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Notification of relapse and other previously treated tuberculosis in the 52 health districts of South Africa

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SUMMARY

OBJECTIVE: To investigate the extent to which relapse and other previously treated tuberculosis (TB) contribute to the notified TB burden in South Africa.

DESIGN: We conducted an ecological analysis at the level of the 52 South African health districts using national electronic TB register data. We included all bacteriologically confirmed TB cases treated for presumed drug-susceptible TB in 2011. Treatment history information was based on recorded patient categories (new vs. retreatment).

RESULTS: Relapse and other previously treated TB cases constituted between 7.6% and 40% (median 17%, interquartile range 12–22) of all bacteriologically confirmed TB cases in the 52 South African districts. Multivariable analysis suggested that districts with higher proportions of previously treated TB cases had higher TB case notification rates ($P < 0.001$), lower estimates of antenatal human immunodeficiency virus (HIV) prevalence in the district population ($P < 0.001$) as well as lower HIV co-infection rates ($P < 0.001$) among new TB cases.

CONCLUSION: Relapse and other previously treated TB cases contributed substantially to the notified TB burden in several South African health districts, particularly those with high case notification rates and lower antenatal HIV prevalence. Additional efforts to prevent TB among previously treated people, such as strengthening treatment monitoring and/or secondary preventive therapy, should be considered.

KEY WORDS: tuberculosis; previous treatment; recurrence; relapse; reinfection

IN TUBERCULOSIS (TB) CONTROL programmes worldwide, a variable proportion of the TB burden is detected among individuals with a history of TB treatment. These are classified as 'relapse cases' if they had completed their previous treatment successfully[1] regardless of whether they were 'true' relapses (i.e., endogenous reactivation of TB) or experienced a new TB episode following reinfection. Other previously treated cases also include those in whom the previous treatment had failed, who were lost to follow-up (LTFU) during treatment and in whom the previous treatment outcome is not known.

Previously treated TB poses unique challenges to TB control programmes. It is more difficult to diagnose than new disease, given the low specificity of radiography[2] and of rapid molecular diagnostic assays,[3] and more often presents as drug-resistant TB.[4] Treatment outcomes are usually less favourable than those among individuals treated for a first episode of TB.[5,6]

The extent to which relapse and other previously treated TB contribute to the overall number of notified TB cases varies considerably among countries. In 2015, previously treated cases represented between 1.5% and 35% of TB case notifications in the 30 high TB burden countries defined by the World Health Organization.[7] The highest proportions (≥30%) are usually found in countries with a high burden of multidrug-resistant (MDR) TB.[8]

An unexpectedly high proportion of relapse and other previously treated TB (~30% over several years[9,10]) has also been reported among notified TB cases in Cape Town, a South African metropole with a high TB incidence. Reports of high local rates of reinfection TB after previous successful treatment,[11,12] particularly among human immunodeficiency virus (HIV) infected individuals,[9] as well as the majority of previously treated cases reporting a history of successful treatment (~75%[9]), suggest that

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poor treatment outcomes alone may not sufficiently explain this observation. The high relative burden of previously treated TB in Cape Town is in contrast to lower proportions reported for South Africa as a whole (7.8% previously treated TB cases in 2015)[7] and other areas in the country,[13–15] suggesting considerable variation at the sub-country level.

Here, we describe the proportion of relapse and other previously treated TB among diagnosed TB cases in the 52 South African health districts. We aimed to investigate if this proportion varied with the local TB case notification rate, estimates of HIV prevalence and outcomes of TB treatment in these districts.

METHODS

Study setting

South Africa has a population of 55 million people[16] and consists of nine provinces and 52 health districts. In 2015, an estimated 7.0 million (13%) people were living with HIV,[17] and an estimated 454 000 people developed TB (57% of whom were HIV-co-infected), a TB incidence rate of 834 cases per 100 000 individuals. Of estimated incident TB cases, 63% were notified/had access to standard TB treatment.[16]

Data sources

Data for TB cases treated in 2011 in South Africa were extracted from the national electronic TB register (ETR.Net).[18] The register was introduced by the National TB Programme in 2003 and is the database of record for all TB cases treated for presumed drug-susceptible TB (i.e., those in whom drug susceptibility test [DST] results were negative for rifampicin resistance, or who were treated for drug-susceptible TB in the absence of DST results). We chose 2011 as the year of analysis due to known inconsistencies of reporting treatment history from 2012 onwards, which is associated with suspension of the category II retreatment regimen in South Africa.

