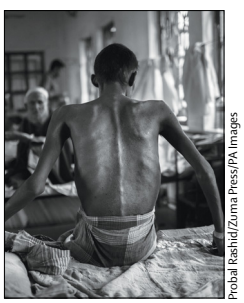
Better data, more tailored tuberculosis therapies



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The WHO End TB Strategy includes all the necessary elements to address the ongoing tuberculosis epidemic, while keeping an eye on the possibility of eliminating tuberculosis in both low-incidence and high-incidence settings.[1,2]

The global threat of multidrug-resistant tuberculosis is clearly acknowledged, with both national tuberculosis programmes and individual clinicians facing severe challenges in managing this severe form of disease.[3,4] Clinicians often need to diagnose multidrug-resistant tuberculosis in disadvantaged populations. They must institute a regimen with a sufficient number of effective drugs, and then support each patient's adherence throughout a long and expensive treatment period during which toxic side-effects frequently occur. Final outcomes are largely suboptimal.[1–6]

Although new drugs (eg, bedaquiline and delamanid)[7,8] and repurposed drugs (eg, linezolid, meropenem, and mefloquine)[9,10] are available and promising, more scientific evidence is necessary to assess their potential impact on the epidemic of multidrug-resistant tuberculosis. They also need to be more easily available globally for sufficient controlled trials to be conducted.

Public health experts and policymakers need to organise a complex management strategy, recommending the correct diagnostic and treatment algorithms, while ensuring—among other priorities—economic sustainability in resource-limited countries.[5]

Comprehensive surveillance of the prevalent drug-resistance patterns of *Mycobacterium tuberculosis* at the regional and national level would be an extremely useful managerial tool to support clinicians and public health experts. Although substantial efforts have been made to describe the existing prevalence of drug resistance,[1] estimations based on point-prevalence surveys might really help.

The study reported by Matteo Zignol and colleagues[11] in *The Lancet Infectious Diseases* provides a multisite overview of population-based drug-resistance patterns in countries with high incidence of drug-susceptible and multidrug-resistant tuberculosis. For the first time in the scientific literature, the investigators provide important information about pyrazinamide and fluoroquinolone resistance. Their retrospective assessment, based on previous surveys of multidrug-resistant tuberculosis, included more than 5000 strains from Pakistan, South Africa, Azerbaijan, Bangladesh, and Belarus.

The prevalence of pyrazinamide and fluoroquinolone resistance varied in different settings. There was an association with rifampicin resistance, particularly when patients were previously exposed to antituberculosis therapy. No significant differences in resistance prevalence were detected among the fluoroquinolones tested (ofloxacin, levofloxacin, and moxifloxacin) within the countries surveyed. A core finding was the highest cross resistance in ofloxacin-resistant mycobacterial strains for levofloxacin (>80%) and moxifloxacin when tested at 0·5 µg/mL (>70%).

Zignol and colleagues' findings describing the prevalence of resistance to fluoroquinolones are original and extremely useful for both clinical and public health purposes; this study is timely and has important implications.

One such implication is that the prescription of pyrazinamide should be carefully evaluated in rifampicin-resistant cases. Rifampicin resistance can now be identified within just a few hours thanks to rapid molecular methods, and, if present, should lead to testing for resistance to pyrazinamide and fluoroquinolones.

Although the overall prevalence of fluoroquinolone resistance in Zignol and colleagues' study was low, the increased prevalence in some settings (eg, Pakistan and Bangladesh) raises concerns and questions the wisdom of empirical prescription of fluoroquinolones to patients with lower respiratory tract infections.

The reader might question whether the resistance patterns identified in this paper can be extrapolated to settings with a superficially similar tuberculosis epidemiology. A certain degree of caution is advisable in assuming that all countries with similar burdens of multidrug-resistant tuberculosis might have similar drug-resistance prevalence, because the statistical power in surveys of relatively rare events is low.

The new WHO-recommended regimen for multidrug-resistant tuberculosis (previously known as Bangladesh regimen), which is expected to increase patients' adherence and programmatic sustainability (being shorter and cheaper), includes pyrazinamide and fluoroquinolones among its core drugs.[12] The variability

in drug resistance patterns calls for understanding of national and subnational epidemiology, and emphasises the need for rapid molecular methods and drug susceptibility testing to exclude drug resistance whenever there is suspicion that it might be present. Only with accurate and timely diagnosis will the spread of drug-resistant tuberculosis be contained.

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