If we can beat Ebola, why not sleeping sickness too?

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The man sits on the edge of the bed, feet touching the floor but incapable of supporting his weight. He doesn't speak and his eyes stare vacantly ahead, despite the eight or ten people who have crowded in to see him. His mother stands nearby, beside herself with despair. He's had these symptoms for a year, she tells us. His brother has to carry him on his back at home in their village.

His name is Ibrahima Sory Camara, and he's in a sleeping sickness clinic in Forécariah, a town in Guinea, West Africa. Camara may be experiencing many other symptoms that he can't tell anyone about: sleeping sickness can also cause headache, severe itching, apathy, aggression, confusion, insomnia at night, and in the day the overwhelming desire to sleep that gives the disease its common name.

If left untreated, the disease is almost invariably fatal, as the parasite that causes it eventually reaches the brain. But severe cases are rare in Guinea these days. The number has fallen dramatically since the 1990s, thanks to a national programme to catch infections early and to control the flies that spread it. But it seems impossible to get the number all the way to zero – and no one knows why.

Guinea is constantly fighting disease. It was here, in 2013, that the first known victim of the Ebola outbreak died, a two-year-old boy. The ensuing epidemic spread rapidly through the country and its neighbours Liberia and Sierra Leone, eventually killing more than 11,000 people. Guinea was declared Ebola-free in 2016. Yet sleeping sickness, a disease

that killed millions in the 20th century, lingers on – as does the threat of a new epidemic. Why?

I met Camara earlier this year when I went to Guinea with a group of scientists who think they may have the answer to this conundrum. If their theory is correct, it would fundamentally change our understanding of this disease. It might explain why sleeping sickness is able to cling on despite the national programme's best efforts. And it could even lead to a paradigm shift in tactics as Guinea tries to eliminate sleeping sickness for good.

It's 6am on a warm May morning and I am waiting for the sunrise and a truck to take me to Missira, a village on the Guinean coast. I'm travelling with a team from the national programme fighting sleeping sickness – they've been visiting villages in the area for the past two weeks and this is their last day in the field.

We bounce along rust-red roads, stopping only to pick up some bread along the way. Since gaining independence in 1958, Guinea has retained some French culture, not least its official language and a love of freshly baked baguettes. We pass many bikes and motorbikes on the early-morning roads with loaves sprouting out of their panniers. These, along with a cup of instant coffee and a bit of cheese, are the basis of our breakfast when we finally reach Missira around 8am.

I learn later that another name for sleeping sickness here translates as "the sickness at the end of the track" – and Missira is literally at the end of the track, for the road leads straight to the edge of the Atlantic Ocean. We're close to the mangroves where people hunt, fish and grow crops. Mangroves are also home to tsetse flies, which carry the sleeping sickness parasite and whose bites are the source of all human infections. And that's why we're here today – to test everyone in Missira for signs of the parasites in their blood.

The team – 10 or 12 scientists, health workers and local representatives, all but one from Guinea – get smoothly on with setting up for the day. Tables form stations for every stage of the process: registration, then a finger-prick to take blood, the test itself, and somewhere more private for a consultation with the nurse if the test is positive. Here, the nurse will check for swollen lymph nodes in the neck, before they take more blood to try and spot parasites wriggling about under the microscope.

These field tests aren't perfect, although they are relatively accurate considering they can be done anywhere there's a power source (a car battery is enough). But not everyone who tests positive will actually be infected. Some will be false positives, while others may have antibodies to the parasites – which are what the test detects – but not any actual parasites in their blood. So anyone who tests positive today will be invited to the clinic in Forécariah for more tests and only then – if required – receive treatment.

This approach, which is how Camara was diagnosed a few days ago, is called active surveillance. Unlike passive surveillance, which relies on having the capacity to diagnose and treat people who come to a health centre with symptoms, active surveillance means regularly testing everyone in specific areas. In other countries, when cases of sleeping sickness have fallen to similarly low levels, the World Health Organization (WHO) has recommended that passive surveillance is enough. But the man in charge of fighting sleeping sickness in Guinea wants to keep throwing everything he can at the disease because he knows what will happen if they step back before it has been eliminated.

