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Sputum smear-positive tuberculosis among previously treated individuals in the Western Cape Province, South Africa

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Tuberculosis remains a serious threat to human wellbeing in South Africa and elsewhere. Behind India and China, South Africa currently ranks 3rd in the list of countries by estimated total number of incident tuberculosis cases. In 2011, about 390,000 tuberculosis cases were reported in the country, 83% of whom were co-infected with HIV, and an additional 20,000 to 210,000 incident cases were estimated to have occurred unknowingly to the National Tuberculosis Control Programme (1).

It is of note, that a considerable share of South Africa's tuberculosis burden affects those people who have previously been treated for tuberculosis – many of them successfully. In 2011, almost one out of every eight notified tuberculosis cases had a history of previous treatment (1). The number of re-treatment cases after treatment success was more than seven times higher than the number of cases after failure of treatment and almost four times higher than the number of cases that had defaulted, i.e. that interrupted treatment for at least two consecutive months. Re-treatment tuberculosis was recently shown to contribute significantly to both HIV-associated and non-HIV associated tuberculosis in the City of Cape Town (2).

Studying the rate of re-treatment for smear positive tuberculosis

In this context, we recently published the results of a retrospective cohort study that was conducted using tuberculosis treatment register data from two communities in suburban Cape Town (3). The purpose of this study was to investigate, among tuberculosis patients who had either successfully completed or defaulted from their treatment, the rate of subsequent re-treatment for smear-positive tuberculosis. We further aimed to investigate, among patients who did not complete their treatment, whether sputum conversion prior to defaulting and the duration of treatment were associated with smear-positive tuberculosis re-treatment.

In this treatment register-based cohort study, we included all (index) treatment episodes of sputum smear-positive tuberculosis cases who had been treated for smear-positive tuberculosis in the communities between 1996 and 2008 and who had either completed or defaulted from this treatment episode. A probability record linkage algorithm was used to link subsequent treatment episodes recorded in the treatment register to individual persons. The rate of subsequent re-treatment for sputum smear-positive tuberculosis was measured for both groups of patients.

High risk of smear-positive tuberculosis in defaulters

We show in the published study that the hazard rate of re-treatment for smear-positive tuberculosis was between 3- and 5.26-times higher in tuberculosis cases who had defaulted from treatment compared to successfully treated cases. By the end of the second year after the date when the patient had defaulted, 27.9% had already experienced a re-treatment episode for documented sputum smear-positive tuberculosis compared to 5.8% after treatment success.

Among treatment defaulters, the rate of smear-positive tuberculosis re-treatment was depended on whether the patient had converted to smear-negative at the end of the second month of treatment. Furthermore, there was an inverse linear relationship between the duration of the first treatment episode until the date of default and the rate of subsequent re-treatment for smear-positive tuberculosis. Both age at the time of the index treatment episode and the smear-grade, i.e. the density of acid-fast bacilli found in the diagnostic sputum, were positively associated with subsequent re-treatment, independent of what the later treatment outcome had been.

To our knowledge, this the first study demonstrating a high risk of smear-positive tuberculosis in patients who had been non-adherent to a full course of treatment before. Our results suggest that tuberculosis was initially contained in the majority of defaulters but worsened again soon after stopping the treatment. Although the rate of re-treatment was substantially higher among defaulters, cases after treatment success account for the vast majority of smear-positive re-treatment cases, due to the fact that far more tuberculosis cases were successfully treated than had defaulted, and the rate of re-treatment after success was lower in the first two years but remained constantly high in the following years.

True rate of smear-positive tuberculosis might even be higher

We believe that our rates of re-treatment underestimate the true rate of smear-positive tuberculosis among previously treated tuberculosis cases in the communities, because we were unable to account for tuberculosis cases who experienced a

subsequent episode of smear-positive tuberculosis after treatment success or default without being diagnosed or being diagnosed but without being treated. Furthermore, the denominator in our rate estimate included person-years at risk for previously treated tuberculosis cases who might have moved away from the area or who might have died. Therefore we expect that the true rate of smear-positive tuberculosis among previously treated tuberculosis cases is even higher. Our study is also limited by the fact that we were unable to control for other known risk factors of disease recurrence such as residual lung cavitation at the end of the first treatment episode, greater area of involved lung tissue and positive sputum culture two month after the start of the first treatment episode (4). In addition, we were unable to determine the effect of HIV co-infection, a known risk factors for tuberculosis recurrence (5), on the risk of smear-positive tuberculosis among previously treated cases. The proportion of tuberculosis cases who were co-infected with HIV in our setting was relatively small compared to other areas in the Western Cape Province.

Implications for tuberculosis control

The results of our study have implications for tuberculosis control as they emphasize the need to ensure treatment adherence in order to prevent subsequent smear-positive tuberculosis and, possibly, related adverse health effects such as chronic pulmonary impairment (6), death (7), and acquisition of drug-resistance (8). High rates of smear-positive tuberculosis after previous treatment raises questions about the extent to which previously treated tuberculosis cases contribute to on-going tuberculosis transmission in the communities. Den Boon et al. had published the results of a tuberculosis prevalence survey conducted in the same communities (9). During this survey, 18 smear-positive tuberculosis cases were detected in a randomly selected household sample, 10 (56%) of whom had had a history of previous treatment. If these cases were representative of all infectious source cases in the communities, than it is reasonable to conclude that previously treated tuberculosis cases contribute significantly to transmission. This study and our results suggest that disease recurrence might play an important role for the burden of tuberculosis in the communities.

The study presented here forms part of a larger on-going research project in which we investigate the burden and underlying causes of recurrent tuberculosis and the risk of progression to multidrug-resistant (MDR) tuberculosis among patients with multiple episodes of tuberculosis (treatment).

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