**RISK FACTORS FOR MULTIDRUG RESISTANT TUBERCULOSIS IN AFRICA: A META-ANALYSIS**

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**Abstract**

The rising HIV-infection rates, poverty and ineffective control programs have contributed to the high incidence of tuberculosis (TB) in Africa over the past few years. Multidrug resistant tuberculosis (MDRTB) is spreading rapidly in African countries. This meta-analysis examines risk factors for MDRTB in Africa.

**Methods:** Published studies investigating the risk factors for MDRTB in Africa were collected from PubMed and Embase databases. A random effects model in the Comprehensive Meta-analysis V2 software was used for a meta-analysis, to obtain pooled risk estimates of associations between previous TB treatment and HIV-status with MDRTB development.

**Results:** Twenty-two eligible papers were reviewed. The risk of developing MDRTB was greater in patients who had previous treatment in Africa (OR 7.7; 95% CI 3.7, 16.3), and highest in Western African countries (OR 8.986; 95% CI 4.198-19.261). The heterogeneity between the studies was high ($I^2 = 85.94$, $P < 0.001$) and it was not explained by location and study design. HIV infection and MDRTB in Africa were not significantly related. The risk of working in mines in Africa was associated with MDRTB development (OR 0.02; 95% CI 0.09-0.83).

**Conclusions:** TB treatment history was found to be the strongest risk factor for MDRTB in Africa. Complete treatment programs and effective monitoring and surveillance can help successful treatment, and decrease the incidence of MDRTB in Africa.

**Keywords:** tuberculosis risk factors WHO DOTS meta-analysis drug resistance

**Introduction**

Tuberculosis (TB) is a leading cause of death from infectious disease in Africa and it was declared an emergency by the World Health Organization (WHO) in 2005.(1,2,3) Sub-Saharan Africa has the highest incidence of TB in the world, with a high infection rate among HIV-positive patients.(3,4) High HIV incidence rates, the growing population, widespread poverty and ineffective control programs have contributed to the TB epidemic in Africa.(3,5) The emergence of antituberculosis drug resistance over the past few years has been a further impediment in preventing the spread of TB.
prevalence could be attributed to the recent introduction of rifampin in these countries, the use of rifampin-free treatment regimens in the continuation phase of therapy, and the growing use of direct observation of treatment. Lack of access to treatment may also contribute to the low prevalence of MDRTB. There is however insufficient information about drug resistance in several African countries with a very high incidence of tuberculosis, because of no surveillance in those regions.

With the emergence of the extensively drug resistant tuberculosis (XDRTB) strain in South Africa, it has become more important to identify the determinants of drug resistance and take immediate remedial measures. While many studies have dealt with the prevalence of MDRTB in African countries, very few studies have focused on the predictors for MDRTB in Africa in particular. The aim of this meta-analysis was to review published studies reporting the risk factors of MDRTB in Africa to obtain a better understanding of the situation in those countries.

**Methods**

**Selection of papers**

A review of published studies focusing on risk factors for MDRTB in Africa was carried out through a comprehensive search on PubMed (1995 to 2007) and Embase (2000 to 2007). Articles from Medline were obtained from PubMed. A combination of the following terms was used as free text and phrases: risk factors, multidrug-resistant tuberculosis, Africa, epidemiologic determinants, surveillance, surveys, transmission, spreading, predictors and treatment outcome.

**Research design**

Studies that reported information allowing the calculation of estimates of association between MDRTB and other risk factors in Africa were included in the analysis. Studies were excluded if they were restricted to specific study groups such as HIV-infected individuals, previously treated TB cases, or previ-