Mamadou Camara, no relation to Ibrahima, is a biologist and director of Guinea's programme against sleeping sickness. He tells me that the disease has been recognised as a major problem for decades.

It killed millions of people in the 20th century, in a series of devastating

epidemics as well as the slower, persistent death tolls of endemic disease. In the 1940s, the number of reported cases across Africa was around 50,000 a year, with the real number likely to have been much higher. By the end of the 1960s, after sustained internationally supported efforts dropping insecticide from aircraft to kill the flies, and culling wild animals suspected of harbouring the disease, cases of sleeping sickness fell to just 5,000 a year.

But leaving that small foothold for the disease proved a disastrous mistake. By the 1990s, cases of sleeping sickness had soared back almost to the levels of 50 years earlier. Was there something we hadn't understood about this infection? And will that same gap in our knowledge stop us eliminating sleeping sickness this time around, too? A 2017 Lancet article says that neglecting sleeping sickness, "either because of social or political instability or the tyranny of success, will inevitably lead to resurgence".

Active surveillance has been enough to get rid of the infection in many countries and regions since the 1990s. But in three small areas of Guinea, including the villages around Forécariah, the disease just won't die out. The national programme here now includes vector control – targeted ways to trap and kill tsetse flies – which has helped, but there always seem to be a few more cases cropping up. Since 2004, there have been between 50 and 100 reported cases a year in Guinea. There was a dip to 33 in 2014 and just 29 in 2015, but this was due to under-reporting during the Ebola epidemic. In 2016, after the end of Ebola, 107 cases were reported – the highest for 13 years.

Camara says the disease is back under control now, thanks to the actions of his team, the ministry of health, and the international partners who provide resources for surveillance and vector control as well as funding research to better understand the parasite and how it spreads.

Jose Franco is the WHO's Medical Officer for the Department of Control of Neglected Tropical Diseases. He says that, although it can be hard to keep pushing when cases fall so low, it is not the number of cases being treated that should be counted but "the number of cases you are avoiding".

"You are always working," he explains. "Detecting cases, treating them, and complementing in some areas with vector control… In some countries, they are not detecting cases for some time, they have a good health system, then in these cases we are now working more in setting up a surveillance system, mainly based on passive screening.

"We have to adapt these strategies according to the evolution of the disease and the evolution of the country."

The WHO's current aim is to eliminate the disease in 80 per cent of endemic areas by 2020. In this instance, "elimination" is a technical term, meaning transmission is so low that it is no longer a public health problem in the country. It doesn't mean there are zero cases – and this worries Camara, because he knows that history shows it can always come roaring back.

So as well as active surveillance and vector control, Camara is a big supporter of more scientific research into sleeping sickness, to figure out why it is clinging on in Guinea, and whether a change in approach could help them make further progress – and, maybe one day, eradicate it altogether.

Somewhat surprisingly, there are no positive results in Missira today, meaning no one has to come back to the clinic for more tests. Over the fortnight that the team have been testing villages around Forécariah, around 25 people have been invited to go to the treatment centre in town. They will all arrive there tomorrow for further tests, and treatment if

they need it. While they are there, if they are willing, they can also take part in research to test a new hypothesis about sleeping sickness and just why it is proving so stubborn in Guinea.

Annette MacLeod is a Wellcome Senior Research Fellow at the University of Glasgow. She's been investigating the parasites that cause sleeping sickness, called trypanosomes, since her PhD. She says she always found bugs fascinating – "disgusting and beautiful at the same time" – but it's the potential to use science to rid people of this infectious disease that attracted her to the field.

"An infectious disease can be cured," she says. "Whereas an inherited disease, it's a lot more tricky to actually do anything."

