Executive summary

South Africa is one of the 22 highest tuberculosis (TB) burdened countries globally and the occurrence of laboratory-confirmed multi drug resistant TB (MDR–TB) and extensively drug resistant TB (XDR-TB) has long been recognized in South Africa. A drug resistance survey (2012-2014) to quantify and delineate the extent of drug resistance in new and retreatment TB patients nationally and provincially in South Africa, as well as to compare findings with the previous survey (2001-2002) was undertaken based on WHO guidelines. The prevalence of MDR-TB nationally in the latest survey was measured at 2.1% in new cases and 4.6% in retreatment cases with an overall, MDR-TB estimate of 2.8%. Compared to the previous survey, the MDR-TB prevalence has remained relatively stable over the ten-year period. The highest rate observed was in Mpumalanga province with an overall rate of 5.1%. Contrasted to the MDR-TB prevalence nationally, the rate of any rifampicin-resistance prevalence has increased since the previous survey, primarily seen among new cases, and almost doubling from 1.8% to 3.4%, highlighting the likely role of transmission. Second-line drug resistance prevalence among MDR-TB cases was for the first time evaluated in this survey and the findings are concerning. The prevalence of resistance to ethionamide and pyrazinamide, both used empirically in the treatment of MDR-TB, was found to be high at 44.7% and 59.1% respectively. Additionally, resistance levels to the key drug classes, fluoroquinolones and injectable agents, were both 13%, highlighting the relatively high frequency of pre-extensively drug-resistant tuberculosis cases among those with MDR-TB. These findings highlight emerging threats to drug resistant TB control requiring urgent intervention.

Introduction

South Africa is one of the 22 highest tuberculosis (TB) burdened countries globally and has the second highest TB incidence rate in the world.1 The first national survey of TB drug resistance in South Africa was undertaken between 2001 and 20022. The study reported an overall multi drug resistant TB (MDR-TB) rate in South Africa of 1.6% (95% CI: 1.1%-2.1%) in new cases and 6.6% (95% CI: 4.9%-8.2%) in retreatment cases.
Although the MDR-TB prevalence appears to be low among primary TB cases, this needs to be interpreted in the context of a high incidence of TB in South Africa. In the WHO Global TB Report 2015, South Africa had the second highest absolute number of notified rifampicin-resistant (RR)/MDR cases globally (18,734), with India ranked number one (25,748) but the latter having a population 20 times that of South Africa. The occurrence of laboratory-confirmed extensively drug resistant TB (XDR-TB), a more resistant form of MDR–TB, has long been recognized in South Africa, and was managed as difficult-to-treat MDR-TB cases. An outbreak of XDR-TB was reported in 2005 at the Church of Scotland Hospital in Tugela Ferry, KwaZulu-Natal province and was followed by a report of the emergence of “totally drug-resistant” TB in Eastern Cape province based on strains collected during the period 2008-2009.

Routine notification data has shown that the treatment success rate is approximately 50% in MDR-TB cases and 20% in XDR-TB patients. Furthermore, many of these unsuccessfully treated patients die. The situation has however improved with the introduction of bedaquiline for which early programme data suggests improved outcomes. The current WHO recommendation is to conduct a TB drug resistance survey every five years and a new survey was long overdue to quantify and delineate the extent of drug resistance in new and retreatment TB patients nationally and provincially in South Africa, as well as to compare findings with the previous survey.

Methods

A survey aimed at providing MDR–TB estimates for each province and nationally was designed using a population-based cross-sectional study according to WHO guidelines. Clusters were randomly selected and were either individual healthcare facilities or a combination of facilities. Patients were eligible for inclusion in the survey if they were older than 18 and presented as a presumptive TB case, according to WHO/International Union against Tuberculosis and Lung Disease (IUATLD) definitions.

All consecutive presumptive TB cases, who provided informed consent at selected facilities during the survey period, had a case report form (CRF) completed through direct patient interview by a healthcare worker at the health facility and in addition had a survey-specific sputum sample collected, were included. The CRF with the corresponding sample was sent to the Centre for Tuberculosis at the National Institute for Communicable Diseases in Johannesburg, where smear microscopy, liquid mycobacterial culture and HIV testing on sputum was performed. This was followed by drug susceptibility testing against a panel of first-line and second-line anti-TB drugs on Mycobacterium tuberculosis-confirmed isolates. Data from the CRF and the laboratory testing process were collated and analyzed.