ETR.Net includes case-based data captured from paper-based treatment registers at the sub-district-level. The study data were validated and cleaned; duplicate entries and case records kept in the register despite pretreatment confirmation of drug-resistant TB, had been removed. We also used published population census estimates for 2011[19] to calculate district-level TB case notification rates, and HIV prevalence estimates from the 2011 National Antenatal Sentinel HIV prevalence survey.[20]

Study definitions

We relied on standard definitions for TB recording and reporting in South Africa.[21] The term 'bacteriologically confirmed' is reserved for TB cases in whom *Mycobacterium tuberculosis* was confirmed using Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA), smear microscopy or culture. Previously treated TB cases included relapse (retreatment after treatment success) and other previously treated cases (Table 1). The latter included the categories 'retreatment after failure', 'retreatment after loss to follow-up' and 'other retreatment'.

Study design

We conducted an ecological analysis at the level of the 52 South African health districts. The study population included all bacteriologically confirmed TB cases (adults, children, all forms of TB) who started treatment for presumed drug-susceptible TB in 2011. The outcome measure (dependent variable) was the proportion of previously treated TB cases, expressed as a proportion of all bacteriologically confirmed TB cases. We considered explanatory variables describing rates of TB and HIV in the district population, as well as HIV co-infection and treatment outcomes among TB cases with a first treatment episode (Table 1).

Data analysis

We used STATA v14.2 (Stata Corp, College Station, TX, USA) for data analysis. Our analysis comprised descriptive statistics for previously treated TB cases and their subcategories (relapse vs. other previously treated). We investigated district-level associations between the outcome measure (i.e., the proportion of previously treated TB) and each of the explanatory variables. The Spearman correlation coefficient (r) and its two-tailed significance was estimated. Then, we included significantly associated explanatory variables in a generalised linear model with a logit link of the binomial family[22] to evaluate the independence of univariable associations. Secondary analysis was based on all TB cases (i.e., by including also those who were clinically diagnosed or for whom bacteriological results were not documented). To assess if the results of our analysis were robust to temporal trends in HIV co-infection and treatment outcomes, we replaced same-year estimates with those among new TB cases treated in the preceding 2 years.

Ethics statement

This study forms part of a larger study whose protocol was approved by the Ethics Committee of the Faculty of Medicine and Health Sciences of Stellenbosch University, Tygerberg, South Africa (N16/07/088). The South African National Department of Health (Pretoria, South Africa) gave consent to use the ETR.Net data and to publish the results.

RESULTS

Overview of the study population

In 2011, 182 455 bacteriologically confirmed TB cases were treated for presumed drug-susceptible TB in South Africa. Bacteriologically confirmed cases

Table 1 Study definitions

Description	Definition/explanation
Subcategories of previously treated TB cases	
Relapse	TB cases recorded in the treatment register under the standard patient category 'relapse', assigned to patients who were declared 'cured' or 'treatment completed' at the end of a prior TB treatment episode and have now developed TB again
Other previously treated	TB cases recorded in the treatment register under the standard patient categories: • 'Retreatment after failure': TB cases who received treatment and remained or became smear- or culture-positive at the end of the treatment period • 'Retreatment after loss to follow-up': TB cases who completed ≥1 month of treatment and returned after interrupting treatment for ≥2 consecutive months • 'Other retreatment': TB cases who were previously treated but the outcome of previous treatment was not known
Dependent variable (district-level)	
Proportion of previously treated TB cases	Previously treated TB cases (including both subcategories 'relapse' and 'other previously treated') as a proportion of all (new and previously treated) TB cases
Explanatory variables (district-level)	
TB case notification rate	New and relapsed TB cases per 100 000 of the district population
HIV prevalence	Percentage of HIV infection in the district population (estimated among pregnant women attending antenatal care)
HIV co-infection among new TB cases	Percentage of new TB cases with documented HIV-positive status; HIV status is usually recorded on the basis of either a positive HIV test conducted at the beginning of TB treatment or positive HIV status self-reported by the patient
Treatment success	Percentage of new TB cases who were bacteriologically cured and those who completed their treatment and were considered successfully treated (but without bacteriological confirmation of cure)
Death during treatment	Percentage of new TB cases who died during TB treatment (from any cause)
Loss to follow-up from treatment	Percentage of new TB cases who were LTFU during TB treatment (i.e., those who interrupted their treatment for ≥2 consecutive months)

TB = tuberculosis; HIV = human immunodeficiency virus; LTFU = lost to follow-up.

represented 46% of all TB cases, and included few children cases and extra-pulmonary TB cases (Table 2). Of the 182 455 bacteriologically confirmed TB cases, 35 633 (20%) had been treated previously, the majority (21 084, 59%) of whom were relapse cases. Characteristics of new and previously treated TB cases are shown in Table 3.

