotic that is really best for treating *Staph aureus* (methicillin or one of its cousins like oxacillin). And the way that that happened was that it acquired a gene that makes it resistant to those antibiotics.

[Sarah Gregory] You typed 600 MRSA isolates from 51 hospitals in Rio de Janeiro from 2014-2017. Why did you do this?

[Paul Planet] MRSA is really a global problem, but it also has a really interesting pattern around the globe where different strains or different kinds of MRSA appear and disappear in sort of epidemic waves in different parts of the world. And we were working (and had been working) for some time with a group in Rio de Janeiro to try to understand what sorts of MRSA were circulating at any given time, and we had actually already seen that certain clones of MRSA (certain lineages of MRSA) were really dominant at different times in the past and we wanted to see what was going on currently because it is not always obvious just by looking at the information available from hospitals what's going on with different lineages. So we had this opportunity and this great collaboration with Agnes Figueiredo down in Rio to try to really nail down what was going on with the epidemiology of MRSA in South America in Rio.

[Sarah Gregory] And what did you find?

[Paul Planet] So we found something really interesting, something that we may have expected by the patterns that we've seen in other parts of the world. But we found that the old circulating kinds of MRSA that we had seen in previous years had been completely replaced by a new strain of MRSA (or a new group of strains of MRSA) that the old strains that we had seen circulating in infected people in hospitals were almost extinct. There was still remnants of them, but they had been completely replaced by this new MRSA.

[Sarah Gregory] You also did analysis of 200 whole-genome isolates. What did that reveal?

[Paul Planet] Whole-genome analysis gives you the ability to get down to a really fine-grained analysis of what are the actual organisms that are circulating in a given place. And it can even get you down to understanding what organisms are being transmitted and who transmitted which analysis to whom. But the reason to do whole-genome analysis here is we really wanted to understand how this new kind of MRSA that we saw emerging in hospitals in Rio was related to other kinds of emerging lineages in other places and also to the previous ones from Rio.

What we found was that many of these isolates of this emerging lineage grouped together very tightly in a phylogenetic tree, suggesting that they had been introduced to Rio in a single event and were spreading within Rio and between all of those hospitals that we had surveyed.

[Sarah Gregory] You used molecular clock analysis to hypothesize when this lineage began. First of all, what is molecular clock analysis?

[Paul Planet] Molecular clock analysis is something that has been around for a while, and it sort of relies on the information in DNA and the mutation rate to try to understand how long things have been changing. So you can use the observed differences between nucleotides—between different isolates that you get from the field—and then you can ask the question, "How long would it have taken for these mutations to have a rhythm going back then?". And that gives you this molecular clock where you can take things in the present day and work backwards to see when they probably arose.

[Sarah Gregory] And what did it tell you about the lineage expansions into Rio de Janeiro?

[Paul Planet] What it tells us is something actually a little surprising, but it also gave us a very strong sense that this lineage had come in around 2009 and had begun to spread around 2009. So it also gives us sort of a timeframe for how quickly changes can happen in the epidemiology of a strain that's becoming epidemic. So just between 2009 and by the end of our study in 2017, this clone had become the dominant clone all across Rio.

[Sarah Gregory] And then multivariate analysis showed an association between bloodstream infections and the lineage that includes the RdJ clone. Tell us about that.

[Paul Planet] Yeah, so this was something that was really surprising to me. There has always been a sense that certain kinds of MRSA may be more likely to cause disease than others. But it has been really hard to nail that down. There are clones that have been circulating in the United States, for instance, that seem to cause more skin and soft tissue infection. But we really didn't expect to find that one clone of MRSA was actually going to be more closely linked to certain clinical outcomes, and at least with the first task for our analysis here, it does seem that this new emergent clone is more likely to be found from bloodstream infections. It's something that we really need to do further studies to make sure that this is actually the case, but it has large implications for how we deal with the threat of this new epidemic and MRSA clone.

[Sarah Gregory] This clone also was better able to evade immune function. Why and how does it affect people who get it?

[Paul Planet] This is a question that we really are currently diving into. As I said, we didn't really expect that this clone would have an epidemiology that suggested that it was more likely to cause systemic infections. But when we saw that we wanted to get a first pass at how that might be happening. And one possibility, and this is also known from other *Staph aureus* research, is that *Staph aureus* has a lot of tools at its disposal for evading immune cells. And as a first look at this we looked at this clone's ability to evade human monocyte antibacterial cells in culture and it seems to live better in the presence of those cells. And we don't yet know the molecular reason for that, but it's something that we're very interested and currently investigating.

[Sarah Gregory] Okay. So this is actually pretty complicated. Can you kind of summarize and tell us again how all this leads to multidrug-resistant MRSA?