The survey received ethical approval from the University of Witwatersrand Research Ethics Committee on the 26/11/2010 (Ethics clearance No. M081022). Clearance was also received from the Centers for Disease Control and Prevention, Atlanta, USA. The survey was initiated after consultation and approval from the respective provinces and the South African National TB Control Programme.

Results

The South African Tuberculosis Drug-Resistant Survey (DRS) of 2012-2014 was the largest TB DRS conducted...
in the country to date with 200,358 persons screened from 464 randomly selected facilities in all nine provinces. A total of 10,044 culture confirmed TB cases was identified. These underwent both first- and second-line drug susceptibility testing. Nationally, 22% of culture positive TB cases reported prior treatment for TB and the highest incidence was in the Western Cape at 35%. HIV co-infection was 63.2% nationally and ranged between 47.4% (Western Cape) and 76.8% (Mpumalanga).

The prevalence of MDR-TB nationally was measured at 2.1% (95% CI: 1.5%-2.7%) in new cases and 4.6% (CI 95%: 3.2%-6.0%) in retreatment cases with an overall MDR-TB estimate of 2.8% (95%CI: 2.0%-3.6%) (Table 1). Compared to the previous survey of 2001-2002, the prevalence of MDR-TB has remained relatively stable over the ten-year period with the overall MDR-TB rate in the previous survey being 2.9% (95% CI: 2.4%-3.5%).

Provincial MDR-TB prevalence varied with six of nine provinces showing MDR-TB rates below 2% among new cases in the current survey. The highest rate observed was in Mpumalanga province with an overall rate of 5.1% (95% CI: 3.7%-7.0%), including both new and previously treated cases, which was higher than the national rate (2.8%; 95% CI: 2.0%-3.6%). This is of particular concern requiring urgent intervention.

Contrasting with the MDR-TB prevalence nationally, rifampicin-resistance prevalence has increased since the previous survey, with the overall prevalence at 4.6% (95% CI: 3.5%-5.7%) nationally in the current survey, compared to 3.4% (95% CI: 2.8%-3.9%) in the previous survey. The increase was primarily seen among new cases, almost doubling from 1.8% (95% CI: 1.3%-2.3%) to 3.4% (95% CI: 2.5%-4.3%), highlighting the likely role of transmission. Rifampicin mono-resistance (RMR), which showed a low prevalence in the previous survey, has emerged as a concern. It was below 0.5% overall in the previous survey but has increased to 1.7% in the current survey. Provincial variation was observed in RMR-TB cases with several provinces showing similar prevalence rates of MDR and RMR-TB cases while Limpopo province showed higher RMR-TB prevalence than MDR-TB. The reason for the emergence of RMR-TB in the context of standardized combination therapy is unclear and should be further investigated. The prevalence of isoniazid resistance (9.3%; 95% CI: 7.9%-10.7%) was higher than that of rifampicin resistance (4.6%; 95% CI: 3.5%-5.7%). A notable increase in isoniazid mono-resistance (IMR) was observed between the current survey (4.9%; 95% CI: 4.1%-5.8%) and the previous survey (2.7%; 95% CI: 2.2%-3.2%).

Second-line drug resistance prevalence among MDR-TB cases was evaluated for the first time in this survey and the findings are concerning (Table 2). The prevalence of resistance to ethionamide and pyrazinamide, both used empirically in the treatment of MDR-TB, was found to be high at 44.7% (95% CI: 25.9%-63.6%) and 59.1% (95% CI: 49.0%-69.1%) respectively. This compromises the effectiveness of the standard MDR-TB regimen and could lead to further selection of resistance to other drugs. Additionally, resistance levels to the key drug classes - fluoroquinolones and injectable anti-TB agents - were both 13% (95% CI: 5%-21%), highlighting the relatively high frequency of pre-extensively drug-resistant TB (XDR) cases among those with MDR-TB confirmation, and the need to identify these cases early.
Table 1: National first-line drug resistance estimates among new and previously treated TB cases, 2012-14 survey, South Africa.

