

Trends in drug-resistant tuberculosis in a gold mining workforce in South Africa,

2002 – 2008

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SUMMARY

Setting and objective: To describe trends in drug-resistant tuberculosis in two gold mining workforces, South Africa, 2002-8.

Design: Tuberculosis programme data analysis.

Results: Tuberculosis case notification rates decreased between 2002-8, from 4006 to 3018/100000 and 3192 to 2468/100000 for companies A and B respectively. HIV prevalence exceeded 80% in tuberculosis episodes with known status. The proportion of tuberculosis episodes with multi-drug resistance (MDRTB) increased: among previously treated cases, from 6/129 (4.7%) to 17/85 (20.0%) and from 4/38 (10.4%) to 7/28 (25.0%) in companies A and B respectively (tests for trend, $p < 0.001$ company A; $p = 0.304$ company B). Case notifications of MDRTB increased during 2002-8, from 39.8 to 122.9/100000/year in company A and 57.8 to 96.8/100000/year in company B. Coverage of second-line drug susceptibility testing among MDRTB episodes was low. Previous treatment exposure was a strong risk factor for MDRTB (prevalence ratio 8.78 [95% confidence interval 5.94 – 12.97] in previously treated versus untreated).

Conclusion: Despite decreasing tuberculosis notifications overall, notifications of MDRTB and proportions of episodes with MDR increased in the larger company. Cure must be ensured in first episodes to prevent acquired resistance. Improved coverage of culture, drug susceptibility testing and HIV testing is required to allow treatment to be optimised.

Keywords: Multi-drug resistance, HIV, drug susceptibility testing, isoniazid, rifampicin

INTRODUCTION

Tuberculosis case notification rates (CNR) among gold miners in South Africa are very high, exceeding 4000/100000 in 1999 [1], compared with 960/100000 nationally in South Africa in 2008 [2], attributable to high prevalence of HIV (29% in 2001) and silicosis [3, 4]. In the 1990s, the proportion of tuberculosis episodes with multi-drug resistance was stable and relatively low in miners [5, 6], estimated at 1.0% and 2.8% among previously untreated and previously treated episodes respectively [5]. More recently in South Africa, transmission of drug-resistant tuberculosis and resistance to second line antituberculous agents has been reported in association with HIV treatment facilities [7] and gold miners [8].

The aims of this study were: 1) to describe trends in CNR and prevalence of drug resistance among tuberculosis episodes from 2002-8; 2) to analyse the effect of previous tuberculosis treatment and HIV infection on drug resistance in a gold mining workforce, in a period preceding a large-scale tuberculosis prevention intervention.

STUDY POPULATION AND METHODS

We analysed routine data from 2002-8 in two mining companies in Gauteng province, South Africa (companies A and B). From 2006, companies participated in "Thibela TB", a cluster-randomised trial of community-wide isoniazid preventive therapy (IPT) [9]. Of seven mine shafts contributing data for this analysis, two were intervention (starting June and July 2007) and five control clusters.

Tuberculosis episodes were included in this study if treatment started between 1st January 2002 and 31st December 2008. Episodes were then included in analysis of drug resistance if they were culture positive for *Mycobacterium tuberculosis* (without concurrent non-tuberculous mycobacteria (NTM)), with drug susceptibility testing (DST) results available for at least isoniazid and rifampicin.

Policy in both companies from 2002-8 was to perform culture and DST for rifampicin and isoniazid routinely for retreatment cases and cases responding poorly to treatment. Company A also routinely tested previously untreated cases. Second-line DST was only performed among multi-drug resistant tuberculosis (MDRTB) episodes after 2006. Medical records (electronic where available, supplemented by paper records), laboratory records and tuberculosis registers were reviewed retrospectively. For paper-based source data, for logistic reasons, complete data were only extracted for episodes with DST results.

Definitions

The CNR was defined as the number of tuberculosis treatment episodes recorded in the tuberculosis register during a given period of time, per 100000 population, with denominators calculated as below (see "data analysis").

HIV status was defined as positive if a positive rapid test or ELISA result was recorded before tuberculosis treatment was started or up to six months afterwards, and negative if a negative result was recorded after the start of tuberculosis treatment or up to six months before.

Drug resistance in previously untreated versus previously treated cases was defined as drug-resistant tuberculosis occurring in an individual with fewer than 30 versus 30 or more days previous tuberculosis treatment exposure. Changes in drug susceptibility during treatment were also counted as episodes of drug resistance in previously treated cases and included in calculating CNR for drug-resistant tuberculosis and prevalence ratios for drug resistance by treatment history and HIV status.

MDRTB was defined as *M. tuberculosis* resistant to at least rifampicin and isoniazid.

Rifampicin and isoniazid monoresistance were defined as *M. tuberculosis* resistant to rifampicin but not isoniazid and isoniazid but not rifampicin, respectively.