But sleeping sickness has proved trickier than she expected: "Now we're realising that it's a lot more complicated and you can't just look at the pathogen on its own. It's very much about the whole parasite interaction and how we can interfere with that to combat the disease."

Trypanosomes have co-evolved with people and tsetse flies for thousands of years. They cannot proliferate without spending some of their life cycle in humans and some of it in flies, switching between species when the flies bite people to take blood meals.

Based on what we know, however, sleeping sickness should have died out long ago.

Most people who are diagnosed with sleeping sickness have a very low concentration of parasites in their blood. And when a tsetse fly feeds, it will slurp only a tiny drop. So, most of the time, a fly wouldn't ingest any parasites from an infected person. Mathematical models – based on how many flies there are, how often they feed and so on – show that sustained transmission of trypanosomes ought to be impossible.

And yet people continue to get infected. How can this paradox be explained?

A new clue came from MacLeod's longtime collaborator, Bruno Bucheton, a French scientist based in Guinea who has previously been stationed in Sudan and Burkina Faso working for the Institut de Recherche pour le Développement. Working closely with the active surveillance teams in Guinea, he noticed that there were a surprisingly high number of false positives.

Of course, this could have been due to a lack of accuracy in the field test – the rarer a disease gets, the lower a test's predictive power will be, because false positives start to outnumber true positives. But because the team were testing the same people repeatedly over a number of years, Bucheton was able to track everyone who got a presumed false positive result. About a third of them tested negative the next time, as expected. However, another third went on to develop sleeping sickness – so maybe the earlier test had been right, but the concentration of parasites in their blood had been just too low to be detectable.

Even more interesting were the final third, who consistently tested positive for antibodies despite having no discernible parasites in their blood and never showing any signs of the disease. Why would their bodies produce antibodies if there weren't any parasites?

MacLeod tells me of a case in the UK, a man from Sierra Leone who had not been back for nearly 30 years when he suddenly developed sleeping sickness. He must have harboured some parasites undetected, without any symptoms, for decades. If a significant number of people were infected with hidden parasites like this, could they be acting as a reservoir for the trypanosomes and tipping the mathematical equations back in favour of transmission?

There was a problem with this hypothesis, though: how could these people be transmitting trypanosomes to flies if they didn't have any in their blood? The answer, according to MacLeod, is that we should have been looking elsewhere.

"You need to understand how the tsetse fly feeds," she explains. "They're like flying chainsaws – they've got serrations all down their mouth parts, and they probe up and down and kind of mash up the skin and then suck on the flow of blood and lymph, interstitial fluid and everything that's there."

So the parasites don't necessarily need to be in the blood to be ingested by the fly – they could just as easily be in these other fluids or, as MacLeod and Bucheton thought, in the skin itself.

In hindsight, this wasn't such a radical idea. People with sleeping sickness often experience intense itching on their chests and backs – old textbooks show pictures of people who have scratched their skin raw as a result. One historical reference MacLeod found even said that sleeping sickness was "primarily a skin disease". But in an age of genetics and blood tests, most researchers seem to have lost sight of this side of it.

So what would it mean, practically, if this hypothesis is true? Well, if you can have a trypanosome infection in your skin without any discernible parasites in your blood, it would mean thousands of people across Africa have been told they are clear when they are, in fact, infected and could be passing the infection to flies and then on to other people. It could even mean that all of these people would have to be treated too if we want to stop transmission of the disease once and for all.

Experiments with mice showed that parasites in the skin could indeed be transmitted when flies fed, but MacLeod, Bucheton and their colleagues

needed to find out if there really were people who had parasites in their skin and not their blood. To do that, Bucheton invited MacLeod to Guinea.

Before she could go, however, she needed to wait for an outbreak of another infectious disease to die down, and for its effects to be repaired. This other disease was Ebola.

I've heard conflicting accounts of what happened outside the village of Tanéné at the end of May 2015. What's agreed is that a woman from Tanéné was suspected to have Ebola. Whether she was living there or travelled back there in the dead of night is unclear. Either way, when the authorities went to investigate and, if necessary, take her to an Ebola treatment centre, young men from her village – probably including her brother – objected and tried to turn them away.

