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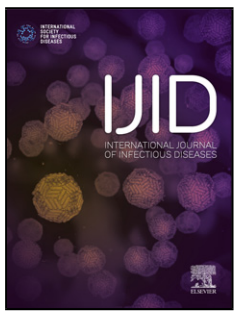

Rate of treatment success and associated factors in the program for drug susceptible tuberculosis in the Forest Region, Republic of Guinea, 2010-2017: a real-world retrospective observational cohort study

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Rate of treatment success and associated factors in the program for drug susceptible tuberculosis in the Forest Region, Republic of Guinea, 2010-2017: a real-world retrospective observational cohort study

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Highlights

- Drug susceptible tuberculosis program in the Forest Region, Republic of Guinea.
- The WHO goal of 90% treatment success remains elusive in rural areas.
- TB-HIV coinfection remains a major risk factor for low treatment success.
- Older age and long travel distance is also associated with low treatment success.

Abstract

OBJECTIVES: To analyze the treatment success rate (TSR = sum of cured or treatment completed) in the tuberculosis (TB) program for drug susceptible TB (DS-TB) of the “Centre Hospitalier Régional Spécialisé” in Macenta, Forest Region, Republic of Guinea.

METHODS: This cohort study included patients starting treatment for DS-TB between 2010 and 2017. Data collection was part of the documentation for the national TB program. Descriptive analysis was applied to determine TSR in various patient groups. Further, we performed logistic regression to determine factors influencing TSR, in new and relapse cases versus all other previously treated cases. A subgroup analysis for only microbiologically confirmed pulmonary TB was added.

RESULTS: We included 3,969 patients. TSR increased from 68.3% in 2010 to 80.8% in 2017 ($p<0.001$). Mortality (11.2%) occurred mainly in early treatment months, while loss to follow-up (5.9%) increased towards later treatment months. Risk factors for low TSR were advanced age, positive HIV status, long travel distances (>100km) to the clinic and late drug refill.

CONCLUSION: TSR in the Forest Region of Guinea remains below the WHO goal of 90%. Reaching this target remains a challenge in rural areas with high early mortality and increased risk of loss to follow-up.

Keywords

Drug susceptible tuberculosis, sub-Sahara Africa, Republic of Guinea, End TB Strategy, treatment success rate, TB-HIV co-infection

Introduction

In recent years, tuberculosis (TB) was the 10th leading cause of death worldwide and the 7th leading in low-income countries (WHO 2016). In 2017, 25% (2.48 million) of the *estimated* 10 million cases developing active TB worldwide were estimated to live in the WHO African Region. To contain the TB epidemic, the WHO developed the "End TB" strategy in 2015, as part of the Sustainable Development Goals (Johnston 2016). Compared to 2015, the final target of "END TB in 2035" aims for ≥ 90% treatment success rate (TSR); a reduction by 95% in number of TB deaths, and a reduction of the TB incidence rate by 90% to ≤ 10 cases per 100'000 population per year (WHO 2015).

TB incidence in the Republic of Guinea (from now on: Guinea) in 2017 was estimated at 176 cases per 100,000 population. Nationally in 2017, there were 13,752 new and relapse TB cases (incident cases) registered, of which 73% were bacteriologically confirmed and 83% knew their HIV status (WHO 2018a). Among these, 25% were TB-HIV co-infections. The people affected are around one third women (35%), a bit less than two third men (54%) and 11% children under 15 years (WHO 2018b). The proportion of TB-HIV co-infection is higher in the regions at the border with Sierra Leone and Côte d'Ivoire (Ministry of Health Guinea 2019).

In 2017 in the WHO Africa Region, TSR reached 82% in incident cases, while Guinea reported 88% TSR in 2017 (WHO 2019). From internal analyses of the TB program in Macenta, this high TSR appeared unrealistic for our setting. We therefore aimed to

understand the TSR for the TB program in Macenta and potential reasons for the anticipated lower TSR.

To our knowledge this is the first publication of TB data in Guinea outside of the aggregated national data.

Objectives

To understand TSR of people living with tuberculosis (PLTB) who are enrolled in the tuberculosis program for people with drug susceptible tuberculosis (DS-TB) at the "Centre Hospitalier Régional Spécialisé" (CHRS) in Macenta, we defined our objectives as follows:

1. To characterize the total number of people with DS-TB starting anti-tuberculosis treatment (ATT) between 2010 and 2017 and to assess TSR according to treatment history.

2. To assess the predictors for TSR in the following patient categories according to previous treatment history: a) in incident cases and b) in all other previously treated patients.

Methodology

Study design and setting

This is a retrospective observational cohort study; we report according to the STROBE (checklist in supplements) statement (Von Elm et al. 2007). It was conducted in Macenta, 800km southeast of the capital Conakry. Macenta is the capital of the homonymous prefecture in the administrative region of N'Zérékoré. Its

population of 1.6 million accounts for 15% of the population of Guinea (République de Guinée 2018).

The CHRS is a national reference center for HIV, leprosy and TB, including multidrug- or rifampicin-resistant TB (MDR/RR-TB). The hospital is a public-private partnership between the Ministry of Health and Public Hygiene of Guinea and SAM global, a faith-based non-profit organization. Antiretroviral treatment (ART), leprosy treatment and ATT are free-of-charge for PLTB and provided to the CHRS by the respective national programs.

