Close research partnership with African scientists helps solve mystery of malaria-like illnesses

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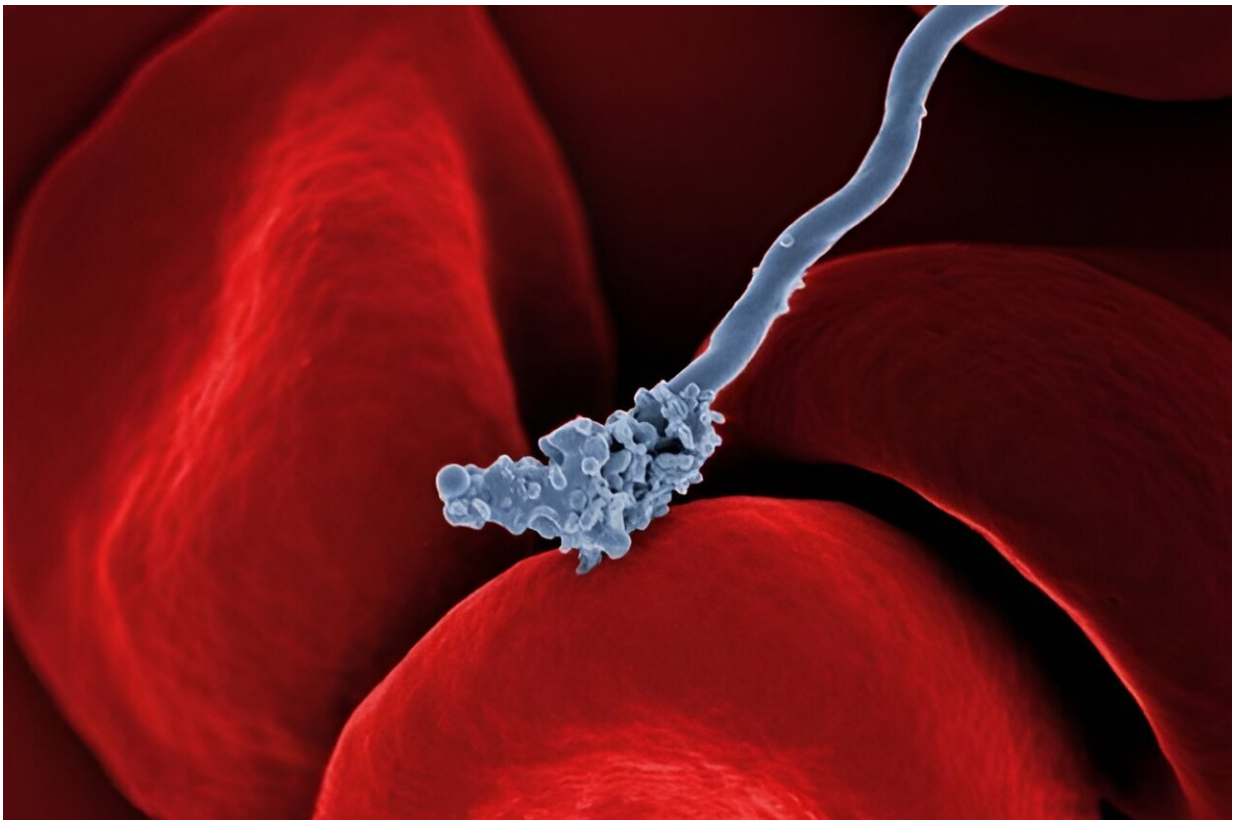

Tick-borne bacteria Borrelia (blue) interacts with red blood cells. The bacteria causes infections with malaria-like symptoms. Credit: National Institute of Allergy and Infectious Diseases, National Institutes of Health via U.S.

Malaria prevalence has decreased drastically over the past two decades, but clinics in West Africa are still full of patients with fevers and symptoms similar to, but not exactly like, malaria.

Little is known about the pathogens that cause these infections, and so these "non-malarial febrile illnesses" (NMFI) often fly under the radar of infectious disease surveillance programs because researchers don't know which pathogens to look for. Understanding how genomics could help detect and identify these mysterious infections has been the focus of a multi-year research partnership between University Cheikh Anta Diop in Dakar, Senegal and the Broad Institute of MIT and Harvard.

We sat down with two members of this research team, ZoÃ« Levine and Katie Siddle, to discuss their most recent work, a study published last month in *Nature Communications* that used two types of genetic sequencing to analyze blood samples from patients in Senegal and identify NMFI-causing pathogens.