<table>
<thead>
<tr>
<th>Country (date)</th>
<th>Design (reference)</th>
<th>Sample size (N)</th>
<th>MDR-TB (n)</th>
<th>Factors</th>
<th>Odds ratio estimates</th>
</tr>
</thead>
<tbody>
<tr>
<td>Botswana (1995-96)</td>
<td>Systematic random survey (16)</td>
<td>551</td>
<td>7</td>
<td>Age in years: 30-39</td>
<td>1.5 (0.2–8.3) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>40-49</td>
<td>5.7 (0.9–36.0) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Over 50</td>
<td>0.4 (0–3.5) *</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lived outside Botswana</td>
<td>9.4 (1.1–216) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Lived in South Africa</td>
<td>13.3 (1.5–306) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worked in the mines</td>
<td>11.7 (1.3–267) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Worked in South African mines</td>
<td>13.3 (1.5–306) *</td>
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<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Had HIV/AIDS</td>
<td>0.9 (0.8- 2.4) *</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Female sex</td>
<td>2.5(1.2–5.2) §</td>
</tr>
<tr>
<td>Equatorial Guinea (2001)</td>
<td>Laboratory study (17)</td>
<td>499</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>South Africa (1993-1997)</td>
<td>Reviewed drug susceptibility records (18)</td>
<td>2404</td>
<td>13</td>
<td>Previous treatment</td>
<td>2.03 (1.46–2.82) ±</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Treatment failure</td>
<td>18.74 (1.76–475) ±</td>
</tr>
<tr>
<td>South Africa (2003-2005)</td>
<td>Laboratory survey (19)</td>
<td>665</td>
<td>17</td>
<td>Under 13 years of age</td>
<td>2.84 (1.29- 6.28)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-Prior TB for 6 to 11 months</td>
<td>7.6 (2.6- 22.4)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>-More than 12 mo</td>
<td>13.7 (4.5–41.6)</td>
</tr>
<tr>
<td>Sierra Leone, Swaziland, Lesotho (1994-1995)</td>
<td>Cross-sectional study (12)</td>
<td>1419</td>
<td>40</td>
<td>Clustering</td>
<td>0.02 (0.09–0.83) ±</td>
</tr>
<tr>
<td>South Africa (2000)</td>
<td>Prospective population-based cohort study (20)</td>
<td>419</td>
<td>24</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Table 2. Risk estimates of MDRTB from different studies.**

* The reference group is susceptible new cases. Bi-and multi-variable analysis was performed.

§ Risk factors for resistance among new cases was observed ± versus other cases resistant to more than one drug

±Adjusted for age-group and other variables.

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**Table 1. Prevalence of multidrug resistance tuberculosis among new cases of tuberculosis in Africa (1997-2000).**

*Ref 8, **Ref 44.

<table>
<thead>
<tr>
<th>African country or region</th>
<th>Prevalence of MDRTB % of patients (95% CI): 1997-1999 *</th>
<th>Prevalence of MDRTB % of patients (95% CI): 2000 **</th>
</tr>
</thead>
<tbody>
<tr>
<td>Benin</td>
<td>-</td>
<td>0.3 (0-0.9)</td>
</tr>
<tr>
<td>Botswana</td>
<td>0.5 (0.1-1.4)</td>
<td>0.5 (0-1.0)</td>
</tr>
<tr>
<td>Central African</td>
<td>1.1 (0.4-2.5)</td>
<td>1.1 (0.0-2.0)</td>
</tr>
<tr>
<td>Republic (Bangsi)</td>
<td>0.6 (0.1-1.6)</td>
<td>0.6 (0-1.2)</td>
</tr>
<tr>
<td>Guinea</td>
<td>-</td>
<td>5.3 (2.9-7.8)</td>
</tr>
<tr>
<td>Ivory Coast</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Kenya</td>
<td>-</td>
<td>0.0</td>
</tr>
<tr>
<td>Morocco (Casablanca)</td>
<td>2.2 (1.1-3.8)</td>
<td>2.2 (0.9-3.4)</td>
</tr>
<tr>
<td>Mozambique</td>
<td>3.5 (2.5-4.8)</td>
<td>3.5 (2.4-4.6)</td>
</tr>
<tr>
<td>Sierra Leone</td>
<td>0.9 (0.0-4.7)</td>
<td>0.9 (0-2.5)</td>
</tr>
<tr>
<td>South Africa</td>
<td>1.5 (0.7-2.8)</td>
<td>1.5 (0.6-2.4)</td>
</tr>
<tr>
<td>Swaziland</td>
<td>-</td>
<td>0.9 (0-1.9)</td>
</tr>
<tr>
<td>Uganda</td>
<td>0.5 (0.1-1.9)</td>
<td>0.5 (0-1.3)</td>
</tr>
</tbody>
</table>
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The Comprehensive Meta-analysis V2 software was used for statistical analysis.(15) For studies that reported the odds ratios with the 95% confidence interval (CI) for the risk factors for MDRTB, the results were directly reported. Random effect models were used to obtain pooled risk estimates and odds ratios with their 95% CI and their corresponding forest plots were obtained. Heterogeneity between the studies reviewed was quantified using the I² statistic and the corresponding P-value. The risk factors used in the analysis to determine and association with MDRTB were previous treatment, treatment based on study location and HIV status.

Results

A total of 391 articles were reviewed from the PubMed search on the risk factors for drug resistant tuberculosis in Africa of which 31 articles met the inclusion criteria. Eleven studies were excluded from the analysis because of insufficient information for calculating the risk estimates. Two articles were selected from the Embase database.