We only included data from people with DS-TB, treated with category 1 (6 months, 2HRZE/4HR)[1] or 2 (prolonged to 8 months and including streptomycin, 2HRZES/1HRZE/5HRE)[1] regimens, and enrolled in the TB program at the CHRS between 01.01.2010 and 31.12.2017. PLTB were followed up until end of treatment, or until any other WHO TB outcome defined in the following sections was met, i.e. for a maximum of 8 months of treatment. The follow up for microbiologically confirmed pulmonary TB was performed by 3 sputum controls after ATT start, at month 2 (for category 1) respectively month 3 (for category 2) as well as at month 5 and at the end of treatment. There was no systematic follow-up plan in place during the study period, outcome data of patients lost to follow-up were partially retrieved from peripheral health posts during supervision visits. We analyzed outcomes per TB diagnosis – therefore some patients contributed more than 1 TB episode to the analysis.

Clinical management of tuberculosis at the CHRS

[1] H: isoniazid R: rifampicin Z: pyrazinamide E: ethambutol S: streptomycin

The ATT at the CHRS follows the national guidelines published by the “Programme National de Lutte Antituberculeuse” (PNLAT), based on the WHO recommendations (Ministry of Health Guinea 2019). Culture-based drug susceptibility testing was not available at the CHRS for the study period. Pulmonary TB (PTB) testing is performed by sputum microscopy (Ziehl-Neelsen staining). A chest x-ray supports the diagnosis of clinical PTB if sputum is not available or if sputum is negative while clinical suspicion is high. Extrapulmonary TB (EPTB) was mainly diagnosed clinically. Since November 2016, molecular testing with GeneXpert has been available with a higher sensitivity to detect *Mycobacterium tuberculosis*. GeneXpert based diagnostics were primarily reserved for people living with HIV (PLWH) with negative sputum microscopy. ATT follows the directly observed treatment strategy (DOTS) during the intensive phase. Newly diagnosed PLTB were tested for HIV and – in case of a positive result – started on ART within 2-8 weeks of starting ATT.

Definitions and outcomes

We applied the following WHO TB outcome definitions (WHO 2020):

Cured: Bacteriologically confirmed TB at treatment start and smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: Completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative.

Treatment failed: Sputum smear or culture is positive at month 5 or later during treatment.

Died: Death due to any reason before starting or during treatment.

Loss to follow-up (LTFU): No treatment started, or treatment interrupted for 2 consecutive months or more.

Not evaluated: No assigned treatment outcome, including cases “transferred out” to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.

Treatment success: Percentage of all PLTB declared “cured” or “treatment completed”

We applied the following WHO TB case definitions (WHO 2020):

Bacteriologically confirmed TB case: has a biological specimen that is positive by smear microscopy, culture or WHO approved rapid diagnostics.

Clinically diagnosed TB case: does not fulfill the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner (including cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation).

As a measure of the distance from home to the clinic, we calculated the kilometers by road, using Google maps. This is a simplification as river crossings and poor quality of roads can have a much larger impact on the actual travel time than the kilometers per se. Since exact addresses are inexistent, the nearest settlement was taken to measure distance within Guinea. For foreign nationals no exact address was reported, therefore they were classified as own group. As Ebola period we defined the main epidemic Ebola period in Macenta that lasted from August through December 2014. During this time, patient numbers declined considerably at the CHRS, resulting in a 53% drop in new TB diagnoses compared to the same months

of 2013 (Leuenberger 2015). We suspected that treatment success might be substantially worse for PLTB enrolled during those months.

Data collection

Data were extracted from the CHRS electronic patient management system. It contains all items of the national documentation required by the PNLAT plus additional points relevant for management at the CHRS. We extracted data on age, sex, place of residence, year of registration, and clinical data relevant to TB and HIV status.

Statistical analysis

We used descriptive statistics to assess baseline characteristics of all patients starting ATT for drug-susceptible TB between 2010 - 2017. For continuous data we used summary statistics. The Mann-Whitney U test was used, verifying the non-adherence of the data to the Gaussian distribution. In investigating the association between categorical variables, we used Pearson's chi-square test. In case of a cell count less than five, Fisher's exact test was performed.

We stratified patients according to WHO TB categories in a) incident cases and in b) all other retreated patients.

We used logistic regression to assess factors that might influence treatment success as defined according to our conceptual framework. These were the following variables: age in 10-year strata (following the WHO definitions), year of ATT start, sex, distance from the CHRS (grouped in Macenta town, distance from CHRS ≤100km respectively >100km and neighbouring countries), Ebola period in Macenta, HIV and ART status, clinical manifestation and bacteriologically confirmed versus

clinically diagnosed TB. All variables were included in the analysis, as all of them can have an effect as confounders.

In a subgroup analysis we included only bacteriologically confirmed PTB to assess the program in the “true positive” TB cases. For this analysis we added an additional variable - late treatment refill - to assess whether this predicted treatment failure. Late treatment refill was defined as a microbiological control later than 2 months (for treatment category 1) or later than 3 months (for treatment category 2) after ATT start. This proxy was taken since refill dates were not systematically recorded.

All statistical analyses were performed with Stata version 16.0. (StataCorp. 2019)

Results

4,089 PLTB were registered in the tuberculosis program between 2010 and 2017, of whom 2.9% (120) were people with MDR-TB and therefore excluded from our analysis. The remaining 3,969 people with DS-TB were included in the primary descriptive analysis. In the logistic regression analysis, 3,679 incident cases were included. Figure 1 shows the number of participants at each stage and where patients were excluded due to missing parameters.

Figure 1: Flow diagram showing the numbers of participants at each stage.

Legend figure1: TB – tuberculosis, PTB – pulmonary TB, LTFU – loss to follow up, NE – not evaluated.

