Clare : Hello and welcome, I'm Clare and you're listening to Microbe Talk, the podcast by the Microbiology Society. Our final podcast to finish a year of interesting discussions, insightful collaborations and exciting new research, is a conversation on antimalarial drug resistance.

In this episode of Microbe Talk I spoke to Adam Aspinall who's Senior Director in the Access and Product Management team at Medicines for Malaria Venture. Keep listening to find out more about Malaria, Antimalarial drug resistance and the work that Medicines for Malaria Venture is doing to support new drug discovery.

Adam: Hello, my name's Adam Aspinall. I work for Medicines for Malaria Venture in Geneva, Switzerland, and I'm Senior Director in the Access and Product Management team.

Clare: Perfect, and good place to start with me. Could you explain what Medicines for Malaria Venture is, who they are, and what they do?

Adam: Sure. Medicines for Malaria Venture, or MMV for short, is what's called a product development partnership. And they were set up essentially to address a market failure because for many neglected diseases there's no incentive for pharmaceutical companies to develop new drugs because in the case of antimalarials, for example, they cost a penny a bucket full. They're not very profitable compared with many of the newer drugs that come along. And so we take donor funding and we apply it to reduce the risk for pharma companies to develop new drugs.

Adam: And typically, that might include funding development studies up to Phase 2, or in some cases, Phase 3. And in return for that, the pharma company will agree to commercialize the product wherever it's needed at a no-profit, no-loss basis.

Clare: So we're here to speak on a topic that actually has a bit of crossover between the Microbiology Society and our Knocking Out AMR project and the work that MMV is working on, specifically antimalarial resistance. So, I suppose actually just starting off with, what is antimalarial drug resistance would be a good question.

Adam: Sure, that's a good question to start off with.

So malaria is caused by the *Plasmodium* parasites and the most common type of parasites, *Plasmodium*, found in Africa, is the *Plasmodium falciparum* parasite, and that's also the one that causes the most severe disease.

Adam: And the thing about *Plasmodium*, for tiny organisms, they're incredibly clever. And they're very good at finding loopholes in the defenses of antimalarials. And so the one certainty with antimalarial, similar to antibiotics, is that eventually they'll find ways to evade the effectiveness of antimalarial drugs. And when that happens the drugs start to fail and we have a problem on our hands.

Clare: So obviously malaria is caused by a parasite. Is antimalarial drug resistance different and the way that you approach it and treat it is it different to how you would perhaps approach antibiotic resistance for example?

Adam: I think there are many similarities and many parallels. Essentially, you have to make it harder for the parasite to evolve resistance by exposing it to, for example, to different drugs, perhaps with different mechanisms of action.

Adam: And there are other procedural approaches you can use as well such as diversifying drug use as well as obviously developing drugs with new mechanisms of action and using those which perhaps haven't had so much use in the past.

Adam: We repurpose, we look at combining different drugs to try and stay one step ahead all the time. So in that sense, I think there are many similarities between antimalarial resistance and antibiotic resistance.

Clare: At the moment, what is the sort of state of play with antimalarials? How many are there? What's access like in the places that need it? What's the sort of current sort of situation, I suppose?

Adam: So right now, the gold standard of treatment and the recommended treatment from the WHO are the artemisinin-based combination therapies or ACTs. And, at the moment, there are six approved ACTs. And these have been in use since the early 2000s. The issue we have with the current antimalarials is that although there are six approved ACTs, in most African countries, in particular, 80% of ACT use is in the form of one drug, which is artemether-lumefantrine, or AL.

Adam: And that means effectively, many countries have all their ACT eggs in one basket. And that really is an issue, because if you start seeing resistance to AL and they don't have other drugs currently approved at a country level, then they have a real issue and a big threat.

Adam: In terms of access, generally ACT access is pretty good. Funding is always an issue and by the very nature of the countries that most of these drugs are used in, funding is a problem. The donor organizations such as The Global Fund and the President's Malaria Initiative do fund the majority of ACTs use in the public sector, at least in Africa.

Clare: And I suppose that actually brings me quite nicely on to my next question. There's a worrying rise of antimalarial drug resistance. What can be done? What can organisations like MMV do to tackle this?

Adam: Yeah, well, I think everybody in the global malaria community is really concerned about the current situation. There are a number of things that we can be doing. The first thing to say is that the WHO did introduce its strategy to respond to antimalarial resistance in Africa in 2022.

And that contains four key pillars, and it covers everything from research and development to how to use the current tools to repurposing existing medicines.

A couple of examples of things that we're involved with: a key part of the response right now is to diversify ACT use, which means using other drugs, not just artemether-lumefantrine, which is the gold standard.

