Drug-resistant tuberculosis: The rise of the monos

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The diagnostic and therapeutic landscape of tuberculosis has never been more dynamic: efficacious 1-month-preventive treatment regimens;[1] rapid and improving tuberculosis assays; WHO guidelines that include shorter-course regimens for multidrug-resistant (MDR) and isoniazid monoresistant strains; policy on use of novel-class drugs such as diarylquinalone (bedaquiline) and the nitroimidazoles (delaminid and pretominid); and repurposing existing drugs such as linezolid, clofazamine, and imipenem.[2–5] The timely report by Nazir Ahmed Ismail and colleagues[6] in the *Lancet Infectious Diseases* contributes to this landscape by describing the prevalence of combinations of drug resistance in *Mycobacterium tuberculosis* detected in adults attending South African health facilities with at least one symptom suggestive of tuberculosis, in a survey done between 2012–14. The report provides the most comprehensive and recent estimates of drug resistance in South Africa and compares with those from a previous survey from 2001–02[7] that used similar methods, and will assist policy, clinical, and pharmacological practice for management of tuberculosis.

South Africa's extreme burden of the HIV–tuberculosis syndemic has increased the prevalence of drug-resistant tuberculosis. Indeed, at our MDR clinic and hospital in Matlosana (North West Province, South Africa), more than 60% of patients with any rifampin resistance are co-infected with HIV. However, the report by Ahmed Ismail and colleagues[6] did not include either basic or comprehensive HIV data; stratification by HIV status was reported only for adults with any rifampicin resistance and for those with MDR tuberculosis. Most cases of rifampicin monoresistant (RMR) tuberculosis were detected in HIV-infected individuals who had primary RMR tuberculosis, making it unlikely that this strain was selected because of interactions between rifampicin and efavirenz. Other studies[8,9] have shown similar interactions between RMR-tuberculosis and HIV infection, and among individuals with HIV infection, lower CD4 cell counts seemed to be a risk factor for RMR tuberculosis.

An important finding of Ahmed Ismail and colleagues' study debunks the dogma that rifampicin monoresistance equates to multidrug resistance. Indeed, rifampicin monoresistance accounted for almost half the total rifampicin resistance detected in some provinces of South Africa, and worryingly, rifampicin resistance had almost doubled compared with findings from the previous survey.[7] Because current treatment guidelines do not discriminate between MDR-tuberculosis and RMR-tuberculosis, we might be overtreating RMR-tuberculosis. Regimens of shorter duration that contain fewer drugs, are antiretroviral friendly, and avoid injectable agents would be appropriate, especially if RMR-tuberculosis is less virulent, or has a better prognosis than MDR-tuberculosis.

Ahmed Ismail and colleagues[6] reported that the prevalence of isoniazid-monoresistant tuberculosis more than doubled from 2·7% (95% CI 2·2–3·2) in a survey in 2001–02 to 4·9% (4·1–5·8) in 2012–14. Isoniazid preventative treatment might be a potential risk factor for isoniazid-monoresistant tuberculosis, despite findings from clinical trials of preventive treatment not supporting this concept. However in Ahmed Ismail and colleagues' study,[6] isoniazid-monoresistant tuberculosis was not typed and the frequencies of *kat*G and *inh*A genes, either alone or in combination, were not reported. Knowing data for these genes would assist with treatment decisions regarding giving either high-dose isoniazid or adding ethionamide to the MDR treatment regimen. Similarly quinolone resistance was not reported for patients with isoniazid monoresistance in this study—the prevalence of quinolone resistance in individuals with isoniazid-monoresistant tuberculosis would assist when considering the new WHO treatment guideline for isoniazid-monoresistant tuberculosis in which levofloxacin is recommended for 6 months.[5]

Sputum cultures were phenotypically tested, which despite being cumbersome had strengths, because resistance that is not genotypically detected might be diagnosed with Löwenstein-Jensen media rather than automated culture with sensitivity.[10] The Xpert MTB/RIF (Cepheid, Sunnyvale California) and line probe MTBDR plus (Hain Lifescience, Nehren, Germany) do not detect the rifampin-resistance mutation *Ile 491 Phe rpo* B.[11] This is of concern because a survey of MDR-tuberculosis in Swaziland,[12] which borders three provinces of

South Africa, reported a third of isolates having the *rpo* B mutation and the prevalence of this mutation in South Africa remains unknown. Therapy for drug-sensitive tuberculosis will be routinely prescribed if isoniazid resistance is not routinely tested for, and if rifampicin resistance mutations are missed.

A high proportion of the tuberculosis cases in Ahmed Ismail and colleagues' study[6] were resistant to ethionamide and pyrazinamide (44·7% and 59·1%, respectively). The new recommended short-course MDR treatment regimen for South Africa includes both drugs in the initial intensive and continuation phases. We therefore recommend that routine testing for pyrazinamide and ethionamide resistance be done at initiation of MDR therapy, because almost half of patients with MDR tuberculosis could receive only three effective drugs, which can lead to poorer outcomes.[13]

Surveys of resistance patterns are tools for planners, guideline drafters, and society at large. In undertaking such surveys, crucial information should be collected including HIV serostatus, CD4 cell count, and current antiretroviral therapy. They should also report molecular diagnostic and resistance results, and phenotypic sensitivity testing of currently used and investigative new drugs with activity against drug-resistant tuberculosis.

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Urban transmission of tuberculosis in China

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Tuberculosis control in urban settings is a huge challenge. Risk factors and conditions favouring transmission of tuberculosis include increasing spatial proximity and large population influxes.[1] Worldwide, migration starts in poorer, rural places and ends in large urban centres.[2] Cities become important hubs for the transmission of infectious diseases and have higher rates of tuberculosis infection than do rural areas.[3]

In *The Lancet Infectious Diseases*,[4] Chongguang Yang and colleagues investigate the effect of internal migration on tuberculosis transmission in a large, prospective, epidemiological study based in the Songjiang district of Shanghai, China. They combined molecular-guided epidemiological methods with a temporospatial data analysis to reconstruct putative transmission networks among migrants originating from rural areas and native residents of the city. Similar to other Chinese megacities, Shanghai has experienced a steady population increase over the past decades, with an estimated population of 24 million in 2013, and a predicted population of