Objective 1: Patient characteristics and treatment success rates

Overall, 2,517 (63.4%) male and 1,452 (36.6%) female patients – including 216 (5.4%) children under 15 years – were treated (Table 1). One third (36.3%) were from Macenta town, 60.8% from Guinea beyond Macenta, and 2.9% from neighboring

countries. The TB characteristics and HIV status at ATT start are shown in Table 2. The key changes between the years 2010 and 2017 are the following: an increase from 36.0% up to 43.7% in patients coming from a distance of more than 100km; an increase of people tested for HIV from 75.6% up to 94.6%; an increase of PLWH on ART at ATT start from 20% up to 81.2%; and a decrease of bacteriologically confirmed TB cases from 70.1% down to 60.3%.

Of the 3,969 patients treated within these eight years, 115 were treated twice and one patient was treated three times at the CHRS.

Table 1: Patient demographics, including all patients diagnosed with a drug susceptible tuberculosis between 2010 and 2017 at the CHRS in Macenta.

Legend table 1: Treatment success is defined as the sum of the category "cured" or the category "treatment completed". Unfavorable treatment outcome includes all treatment outcomes other than treatment success.

Table 2: Tuberculosis characteristics and HIV status at inclusion in TB program and diagnosed with drug susceptible tuberculosis between 2010 and 2017 at the CHRS in Macenta

Legend table 2: Treatment success is defined as the sum of the category "cured" or the category "treatment completed". Unfavorable treatment outcome includes all treatment outcomes other than treatment success.

An overall TSR of 75.7% was achieved over these 8 years (75.5% for men and 76.1% for women), with a clear increase from 68.3% in 2010 to 80.8% in 2017. Excluding the 154 patients, that were transferred out during the treatment and are

defined as “not evaluated”, the remaining 3,815 patients reach a TSR of 78.4%. However, according to WHO outcome definitions, we kept patients transferred out in the outcome category “not evaluated”. Figure 2 shows TSR for each year.

The success rate for incident cases was 76.3% (Figure 3**Error! Reference source not found.**) but only 67.1% for all other retreated cases. Figure 4 shows the strong negative impact of a positive HIV status on the TSR and Figure 5 shows the TSR for bacteriologically confirmed versus clinically diagnosed TB cases.

Of the 443 (11.2%) patients who died during treatment, almost half (48.8%) died during the first month of treatment, 23.0% during the second and slightly more than 25% in either month three or four of treatment. The number and proportion of LTFU (234, 5.9%) however increased over the duration of treatment: 23.1% of these occurred in the first two months and 55.6% after month three of treatment.

Figure 2: Evolution of the treatment success rate 2010 - 2017

Legend figure2: Treatment success rate, defined as the sum of categories “cured” or “treatment completed” in people diagnosed with drug susceptible tuberculosis, shown for all patients grouped by year of registration. The shaded bars show treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate the treatment success rate.

Figure 3: Overall treatment success rate and stratified according to history of previous anti-tuberculosis treatment

Legend figure3: Treatment success rate, defined as the sum of “cured” or “treatment completed”, in people diagnosed with drug susceptible tuberculosis, shown for all patients, incident cases (new and relapse cases) and all other retreated patients (all retreated cases except “retreatment after relapse”). The shaded bars show treatment

success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate treatment success rate.

Figure 4: Treatment success rate according to HIV status

Legend figure 4: Treatment success rate, defined as the sum of "cured" or "treatment completed" in people diagnosed with drug susceptible TB, and shown for people not living with HIV versus people living with HIV on ART and not on ART at start of anti-TB treatment. The shaded bars show treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate treatment success rate. TB – tuberculosis, ART – antiretroviral therapy

Figure 5: Treatment success rate according to bacteriologically confirmed or clinically diagnosed TB cases

Legend figure 5: Treatment success rate, defined as the sum of "cured" or "treatment completed" in people diagnosed with drug susceptible TB, and shown for bacteriologically confirmed TB and clinically diagnosed TB. The shaded bars show treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate treatment success rate. TB – tuberculosis

Objective 2: factors associated with treatment success

After excluding patients with missing data on treatment history, distance or type of TB disease (see table 3 in supplements) the remaining 3679 patients diagnosed with incident TB were included in the main logistic regression. Figure 6 shows the crude and adjusted odds ratio (OR) and confidence interval (CI) from logistic regression. After adjusting for the above-named factors, we showed that older patients have lower odds of treatment success than patients between 25 and 34 years of age (reference age group). Furthermore, lower odds of treatment success were observed

for people coming from places >100km from the CHRS (OR 0.77, 95% CI 0.64 – 0.93) compared to people coming from Macenta, PLWH on ART at start of ATT (OR 0.34, 95% CI 0.27 – 0.43), PLWH not on ART at start of ATT (OR 0.27, 95% CI 0.20 – 0.36) compared to people not living with HIV; as well as patients with clinically diagnosed TB (OR 0.81, 95% CI 0.66 – 1.00) as compared to patients with bacteriologically confirmed TB. Conversely, the odds of achieving treatment success increased by 8% per calendar year (OR 1.08, 95% CI 1.04 – 1.12).

Figure 6: Crude and adjusted odds ratio (95% confidence interval and p-value) from logistic regression analysis identifying factors associated with treatment success in new and relapse TB cases

Legend figure 6: Logistic regression for crude and adjusted odds ratio. OR – odds ratio, CI – confidence interval, TB – tuberculosis; CHRS - Centre Hospitalier Régional Spécialisé in Macenta; ART - antiretroviral therapy, Ebola - months of the main epidemic Ebola period in Macenta (August - December 2014); year of anti-TB treatment start refers to the years 2010-2017, the OR is given per later year of registration and compared to the respective previous year, for example treatment success of 2011 compared to 2010 and treatment success of 2012 compared to 2011 etc. (Jann 2014)

Logistic regression for all other retreated patients (excluding the relapse cases), showed fewer significant factors due to small numbers (n = 149).