Previously treated TB at the district level

The proportion of bacteriologically confirmed TB

Table 2 Overview of TB cases in South Africa who started treatment for presumed drug-susceptible TB in 2011

	Bacteriologically confirmed*				Total	
	Yes		No			
Variable	*n*	Col%	*n*	Col%	*n*	Col%
Total	182 455	–	216 943	–	399 398	–
Treatment history						
New	146 822	80.5	186 606	86.0	333 428	83.5
Previously treated, relapse	21 084	11.6	8 038	3.7	29 122	7.3
Previously treated, other	14 549	8.0	22 299	10.3	36 848	9.2
Sex						
Female	81 372	44.6	104 319	48.1	185 691	46.5
Male	101 083	55.4	112 624	51.9	213 707	53.5
Age, years						
0–14	4 121	2.3	45 145	20.8	49 266	12.3
≥15	178 334	97.7	171 798	79.2	350 132	87.7
Site of TB disease						
Extra-pulmonary	1 828	1.0	50 360	23.2	52 188	13.1
Pulmonary	180 627	99.0	166 583	76.8	347 210	86.9
Information on HIV status						
Not documented	27 806	15.2	45 626	21.0	73 432	18.4
Documented	154 649	84.8	171 317	79.0	325 966	81.6
HIV status (among documented)						
Negative	59 758	38.6	53 122	31.0	112 880	34.6
Positive	94 891	61.4	118 195	69.0	213 086	65.4

* Bacteriological confirmation (using any method) documented in the TB treatment register.
TB = tuberculosis; HIV = human immunodeficiency virus.

Table 3 Characteristics of bacteriologically confirmed new and previously treated TB cases in South Africa, 2011

Variable	New cases		Previously treated cases	
	n	Col%	*n*	Col%
Total	146 822	100.0	35 633	100.0
Sex				
Female	67 953	46.3	13 419	37.7
Male	78 869	53.7	22 214	62.3
Age, years*				
0–14	3 863	2.6	258	0.7
≥15	142 959	97.4	35 375	99.3
Site of TB disease				
Extra-pulmonary	1 608	1.1	220	0.6
Pulmonary	145 214	98.9	35 413	99.4
Information on HIV status				
Not documented	23 132	15.8	4 674	13.1
Documented	123 690	84.2	30 959	86.9
HIV status (among documented)				
Negative	47 838	38 7	11 920	38.5
Positive	75 852	61.3	19 039	61.5
Treatment outcome†				
Treatment success	102 420	79.1	21 540	69.1
Lost to follow-up	7 999	6.2	3 813	12.2
Died‡	7 438	5.8	2 259	7.2
Failure§	1 423	0.7	541	0.8
Transferred out	5 916	4.6	1 582	5.1
Not evaluated	4 252	3.3	1 451	4.7

* Median age: 34 years among new and 38 years among previously treated TB cases.
† Excludes treatment outcomes for 17 343 new and 1451 previously treated TB cases who moved during treatment and their outcomes were thus documented in another reporting unit.
‡ The proportion of TB cases who died during treatment varied by HIV status. Among new cases, it was 2.6 times higher among HIV-positive (5006/65 929, 7.6%) than among HIV-negative (1280/43 913, 2.9%) individuals. Among previously treated cases, it was 2.0 times higher among HIV-positive (1462/16 207, 9.0%) than among HIV-negative (493/11 020, 4.5%) individuals.
§ Includes 526 new and 304 previously treated TB cases in whom TB treatment was discontinued due to detected rifampicin-resistant TB.
TB = tuberculosis; HIV = human immunodeficiency virus.

cases with a history of previous TB treatment varied at the district level between 7.6% and 40% (median 17%, interquartile range [IQR] 12–22) (Figure 1A). The majority were relapse cases (median 61%, IQR 50–70). Relapse was more common than other previously treated TB, particularly in districts with a high proportion of previously treated cases overall (Figure 1B).

We observed a strong association between higher TB case notification rates per 100 000 population and the proportion of previously treated TB among bacteriologically confirmed TB cases in the districts ($r = 0.75$, $P < 0.001$; Figure 2A). Estimates of district-specific antenatal HIV prevalence were inversely associated with the proportion of previously treated TB cases ($r = –0.45$, $P < 0.001$) (Figure 2B). We also found a strong inverse association between the proportion of HIV co-infections among new cases and the proportion of previously treated TB cases ($r = –0.70$, $P < 0.001$) (Figure 3A).