<table>
<thead>
<tr>
<th>TB resistance</th>
<th>New (%, 95% CI)</th>
<th>Previously treated (%, 95% CI)</th>
<th>Overall (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDR</td>
<td>2.1 (1.5-2.7)</td>
<td>4.6 (3.2-6.0)</td>
<td>2.8 (2.0-3.6)</td>
</tr>
<tr>
<td>Any rifampicin</td>
<td>3.4 (2.5-4.3)*</td>
<td>7.1 (4.8-9.5)</td>
<td>4.6 (3.5-5.7)</td>
</tr>
<tr>
<td>Rifampicin mono(^\d)</td>
<td>1.4 (0.9-1.8)</td>
<td>2.5 (1.2-3.7)</td>
<td>1.7 (1.1-2.2)</td>
</tr>
<tr>
<td>Rifampicin mono (strict)(^1)</td>
<td>0.9 (0.5-1.3)*</td>
<td>1.8 (0.7-2.9)</td>
<td>1.1 (0.6-1.7)*</td>
</tr>
<tr>
<td>Rifampicin mono (other)(^2)</td>
<td>0.4 (0.1-0.7)*</td>
<td>0.7 (0.2-1.2)</td>
<td>0.5 (0.2-0.8)*</td>
</tr>
<tr>
<td>Any isoniazid(^\d)(^\d)</td>
<td>7.6 (6.4-8.7)</td>
<td>11.1 (9.1-13.1)</td>
<td>9.3 (7.9-10.7)</td>
</tr>
<tr>
<td>Isoniazid mono</td>
<td>5.5 (4.6-6.5)</td>
<td>6.5 (5.1-7.9)</td>
<td>6.1 (5.1-7.1)</td>
</tr>
<tr>
<td>Isoniazid mono (strict)(^1)</td>
<td>4.5 (3.6-5.3)*</td>
<td>5.5 (4.3-6.8)*</td>
<td>4.9 (4.1-5.8)*</td>
</tr>
<tr>
<td>Isoniazid mono (other)(^2)</td>
<td>1.1 (0.3-1.8)</td>
<td>1.0 (0.4-1.6)</td>
<td>1.1 (0.4-1.7)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>2.0 (1.2-2.8)*</td>
<td>3.5 (2.2-4.8)</td>
<td>2.5 (1.7-3.3)*</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>3.9 (2.8-5.1)</td>
<td>5.1 (3.8-6.5)*</td>
<td>4.5 (3.5-5.5)*</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>2.9 (2.2-3.6)</td>
<td>5.2 (3.8-6.7)</td>
<td>3.7 (2.9-4.5)</td>
</tr>
</tbody>
</table>

\(^\d\) rifampicin-resistant & isoniazid susceptible
\(^\d\(^\d\) rifampicin susceptible & isoniazid resistant
\(^1\) strict (without resistance to another first line drug: streptomycin/ethambutol)
\(^2\) other (with resistance to another first line drug: streptomycin/ethambutol)
*non-overlapping 95% confidence intervals between 2012-14 and 2001-2

Table 2: National second-line drug resistance among MDR-TB cases, 2012-14 survey, South Africa.

<table>
<thead>
<tr>
<th>Drug</th>
<th>Overall (%, 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Pyrazinamide</td>
<td>59.1 (49.0-69.1)</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>44.1 (30.2-58.0)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>63.0 (52.8-73.2)</td>
</tr>
<tr>
<td>Ethionamide</td>
<td>44.7 (25.9-63.6)</td>
</tr>
<tr>
<td>P-aminosalicylic acid</td>
<td>5.3 (2.2-8.3)</td>
</tr>
<tr>
<td>Second-line injectable</td>
<td>13.0 (5.0-20.9)</td>
</tr>
<tr>
<td>Ofloxacin</td>
<td>13.0 (5.0-21.0)</td>
</tr>
<tr>
<td>XDR-TB</td>
<td>4.9 (1.0-8.8)</td>
</tr>
</tbody>
</table>
Discussion
South Africa has experienced a stable MDR-TB epidemic spanning a ten-year period. However, resistance to individual drugs is on the increase. The concerning increase in rifampicin mono-resistance, primarily among new cases, is suggestive of transmission although the underlying reasons for its occurrence may relate to sub-optimal dosing of rifampicin, the bioavailability of rifampicin being affected by drug interactions, and intermittent compliance with treatment.\(^7\)\(^8\)

The use of Xpert MTB/RIF as the primary diagnostic tool\(^9\) will be important for detecting those cases with rifampicin resistance early, together with rapid initiation of therapy to halt further transmission.