The subgroup analysis of microbiologically confirmed incident PTB cases, including 2,082 patients with sputum results at predefined months, showed a lower TSR (OR 0.50, 95% CI 0.35 – 0.71) in patients with late drug refill at month 2 respectively 3, compared to patients with drug refill on schedule.

Discussion

We found an improvement of the overall TSR from 68.3% in 2010 to 80.8% in 2017. The WHO goal of 90% TSR was not reached due to 443 (11.2%) deaths, 234 (5.9%) LTFU and 158 (4.0%) patients without evaluated treatment outcome. The most significant risk factors for not achieving treatment success were a positive HIV status, older age and greater distance from home to the CHRS.

Our data are generalizable for PLTB in Guinea, given a similar distribution of sex, age and clinical manifestation as depicted in the WHO tuberculosis profile of Guinea in 2017 (WHO 2018b).

TB as a disease of poverty is reflected in the high early death rate in our population, reflecting late health-seeking behavior. Patients are diagnosed late, often after having tried out local remedies before consulting TB clinics since these often involve more financial investments due to longer travel times and higher costs for transport, food and lodging, even if basic diagnostics and treatment are free of charge. Other obstacles to early treatment are logistical challenges of the health care system (drug stock-outs / often long turn-around times for results). The WHO recommends integrated HIV and TB services with decentralized delivery of services for both infections (WHO 2015), but experience in Macenta shows that frequent stock-outs in smaller sites drive patients towards larger centers – at the cost of longer travel times and increased financial expenses for patients. This is seen in the increase of patients over time travelling from a distance of more than 100 km to reach the CHRS.

TB-HIV co-infection proved to be a major detrimental factor for treatment success in our study. This stands in contrast to the WHO data for Guinea in 2017 that show an equal success rate for people co-infected with TB-HIV: 88% for all incident cases and

85% for PLWH in 2017 (WHO 2019). In our setting, patients were often diagnosed with HIV at the time of TB diagnosis (36.4% of our PLWH were not yet on ART at time of TB diagnosis); hence already presenting with an opportunistic infection and advanced immune deficiency. But not only the immune deficiency, also the pill burden or side effects of a dual treatment of TB and HIV affect the adherence to medication intake and consequently the TSR (Gebremariam et al. 2010). Guinea is a country with a generalized HIV epidemic, but a low HIV prevalence of 1.4% in adults (UNAIDS 2019). The country has poorer HIV-related performance indicators than most high-prevalence Southern African countries. Country-wide indicators regarding the percentage of patients who know their HIV diagnosis, who are on ART and who are virally suppressed are unknown. Accentuated by the rural surroundings in the Forest Region, HIV diagnosis is often not considered and therefore missed at earlier stages. Also, according to the UNAIDS report 2019, Guinea is a country with a very high level of stigma towards PLWH, whereby approximately 70% of people responded they would not buy vegetables from a shopkeeper known to be living with HIV. All these factors additionally contribute to delayed health-seeking behavior and delayed detection of HIV or TB through the health care system. We therefore argue that our figures with a markedly lower TSR in PLWH (61.2% for those already on ART and 53.6% for those not yet on ART) represent a realistic capture of the mentioned difficulties for people co-infected with HIV-TB and living in rural Guinea.

In the context of sub-Sahara Africa, our results are comparable regarding the factors associated with a poor treatment success. The significant influence of TB-HIV co-infection on poor treatment success of ATT is shown in several studies from sub-Saharan Africa (Gabida et al. 2015; Oshi et al. 2015; Asres et al. 2016; Zenebe and Tefera 2016). Different studies from Ethiopia and Nigeria show, that especially lack of access to health facilities but also older age, is associated with poor treatment

success (Ige and Oladokun 2011; Tadesse et al. 2013; Ofoegbu and Odume 2015; Gebrezgabiher et al. 2016; Zenebe and Tefera 2016; Woimo et al. 2017). The range of treatment success varies a lot between the countries and regions in sub-Saharan Africa. A systematic review and meta-analysis (covering studies from 7 countries) over the years 2008-2018 showed a TSR of 76.2% among bacteriologically confirmed PTB cases, which is comparable to our TSR of 78.2% (Izudi et al. 2019).

This study has some limitations. It is based on data from a single reference hospital with local circumstances that may have had an impact on data quality: data handling errors occurred due to transcription from paper-based national TB program ledgers to the electronic register, and different reporting requirements by the Ministry of Health over these eight years complicated the adjustment of the data. Another weakness, the lack of resources and the difficult logistical setting of the CHRS (2 days travel away from the capital with unsealed access roads) is illustrated in the late introduction of GeneXpert based molecular testing of MDR/RR-TB cases. As a well-known difficulty in resource-poor settings, limited diagnostic possibilities result in a certain number of false positive TB diagnoses, e.g., any severe chronic lung illness (potentially cancer or fibrosis etc.) will be primarily attributed to TB. This will explain the lower TSR in non-microbiologically confirmed TB. A systematic limitation is given by the pre-defined WHO definitions, resulting in a larger number of patients with the outcome “not evaluated” because patients transferred-out are assigned to this category.

The main strength of the study is the center’s function as one of the two national reference centers for TB and the one not situated in the capital city. Its importance in the Forest Region, resulting in a high number of PLTB arriving from outside the actual municipal area, allows a deeper insight into the TB situation for the south-

eastern part of the country. This study is the first publication of TB data in Guinea outside the aggregated national data, which enables an independent view on the situation of the Forest Region of Guinea. Another strength of the study is the improvement in TSR over these eight years due to better care for people with TB-HIV co-infection, shown in a higher HIV testing rate (89%) compared to the 81% in the national data and an increase of PLWH on ART from 20% in 2010 up to 81.2% in 2017. Furthermore, a higher treatment success over these eight years could be reached due to the decrease of 3.4% in deaths, despite fewer bacteriologically confirmed TB cases.

