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# The disconnect between a national tuberculosis drug resistance survey and treatment outcomes: a lost opportunity

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## SUMMARY

We linked results from the Fourth Botswana National Drug Resistance Survey (DRS), 2007–2008, to patient records from the national Electronic Tuberculosis Registry to determine treatment outcomes. Of 915 new patients, 651 (71%) had treatment data available. Completion or cure was achieved for 10/15 (67%, 95%CI 42–85) with isoniazid monoresistance, (6/16, 38%, 95%CI 18–61) with multidrug resistance, while 73% (391/537, 95%CI 69–76) were susceptible to first-line drugs. The analysis was limited because of unavailable treatment records and undocumented outcomes. Prospective analyses following DRSs should be considered to ensure adequate outcome data.

### Keywords

drug; resistance; survey; treatment; outcome

IN MANY SETTINGS with a high tuberculosis (TB) burden, drug susceptibility testing (DST) is unavailable, and standardized treatment regimens are given based on patient category (new or retreatment).[1] Outcomes of treatment with standard regimens for cases of drug-resistant TB are not well characterized. In particular, the adequacy of standard first-line treatment in cases with isoniazid (INH) monoresistance has been challenged, highlighting the need to examine this issue further.[2–5] In Botswana, the Fourth National Drug Resistance Survey (the survey) conducted from 2007 to 2008 provided DST results for over 1 000 patients.[6] Our objective was to assess differences in treatment outcome between cases by DST result.

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*Conflict of interest:* none declared.

## ASPECT OF INTEREST

All cases from the survey with complete DST results for INH, rifampin (RMP), ethambutol and with documented treatment category were included in the analysis.[6] INH and RMP resistance was confirmed at two laboratories, and at a third for discrepancies. Records from the Botswana National Electronic Treatment Register (ETR) for all cases registered from 2007 to 2008 were cross-matched to electronic DRS records by patient name with probabilistic matching using LinkPlus beta version (Centers for Disease Control and Prevention, Atlanta, GA, USA).[7] Patients' sex and age were also compared. We reviewed paper district TB registers from 2007 to 2008 and extracted data from the national electronic multidrug-resistant TB (MDR-TB) database and paper MDR-TB treatment records. Treatment outcome was derived from the MDR-TB treatment outcome for patients who received MDR-TB treatment and from the ETR or paper registers for all others. New cases were treated with the standard new patient regimen, and retreatment cases with the standard retreatment regimen with first-line drugs.[1,8] Treatment regimens for MDR-TB varied.

## RESULTS

A total of 1052 survey cases (915 documented as 'new' and 137 as 'retreatment') were reviewed. A total of 1139 potential treatment records (including multiple records for some patients) were found. All MDR-TB cases were included in the analysis; other cases meeting criteria detailed in the Figure were included. A total of 148 cases — 118/915 (13%) new and 30/137 (22%) retreatment cases — matched no treatment record by name (i.e., had no evidence of being registered for treatment). In summary, 651/915 (71%) new and 48/137 (35%) retreatment cases had treatment records that met the inclusion criteria for analysis. Comparing all cases to the subset included in analysis, among cases documented as new in the survey, 82% (749/915) had isolates susceptible to first-line drugs compared to 82% (537/651) among the subset with valid treatment records that were included in the outcome analysis. Among cases documented as retreatment in the survey, 77% (105/137) were susceptible to first-line drugs compared to only 65% (31/48) of those with valid treatment records.

Overall, 17% (106/635, 95% confidence interval [CI] 14–20) of new cases and 32% (13/41, 95%CI 20–47) of retreatment cases did not have final treatment outcome recorded ('not evaluated') (Table), including 68/635 (11%, 95%CI 8–13) new cases and 9/41 (22%, 95%CI 12–37) retreatment cases who transferred out or moved but did not have a final treatment outcome recorded in the ETR. Among new cases, the proportion with treatment completion or cure was 67% (10/15, 95%CI 42–85) for cases with INH monoresistance and 73% (391/537, 95%CI 69–76) for those with susceptibility to first-line drugs; among cases with documented treatment outcome, the proportion with an unfavorable outcome (lost to follow-up, failed, died) was 23% (3/13, 95%CI 8–50) for cases with INH monoresistance compared to 14% (63/454, 95%CI 11–17) for cases susceptible to first-line drugs, although this difference was not statistically significant (Fisher's exact test, $P = 0.41$).