Of the studies selected for review, 7 were cross-sectional studies, 2 were retrospective descriptive studies and 9 were prospective laboratory studies and prospective surveys. The 9 African countries represented in this review included South Africa, Botswana, Mozambique, Benin, Cameroon, Uganda, Ethiopia, Rwanda and Burundi.

Patients with MDRTB in Africa were more likely to have previously been treated for TB with a pooled risk estimate 7.71 times greater than that for MDRTB in new TB patients, Figure 1. The association between previous treatment and MDRTB was not significant in 5 of the 21 studies reviewed. The odds of developing MDRTB favored previously treated cases in only 2 of the studies. The heterogeneity between the studies (I²=85.94, P<0.001) was not explained by location, study design and HIV status of the patients. Age, district, country of origin, residence in another country, history of familial TB, HIV status, sputum smear result, alcohol consumption, tuberculin skin test, chemoprophylaxis and clinical presentation were not found to be significant risk factors for MDRTB.(17,18,21-24) One study found an association between female sex and MDRTB, Table 2. Children in community-based groups and hospitals did not differ based on drug susceptibility.(19) A significant association was found between working in mines and MDRTB prevalence in some studies, Table 2, while others reported non-significant differences in MDRTB levels among mining clusters and non-clusters.(20,22)

For this study, forest plots for risk estimates of MDRTB in previously treated cases and new cases were calculated in Southern, Central, Western and Eastern African countries. The pooled risk estimates

<table>
<thead>
<tr>
<th>African countries</th>
<th>Patients with culture-positive MDRTB (n)</th>
<th>Patients treated under DOTS-Plus (n)</th>
<th>Patients successfully treated (n)</th>
<th>Deaths averted (n)</th>
<th>Cost per patient treated under DOTS-Plus (USD)</th>
<th>Total costs (USD)</th>
</tr>
</thead>
<tbody>
<tr>
<td>high prevalence of HIV/AIDS</td>
<td>147,000</td>
<td>18,000</td>
<td>13,000</td>
<td>3,000</td>
<td>2,273</td>
<td>46 millions</td>
</tr>
<tr>
<td>low prevalence of HIV/AIDS</td>
<td>58,000</td>
<td>11,000</td>
<td>8,000</td>
<td>2,000</td>
<td>1,979</td>
<td>26 millions</td>
</tr>
</tbody>
</table>
for previously treated cases were found to be the lowest in the Central African countries of Rwanda and Burundi (OR 4.2; 95% CI 2.186-8.07). Benin and Cameroon in Western Africa had pooled risk estimates similar to the Eastern African countries of Uganda and Ethiopia (OR 8.986; 95% CI 4.198-19.261 and OR 8.83; 95% CI 1.978-39.429) respectively. South Africa, Botswana and Mozambique in Southern Africa had a pooled odds ratio favoring newly treated cases as well (OR 7.836; 95% CI 2.667-23.022).

I found no significant association between a patient's HIV status and the development of MDRTB, Figure 2. HIV-negative patients were more prone to MDRTB than patients with HIV infection (OR 0.753; 95% CI 0.448-1.265).

Four of the 5 studies reviewed for HIV-infection being a risk factor for MDRTB were from countries in Southern Africa.

**Discussion**

**Effect of previous treatment**

The history of previous treatment has been found to be a good indicator of MDRTB development.(12,23,26) Studies from other continents reported the prevalence of MDRTB to be up to 10 times higher after unsuccessful treatment.(10,25) The meta-analysis showed a strong association between previous treatment and the development of MDRTB. When classified by location, the studies in Western and Eastern Africa were found to have the highest risk of MDRTB development in previously treated cases. This could be because of higher DOTS coverage in those countries as compared to Rwanda and Burundi.(7) A high prevalence of HIV infection in previously treated TB patients in sub-Saharan Africa could increase the number of MDRTB cases. This increase could be attributed to both TB relapse in patients with HIV/AIDS and the long-term use of rifampicin and isoniazid to treat other opportunistic infections.(27)

While prolonged TB treatment results in an increase in MDRTB, shorter periods of treatment also give rise to MDRTB if they are inadequate and inappropriate.(12) Few studies reviewed enlist specific reasons for previous treatment failure in Africa, such as loss to follow-up, defaulting and death. A measurement bias could arise when patients do not report previous treatment, leading to differential misclassification of patients based on previous treatment.

**Association between HIV-infection and MDRTB**

While studies in the other countries have indicated that HIV/AIDS patients were more likely to develop drug resistance, the studies reviewed in this analysis from Africa have shown a non-significant association between a patient's HIV-status and MDRTB. This was a surprising finding given the high prevalence of HIV/AIDS in sub-Saharan Africa, the high TB relapse rates among HIV/AIDS patients, and the rapid progression of resistance in these immunocompromised individuals. The small number of studies available for review and the high mortality rate among these individuals could have resulted in non-significant associations.