There was no association between the treatment success rate among new TB cases and the proportion of previously treated TB cases ($r = –0.03$, $P = 0.842$) (Figure 3B). However, upon univariable analysis, both lower proportions of death during TB treatment ($r = –0.29$; $P = 0.035$) (Figure 3C) and higher proportions of loss to follow-up from TB treatment ($r = 0.59$, $P < 0.001$) (Figure 3D) were associated with higher proportions of previously treated TB.

Upon multivariable analysis, TB case notification rates ($P < 0.001$), antenatal HIV prevalence ($P < 0.001$) and HIV co-infection ($P < 0.001$) among new TB cases remained independently associated with the proportion of previously treated TB cases (Table 4). Upon inclusion of TB cases without documented bacteriological confirmation in the analysis, and replacement of same-year estimates of HIV co-infection and treatment outcomes with those from the preceding 2 years did not change the observed associations meaningfully.

DISCUSSION

We showed that previously treated TB cases, partic-

Table 4 Generalised linear regression of the proportion (fraction) of previously treated TB among bacteriologically confirmed TB cases in the 52 South African health districts, 2011; the model explains 87% of the variation in the observed proportions of previously treated TB

Variable	Univariable regression			Multivariable* regression		
	OR	95%CI	*P* value	OR	95%CI	*P* value
Total population						
TB case notification rate (per 1000 population)	1.321	1.247–1.400	<0.001	1.161	1.108–1.216	<0.001
Antenatal HIV prevalence, %	0.969	0.957–0.982	<0.001	0.987	0.977–0.994	<0.001†
New TB cases						
Age, years, median	0.954	0.890–1.022	0.180	—		
Sex: male, %	1.064	1.026–1.103	0.001	1.027	1.013–1.042	<0.001
HIV co-infection, %	0.973	0.968–0.978	<0.001	0.985	0.980–0.990	<0.001‡
Treatment success, %	1.005	0.983–1.027	0.670	—		
Death during treatment, %	0.892	0.837–0.951	<0.001	0.968	0.935–1.001	0.058
Loss to follow-up from treatment, %	1.146	1.088–1.207	<0.001	1.017	0.987–1.047	0.265

* Adjusted for all other variables in the model, except where indicated.
† Adjusted for all other variables except for HIV co-infection among new cases (due to collinearity).
‡ Adjusted for all other variables except for HIV prevalence in the population (due to collinearity).
TB = tuberculosis; OR = odds ratio; CI = confidence interval; HIV = human immunodeficiency virus.