Of 32 patients with MDR-TB, 16 were documented as treated with MDR-TB regimens. Of these, 6 had completion or cure, 7 had an unfavorable outcome, and 3 had outcome not

evaluated (2 on treatment at time of data collection, 1 stopped) (Table). Among the remaining 16, 7 were treated with standard regimens, 3 had potential standard treatment records excluded from analysis, and 6 had no treatment record.

## DISCUSSION

This analysis was limited by the small proportion of cases with available treatment records, and of these, with documented final outcome. A large proportion of treatment records that were matched by name were excluded based on incongruent classification, timing or location of treatment. Some of these records may have been incongruent because they did not belong to the same patient. However, this finding also suggests that in some cases treatment classification may not be correctly recorded at the time of specimen collection for the survey or of registration for anti-tuberculosis treatment, that some patients may experience large gaps in timing between diagnosis and treatment, and that some patients may be highly mobile, with diagnostic evaluation at one site and treatment elsewhere. Furthermore, for some patients we found no documentation of registration for anti-tuberculosis treatment (apparent 'primary default').[9] If these patients truly did not initiate treatment despite being diagnosed with TB, this would indicate an important missed opportunity for reducing patient morbidity and mortality, and for reducing transmission, including of drug-resistant TB.

A larger proportion of records were unavailable for analysis for retreatment than for new patients. The reasons for this are not known, but it is notable that many retreatment cases were excluded for apparent incongruent treatment classification between survey and treatment records. Use of patient-rather than episode-based electronic systems (e.g., the Smart Care System, Smart Care, Lusaka, Zambia; http://www.smartcare.org.zm/Home.aspx) could help prevent misclassification of previously treated patients as 'new'. Routine testing for RMP resistance (e.g., using Xpert®MTB/RIF, Cepheid, Sunnyvale, CA, USA) and the use of patient-based electronic databases could ensure proper follow-up for patients with MDR-TB.

Although there is guidance for MDR-TB program management and outcome reporting and for conducting drug resistance surveys, guidance on surveys does not address analysis of treatment outcome.[8,10,11] Because drug resistance surveys represent a large investment in laboratory testing, yield of these data should be maximized. Given the limitations of retrospective review as described here, to better understand the outcomes of standardized treatment regimens under program conditions for TB cases with various patterns of drug resistance, prospective analyses of anti-tuberculosis treatment outcomes in anti-tuberculosis drug resistance surveys should be considered.

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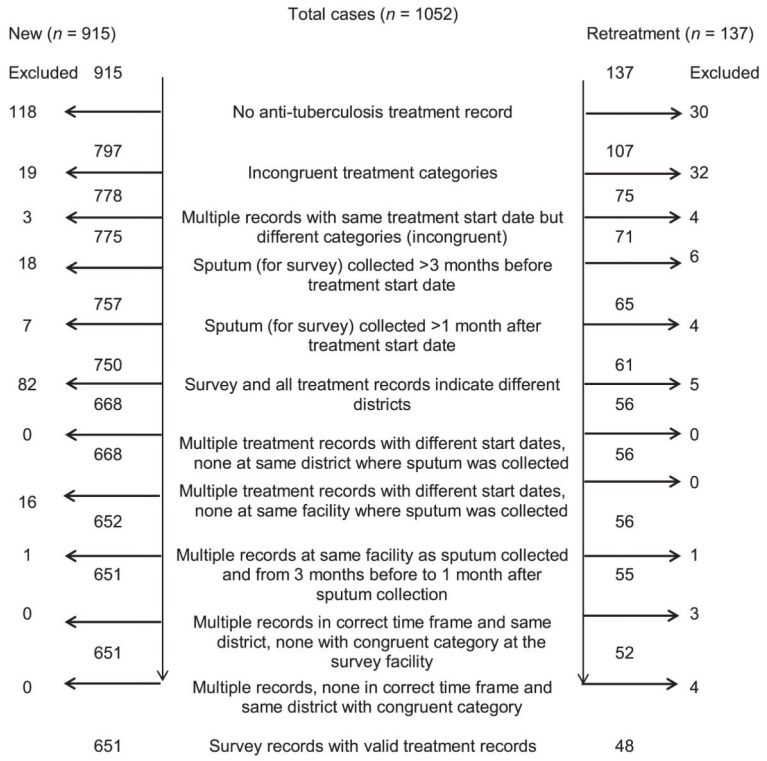


**Figure.**

Flow chart of cases included in outcome analysis. Note: Records were included if they were for MDR-TB cases or for non-MDR-TB cases if 1) treatment category was congruent with that of the survey record (new or retreatment), 2) date of sputum collection for the survey was within 3 months before to 1 month after the anti-tuberculosis treatment start date, and 3) site of anti-tuberculosis treatment and of sputum collection for the drug resistance survey were in the same district. If multiple treatment records matched the above criteria and two records had the same name and same treatment start date and at least one matched by district, both records were used; otherwise, only records from the same facility where sputum was collected for the survey were used. Exclusion criteria were applied sequentially as described from top to bottom of this figure. Some records may have met multiple exclusion criteria. Total numbers of new and retreatment records included in analysis include MDR-TB cases. MDR-TB = multidrug-resistant tuberculosis.