We have newer drugs such as DHA piperaquine, for example, and Pyramax. These have a relatively low drug pressure and they certainly have a place. The reason they haven't been used more widely up till now is because they're a bit more expensive. But using the newer drugs and finding funding for them is definitely part of the picture.

And there's an approach called multiple first-line treatment, which is a very interesting approach to diversifying drug use. It assumes that you have more than two first-line antimalarials available in a country or in a population simultaneously. And that makes it harder for the parasites to evolve resistance. And MMV has funded the first two large-scale pilots of MFT, one in Kenya and the other one in Burkina Faso. Both took different approaches. In Kenya, they used a rotational approach. So, in other words, rotating drugs every year or so. And in Burkina Faso, they stratified drug use. So patients under five got one drug, everybody over five got a different one, and pregnant women got a third drug. And the takeaway from those pilots was that operationally, MFT was a feasible intervention, and it could be done. So that's one approach.

A second project that we're working on at the moment with our partners in MORU in Bangkok, and Fosun Pharma and Marubeni, is to develop a triple ACT. And that's where you have the artemisinin component paired with two partner drugs instead of one. Again, to make it harder for the parasites to evolve resistance. The most advanced of these at the moment is AL plus amodiaquine and that's just about to start in Phase 3 studies early next year. So that's triple ACTs.

But ultimately, if you're concerned about artemisinin resistance, then the best solution is to have non-artemisinin-based combinations. And so, we're working with our partner Novartis to develop a drug called ganaplacide, which is paired with lumefantrine. And that's in Phase 3 right now, and it's looking very encouraging. We just have some early results which show that it's at least as effective as artemether-lumefantrine. And this could be a really key tool in the fight against resistance.

Clare: You mentioned drug pressure there. Could you explain what that is?

Adam: Yeah, well when you've got a drug that's been used for a long time such as artemether-lumefantrine, there's a huge amount of this drug used and it's easier for the parasite to evolve resistance against it. When you've got drugs that have had very little use, relatively speaking, such as DHA-piperaquine, for example, then it makes it harder for the drug to evolve resistance and they can potentially be more effective.

Clare: So you kind of, I suppose, covered creating new antimalarials there and you've also covered, I suppose you'd call it like stewardship, I suppose, of the drugs that you have already, ensuring that there's not too much of a reliance. Are MMV involved in any other sort of interventions in sort of drug resistance.

Adam: No, stewardship is a great word. And it's a really important one when you're faced with this fast-evolving resistance landscape. You have to use, until you have new drugs available, you have to make the most of what you've got. Part of it is looking at how you can be more efficient with what we have right now. And I think the triple ACTs are a great example of how you can put together two existing drugs to come up with something that's more efficient.

Adam: But there are other things that we can do too. One of the WHO recommendations currently is that in areas of resistance, one approach is to block transmission using a drug such as primaquine, for example. Adding primaquine to an ACT so that every patient who's treated for malaria gets a transmission-blocking agent is really low-hanging fruit. It's something that every country can be doing.

Primaquine is really cheap. It's easy to use. I think one of the problems in the past is that there haven't been a lot of WHO prequalified versions of primaquine in the right doses and there hasn't been a child friendly formulation. That's actually changing now and we're also working with one of our partners Fosun Pharma to develop a co-blister ACT plus primaquine which will improve compliance and make it much easier to prescribe.

Clare: And when you mentioned reducing transmission can you explain what you mean by that how the drug does that?

Adam: Sure so if you're bitten by a mosquito which is infected with the *Plasmodium* parasite, that will inject the parasites into your bloodstream they will multiply. If you're then bitten by another mosquito those parasites are transmitted to that mosquito which then pass them on to another person locally. So, if you can break that cycle by blocking the transmission, then it makes it much easier ultimately to achieve elimination.

Clare: Interesting. Yeah, makes perfect sense. Would you say that there's potentially limitations in things like infrastructure and healthcare structures and things like that in particular areas that could be improved and could help the work that MMV is trying to do?

Adam: There's always limitations in most lower- and middle-income countries. And even in some of the higher-income countries, we've seen that healthcare systems are always creaking under the strain. So there's a need for improved regulation and helping strengthen local regulatory agencies in particular. One of the other things that does concern us, and which also plays into the whole area of resistance, is the availability of falsified and substandard medicines. Because if you have an antimalarial that only contains, for example, 20% of the active pharmaceutical ingredients, that in itself can induce the development of resistance. So preventing entry into the supply chain of falsified and substandard medicines and improving medicines quality is really key.

Adam: And part of that will happen through strengthening regulatory agencies, improving detection technology, making it more affordable and increasing training.

Clare: Yeah, yeah. The multi-pronged approach is always something that comes up a lot. It's cross-disciplinary, it's multi-pronged and that's I think the way that you can almost sort of spread your bets and make sure you're covering sort of every angle.