Data analysis

In order to avoid counting re-registrations of the same tuberculosis disease episode, which can occur when treatment is interrupted and then restarted, we excluded re-registrations for the same individual within six months after the planned end of treatment, unless there was a change in drug susceptibility between registrations, for calculations of CNR for and proportions with resistance. In calculating DST coverage (company A), episodes with mixed *M. tuberculosis* and NTM isolated were excluded from numerator and denominator to allow for difficulties in interpreting DST. Episodes included in the calculation of CNR, but excluded from estimates of episodes with DST, comprised those excluded for re-registrations; cultures not done; culture negative; no DST; cultures positive for NTM only or mixed *M. tuberculosis*/NTM. Prevalence ratios were analysed using combined data from both companies. For calculating proportions with drug resistance, denominators comprised episodes with DST available. Based on existing literature [10] we anticipated that previous treatment would be the main risk factor for drug resistance. We also investigated the role of HIV infection. Chi-squared tests were used to compare proportions and the score test for trend to assess for linear trend. The Poisson model was used to assess for linear trend and departures from linear trend in CNR by year. Where there was evidence for departure from linear trend the p-value for the overall test is quoted.

Company workforce data (mean workforce size each calendar year) were used to estimate denominators for CNR. Company A provided monthly figures from September 2003; company B provided 1-8 figures annually from September 2003. September 2003 denominators were used for earlier estimates. Permanent employees and short term contractors were included in denominators, since both contributed to numerators.

Data were entered using EpiData (www.epidata.dk) and analysed using STATA v10 (STATA Corporation, Texas).

Laboratory methods

From 2002 laboratories serving mine health services performed culture and DST using BACTEC™ Mycobacterial Growth Indicator Tube 960 system [BD Diagnostics System, Sparks MD].

Ethical approval

Research Ethics Committees of the London School of Hygiene and Tropical Medicine and the University of KwaZulu Natal approved the study.

RESULTS

Study population

Workforce size, 2002-8, ranged from 15239 to 19476 (company A) and from 6671 to 8414 (company B). Median age was 42 years (interquartile range [IQR] 37, 47 years) for company A and 44 years (IQR 40, 48) for company B.

Numbers included in analysis and case notification rates (CNR)

In company A, with 4268 tuberculosis episodes registered from 2002-8, CNR decreased from 4006/100000 in 2002 to 3018/100000 in 2008 (overall $p < 0.001$). Of 4268 episodes registered, exclusions from the analyses for this study were: 1807 not culture positive; 78 re-registrations; 133 mixed *M. tuberculosis*/NTM; 243 lacked DST for isoniazid and/or rifampicin. Therefore 2007/4268 (47.0%) registered, culture positive *M. tuberculosis* episodes with DST for rifampicin and isoniazid were included in analyses for company A (figure 1). Of these, 617/2007 (30.7%) were retreatment episodes. Five episodes with change in drug susceptibility during treatment were also included.

For company B, 1472 episodes were registered from 2002-8 and CNR decreased from 3192/100000 in 2002 to 2468/100000 in 2008 (test for trend, $p < 0.001$). Of 1472 episodes registered, exclusions from the analyses for this study were: 1014 not culture positive or culture positive with DST not available for rifampicin and/or isoniazid; 43 re-registrations. Therefore 415/1472 (28.2%) registered, culture positive *M. tuberculosis* episodes with DST for rifampicin and isoniazid were included in the below analyses for company B (figure 1). Of these, 200/415 (48.2%) were retreatment episodes. Four episodes with change in drug susceptibility during treatment were also included.

CNR and numbers of culture-positive *M. tuberculosis* episodes with DST for rifampicin and isoniazid after all exclusions are shown in figure 2.

Coverage of drug susceptibility testing

For company A, first-line DST (at least rifampicin and isoniazid) was done in 2007/2250 (89.2%) of *M. tuberculosis* culture-positive episodes. For episodes registered as retreatment episodes, DST coverage was 617/691 (89.3%) in total and 82/82 (100%) in 2008. Coverage was not calculable for company B as complete data were only collected on episodes with DST available.

HIV prevalence

In company A, from 2002-8, HIV status was documented for 1329/2012 (66.1%) episodes with DST available. Of these, 1160 (87.3%) were HIV-infected. The prevalence of HIV infection increased from 149/173 (86.1%) in 2002 to 153/167 (91.6%) in 2008 (test for trend $p = 0.086$).

In company B, from 2002-8, HIV status was documented for 157/419 (37.5%) episodes with DST available. Of these, 135 (86.0%) were HIV-infected.

Trends in drug-resistant tuberculosis: case notification rates (previously treated and untreated cases combined)

In company A, MDRTB CNR increased from 39.8/100000/year in 2002 to 122.9/100000/year in 2008 (test for trend $p=0.004$) and CNR for isoniazid monoresistant episodes changed by year (overall $p<0.001$) without linear trend. CNR for rifampicin monoresistant episodes was 17.1/100000 in 2002 and 55.3/100000 in 2008. In company B, MDRTB CNR increased from 57.8/100000/year in 2002 to 96.8/100000/year in 2008 and CNR for isoniazid monoresistant episodes was 72.2/100000 in 2002 and 72.6/100000 in 2008, neither showing evidence of linear increase (tests for trend, $p=0.65$ and $p=0.73$ respectively) (figure 3).