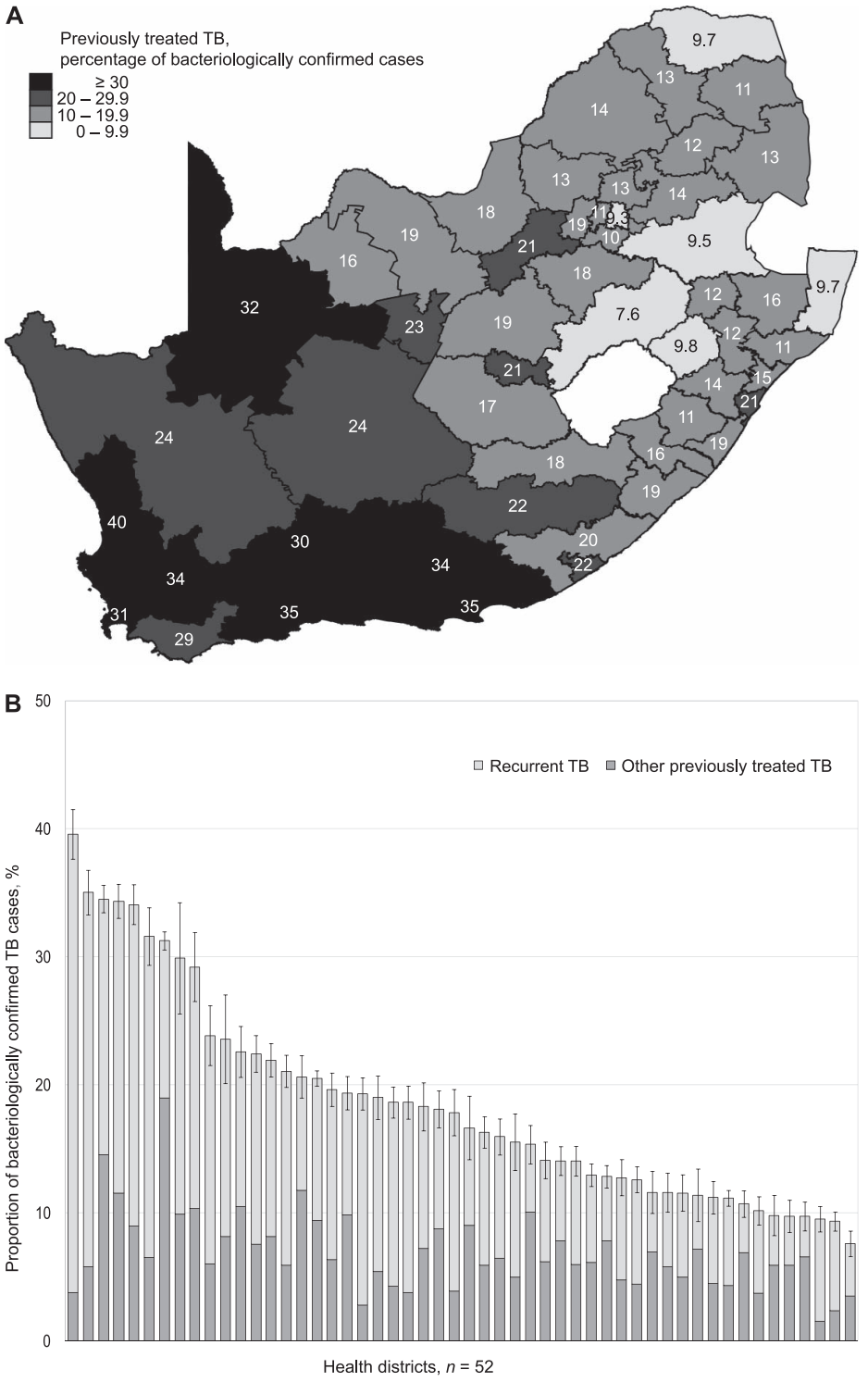

Figure 1 Relapse and other previously treated TB cases as a proportion of all bacteriologically confirmed TB cases in the 52 South African districts, 2011. **A)** Overall proportions; **B)** subcategories of previously treated TB; error bars denote 95% confidence intervals of total proportions.

ularly those with prior successful treatment (relapse), constituted a large proportion of notified TB cases in several parts of South Africa (i.e., between 20% and 40% of bacteriologically confirmed TB in 19 of the 52 districts). Our findings compare well with data from a recent national drug resistance survey (2014) which showed that between 14% and 35% of TB patients sampled in the nine provinces had a history of previous TB treatment.[23] Our findings are consistent with high rates of TB after successful treatment reported from several high-incidence communities in Southern Africa.[12,24–26] They are also consistent with

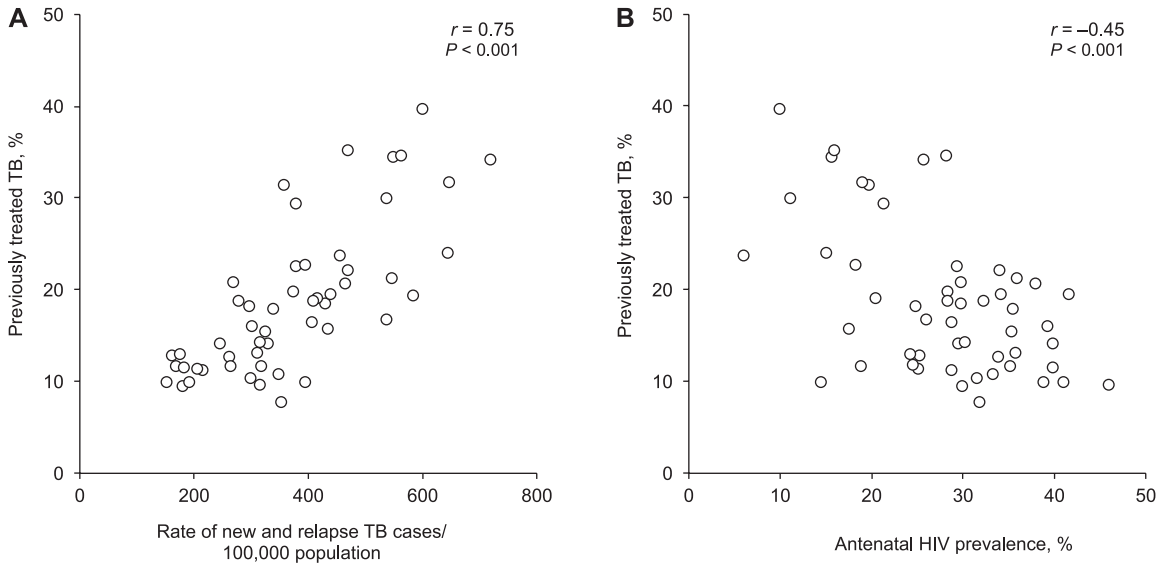

Figure 2 Correlation between the proportion of previously treated TB among bacteriologically confirmed TB cases and each of the following: **A)** TB case notification rate, and **B)** population-level HIV prevalence in 52 South African districts, 2011.