Adam: There is something else we can do as well yes and this is this is really important. In order to make sure that people finish the full course of treatment which of course is essential if you're trying to mitigate against the development of resistance, the shorter the duration of treatment and the less tablets they have to take, the better when it comes to increasing compliance.

So one of the key parts of our strategy is to develop drugs that ultimately, we hope, will just be a single-dose cure. So you could take one tablet and that will be the cure for malaria. Right now, if you're using AL, patients have to take that twice a day for three days. And we know from the studies that have been done that compliance is at best suboptimal and at worst really poor.

Adam: So anything we can do to shorten the duration of treatment, so one day, two days, ideally single dose, is a big part of that. And at the same time, we have to make sure that the drugs we develop are both palatable and easy to take. And so child-friendly medicines, particularly antimalarials, are really, really important. In the past, adult tablets tended to be crushed with the back of a spoon and given to kids. The problem there is they're incredibly bitter. And so the kids would often vomit or spit out at least part of the drug. And that means, again, they're vulnerable to the emergence of resistance.

Clare: That's really interesting. That's an element that I hadn't quite considered before. How has the vaccine changed the way in which we can tackle antimalarial drug resistance?

Adam: Yeah, we think vaccines are a really important addition to the armamentarium and we certainly welcome their introduction. Right now, there are two, RTS,S and R21, and we think that they really will change the paradigm as they become more widely available. They're not without their limitations. Right now, one of the problems is they have to be given monthly. For example, there is a cost attached to them, which in many cases is higher than the cost of treatment. There's also an issue at the moment with the supply availability, which is not infinite. But in the fullness of time, I think these are going to become really important. At the moment, we have this jigsaw of interventions such as the vaccines. We have chemo preventative interventions such as seasonal malaria chemo prevention. We have the treatments.

And of course, we have vector control, which is an incredibly important part of the mix. And as we get the new generations of vaccines coming along and the costs come down or the supply goes up, I think they're going to be an incredibly important part of the mix.

Clare: I wanted to specifically ask about the product development partnership model that you explained earlier. What is it specifically that means that it's more effective or has perhaps a broader reach, I suppose?

Adam: Sure. Well, I think the obvious starting point is that in many cases, the drugs wouldn't be developed unless a PDP was encouraging their development, because for for-profit companies, there's very little profit in developing new antimalarials. So I think PDPs play a really essential role in encouraging the development of new drugs. And we have expertise in the field that pharma companies can leverage, and we put that together with the facilities that our partner companies have. And it's a really winning combination.

In fact, studies have shown that for every dollar that's invested in a PDP, that's equivalent to around $3 if a pharma company was having to invest that money itself. So it's a very cost effective way of developing drugs.

Clare: Interesting. I think that's well encapsulated the current sort of situation with regards to antimalarial drug resistance. I've got my final question if I may. In an ideal world what would you like to see happening in the next five years, next 10 years to kind of support the work that MMV are doing, the work that you guys are doing in kind of tackling this issue? What changes would you love to see?

Adam: Well I mean the obvious question is the one about funding. Funding is always limited. We're all facing, I think, a big squeeze post COVID. There are some uncertainties with recent political developments about how that's going to affect funding as well. So increased funding is really important.

I think what we've seen from other disease areas is the closer you get to elimination, the less funding becomes available because governments look at it and think, ah, they don't need any more funding because they're almost there. And of course, that couldn't be further from the truth because it's that last mile which is the most important. Because if you can't eliminate those last few parasites, for example, you're not going to eliminate the disease. So funding right up to the end is critically important. So if there's one thing I would hope for over the next five to 10 years, it's a stabilisation of the funding situation. Our biggest funder, which is the Bill & Melinda Gates Foundation, is doing incredible work in funding not just malaria, but other disease areas too.

We have many other very committed funders, but everybody's facing the same pressures at the moment and funding is always going to be limited.

Clare: Yeah, I've teased you, there's one more question, sorry. Our listeners are obviously microbiologists, is there anything you'd like to direct them to in terms of resources or anything that they can do to potentially sort of get involved and raise awareness? Any suggestions?

Adam: No, with pleasure. Our website is mmv.org and on that website you'll find a whole bunch of resources, not just about the disease area, but also on specialist part of it, such as, for example, severe malaria. We have the Severe Malaria Observatory and many others as well. And we'd be delighted to have them visit.

Clare: Brilliant. I'll pop that in the description for this podcast. Adam, it's been an absolute pleasure. It's been really interesting to find, pick your brain and get your insights on such an important topic that needs to be discussed. Yeah, it was really lovely having you. Thank you very much.

Adam: Thank you so much.

Clare : Thanks again to Adam for his time and thank you for listening. Youve been listening to Microbe Talk. If you liked this episode, please leave a like or a comment wherever you're listening.