Trends in drug resistance among previously untreated cases

In company A, the proportion of previously untreated cases with MDRTB rose from 2/245 (0.8%) in 2002 to 3/125 (2.4%) in 2008 (test for trend, $p=0.005$). In company B, few MDRTB episodes were registered among previously untreated cases (figure 4).

Trends in drug resistance among previously treated cases

In company A, MDRTB occurred in 6/129 (4.7%) of episodes with previous treatment exposure in 2002 and 17/85 (20.0%) in 2008 (test for trend $p<0.001$). Rifampicin monoresistance occurred in 2/129 (1.6%) in 2002 and 7/85 (8.2%) in 2008 (figure 5).

In company B only two episodes were rifampicin monoresistant. MDRTB occurred in 4/38 episodes (10.4%) in 2002 and 7/28 (25.0%) in 2008 (test for trend, $p=0.304$) (figure 5).

Second-line DST

From 2002-8, in company A, 88/124 (71.0%) of MDRTB cases were tested for ethambutol and streptomycin susceptibility and 48/88 (54.5%) were resistant to both drugs. In company B, 11/44 (25.0%) of MDRTB cases were tested: 8/11 were streptomycin resistant, with 3/8 also ethambutol resistant.

For company A, 7/69 MDRTB episodes in 2006-8 had second line DST results available. In company B, second line DST was documented in 1/20 MDRTB episodes in 2006-8.

Drug resistance by previous treatment exposure and HIV status

Table 1 shows the proportions with drug resistance among previously treated versus untreated episodes. Previous treatment was a strong risk factor for drug resistance, with prevalence ratio for MDRTB of 8.78 (95% confidence interval [CI] 5.94 – 12.97) and for rifampicin monoresistance of 6.11 (95% CI 2.60 – 14.37) in previously treated versus untreated cases. Previous treatment exposure was less strongly associated with isoniazid monoresistance (prevalence ratio 1.45 [95% CI 1.15 – 1.83]). Results were very similar when stratified by company (data not shown).

Among previously untreated episodes, there was no evidence of association between HIV infection and MDRTB, with prevalence ratio for HIV-infected versus HIV-uninfected of 0.95 (95% CI 0.28 – 3.15) (table 2). Among previously treated cases, 87/500 (17.4%) episodes were MDRTB among HIV co-infected, versus 8/72 (11.1%) among HIV uninfected (prevalence ratio 1.57 [95% CI 0.79 – 3.09]). There was no evidence for interaction between HIV status and previous treatment exposure ($p=0.202$).

Among previously treated cases, HIV infection was not associated with rifampicin resistance. 102/500 (20.4%) episodes were rifampicin resistant (monoresistant or MDRTB) among HIV

infected, versus 9/72 (12.5%) among HIV uninfected (prevalence ratio 1.63 [95% CI 0.86 – 3.08]) (table 2).

DISCUSSION

Although CNR among miners have fallen since 2002, they remain very high. Reasons for the observed decrease are not clear, but may include higher antiretroviral therapy coverage, which we will investigate in future work. We do not know of any factors that may have caused completeness of notifications to change over the study period. High CNR may partly be attributed to case detection through annual workforce surveillance by chest radiograph. Comparisons with South African national rates must consider the denominator population of a workforce with strong tuberculosis risk factors.

Despite CNR decreasing overall, MDRTB CNR in company A increased. Although several factors may be contributory, including artefact due to higher DST coverage, we consider this to be unlikely to account for all the increase in MDRTB CNR seen here; which is more likely to be a true increase as rifampicin resistance is superimposed on existing isoniazid resistance. Isoniazid monoresistance CNR changed by year in company A, but without evidence of linear increase in either company. Previous studies suggest that rifampicin levels are reduced among HIV-infected individuals [11] and that individual pharmacokinetic variability accounts for some rifampicin resistance [12]. Drugs used in mine health services are obtained from approved national sources and rifampicin under-dosing is unlikely. We do not have data on treatment adherence in this population but are not aware of any factors that may have caused it to change with time.

Proportions with rifampicin- and multi-drug resistance are higher than reported previously in similar populations [5, 6]. Such resistance was associated with previous treatment exposure, consistent with acquisition of resistance due to previous inadequate treatment, as seen in a

similar workforce [13]. However, two studies using genotyping, one in a mining population, suggest that circulating MDR strains are also transmitted among previously treated individuals [8, 14] and this will account for a proportion of the resistance seen here.

HIV infection was not a strong risk factor for drug resistance. A South African national survey in 2001-2 suggested some association between HIV infection and MDRTB in previously treated cases [15]. Similarly for rifampicin monoresistance, these results do not exclude an effect of HIV infection among previously treated cases, but numbers are insufficient to conclude that observations are not due to chance. International data, collated in a systematic review, were also inconclusive on this point [16].

There is inherent uncertainty regarding population CNRs of drug-resistant disease in this observational study as numerators are relatively small. Bias cannot be excluded due to suboptimal DST coverage. DST may have been more likely to be performed when resistance was suspected, resulting in overestimation of observed proportions, where DST was not done systematically. It is unlikely that changes in proportions with MDRTB are entirely due to changes in testing coverage as our data show increased DST coverage over the study period, which may reflect less selective, more routine testing, or possibly an increase in proportions with suspected drug resistance.