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**Table**

Treatment outcome by patient category and drug resistance pattern among cases enrolled in the survey with available anti-tuberculosis treatment records

| | Treatment outcome | | | | | |
|---|---|---|---|---|---|---|
| | **Completed or cured *n* (%)** | **Lost to follow-up *n* (%)** | **Died *n* (%)** | **Failed *n* (%)** | **Not evaluated *n* (%)** | **Total** |
| Resistance patterns | | | | | | |
| New patients [*] | | | | | | |
| First-line susceptible [†] | 391 (73) | 34 (6) | 28 (5) | 1 (0) | 83 (15) | 537 |
| INH-monoresistant | 10 (67) | 1 (7) | 1 (7) | 1 (7) | 2 (13) | 15 |
| RMP-monoresistant | 3 (60) | 0 (0) | 1 (20) | 1 (20) | 0 (0) | 5 |
| SM-monoresistant | 36 (68) | 2 (4) | 3 (50) | 0 (0) | 12 (23) | 53 |
| PZA-monoresistant | 2 (33) | 1 (17) | 0 (0) | 0 (0) | 3 (50) | 6 |
| EMB-monoresistant | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 |
| Polyresistant [‡] | 7 (39) | 1 (6) | 2 (11) | 2 [§] (11) | 6 (33) | 18 |
| Total | 450 (71) | 39 (6) | 35 (6) | 5 (1) | 106 [¶] (17) | 635 |
| Retreatment patients [*] | | | | | | |
| First-line susceptible [†] | 11 (35) | 6 (19) | 4 (13) | 0 (0) | 10 (32) | 31 |
| INH-monoresistant | 1 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 1 |
| RMP-monoresistant | 2 (40) | 1 (20) | 0 (0) | 0 (0) | 2 (40) | 5 |
| SM-monoresistant | 2 (100) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 2 |
| PZA-monoresistant | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 |
| EMB-monoresistant | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 (0) | 0 |
| Polyresistant [‡] | 1 (50) | 0 (0) | 0 (0) | 0 (0) | 1 (50) | 2 |
| Total | 17 (41) | 7 (17) | 4 (10) | 0 (0) | 13 [#] (32) | 41 |
| MDR-TB regimen [**] | | | | | | |
| New [*] | 1 (17) | 1 (17) | 2 (33) | 0 (0) | 2 (33) | 6 |
| Retreatment [*] | 0 (0) | 0 (0) | 1 (100) | 0 (0) | 0 (0) | 1 |
| MDR-TB | 6 (38) | 5 (31) | 2 (13) | 0 (0) | 3 [††] (19) | 16 |
| Total | 7 (30) | 6 (26) | 5 (23) | 0 (0) | 5 (23) | 23 |

[*] All new patients had standard treatment for new cases (2HRZE/4HR) except one with treatment ‘other’; all retreatment patients had the standard retreatment regimen (2HRZES/1HRZE/5HRE), with the exception of one patient with MDR-TB who was treated with treatment regimen ‘other’.

[†] Susceptible to INH, RMP and EMB and no documented resistance to PZA.

[‡] Resistant to two or more drugs; may include INH or RMP, but not both.

[§] Later treated with MDR-TB regimen based on initial DST result showing MDR-TB. One had completed or cure, one stopped the MDR-TB regimen based on subsequent DST showing no MDR-TB.

[¶] Includes 68 noted as transferred out (to another reporting district) or moved (to another facility in the same reporting unit), but no final treatment outcome is available.

[#] Includes 9 noted as transferred out (to another reporting district) or moved (to another facility in the same reporting unit), but no final treatment outcome is available.

[**] Resistant to at least INH and RMP.

[††] One case stopped treatment at 19 months after sputum conversion; two cases were on treatment at time of data collection.

INH, H = isoniazid; RMP, R = rifampicin; SM, S = streptomycin; PZA, Z = pyrazinamide; EMB, E = ethambutol; MDR-TB = multidrug-resistant tuberculosis.