The sequencing detected a variety of bacterial, viral, and other pathogens, with tick-borne bacteria Borrelia being the top culprit. Levine and Siddle say that these findings could improve the precision of diagnostics and treatments in areas with high numbers of NMFI cases.

First author ZoÃ« Levine is an MD-Ph.D. candidate at Harvard Medical School and graduate student in the lab of Pardis Sabeti at the Broad. Corresponding author Katie Siddle was a postdoctoral fellow in the Sabeti lab at the time of the study and is now an assistant professor at

Brown University.

Why did you and your colleagues in Senegal decide to do this study?

Siddle: This project was somewhat born out of a sense that there was relatively limited diagnostic testing available. Senegalese clinicians told us that lack of diagnostics was a source of frustration for them. There are a lot of patients that they couldn't treat unless it was malaria or a small host of other diseases.

Senegal has a very strong clinical infrastructure, including a strong hospital network with incredible resources like West Africa's Reference Center for Infectious Disease Diagnostics. They can conduct a huge amount of diagnostic surveillance in response to outbreaks, but the routine day-to-day diagnostics available to clinicians in outpatient centers are, as we understand, largely limited to microscopy and rapid tests for malaria.

What surprised you most about your findings?

Siddle: We went into this study expecting viral infections to be more prevalent, not only because that is the question we were most familiar studying, but also because we were specifically interested in these cases of ambulatory fever, which are these patients who were unwell but not severely unwell. There was a prevailing idea at the time that these ambulatory fevers were more likely caused by viral infections than bacterial infections because bacterial infections are often associated with more severe disease manifestations.

Levine: Tick-borne bacteria, like Borrelia and Rickettsia, have been known to circulate in Senegal for many years. They haven't been studied

in this part of Senegal before, so we didn't know what prevalence to expect there. We were surprised that Borrelia was by far the most common identifiable pathogen in our dataset.

You found a significant number of patients infected with multiple pathogens. What implications do these NMFI co-infections have for public health?

Levine: We saw a few Borrelia-malaria co-infections. There's some evidence that co-infection with Borrelia makes people more likely to develop severe malaria. That's interesting from a public health perspective because oftentimes in a clinical setting, if someone tests positive for malaria, the doctor will give them antimalarials and stop there. But maybe the patient should also take a Borrelia test in case the patient has that risk factor for more severe disease.

We also saw a few Rickettsia-malaria co-infections, which raise a lot of questions because the particular type of Rickettsia that we found is speculated to be more of a harmless co-transmission than a pathogen. It's hard to say whether or not it's actually contributing to the disease or just kind of along for the ride.

In 70% of the study's NMFI cohort, no pathogens were detected. Why do you think that was the case?

Levine: I think there's a lot of different factors going on here. Some people might have a non-infectious cause of their fever. Maybe they had a past infection that's causing prolonged symptoms. By the time we're collecting patients' samples, whatever pathogen was there may no longer be in their blood at detectable levels. And our detection methods aren't perfect; we weren't able to look for every known pathogen, especially if they've never been sequenced before.

How did you collaborate with your colleagues in Senegal for this project?

Siddle: The team in Senegal has phenomenal expertise both in the clinic and in the lab.

One of the reasons that I've traveled so much there over the years is that this is a close research partnership. We go back and forth all the time, we talk all the time. For this project, there was sequencing being done there, sequencing being done here, and it wouldn't have been possible really without the expertise of the clinicians and the staff in Senegal who made all this happen.

What implications do your findings have for diagnosis, surveillance, and treatment?

Levine: Our findings helped us understand how well current metagenomic sequencing techniques detect pathogens like malaria and Borrelia. However, metagenomic sequencing is expensive and equipment intensive and therefore not practical for everyday use in the clinic.

On a broader level, I think that metagenomic surveillance of febrile disease, like in our study and others, helps us to understand the landscape of pathogens and know where to target resources, such as funding for point of care diagnostic development.

Further, the pathogen genomes generated and publicly shared improve our understanding of the diversity of these key pathogens and therefore allow us to design more accurate diagnostics in the future.

More information: Zoë C. Levine et al, Investigating the etiologies of non-malarial febrile illness in Senegal using metagenomic sequencing, *Nature Communications* (2024). DOI: 10.1038/s41467-024-44800-7

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