HIV status was not documented for all episodes notified, but HIV prevalence among episodes with known status was very high throughout the study period. Strategies for improved HIV testing and treatment coverage are essential to reduce risk of tuberculosis [17], particularly in view of recent evidence [18, 19, 20] and revised World Health Organization recommendations for early antiretroviral therapy for all HIV-infected individuals with active tuberculosis [21]. This is particularly important for those with drug-resistant tuberculosis and HIV, among whom mortality is high [22, 23, 24].

This study was conducted in a period preceding widespread IPT. There has been concern that IPT may lead to increased isoniazid resistance, although there is no evidence for this [25, 26]. Considering that the intervention began in parts of this workforce from June 2007, the period of this analysis is likely to be too early to reflect its impact. Furthermore, IPT is unlikely to have resulted in the increase in MDRTB seen here and there was no evidence of increasing isoniazid mono-resistance.

CONCLUSIONS

Despite decreasing tuberculosis CNR, MDRTB CNR and proportions of episodes with drug resistance increased in the larger company. It is essential to ensure cure of first episodes to prevent acquired resistance and to ensure prompt recognition, treatment and cure of drug-resistant tuberculosis to prevent further resistance and transmission. Tuberculosis control in this high risk population is challenging and improved coverage of culture, DST and HIV testing is essential to ensure appropriate treatment for tuberculosis.

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Author contributions

CLvH: Study design and implementation, data analysis, paper writing

KLF: Study concept and design, statistical and epidemiological input, data analysis, manuscript review

VNC: Study implementation and design, manuscript review

JJL: Statistical advice, data analysis, manuscript review

GJC: Study design, context advice, manuscript review

ADG: Study concept and design, epidemiological advice, paper writing

Other contributions to the study:

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TABLES AND FIGURES

Table 1: Association of antituberculous drug susceptibility patterns with treatment history, 2002 to 2008: Data from companies A and B combined.

Drug susceptibility pattern	Previously untreated episodes n=1547 n (%)	Previously treated episodes n=884 ² n (%)	Prevalence ratio (95% confidence interval)*
Rifampicin and isoniazid susceptible	1359 (87.8)	619 (70.0)	1.0 (reference)
Isoniazid resistant, rifampicin susceptible	152 (9.8)	106 (12.0)	1.45 (1.15-1.83)
Rifampicin resistant, isoniazid susceptible	7 (0.5)	20 (2.3)	6.11 (2.60 – 14.37)
MDR	29 (1.9)	139 (15.7)	8.78 (5.94-12.97)
Isoniazid any resistance	181 (11.7)	245 (27.7)	2.41 (2.03-2.87)

¹Prevalence ratios calculated separately for each drug susceptibility pattern compared with rifampicin and isoniazid susceptible episodes, ratio compares those previously treated with those previously untreated

²Total includes all retreatment episodes, plus 9 changes in DST during treatment of first tuberculosis episodes and 58 first treatment episodes for which DST was done on specimens taken after 30 or more days' treatment exposure

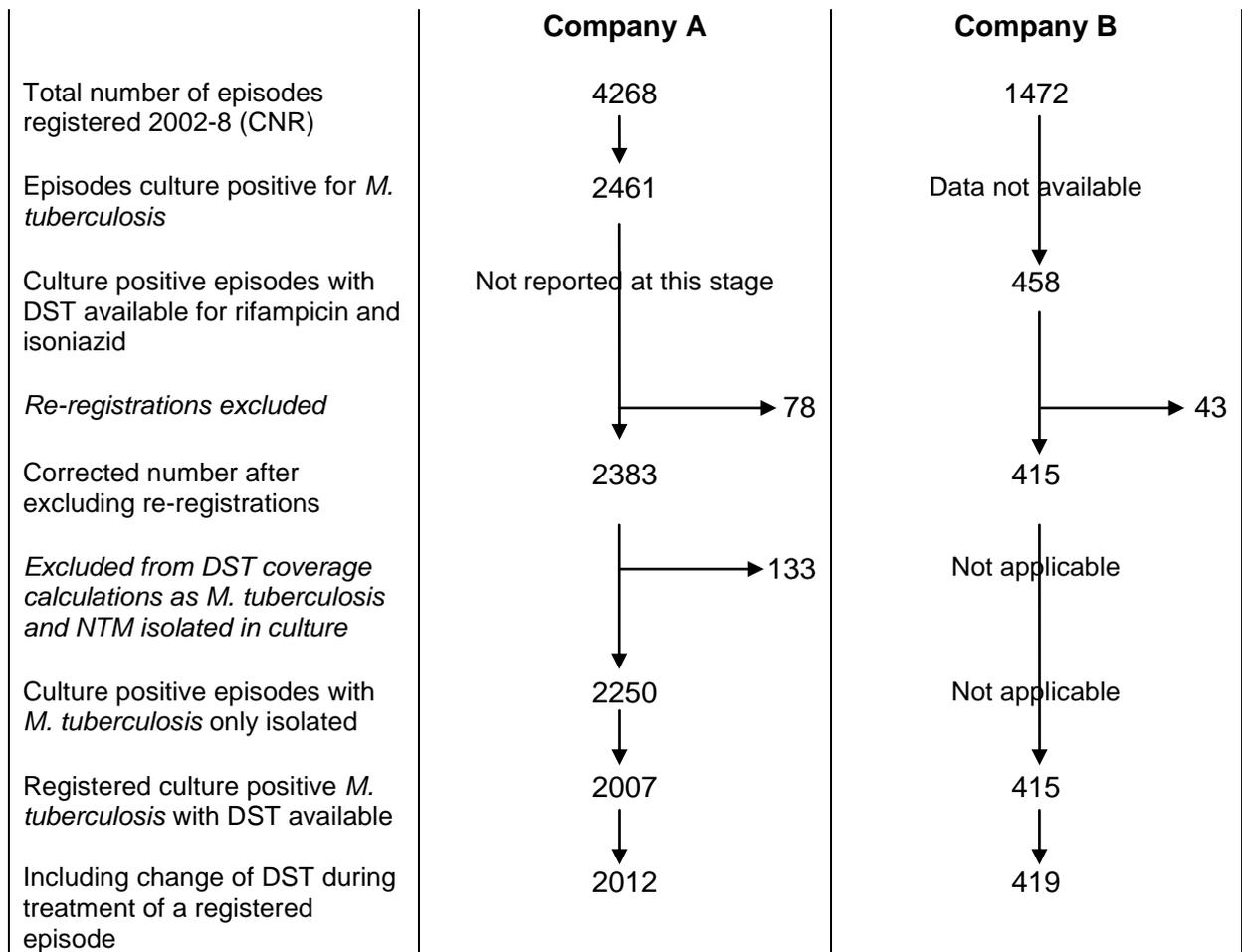
1 **Table 2:** Multi-drug resistance, rifampicin and isoniazid resistance among tuberculosis episodes in HIV- infected and -uninfected individuals in
 2 companies A and B combined