The increased occurrence of isoniazid mono-resistance is also of concern and can be missed with the current national diagnostic algorithm. Although its impact on patient outcomes is poorly defined, rifampicin mono-resistance could potentially impact MDR-TB levels in the future as undetected cases may effectively continue to receive rifampicin mono-therapy. Strengthening the continuation phase regimen needs consideration and the potential role of isoniazid preventative therapy (IPT) as a driver of this increase in the South African context needs to be investigated.\(^10\) Furthermore, the effectiveness of IPT could be reduced as the prevalence of any isoniazid resistance is almost 10% which makes it essential to conduct a risk-benefit assessment.

The province of greatest concern is Mpumalanga which shows higher MDR-TB rates than the national average, as was also observed in the previous survey. This province shares a border with Swaziland, the country with the highest MDR-TB prevalence in the region\(^11\) and with well recognized chronic health system issues. Although the RR/MDR-TB prevalence in Mpumalanga was higher, the rate of isoniazid mono-resistance was similar to that of other provinces.

Rates of resistance to fluoroquinolones and pyrazinamide, both considered companion drugs for new regimens for TB treatment, have shown to be low among TB cases, rendering these regimens suitable for implementation within South Africa. Contrasted with this are the high rates of resistance to ethionamide and pyrazinamide among MDR–TB cases, which may be contributory factors to the poor outcomes seen in these cases. XDR-TB rates nationally were below 5% among MDR-TB cases and lower than the global average, indicating that the problem is not widespread across the country. Taking into consideration the high pre-existent levels of second-line drug resistance and the loss of one or both key drugs among pre-XDR and XDR cases, achieving improved outcomes is likely to require the use of a new regimen incorporating newly introduced drugs.

Recommendations
The findings from the South African TB DRS 2012-14 provide important information which could potentially guide future planning and address the current poor outcomes among drug-resistant TB cases. The following recommendations are made based on the findings of the survey:

- Urgent implementation of interventions in Mpumalanga:
  - Identify potential risk factors for targeted interventions.
  - Improve cross-border cooperation with Swaziland and Mozambique, utilising existing agreements achieved through the SADC declaration.
  - Conduct further research to fully define drivers of resistance in the province.
- Develop interventions to curb IMR and its secondary effects:
Strengthen the current first-line regimen for continuation phase by adding ethambutol with or without pyrazinamide (RHE or RHZE), or institute appropriate measures for early identification of IMR.

Assess the contribution and effectiveness of IPT in the light of increasing cases of resistance.

- Monitor transmission of RMR, research underlying reasons for RMR and institute appropriate interventions:
  - Regularly review transmission data from the surveillance system.
  - Review current rifampicin dosing and conduct rifampicin bioavailability studies in the four- and two-drug combination with and without antiretroviral therapies (ARTs) in areas with high RMR occurrence.
  - Undertake close monitoring of the quality of drugs used in the standard regimen.

- Conduct randomised control trials (RCTs) and review existing standard of care data to assess the effectiveness of existing first and second-line regimens.

- Monitor use of the Xpert MTB/Rif assay for early detection of rifampicin resistance and improve early detection of second-line drug resistance.

- Optimize the existing MDR-TB regimen and consider shortening the MDR-TB regimen with triage algorithm for appropriate patient selection.

- Design an appropriate regimen for pre-XDR/XDR patients using a combination of new drugs.

- Maintain and enhance the routine surveillance system for monitoring existing and new drug resistance and reduce the proportion of diagnosed cases not started on treatment.


Acknowledgements
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References