Conclusion

Despite marked improvement of treatment success over the eight years depicted in this analysis, we showed that the target TSR of 90% could not be reached, due to high early mortality and an increase of LTFU in later treatment months. Advanced age, long travel distances to the hospital, a positive HIV status and late drug refill were associated with lower treatment success. However, the increase of the TSR over the years shows a positive evolution of the tuberculosis program of the CHRS. The more systematic patient recall and reminder system that is planned has the potential to reduce delays of drug refill at month two or three. Furthermore, closer collaboration with the local medical centers that supervise a part of the treatment for PLTB outside of Macenta could result in a better treatment surveillance and thus in a better treatment success with fewer costs and time requirements for patients. Finally, further improvements in TB diagnostics, starting with a wider use of the GeneXpert platform, will enable a more certain exclusion of non-TB cases and thus hopefully a greater TSR for the whole TB cohort in the coming years.

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Conflict of Interest

The authors of this paper declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Ethical Approval

The cantonal ethics committee of Bern, Switzerland, waived submission declaring to be non-responsible.

In Guinea, the data was analyzed within the protocol “Évaluation opérationnelle de la prise en charge des maladies infectieuses et non-transmissibles traitées au Centre Médical de la Mission Philafricaine à Macenta (Etude PRISMA2) » which was accepted by the National Ethics committee of Medical Research (CNERS) in Guinea (N°: 104/CNERS/19).

Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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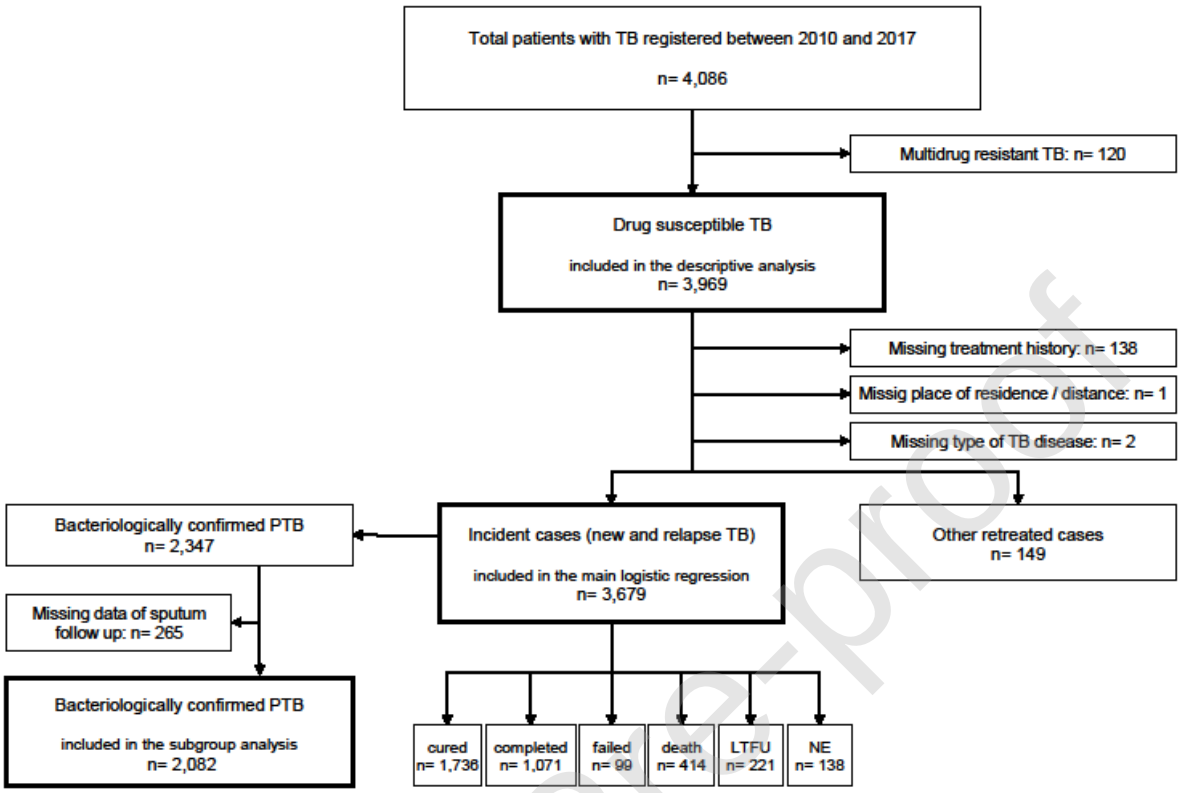
Figure 1: Flow diagram showing the numbers of participants at each stage.



Legend figure1: TB – tuberculosis, PTB – pulmonary TB, LTFU – loss to follow up, NE – not evaluated.