[Paul Planet] I think there are two things that are happening here. One is that there's the multidrug aspect of this new epidemic of MRSA. And then there's also the immunization. So these are two things that are incredibly important for people's health, but they also sort of exist in two different streams. The first one, the evasion of the immune system, is something that could lead to more invasive infection, worse infection, infections that are harder to control. From the multidrug standpoint, not only is this MRSA resistant to methicillin and oxacillin and other penicillin, but it's also resistant to other drugs which we often use to treat MRSA. So drugs like clindamycin—this particular strain is resistant to...many isolates of this strain are resistant to clindamycin, which is another go-to drug for treating MRSA. So this epidemic strain is really operating in two different places that are important for health.

[Sarah Gregory] And how did this happen? How did that happen that it became so resistant?

[Paul Planet] So this is a really important question with a complex answer. It's something that certainly has to do with how we use antibiotics in the clinical setting (in the community as well). But it also has to do with the use of antibiotics right across the board—so the use of antibiotics in animal husbandry and in many contexts across the world. So obviously if we're using too many antibiotics in situations that we don't really need antibiotics, we're going to select for organisms that have antibiotic resistance.

But I think another thing that's worthwhile saying is that sometimes the antibiotic-resistant isolates are...the antibiotic resistance kind of piggybacks on very successful organisms that are successful at spread for other reasons. So I think it's really important to take into account the entirety of the biology of these organisms to understand how resistance is spread. It's certainly related to antibiotic misuse, but it also is related to many other factors—worldwide travel, the ability of these strains to spread from one person to another, and many other things.

[Sarah Gregory] Is there a particular age group or gender that is more affected?

[Paul Planet] So this is another thing that we saw in our data that we really want to follow up on and was a surprise to us. We saw that this MRSA clone was much more likely to be found in the elderly and patients over 60 years old. And we also saw other clones that seemed to be more prevalent in children. Now there are a lot of reasons why this could be, and we really need to sort this out in future studies, but it was a very clear pattern that we saw in this strain in the elderly and it's worthwhile saying that MRSA infection in the elderly and in the very, very young is the most impactful and the most dangerous.

[Sarah Gregory] As we discussed, your study was done in Rio. Can this be extrapolated to the rest of Brazil?

[Paul Planet] Well, we really would like to understand how this might be extrapolated to the rest of Brazil. Rio is obviously a very big city that has many connections to other parts of Brazil, so if I had to guess I would say that it's very likely that this strain would pop up in other parts of Brazil. One of the things that is severely lacking in many countries around the world is that we really don't have very good molecular epidemiology in many places. So when we have the opportunity to do a study like this, we really are only getting a very small snapshot of things that are going on in much bigger geographical regions. But we actually even, in the limited data that we have, we have seen some of these strains pop up in other places in Brazil. So my guess is that this is a much bigger problem than just in Rio, and maybe more than just Brazil.

[Sarah Gregory] But the lineage hasn't exactly actually been found in other countries?

[Paul Planet] Not from the data that we have here. But there are strains that are close relatives that have been found in Europe and in the US even, and I think that it's going to be really important to understand the full global impact of this going forward.

[Sarah Gregory] We mentioned bloodstream infections, but what other kinds of infections does this lineage lead to?

[Paul Planet] So we've seen this lineage in many different kinds of infections. In general, *Staph aureus* can cause infection of almost any tissue in the human body. It is most likely to cause infection in skin and soft tissue. So people have things like boils or pustules—those are usually *Staph aureus*. So almost any lineage of *Staph aureus* can cause those kinds of infections and almost *Staph aureus* lineages can also cause things like pneumonia, urinary tract infection, abscesses, bone infection. In general, whenever we look at a different kind of *Staph aureus*, all of those kinds of infections are in the list. It's just in this particular case, it seems was a little bit more likely to be a bloodstream infection.

[Sarah Gregory] If it is multidrug resistant, is there a way to treat it at all?

[Paul Planet] So happily, yes. We have good, well-tested antibiotics that we can use on these multidrug-resistant MRSA strains. For instance, vancomycin is a tried-and-true antibiotic and all of the isolates that we uncovered here were susceptible to vancomycin. Linezolid was another one that would be effective against it. But the problem then is when we're treating, we just need to be able to pick the right antibiotic.

[Sarah Gregory] What happens if someone is allergic to those antibiotics?

[Paul Planet] Well, that can be a problem. And sometimes we're stuck without a good antibiotic if somebody has multiple antibiotic allergies. There are ways clinically to get around that, but many of these antibiotics—for instance, vancomycin is an antibiotic that you can only give IVs to. It needs to be given essentially in a hospital, at least at first. And with allergies, you need to take extra precaution if you are going to treat as well. So treatment becomes much more complicated with this kind of an organism.

[Sarah Gregory] Is there a way to contain this spread?