recent observations from TB prevalence surveys in the Western Cape Province of South Africa which showed that previously treated adults represented a relatively large subgroup (10–15%) of the adult population and constituted a large proportion of prevalent TB cases detected.[27,28]

The extent to which previously treated people contributed to TB case notifications varied substantially across the districts, and we explored some of the population-level factors associated with this variation. The rate of treated TB cases per 100 000 population determines the relative size of the previously treated subpopulation in the districts. Higher case notification rates may indicate higher forces of infection and reinfection in districts which may drive TB among previously treated people.[29] Molecular studies from settings with a high force of infection have suggested that rates of TB due to reinfection after previous successful treatment are several-fold higher than those of first-time TB.[11,12,24]

We observed an inverse relationship between antenatal HIV prevalence and the proportion of previously treated TB cases. In districts with a high HIV prevalence, a large proportion of the general population was highly susceptible to TB, including those without a history of TB treatment, which possibly resulted in larger numbers of people with first-time TB. Also, HIV-infected people with a first TB episode most likely represented a group of people with more advanced immunosuppression than those who did not develop TB and may thus experience a higher mortality risk during and after TB treatment. We speculate that higher mortality among HIV-infected new TB cases may have contributed to lower proportions of previously treated TB in districts of high HIV prevalence. Our data suggest that HIV co-infected new TB cases had a higher probability of death during TB treatment than non-HIV-infected cases (see ‡ in Table 3 legend), findings that are consistent with earlier research in South Africa.[14]

We did not find evidence that variation in standard treatment outcomes (i.e., lower rates of treatment success or higher rates of loss to follow-up) explained the high proportions of previously treated TB in the districts. Loss to follow-up during treatment may lead to TB reactivation and subsequent retreatment.[11,30] The crude association between loss to follow-up and the proportions of previously treated TB in the districts did not persist when controlling for other variables. This finding is consistent with the observation that most previously treated cases in the districts were classified as ‘relapse’ cases (previous treatment success).

Our study had limitations. It was based on routinely collected data that may have been incomplete and inaccurate. TB treatment history is usually self-reported; under-reporting[31] can contribute to the observed variation in previously treated TB. This was an explorative ecological analysis of indicators measured crudely at the level of health districts and therefore precluded causal inference about the complex individual-level determinants of TB among previously treated people.

By using data from a single year, we assumed that HIV co-infection rates and treatment outcomes in the districts were relatively stable over time in order to be associated with the local burden of previously treated TB. Secondary analysis, in which we considered HIV co-infection and treatment outcomes in previous years, did not change our results meaningfully.