Mamadou Leno, nicknamed "Blo" because he sometimes blows his top like a volcano, tells me he was caught up in the violence. Blo is well known in the area – a lab technician, he is also a social mobiliser for the sleeping sickness programme, working with the community to emphasise the importance of participating in active surveillance. But 18 months into the Ebola outbreak in Guinea, Blo – like practically every other health worker in Guinea – had been commandeered for the new fight against Ebola. Part of his job was checking out suspected cases.

As he approached Tanéné on 31 May, he was met by a group of men. They knew exactly who he was, and why he had come, and they were not there to give him a warm welcome. Despite improved public health information about the epidemic, many people in Guinea were still scared and suspicious, particularly in areas like Tanéné where Ebola had not yet struck. All that these young men knew was that when someone was taken to an Ebola treatment centre, they usually didn't come back, either alive or dead.

In a culture where burial rituals are supremely important, rumours of blood and dead bodies being sold were taken seriously, and had fuelled attacks on health workers early on in the outbreak. The first treatment centre built by Médecins Sans Frontières was attacked within a week, and eight Ebola workers and journalists were killed in the village of Womey in September 2014.

Blo knew he was in trouble when the men started banging on his car. He got out and tried to run for it, but they caught him, beat him and dragged him back to his car. They set it on fire, intending to burn him inside. The only thing that saved him was the women from the village, who persuaded the young men to stop. He was in hospital for two months, during which time he was visited by national radio and TV. When they asked him if he would dare to go back into the field, his response was simple: "I'm a health agent. I'm here to help people. So yes, I'm going back."

Indeed he did, and when the Ebola epidemic was declared over in 2016, he rejoined the sleeping sickness team. Their work was harder now, though: Ebola and the discordant relationships between the government, health workers and communities were still fresh in people's memories. According to Blo, it was the vector control teams who saved the sleeping sickness programme. When these teams went to the villages, carrying the blue and black traps and targets used to lure tsetse flies, people could see they were not the same as the Ebola teams. People would then help to clear roads and tracks so the team could reach the tsetse fly habitats amid the mangroves.

The screening team have been careful to maintain that trust, dispensing with lab coats and making an extra effort to engage people in advance. A specially written play to raise awareness of sleeping sickness was performed a few weeks before surveillance started, and one or two team members go ahead and stay in each village the night before the rest of

the team are due – this means they are able to reinforce the message that as many people as possible should stay in the village and get tested.

Facinet Yansané is one of those who was tested and found positive. Now he has come from his home on an island to have the follow-up tests. The most important is a lumbar puncture to see if there are any parasites in his spinal fluid. If there are, he'll be diagnosed with stage 2 sleeping sickness and given immediate treatment.

Then, whether he's diagnosed with sleeping sickness or not, and if he is willing to help test MacLeod and Bucheton's theory, a dermatologist will take a small chunk of skin out of Yansané's upper back so that they can look for any parasites hiding there. MacLeod has promised that she will dance a jig if they find any parasites in people's skin. The stakes suddenly got a lot higher.

The treatment centre in Forécariah was built specifically for sleeping sickness. However, as the number of cases fell, its use was extended to include leprosy and tuberculosis as well. In 2014/15, it was requisitioned to become an Ebola treatment centre instead. On the ground, I see discarded laminated instructions for how to put on the yellow protective suits that healthcare workers had to wear. There are still scraps of the orange plastic netting used to isolate patients – apparently it is so iconic of the epidemic that it can't be used for anything else in Guinea any more.

It's a stark reminder that sleeping sickness is just one of many life-threatening infections that people in Guinea have to live with.