[Paul Planet] Yeah, absolutely. First, in order to contain the spread, you need to know where it is and that can lead to targeted interventions that can help decrease colonization. In general, *Staph aureus* can be spread from just person to person contact. So simple interventions like washing your hands and hand sanitizers really have an enormous impact on the ability of MRSA to spread. Also things like crowding and overall hygiene have a real impact on MRSA and its ability to colonize within a family, within a household, or even in a hospital.

In many countries that have used very strict MRSA infection measures, you see rates that are a lot lower for MRSA than you see in countries that have been more lax about controlling MRSA. Many countries in Europe, for instance, have very low MRSA rates compared to some other places. That's not only because of the interventions probably, but the interventions of, you know, isolation, hygiene, hand hygiene, make a huge difference.

[Sarah Gregory] And what happens if it isn't contained?

[Paul Planet] Well, I think we have a good example of that in our own history here in the United States where there was an MRSA strain that emerged in the late 1990s that was called USA300, and it was very good at spreading in the community. Prior to that, most MRSA had really been in

hospitals and had been not really a problem in the community. And we had really an epidemic that started around 2000 and quickly spread across the US with cases in every state, and in fact even today many of the cases of MRSA or many of the cases of *Staph aureus* infection in general are due to that uncontained strain. So I think it's really important. We're seeing, you know, this strain mostly in hospitals in Rio right now, and I think it's really important that we're proactive about containing it.

[Sarah Gregory] There seems to be a paucity of studies on these isolates in South America. Why would this be?

[Paul Planet] I think it really comes down to investment in research. And it's not just the case for South America and Latin America, it's also the case in other large, large portions of the world. There's very little known about *Staph aureus* and antibiotic resistance in African nations, for instance. There's places where we've seem to know the most (where we do know the most) about the spread of antibiotic resistance are in places that have the resources to sequence lots of different isolates. And I think it's really...this is an important wakeup call to people that we need to be studying the emergence of antibiotic resistance right across the globe and sort of bolstering research into this rather than cutting it.

[Sarah Gregory] What were the main challenges of doing this study?

[Paul Planet] There were many challenges to this study. I think one of the most important, of course, is that collecting isolates can be an extremely laborious task and Dr. Figueiredo's group in Rio really did an amazing job collecting all 600 isolates, ferrying isolates around by courier back to her lab and then doing all of the characterization that needed to be done. I also thing that one big challenge that we were able to really overcome in this study was linking the kind of techniques that we need to understand this evolution and molecular epidemiology with the reality on the ground. So we were able to, through our collaboration, really get the resources necessary to do the whole-genome analysis but also really make it relevant to something that was actually happening in hospitals in Rio.

[Sarah Gregory] You mentioned a couple surprises earlier. Do you want to recap those, and were there any others?

[Paul Planet] Yeah. So I mean I think the surprises really were the, sort of clarity that this clone was emerging in this particular case and had so clearly replaced other strains. And then the other two, really surprises were the pattern of it appearing more in bloodstream infections and in the elderly. I think one of the things that really intrigues me about the epidemiology of *Staph aureus* is this constant pattern of waves that we're currently very used to looking at epidemic waves in every newspaper every day. But I always have been fascinated by not only what makes certain epidemics rise, but also what makes them fall. And it was really interesting to see this in action over a...relatively a short period of time. And the process that we don't really understand, what is driving these certain clones to take off and what's driving their...maybe more importantly, what's driving them to leave?

[Sarah Gregory] Sort of around that same topic, what do you think were your most important findings?

[Paul Planet] I think the most important finding is that this is something that we need to pay attention to right now. This clone, what we're calling the RdJ clone (for Rio de Janeiro), is something that's clearly emerging. In fact, I would really like to know what's happening right

now with it, you know, with our studies finished collecting in 2017. We started—we've continued to collect as part of our collaboration and we're continuing to look at genomes that are even being sequenced now. But I think the urgency of this finding, that there's something emerging that we need to do something about, is really the most important finding.

[Sarah Gregory] What impact do you hope your findings have on public health? How do you hope they'll be used?

[Paul Planet] I think it's going to be really important to put in place the kinds of interventions that will stop the spread of this clone. It seems to be very good at spreading and very good at causing disease, so we really need to identify it and contain it wherever we can. I think the other important lesson from these studies is that we need to be constantly on top of this. So I would guess that there are...right now, there are other MRSA clones out there that are starting to gain traction and may be the next clone that takes off after the RdJ clone has been contained. So I think that that's really sort of the ongoing awareness, I think, is potentially the most important thing here.

[Sarah Gregory] You mentioned hand hygiene earlier. Do you have any other suggestions or just sort of list again the best ways people can protect themselves and stop the spread of this thing?