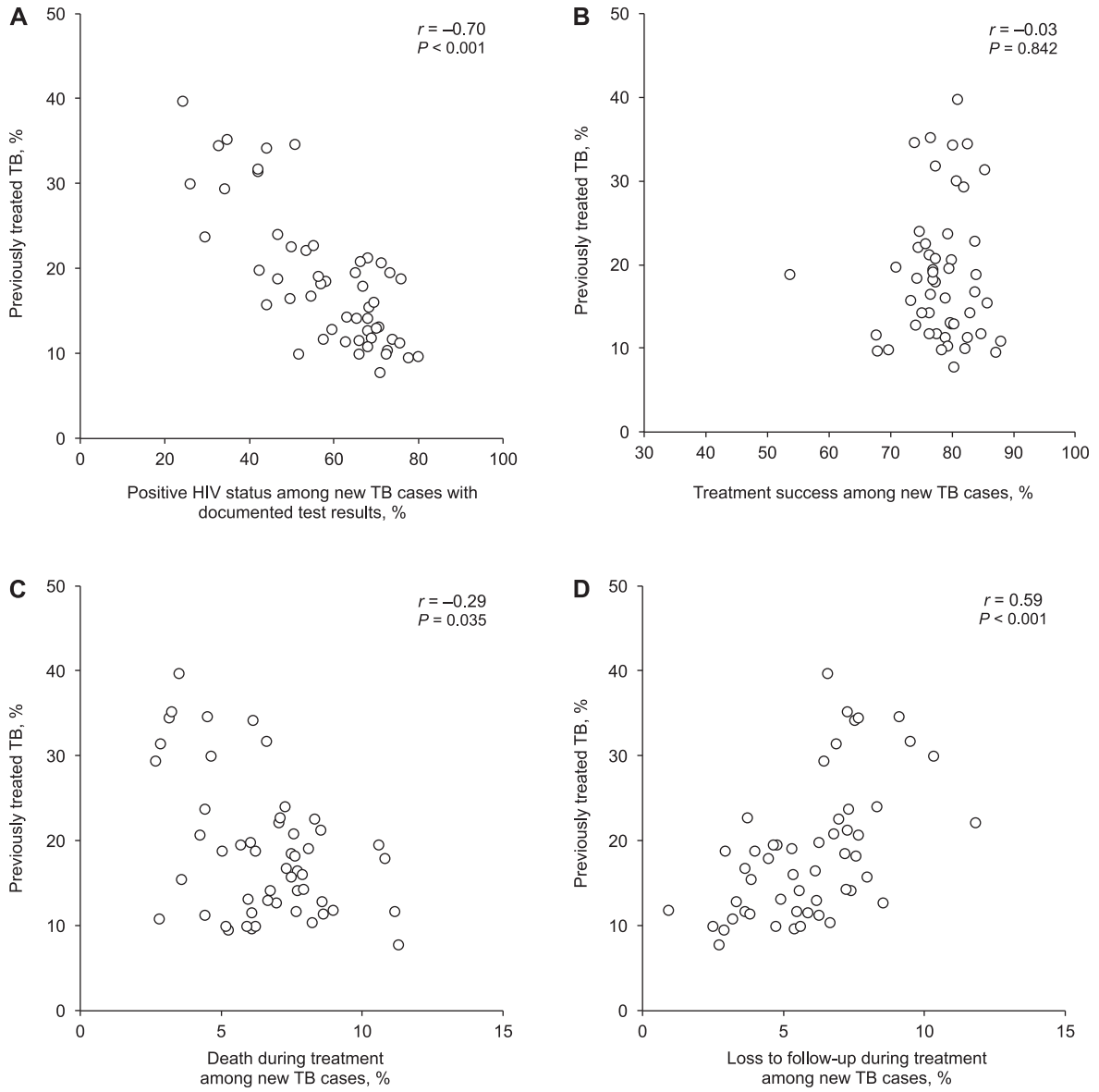

Figure 3 Correlation between the proportion of previously treated TB and the following characteristics of bacteriologically confirmed new TB cases in 52 South African districts, 2011 **A)** HIV status; **B)** treatment success; **C)** death during treatment; and **D)** LTFU during treatment.

However, temporal trends may have contributed to the variation in previously treated TB.

We could not investigate the role of antiretroviral treatment (ART) in the districts. While ART reduces the risk of TB,[32] it is also expected to increase survival among TB patients. Whether the expansion of ART in South Africa will lead to increased survival and more previously treated TB cases or reduce the number of previously treated TB cases due to immune reconstitution and lower the risk of relapse and/or disease progression following reinfection is not known.

Finally, our study was based on TB cases treated for presumed drug-susceptible TB; systematic data on drug susceptibility testing were not available from routinely recorded data sources. The role of drug resistance as a cause or consequence for previously treated TB in the South African districts is not known.

Our findings have implications for TB control. Substantial proportions of previously treated TB cases in several South African districts mean that local TB control programmes face the considerable challenges of diagnosing and treating TB in this group. For example, South Africa has meanwhile implemented Xpert countrywide as the primary diagnostic tool to replace smear microscopy (notably, after data for our study were recorded). In districts in which previous TB treatment is common, the known high false-positive rate of Xpert among previously treated presumptive TB cases[3] is expected to lead to substantial over-diagnosis. Re-treating and curing a large number of former TB patients who are also

more likely to be LTFU during treatment[5,6] may be particularly challenging in these districts. Moreover, repeated exposure to TB drugs represents a key risk factor for acquired drug resistance.[33] Whether drug-resistant TB is more likely to emerge in districts where previously treated TB is common is not known.

Sizable proportions of previously treated TB cases raise questions about the performance of TB treatment under routine programme conditions. Intermittent and irregular treatment, as well as undetected drug resistance, have been identified as risk factors for recurrent TB.[25] Understanding how programme performance relates to the high burden of previously treated TB will therefore be crucial.