Number of episodes	HIV infected: resistant/total ¹ (%)	HIV uninfected: resistant/total ¹ (%)	Prevalence ratio ² (95% confidence interval)	p-value (chi-squared test)
MDR				
Previously untreated	19/795 (2.4)	3/119 (2.5)	0.95 (0.28-3.15)	0.931
Previously treated	87/500 (17.4%)	8/72 (11.1)	1.57 (0.79-3.09)	0.180
Any rifampicin resistance (MDR plus rifampicin monoresistance)				
Previously untreated	21/795 (2.6)	5/119 (4.2)	0.63 (0.24-1.64)	0.340
Previously treated	102/500 (20.4)	9/72 (12.5)	1.63 (0.86-3.08)	0.113
Any isoniazid resistance (MDR plus isoniazid monoresistance)				
Previously untreated	108/795 (13.6)	12/119 (10.1)	1.35 (0.77-2.37)	0.292
Previously treated	144/500 (28.8)	18/72 (25.0)	1.15 (0.75-1.76)	0.503

3 ¹Denominators include all registered episodes with DST available and known HIV status (n=1480) plus six cases of change of drug susceptibility during
 4 treatment in individuals with known HIV status (total=1486)

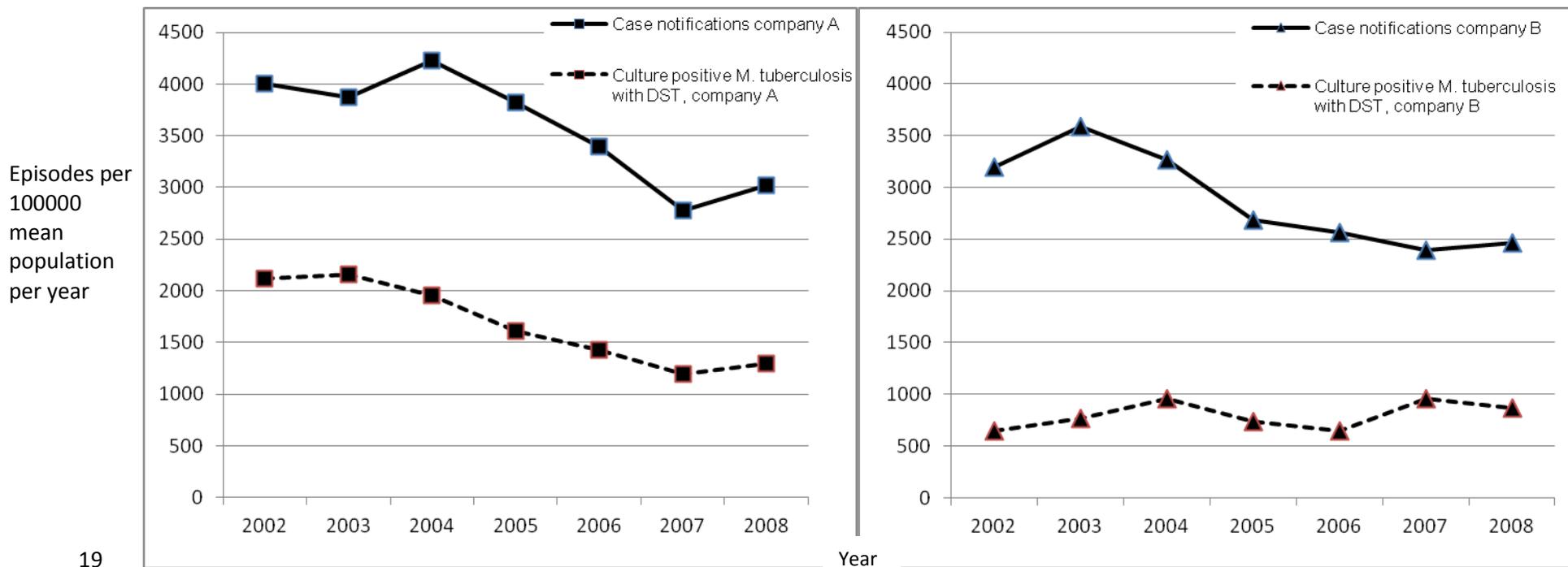
5 ²Prevalence of resistance pattern specified, in HIV infected versus uninfected