**Other risk factors**

In general, the studies reviewed did not report a significant association between age, area of residence and country of origin. Although poverty has been shown to influence drug resistance levels, the studies do not report a relationship between MDRTB and a patient's socioeconomic status. A cohort study of gold miners in South Africa showed that 36% of the miners with MDRTB were from South Africa and the remaining were from neighboring countries. Less than 50% of the miners infected with MDRTB had HIV/AIDS.(30) Clustering in gold mines was found to be a significant risk factor for MDRTB among South African gold miners. Other risk factors could include poverty and treatment inaccessibility among the gold miners.

**Country differences**

The effectiveness of TB control programs has been associated with a decreased prevalence of MDRTB. This is linked to the political and economic framework of the country. Mozambique and Rwanda for instance have relatively high levels of drug resistance compared with Botswana, Swaziland and Zimbabwe because the political turmoil could have led to incomplete treatment programs in those countries. A systematic random survey conducted in Botswana indicated that MDRTB cases were more likely to have lived in neighboring countries like South Africa and worked in South African mines.
MDRTB TREATMENT AND CONTROL

The treatment of MDRTB requires the use of second-line TB drugs. The DOTS-Plus initiative, created by WHO in 1999, has led to dramatic reductions in the prices of second-line drugs in African countries. The performance of the DOTS-plus initiative in Africa is summarized in Table 3. National Tuberculosis Programs (NTP) in many African countries are making progress in developing goals and identifying loopholes in the management of MDRTB.

STUDY LIMITATIONS

First, only 3 studies included in the analysis gave information about the patient's age, sex and location, and 1 study had MDRTB specific information for these parameters. Risk estimates for MDRTB based on age, sex and location could therefore not be calculated.

Second, a complete classification of the treatment status of previously-treated patients such as treatment failure, relapse, return to treatment and the duration of treatment was done in only 2 studies. This made it difficult to evaluate possible effects of inadequate or interrupted treatment on MDRTB development.

Third, no study reported the patient's race, foreign status, BCG vaccination status education level and socioeconomic status so an association between MDRTB and these factors could not be calculated.

Fourth, lack of information about all of these factors prevented determination of the reason for heterogeneity between the studies. Differences in study methodologies could have accounted for the high level of heterogeneity because of variations in study settings, sampling techniques and sample sizes used. Possible confounding factors could also not be determined in the analysis because of insufficient information.

Fifth, only 5 studies had information about a patient's HIV status and MDRTB development. This could have led to non-significant associations. Few reports studied the prevalence of MDRTB in miners and therefore calculations about mining as a risk factor for MDRTB could not be made.

Last, all the studies included in the analysis are from sub-Saharan African countries preventing the comparison of risk factors between these countries and the rest of Africa.

CONCLUSIONS

MDRTB is not yet a serious problem in Africa: rapid detection of incident cases can perhaps prevent the outbreak of extensively drug resistant tuberculosis and other forms of drug resistance.

Because previous treatment history is a major risk factor for MDRTB development, TB control programs must focus on treatment completion rates and effective monitoring and patient follow-up. The political and economic make-up is largely different in African countries, which affect the implementation of NTP. While access to MDRTB treatment is poor, on the one hand; lack of availability of over-the-counter antibiotics magnifies the problem of drug resistance in Africa. Large parts of Africa need to be surveyed to determine levels of drug resistance. Drug surveillance is needed before the implementation of treatment programs to prevent the development of further drug resistance in patients without the MDRTB strain.

There is a strong need for newer cost-effective treatment strategies in the developing nations of Africa to combat more severe forms of drug resistance. MDRTB detection also needs to be simplified to hasten the treatment process. It currently takes as long as 3 months to detect TB drug resistance in patients and there is a heightened risk of transmission of infection in addition to degeneration of the patient's condition in that interim period.

More studies are needed to determine relationships between race and socioeconomic status and MDRTB development. Studies also need to address country-specific issues while studying risk factors for drug resistance in African countries owing to the wide political and cultural diversity in Africa.

Thus a concerted effort by the key players in the healthcare sector would ensure swift detection, prevention of transmission and proper treatment of MDRTB cases in Africa.

Acknowledgments

I would like to thank Dr Laura Pontigia for constant guidance and support, and the librarians at the JW England library, University of the Sciences in Philadelphia for their time and efforts.

References

1.WHO TB Emergency Declaration, issued by WHO Regional Office for Africa. At www.who.int.