High burdens of previously treated TB underscore the need for additional efforts to prevent TB among previously treated people, as emphasised more than one decade ago.[34] A recent modelling study of TB in suburban Cape Town projected that the benefits of targeted case finding and secondary prevention among people who completed TB treatment could extend to the population level.[35]

CONCLUSION

Previously treated people contribute substantially to the diagnosed TB burden in South Africa, particularly in areas with high TB rates. More research is needed to understand individual and health-system determinants that lead to repeated TB episodes. Our analysis supports evidence that previously treated people constitute a large and important TB high-risk group in South Africa. Efforts are warranted to address the specific needs of this group to prevent TB and the adverse health and socio-economic consequences that the disease continues to have in their families' lives.

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RÉSUMÉ

OBJECTIF : Déterminer dans quelle mesure les rechutes et les autres cas de tuberculose (TB) déjà traitée contribuent au nombre de cas notifiées en Afrique du Sud.

SCHÉMA : Nous avons réalisé une analyse écologique au niveau de 52 districts de santé d'Afrique du Sud grâce aux données du registre national électronique de la TB. Nous avons inclus tous les cas de TB confirmés par bactériologie traités pour une TB présumée pharmacosensible en 2011. Les informations relatives aux antécédents de traitement ont été basées sur les catégories de patients enregistrées (nouveau contre retraitement).

RÉSULTATS : Les rechutes et les autres cas de TB déjà traités ont constitué entre 7,6% et 40% (médiane 17% ; intervalle interquartile 12–22) de tous les cas de TB confirmés par bactériologie dans les 52 districts d'Afrique du Sud. L'analyse multivariable a suggéré que les districts ayant les proportions plus élevées de cas de TB déjà traités avaient également des taux de notification des cas de TB plus élevés ($P < 0{,}001$), des estimations plus faibles de prévalence du virus de l'immunodéficience humaine (VIH) anténatal dans la population du district ($P < 0{,}001$) ainsi que des taux plus faibles de co-infection au VIH ($P < 0{,}001$) parmi les nouveaux cas de TB.

CONCLUSION : Les rechutes et les autres cas de TB déjà traités contribuent de façon substantielle au poids de la TB notifiée dans plusieurs districts de santé d'Afrique du Sud, particulièrement ceux qui ont un taux élevé de notification des cas et une prévalence plus faible du VIH anténatal. Il faut envisager des actions supplémentaires de prévention de la TB parmi les patients déjà traités comme par exemple un renforcement du suivi du traitement et/ou un traitement de prévention secondaire.

RESUMEN

OBJETIVO: Investigar en qué medida los casos de recaída y otros casos con antecedente de tratamiento antituberculoso contribuyen a la carga de morbilidad por tuberculosis (TB) que se comunica en Suráfrica.

MÉTODO: Se realizó un análisis ecológico en 52 distritos de salud de Suráfrica a partir de los datos del registro nacional electrónico de TB. Se incluyeron todos los casos de TB con confirmación bacteriológica tratados por presunción de TB farmacosensible en el 2011. La información sobre los antecedentes de tratamiento se fundamentó en las categorías registradas de los pacientes (nuevo contra retratamiento).

RESULTADOS: Los casos de recaída y otros casos de TB con antecedente de tratamiento constituyeron entre el 7,6% y el 40% de todos los casos de TB confirmados bacteriológicamente (mediana: 17%; amplitud intercuartílica 12–22) en los 52 distritos surafricanos. Un análisis multivariante indicó que los distritos con mayores proporciones de casos previamente tratados exhibían tasas más altas de notificación de casos de TB ($P < 0{,}001$), más baja prevalencia de infección por el virus de la inmunodeficiencia humana (VIH) en las mujeres que acudían a los servicios de atención prenatal en el distrito ($P < 0{,}001$) y también tasas más bajas de coinfección por el VIH en los casos nuevos de TB ($P < 0{,}001$).

CONCLUSIONES: Los casos de recaídas y otros casos de TB con antecedente de tratamiento contribuyen de manera importante a la carga de morbilidad por TB notificada en varios distritos de salud de Suráfrica, sobre todo en los distritos con tasas altas de notificación de casos y menor prevalencia prenatal de infección por el VIH. Se debe considerar la posibilidad de invertir esfuerzos complementarios a fin de prevenir la TB en las personas previamente tratadas, por ejemplo el fortalecimiento de la vigilancia del tratamiento, el tratamiento preventivo secundario o ambos.