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EDITORIAL

Do rats pass the sniff test?

CRICETOMYS ANSORGEI. We know them better as African giant pouched rats. Apparently, they don't have great vision, but they make up for that with an excellent sense of smell. APOPO, a Belgian nonprofit organization, has used these rats to detect and destroy landmines in many areas. For this life-saving work, the rats have justifiably earned the moniker of HeroRATs.

But can these heroes detect tuberculosis (TB)? In this issue of the *Journal*, Mulder and colleagues present data on the ability of African rats to detect TB in Tanzania.[1] Sputum from adults with presumptive TB was tested with rats, smear microscopy, Xpert® MTB/RIF, and solid and liquid culture.

Of 771 eligible participants, 345 (45%) were culture-positive for *Mycobacterium tuberculosis*, and 264 (34%) were positive for the human immunodeficiency virus (HIV). The rats were able to detect TB, with a sensitivity of 75% (95%CI 70–80%) when compared with culture. However, this sensitivity, where a rat-positive sample meant that at least two rats out of the team of seven rats had to indicate TB on a sputum sample, came at a cost: specificity was only 41% (95%CI 36–46%).[1] So, rats frequently produce false-positive results. The sensitivity of rats was independent of HIV status, and was significantly higher than smear microscopy. The estimated cost for detecting TB using rats is about $1 per sample.[1]

The authors acknowledge that the rats do not meet the accuracy criteria in World Health Organization (WHO) target product profiles (TPPs)[2] as a standalone TB diagnostic or as a triage test for presumptive TB. However, they argue that rats might help as a triage test, and detect smear-negative patients in high throughput, centralized laboratories or referral hospitals, where several samples can be accumulated and tested by teams of rats.

While the accuracy estimates do not meet TPPs at present, let us imagine it can be improved in future. But will that translate into a scalable test? Here, I worry that rats may not pass the sniff test.

First, replacing (or supplementing) smears at centralized laboratories with rats is not very ambitious. Most TB patients do not access reference laboratories; instead, they are managed (or should be managed) at primary care and district-level facilities. Also, by the time patients (or samples) reach the reference laboratories, they will already have been managed for TB at lower health care levels, and require drug susceptibility testing (DST). Universal DST for all patients with TB is now an End TB target,[3] and rats cannot seem to be able to detect drug resistance.

Second, an ideal triage test is one that can be done at the primary care or community level, to identify those who need to be referred for a confirmatory TB test.[4] However, it seems challenging to decentralize rats to even the primary care level. You need a team of rats working together and they need to be presented with several samples sequentially. As a result, it is not easy to see how peripheral microscopy centres can deploy them. In contrast, molecular tests can detect TB as well as drug resistance, and they can be deployed in both centralized and decentralized settings.[5]

Third, scale-up requires a robust, global supply chain. How does one procure one specific type of rat from Africa, and train them, the way APOPO does? Rats begin training in their infancy, and are trained for 9 months before they pass APOPO's accreditation process. How many groups can conduct such training globally? And if they did, what kind of variations would we see in the results? And, as rats live for only 8 years, a steady supply of trained rats would be essential for the supply chain, along with resources for animal handlers, animal care facilities, and safety compliance.

Finally, there are issues of user acceptance and ambition. Not only must patients accept results from rat detection, but so must doctors, national TB program (NTP) staff, policy makers, and funders. I am not aware of any studies on this, but if I were a patient today, I would want a rapid molecular test such as Xpert. If I were a clinician or an NTP manager, too, I would want rapid molecular tests for my patients. And why not? Over 23 million Xpert cartridges had been procured under concessional pricing globally, and more and more countries are starting to replace smears with Xpert.[6] So, I see no reason to wind the clock back, and scale back our ambition, to a test that has modest accuracy, cannot detect drug resistance, and will be challenging to scale-up.

Given these concerns, the future lies in understanding the biology of rat sniffing, and find a way to detect the volatile compounds that rats are sniffing, and convert that into a standardized, scalable device. While nearly half a dozen companies are working on such technologies,[7] no test is close to policy endorsement.

So, while we wait for a test that can truly pass the sniff test, we would be better off scaling up the WHO-endorsed tools that we already have, and making them more accessible both to our patients and to the

NTPs.[8] We urgently need to bridge the gap between innovation and access.

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