Sakoba Keita was the national coordinator of the Ebola response. He tells me that people stayed away from healthcare facilities during the epidemic because of rumours that that's where you got infected. He says the percentage of people accessing the healthcare they needed fell from

70 per cent before the outbreak to just 30 per cent. Micaela Serafini from Médecins Sans Frontières says more people died because of the impact of the epidemic on other conditions than died of Ebola itself.

While MacLeod and the others wait for the skin biopsy samples to be prepared for inspection, I meet Ibrahima Sory Camara again. After just a few days of treatment, he is walking, albeit at a slow shuffle, making tentative eye contact and speaking in a low whisper as if rediscovering his voice. His mother is now beside herself with relief and gratitude.

A few years ago, the treatments for stage 2 sleeping sickness were pretty bad. One of them contained arsenic and had a 5 per cent chance of killing the patient before it cured the disease. A new combination of drugs called NECT is much safer and more effective. NECT, which combines a previously used intravenous drug with an oral tablet, was launched in 2009 by a partnership including the Drugs for Neglected Diseases Initiative (DNDi) and Médecins Sans Frontières. It is now used to treat all stage 2 patients in West Africa, thanks to drug donations from the pharmaceutical companies Sanofi and Bayer.

But the treatment is still complicated enough that people have to stay in the clinic for 10 days to receive it. If the skin hypothesis turns out to be true, and it's decided that anyone who tests positive should be treated even if they don't have parasites in their blood, this treatment regimen would be a massive hindrance – people just won't want to come to hospital for 10 days, not working, not earning money, to be treated for an infection that isn't bothering them.

A treatment that could be given just in pill form would revolutionise the way the disease is dealt with. More people would be encouraged to attend screening if a positive test simply meant taking pills. DNDi and others are working on developing new sleeping sickness drugs, and in October 2017 DNDi researchers announced that an effective oral

treatment is in the final phase of trials. They are also working on what they hope will be an even simpler, single-dose treatment.

These new drugs might even make it practical to treat those who tested positive only to the field test – often referred to as "seropositive" people – in case they have parasites in their skin.

Even so, Jose Franco at the WHO is sceptical about the need to change the policy. "In some areas, yes, you could do that. Difficult access, areas with insecurity, you don't know when you will be able to go again – yes, in these areas it could be interesting to treat seropositive people. But as a general rule, now I will say not."

MacLeod and Bucheton think everyone with a trypanosome infection should be treated, whether it is in the blood or in the skin. But first they have to find out whether seropositive people really can have a skin infection without any evidence of parasites in the blood.

Back in the lab in Forécariah, there are problems with the microscope slides. Nono-raymond Kuispond Swar, a pathologist from the Democratic Republic of the Congo, the country with the greatest number of sleeping sickness cases, has been overseeing the skin biopsies as well as preparing the slides. It's been a juggle, and other small setbacks have slowed things down even further.

Now it's our last night here – tomorrow the last few people come for follow-up tests and then the team will pack up and head back to the capital, Conakry. Mamadou Camara has come to see how things are going and there's even a party arranged for tonight, at which everyone wants to see MacLeod's victory dance. So on every front, time is running out – and, just to add to the tension, a storm is approaching.

As thunder cracks outside, MacLeod is in the lab, helping with the

staining, and watching in frustration whenever Kuispond goes to the microscope. She's getting nervous that they won't have time to look properly for trypanosomes in the skin here and will have to wait until they are back in Glasgow. Her hope was to get a quick look so that if they did see trypanosomes in the skin of seropositive people here in Forécariah, they could be treated right away. If they don't even get to look, those people will be off home and potentially spreading the infection to their neighbours.

Each biopsy has been rolled gently over a slide so that some of the skin cells – and any parasites – are transferred onto the glass. Then they are treated with fixers and stains, every step involving more waiting.

It starts to rain, and in the humid conditions the slides need even longer to dry. At one point, a gas camping stove is brought out and the slides are balanced near the flame in an attempt to speed things along. As we huddle round the little stove, MacLeod comments that it feels absurd to have come all the way to Guinea just to watch slides dry.

