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I declare that I have no conflicts of interest.

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XDR tuberculosis in South Africa: old questions, new answers

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See Comment pages 1755 and 1757
See Articles page 1798

In *The Lancet* today, Keertan Dheda and co-authors[1] present an interesting report about early treatment outcomes of extensively drug-resistant (XDR) tuberculosis (resistant to isoniazid, rifampicin, any fluoroquinolone, and at least one injectable drug: capreomycin, kanamycin, or amikacin) in South Africa. Culture conversion and mortality, stratified by HIV status, were retrospectively reviewed from the original records of a large cohort of 174 cases diagnosed between 2002 and 2008.

Why is this report relevant? The scientific community is still piecing together the puzzle of XDR tuberculosis, more than 4 years after its first description.[2] In looking more broadly to the issue of XDR tuberculosis, we find the same conundrum that faced the blind men in describing the elephant: is everyone partly right, or are we all mostly wrong?[3]

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In addition to questions generated from the findings of treatment outcome studies of patients with XDR tuberculosis, Dheda and colleagues' results provide additional information for debate. Is XDR tuberculosis a death sentence as the European data indicate, or can we really achieve a high proportion of success as the data from Peru suggest?[4–7] Is the poor outcome in patients with XDR tuberculosis described in KwaZulu Natal related to HIV-positive status as is commonly perceived?[7] Are patients dying despite the availability of antiretroviral treatment?[7] What is the best regimen for treatment of XDR tuberculosis in resource-restricted settings? What is the role of surgery? Are reliable predictors of poor outcome available?

Dheda and colleagues' first finding was that there was no difference in early outcomes (mortality and culture conversion) in individuals with or without HIV infection. This result is important for the design and implementation of treatment programmes to reduce existing stigma associated with co-infection with XDR tuberculosis and HIV, and for advocacy purposes.

The second important finding is that HIV-infected patients treated early with antiretroviral drugs had lower early risk of mortality than did untreated patients, the overall number of deaths being lower than the almost 100% described in KwaZulu Natal although the

proportion of individuals who had culture conversion was still very low.[8,9]

The third important finding was that treatment with moxifloxacin, lack of previous culture-proven multidrug-resistant tuberculosis, and increasing number of drugs used in a regimen were independent predictors of survival. Low body-mass index was a negative prognostic factor, further emphasising the important part played by social determinants, as stressed in the Stop TB Strategy.[10,11]

Last but not least, the outcome of patients with XDR tuberculosis in South Africa was poor despite improved adherence and availability of drugs. Dheda and colleagues correctly advocate for further improvement of the effectiveness of tuberculosis programmes, because more than three-quarters of the cases of XDR tuberculosis had a previously diagnosed multidrug-resistant form of disease with clear evidence of development of super-resistance, and diagnostic and treatment delays.

Today's study has some drawbacks (retrospective design, no final outcomes, laboratory limitations, no full-spectrum drug-susceptibility testing information was available) which limit its capacity to provide a complete answer to the questions posed by us.

The results of today's study (because they have programmatic advocacy value) have both clinical and public health relevance. They provide further hope to patients who are HIV-positive, and show that WHO's recommended strategy for control of tuberculosis and HIV/AIDS is based on solid ground. The results also suggest a switch to a treatment policy focused on a new generation of fluoroquinolones, use of more drugs (when feasible), and use of surgery.[6,12] They also confirm that adverse events associated with second-line antituberculosis drugs (particularly moxifloxacin) are common and severe, which calls for a careful implementation of all aspects (including clinical aspects) of the necessary programmatic scale-up in resource-restricted settings.

Moreover, today's study further stresses the need to look at the patient as one individual affected by two diseases, needing a comprehensive approach beyond the necessary medical treatment, including poverty reduction, psychological support, and all the interventions necessary to alleviate the additional burden of social determinants.[13,14]

To obtain an improved picture of the elephant, the differences between data from KwaZulu Natal and those reported by Dheda and colleagues—besides the differences in data from South Africa, Europe, and Peru—are a matter of interest for the scientific community. Further studies aimed at identification of important differences (eg, in genetic susceptibility, strain virulence, and social determinants) are needed.

Today's study emphasises, once more, that while waiting for the expected new drugs (some are in the pipeline), we urgently need to reinforce health systems and, within these health systems, the disease-programme's effectiveness. Otherwise, the new drugs will lose effectiveness in much less than the time necessary to develop them.

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