[Paul Planet] Yeah. MRSA has a very high prevalence in our community, but it is something that, you know, different studies say different things about how prevalent it is. But, you know, it seems reasonable that a prevalence around 1% in most populations is about right, maybe less than that. But what that gives us is the opportunity to perform hand hygiene, to have behavioral interventions that contain the spread of colonizing MRSA as much as possible. So those kinds of things are—so and again, I'll say it again—hand hygiene and other hygiene aspects like making sure that you don't have people in overcrowded conditions, you don't have people who are using the same towels and linens and things like that. These are things that I tell my patients, you know, to have extra care when you're cleaning your linens and don't use the same towels and things like that.

[Sarah Gregory] So, like a hotel or....? Now you're making me nervous.

[Paul Planet] Yeah.

[Sarah Gregory] Like if you stay at a hotel?

[Paul Planet] I mean, I think most linens when clean are fine to use. And in multiple studies, the major place where MRSA spreads and *Staph aureus*, in general—I think *Staph aureus* is also a problem, it's not just MRSA—but the major place where it spreads is in the household. And one of the problems we know about *Staph aureus* is that it's an extremely hearty organism. It can live on surfaces for days, if not longer than that. So keeping things clean is a really important part of the equation.

[Sarah Gregory] I have a friend who actually got MRSA at a gym just a few blocks away from where we live. Is that common? I mean, what kind of precautions in a gym should people be taking?

[Paul Planet] Well, I think people should be taking the same kinds of precaution. I mean, just thinking about the fact that *Staph aureus* can live on surfaces for a significant amount of time, so it's likely to get on the equipment, it's worthwhile mentioning that, you know, some of the earliest MRSA outbreaks that were not in the hospital, community outbreaks were in places amongst athletic teams and people who were using gyms and people in crowded situations like jails. So those sorts of places, as long as you're taking precautions—wiping things down, using

the wipes that you're given—those are the important steps.

[Sarah Gregory] Does showering like immediately after, is that helpful?

[Paul Planet] Probably. Anything that can reduce the burden. We can't completely seal ourselves off from bacteria that we come in contact with. In fact, we wouldn't really want to seal ourselves off from all contact with bacteria. They are an important part of our lives and are beneficial in many situations. But when you're talking about a pathogen, the most important thing is dose. So if you get a big dose, you're more likely to get infected. And even if you're not killing all of the MRSA by hand sanitizing, you're killing hopefully enough of it that it doesn't cause infection.

[Sarah Gregory] I see. So this is a contact pathogen. We don't get this like COVID or pneumonia or something? Though you did mention pneumonia earlier. You don't get it from aerosols or droplets or anything then, right?

[Paul Planet] No. It's really contact. But once again, it's contact with anything that humans have had contact with. It likes to live on your skin best of all, and also in places that are warm and wet parts of your skin. So the classic place is just inside your nostrils and then in your armpits and groin and places like that. That's where it likes best. But it can also live on other parts of your skin and live on surfaces for some period of time. But it's really contact, it's not at all airborne.

[Sarah Gregory] This study, as so many studies are, was a collaborative effort. Tell us a little bit about how that process works—both challenges and the joys.

[Paul Planet] Yeah. This has been a joy through and through, and also could never have happened if there was not a sort of the structure in place to collaborate. Really, the synergy between the kinds of technologies and analysis methods that we can offer and the microbiological skills of the Figueiredo lab in Rio really came together to make this much more impactful. And it's sort of a symptom of how so much of science is being done now. It's just really important to collaborate, and, you know, most of the best science I think is coming out of broad scientific collaborations. So they're using lots of different resources.

[Sarah Gregory] Dr. Planet, tell us about your job and how you became involved in this study.

[Paul Planet] So I'm a pediatric infectious disease specialist. I have an MD and a PhD in microbiology and evolutionary biology, and I have been interested for a long time in *Staph aureus* and how it evolved and what accounts for this epidemic spread of antibiotic resistance. So the way that this collaboration and this study was born was actually through a global initiative. At the time, I was at Columbia University and there was a request for funding that was put out where there were funds to do a public health project in Rio de Janeiro, and I reached out to Agnes Figueiredo. We barely knew each other at the time, but I knew that she was sort of a pioneer of microbiology in Brazil, and reached out to her and said, "Here's an opportunity for us to understand the molecular epidemiology of emerging MRSA". And the rest is this project. So it was actually having that little bit of extra infrastructure and resources (money, funding) was what really spurred this into action, and of course this has become a much larger collaboration and continue to collaborate on multiple projects to this day.

[Sarah Gregory] Well thank you so much for taking the time to talk with me today, Dr. Planet.

[Paul Planet] Thank you. It was great to be with you.

[Sarah Gregory] And thanks for joining me out there. You can read the November 2021 article, Multidrug-Resistant MRSA Associated with Bacteremia and Monocyte Evasion, Rio de Janeiro, Brazil, online at [cdc.gov/eid](https://www.cdc.gov/eid).

I'm Sarah Gregory for *Emerging Infectious Diseases*.

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