6 **Figure 1:** Flow chart of numbers of tuberculosis episodes included at each stage of results
 7 and analyses



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16 **Figure 2:** Tuberculosis case notifications and episodes of culture positive *M. tuberculosis* with drug susceptibility testing (DST) results available
 17 for at least rifampicin and isoniazid, per 100000 per year, 2002 to 2008, companies A (left) and B (right). Table shows numbers of cases
 18 notified for each year, per company, and number (percentage) culture positive *M. tuberculosis* with DST.



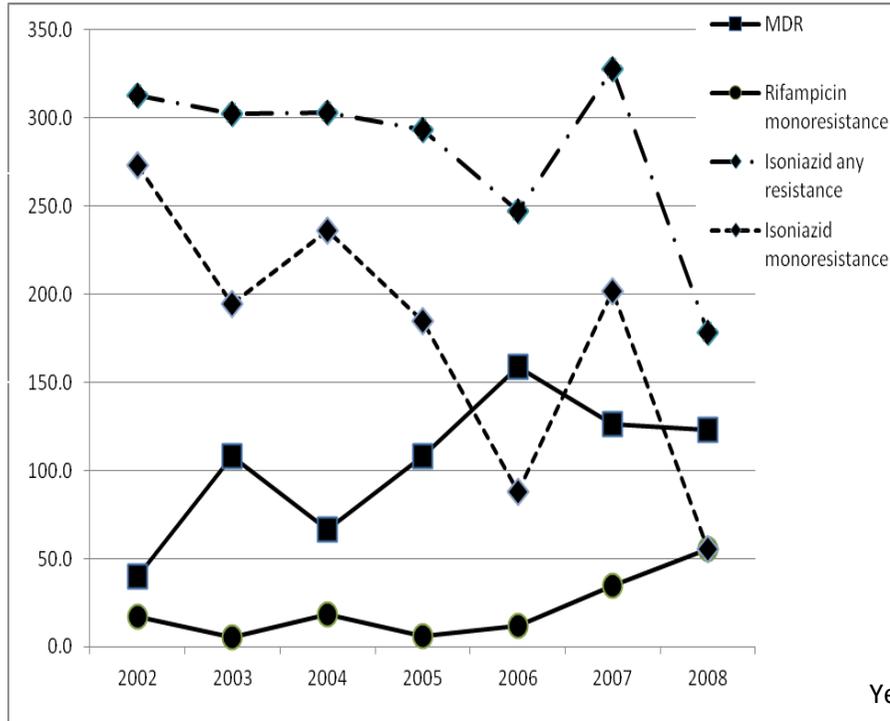
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Year	2002	2003	2004	2005	2006	2007	2008	Total Comp A	2002	2003	2004	2005	2006	2007	2008	Total Comp B
Cases notified	704	717	697	599	578	482	491	4268	221	247	222	189	190	199	204	1472
Number (%) culture positive with DST	373 (53.0)	400 (55.8)	323 (46.3)	252 (42.0)	242 (41.9)	207 (42.9)	210 (42.8)	2007 (47.0)	45 (20.4)	53 (21.5)	65 (29.3)	52 (27.5)	48 (25.3)	80 (40.2)	72 (35.3)	415 (28.2)