Night falls as fast as it always does, and the waiting continues. Kuispond does take the slides to the microscope once, only to declare that they are still not ready. MacLeod is on tenterhooks but also knows that they can't risk losing these precious samples. It would be awful to have taken little chunks out of people's backs only to waste their contribution by rushing.

"They must be dry by now," she says at one point. Kuispond only sighs in response. Reluctantly, the effort is adjourned for tomorrow, but how much time they will have then is not certain.

The hunt begins in earnest the next morning, but it's full of false alarms, as if everyone looking down the microscope has begun to see what they want to see more than anything. Trypanosomes come in two forms depending on where they are in their life cycle, but essentially they look

like tiny worms, thin single cells with a tail – a flagellum – at one end that keeps them always on the move. In textbooks, they easily stand out from other cells, but here it's proving to be like an especially hard game of Where's Wally? – if Wally was a microscopic parasite.

Whenever someone thinks they've seen one, another member of the team comes running to verify the possible sighting. The news is never good.

10.38am: "Where?" "Straight in front of you." "No, it's too small."

10.47am: "Are you talking about that thing right in the middle?" "Yes, sometimes they are more…" "No, I couldn't see that."

11.46am: "Well?" "Voila. But… too short."

4.18pm: "No flagellum." "OK."

4.25pm: "Tell me what you see." "It's curved, it's like a crescent-shaped cell and it looks like it's got a flagellum and – let's have a look and see what the others think. I'm not sure it's the right size."

MacLeod has finally got onto the microscope. She knows Kuispond's painstaking approach is the right way to examine slides, but she has been desperate to just have a quick scan of all of them to see if there are any obvious trypanosomes. And now, with Kuispond in the other room supervising one final biopsy and with just minutes to go before everything has to be packed up ready to leave, she thinks she has seen one.

The first person to arrive is Oumou Camara (no relation to the other Camaras in this piece), a Guinean PhD student who has spent all day poring over the slides with Kuispond. She positions herself at the

microscope and nods. She turns to MacLeod. "I think," she emphasises, "it's a trypanosome."

Mamadou Camara is next in the room. "Annette found it?" he asks, delighted. He looks and gives a big thumbs-up. He hugs MacLeod, who does a little jig to celebrate. Mamadou goes off to get Bucheton and the others. They all agree – it's definitely a trypanosome.

"I told you Annette would find it," says Mamadou, and he slaps a 10,000 franc note (worth about £1) into her hand. "I didn't know there was a reward!" she says, and does another little jig.

"This is what we've been building up towards for a few years now," MacLeod tells me a few minutes later. "It's just fantastic to be here and see it down the microscope."

Had she been worried they'd have to leave without seeing a trypanosome in the skin?

"I really thought that. But no, I was really pleased to find it. Relieved. It means it was all worthwhile. I felt a bit guilty when I saw people going around with big patches on their back where they'd had the skin biopsies. I was thinking, 'Have we done this for no reason? Just chasing something elusive?' But now we have confirmation."

Spurred on by the discovery, the team arrange to have a microscope brought to the hotel in Conakry, so they can keep looking in the time they have before flying home. The floodgates have opened and they are identifying trypanosomes in almost every sample, in both diagnosed patients and undiagnosed seropositives. This is extraordinary because the biopsies are just 2 mm wide and the slides just superficial touch preparations. To find at least one on most of the samples they look at indicates that these people have significant numbers of trypanosomes in

their skin.

We left Guinea knowing that the findings would still have to be confirmed in Glasgow by more advanced microbiology techniques. Now, the team are preparing to publish their findings in a peer-reviewed journal. But what they saw strongly suggests that the skin really could be at least as important as the blood when it comes to diagnosing sleeping sickness and understanding how the disease is spread.

It may take time to convince the WHO and other global health policy makers, but if national plans don't take account of this finding, there may always be thousands of people living with the risk of this potentially fatal disease.

If the policies evolve, however, it might just be possible to eliminate sleeping sickness for good.