Drug-resistant tuberculosis may be under-diagnosed, says genomic analysis in southern Mozambique

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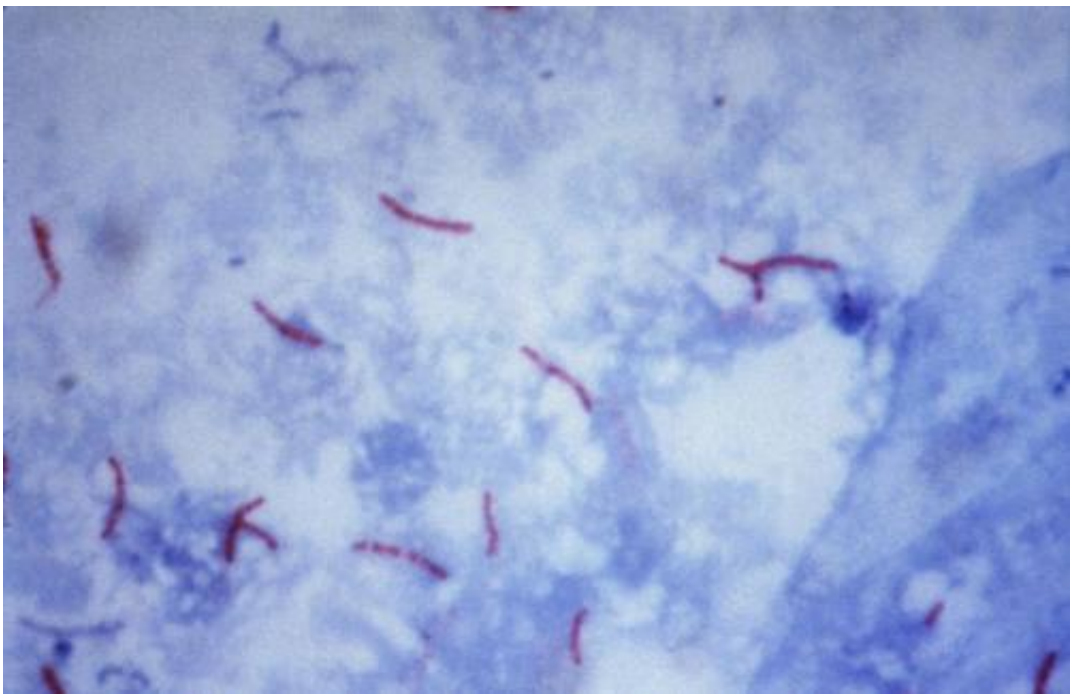

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

A proportion of patients with drug-resistant tuberculosis (TB) receive ineffective treatment due to misdiagnosis by rapid molecular tests,

according to a genomic analysis carried out in southern Mozambique and co-led by the Barcelona Institute for Global Health (ISGlobal), a center supported by "la Caixa" Foundation, and the Institute of Biomedicine in Valencia (IBV), from the Spanish National Research Council (CSIC).

The results indicate that new molecular tests must be developed to detect a broader range of mutations that confer resistance to first-line TB drugs.

Mozambique is one of the countries with the highest burden of drug-resistant TB. The World Health Organization (WHO) recommends the use of the Xpert/Ultra molecular test to identify mutations that confer resistance to the first-line drug rifampicin. However, the test does not detect another mutation that also confers resistance to the drug, which was recently identified in Eswatini and South Africa, two countries that share a border with southern Mozambique. In addition, the test does not detect resistance to another first-line drug, isonoazid.

In this study, the teams of Alberto García-Basteiro, a researcher at ISGlobal and CISM, and Iñaki Comas, from the IBV, joined forces to evaluate the presence of this and other mutations that confer resistance to anti-TB drugs in the region. To do so, they sequenced the entire genome of the bacterium (M. tuberculosis) from more than 600 patient samples collected during two studies (one in 2018 and the other in 2014) in southern Mozambique. Both researchers belong to the CIBER networks of the Health Institute Carlos III.

Resistance to first-line anti-TB drugs but not to newer ones

12.7% of samples (78 out of 612) had one or more mutations conferring resistance to first-line and/or second-line drugs. Ten percent of the

strains were resistant to isoniazid, and four percent were resistant to rifampicin, the main first-line drug.

The mutation reported in Eswatini and South Africa was found in one strain but is likely to have arisen locally. The analysis found two additional mutations conferring rifampicin resistance, which also escaped the Xpert/Ultra test. In addition, a high number of isoniazid-resistant cases were detected, which were also missed by the test.

The good news is that no mutations associated with resistance to two new MDR-TB drugs were found in the region, although a recently published study by another group did find increased resistance to bedaquiline.

Increased surveillance needed

"The strain circulating in Eswatini and South Africa does not appear to have spread significantly to the Manhiça region, but we found evidence that strains with other mutations are being transmitted between Mozambique and other countries in the region," says Comas.

"We observed the circulation of strains resistant to isoniazid but not to rifampicin, and which Xpert/Ultra does not detect," he adds. The authors, therefore, stress the need to increase surveillance and broaden the target mutations beyond those detected by the Xpert/Ultra test.

"Our results provide the most recent figures on the prevalence of antimicrobial resistance by Mycobacterium tuberculosis in this region," says García-Basteiro.

The study is published in the journal *Critical Infectious Diseases*.

More information: Iñaki Comas et al, Monitoring of first-line drug resistance mutations outside the scope of Xpert MTB/RIF Ultra is

needed for successful control of DR-TB in Southern Mozambique, *Critical Infectious Diseases* (2023). DOI: 10.1093/cid/ciad684