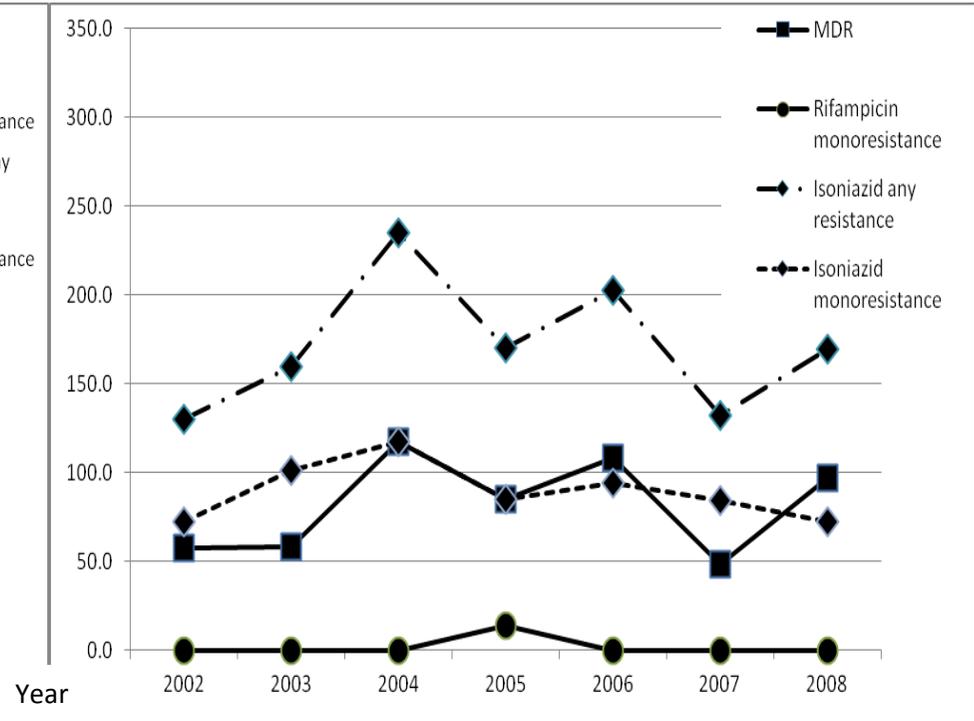
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21 **Figure 3:** Case notification rates for drug-resistant tuberculosis 2002-8: companies A (left) and B (right) Table shows numbers of episodes per
 22 100,000 mean population as plotted

Episodes
per 100000
mean
population
per year



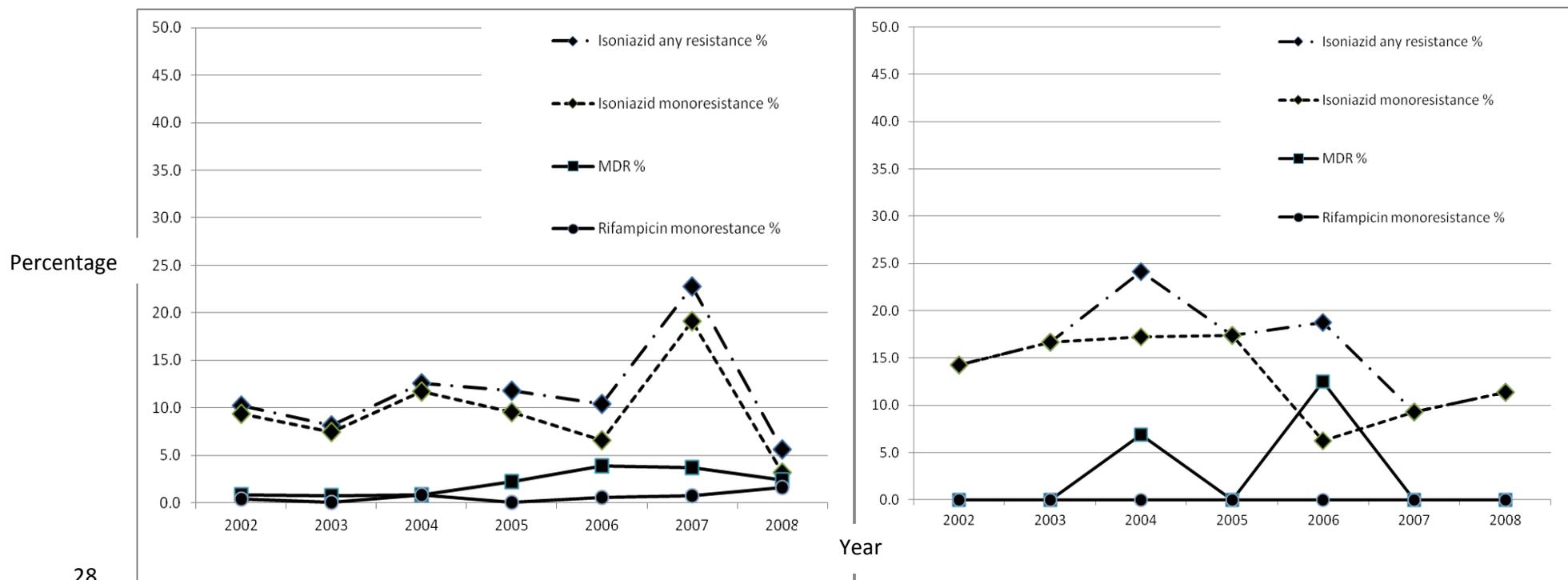
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Number of episodes	2002	2003	2004	2005	2006	2007	2008	2002	2003	2004	2005	2006	2007	2008
MDR	7	20	11	17	27	22	20	4	4	8	6	8	4	8
Rif monores.	3	1	3	1	2	6	9	0	0	0	1	0	0	0
INH monores.	48	36	39	29	15	35	9	5	7	8	6	7	7	6

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25 **Figure 4:** Drug resistance as a percentage of all *M. tuberculosis* culture positive episodes among previously untreated cases, 2002-8:
 26 companies A (left) and B (right)
 27