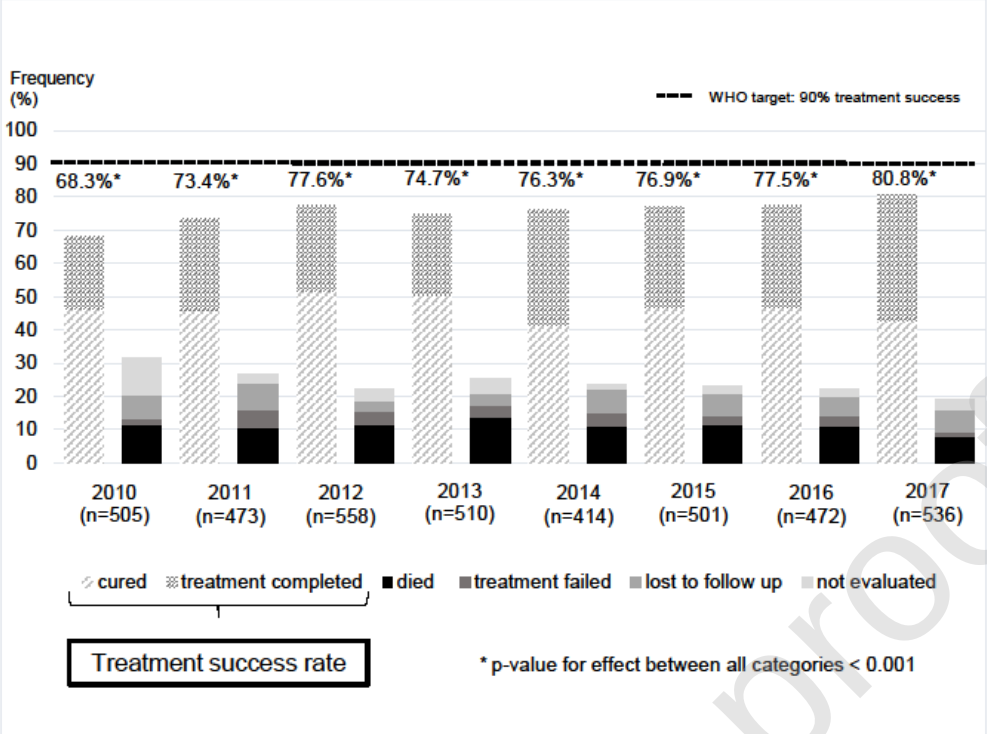


Figure 2: Evolution of the treatment success rate 2010 - 2017

Legend figure2: Treatment success rate, defined as the sum of categories "cured" or "treatment completed" in people diagnosed with drug susceptible tuberculosis, shown for all patients grouped by year of registration. The shaded bars show treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate the treatment success rate.

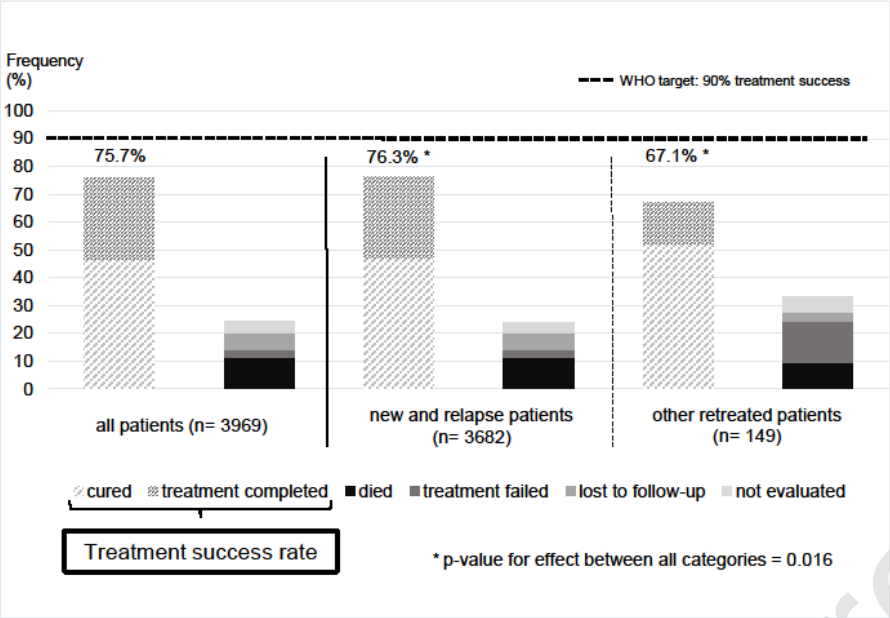


Figure 3: Overall treatment success rate and stratified according to history of previous anti-tuberculosis treatment

Legend figure3: Treatment success rate, defined as the sum of "cured" or "treatment completed", in people diagnosed with drug susceptible tuberculosis, shown for all patients, incident cases (new and relapse cases) and all other retreated patients (all retreated cases except "retreatment after relapse"). The shaded bars show treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate treatment success rate.

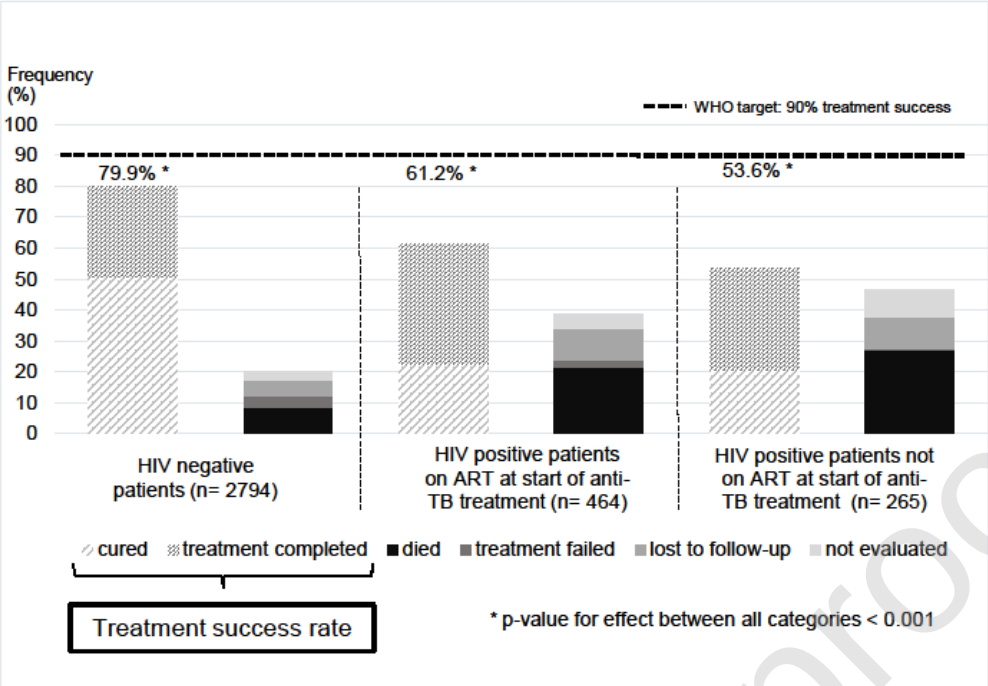


Figure 4: Treatment success rate according to HIV status

Legend figure 4: Treatment success rate, defined as the sum of "cured" or "treatment completed" in people diagnosed with drug susceptible TB, and shown for people not living with HIV versus people living with HIV on ART and not on ART at start of anti-TB treatment. The shaded bars show treatment success, while the filled bars show

treatment outcomes with no treatment success. Percentages indicate treatment success rate. TB – tuberculosis, ART – antiretroviral therapy

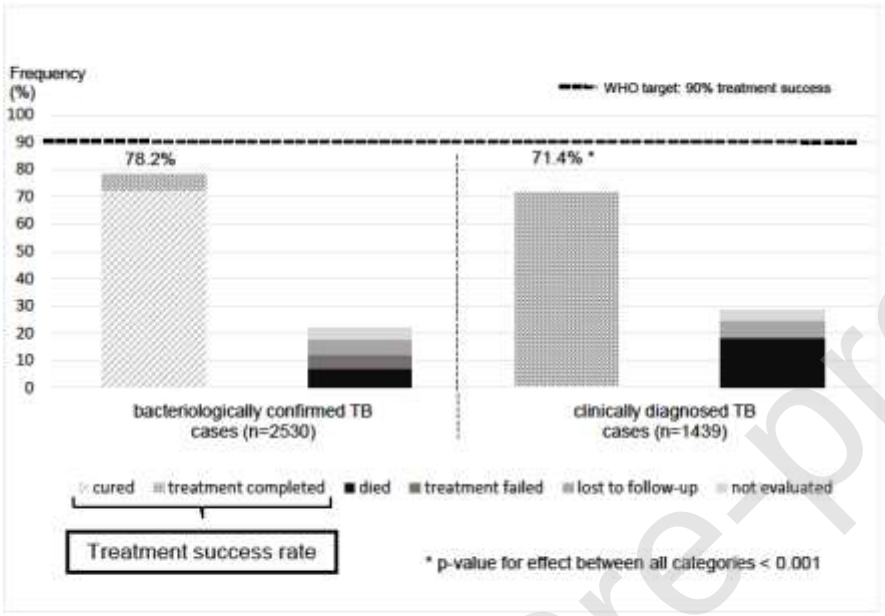


Figure 5: Treatment success rate according to bacteriologically confirmed or clinically diagnosed TB cases

Legend figure 5: Treatment success rate, defined as the sum of "cured" or "treatment completed" in people diagnosed with drug susceptible TB, and shown for bacteriologically confirmed TB and clinically diagnosed TB. The shaded bars show

treatment success, while the filled bars show treatment outcomes with no treatment success. Percentages indicate treatment success rate. TB – tuberculosis

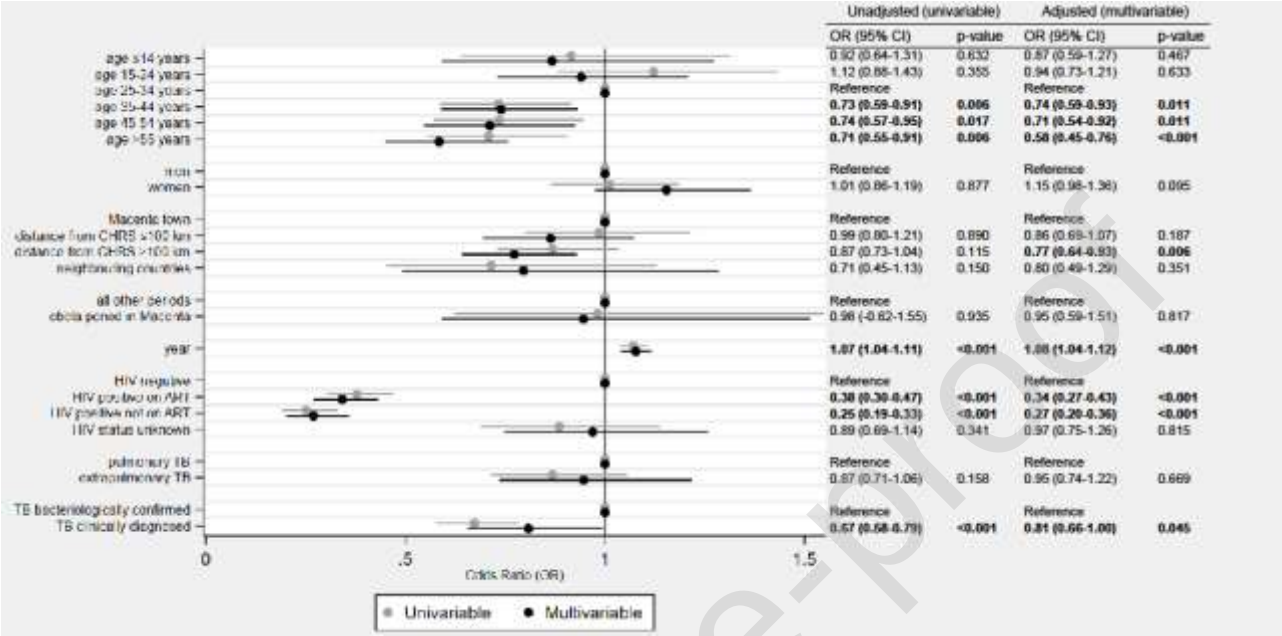


Figure 6: Crude and adjusted odds ratio (95% confidence interval and p-value) from logistic regression analysis identifying factors associated with treatment success in new and relapse TB cases