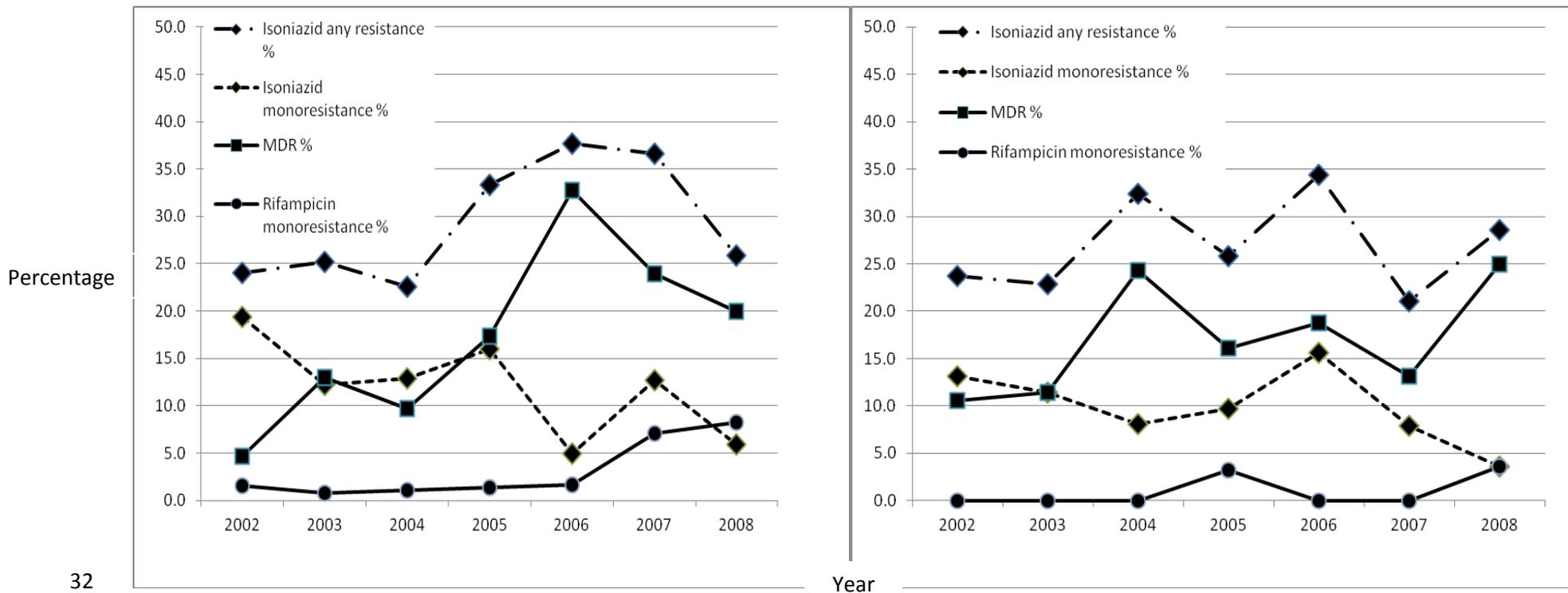


28

Numbers with resistance (%)	2002	2003	2004	2005	2006	2007	2008	2002	2003	2004	2005	2006	2007	2008
MDR	2 (0.8)	2 (0.7)	2 (0.9)	4 (2.2)	7 (3.8)	5 (3.7)	3 (2.4)	0	0	2 (6.9)	0	2 (12.5)	0	0
Rif monores.	1 (0.4)	0	2 (0.9)	0	1 (0.5)	1 (0.7)	2 (1.6)	0	0	0	0	0	0	0
INH monores.	23 (9.4)	20 (7.4)	27 (11.7)	17 (9.6)	12 (6.6)	26 (19.1)	4 (3.2)	1 (14.3)	3 (16.7)	5 (17.2)	4 (17.4)	1 (6.3)	4 (9.3)	5 (11.4)
Total episodes (denominators)	245	270	231	178	182	136	125	7	18	29	23	16	43	44

29

30 **Figure 5:** Drug resistance as a percentage of all *M. tuberculosis* culture positive episodes among previously treated cases, 2002-8: companies
 31 A (left) and B (right)



32

Percentage with resistance	2002	2003	2004	2005	2006	2007	2008	2002	2003	2004	2005	2006	2007	2008
MDR	6 (4.7)	17 (13.0)	9 (9.7)	13 (17.3)	20 (32.8)	17 (23.9)	17 (20.0)	4 (10.4)	4 (11.4)	9 (24.3)	5 (16.1)	6 (18.8)	5 (13.2)	7 (25.0)
Rif monores.	2 (1.6)	1 (0.8)	1 (1.1)	1 (1.3)	1 (1.6)	5 (7.0)	7 (8.2)	0	0	0	1 (3.2)	0	0	1 (3.6)
INH monores.	25 (19.4)	16 (12.2)	12 (12.9)	12 (16.0)	3 (4.9)	9 (12.7)	5 (5.9)	5 (13.2)	4 (11.4)	3 (8.1)	3 (9.7)	5 (15.6)	3 (7.9)	1 (3.6)
Total episodes (denominators)	129	131	93	75	61	71	85	38	35	37	31	32	38	28