Legend figure 6: Logistic regression for crude and adjusted odds ratio. OR – odds ratio, CI – confidence interval, TB – tuberculosis; CHRS - Centre Hospitalier Régional Spécialisé in Macenta; ART - antiretroviral therapy, Ebola - months of the main epidemic Ebola period in Macenta (August - December 2014); year of anti-TB treatment start refers to the years 2010-2017, the OR is given per later year of registration and compared to the respective previous year, for example treatment success of 2011 compared to 2010 and treatment success of 2012 compared to 2011 etc. (Jann 2014)

Table 1: Patient demographics, including all patients diagnosed with a drug susceptible tuberculosis between 2010 and 2017 at the CHRS in Macenta.

	Total	**Treatment success**	**Unfavorable treatment outcome**	**p-value**
Total (%)	3,969 (100)	3,006 (75.7)	963 (24.3)	
Sex (%)				0.684
Men	2,517 (63.4)	1,901 (63.2)	616 (64.0)	
Women	1,452 (36.6)	1,105 (36.8)	347 (36.0)	
Median age in years				<0.001
median (IQR)[a], maximum	34 (25 - 46) max. 99	34 (24 - 45) max. 91	37 (27 - 49) max. 99	
Age categories (%)				0.002
< 15 years	216 (5.4)	168 (5.6)	48 (5.0)	
15-24 years	758 (19.1)	605 (20.1)	153 (15.9)	
25-34 years	1016 (25.6)	792 (26.4)	224 (23.3)	
35-44 years	882 (22.2)	641 (21.3)	241 (25.0)	
45-54 years	535 (13.5)	391 (13.0)	144 (15.0)	
≥55 years	562 (14.2)	409 (13.6)	153 (15.9)	
Year of registration (%)				<0.001
2010	505 (12.7)	345 (11.5)	160 (16.6)	
2011	473 (11.9)	347 (11.5)	126 (13.1)	
2012	558 (14.1)	433 (14.4)	125 (13.0)	
2013	510 (12.9)	381 (12.7)	129 (13.4)	
2014	414 (10.4)	316 (10.5)	98 (10.2)	
2015	501 (12.6)	385 (12.8)	116 (12.1)	
2016	472 (11.9)	366 (12.2)	106 (11.0)	
2017	536 (13.5)	433 (14.4)	103 (10.7)	
Place of residence (%)				0.020
Macenta town	1,440 (36.3)	1,117 (37.2)	323 (33.5)	
Guinea, distance to CHRS ≤ 100km	856 (21.6%)	659 (21.9)	197 (20.5)	
Guinea, distance to CHRS >100km	1,556 (39.2)	1,149 (38.2)	407 (42.3)	
Neighboring countries	116 (2.9)	81 (2.7)	35 (3.6)	
Missing data	1 (0.03)	0	1 (0.1)	
Distance from home to clinic (km) median (IQR)[a], maximum [b]	127 (58 - 350) max. 989	127 (58 - 302) max. 989	133 (80 - 350) max. 732	<0.001

Percentages may not total 100 due to rounding.

[a] IQR – interquartile range; [b] excluding patients from Macenta town, foreign nationals and unknown. As a measure of the distance, we calculated the kilometers by road, using Google maps. CHRS – Centre Hospitalier Régional Spécialisé

Table 2: Tuberculosis characteristics and HIV status at inclusion in TB program and diagnosed with drug susceptible tuberculosis between 2010 and 2017 at the CHRS in Macenta.

	Total n=3,969	**Treatment success**	**Unfavorable treatment outcome**	**p-value**
Treatment category (%)				0.006
1st line – initial regimen	3,700 (93.2)	2,821 (93.9)	879 (91.3)	
1st line – retreatment regimen[c]	269 (6.8)	185 (6.2)	84 (8.7)	
Treatment history (%)				*<0.064
New patients*	3,558 (89.6)	2,714 (90.3)	844 (87.6)	
Retreatment all*	273 (6.9)	194 (6.5)	79 (8.2)	
--- retreatment after relapse	--- 124 (3.1)	--- 94 (3.1)	--- 30 (3.1)	
--- retreatment after loss to follow-up	--- 46 (1.2)	--- 35 (1.2)	--- 11 (1.1)	
--- retreatment after failure	--- 76 (1.9)	--- 51 (1.7)	--- 25 (2.6)	
--- retreatment others	--- 27 (0.7)	--- 14 (0.5)	--- 13 (1.4)	
Missing data*	138 (3.5)	98 (3.3)	40 (4.2)	
Type of tuberculosis disease (%)				<0.001
Bacteriologically confirmed pulmonary tuberculosis	2,521 (63.5)	1,972 (65.6)	549 (57.0)	
Clinically diagnosed pulmonary tuberculosis	762 (19.2)	524 (17.4)	238 (24.7)	
Extrapulmonary tuberculosis	684 (17.2)	509 (16.9)	175 (18.2)	
Missing data	2 (0.1)	1 (0.03)	1 (0.1)	
HIV testing done (%)				0.342
Yes	3,532 (89.0)	2,667 (88.7)	865 (89.8)	
No	437 (11.0)	339 (11.3)	98 (10.2)	
HIV status (%)				<0.001
HIV positive	729 (18.4)	426 (14.2)	303 (31.5)	
HIV negative	2,794 (70.4)	2,233 (74.3)	561 (58.3)	
unknown (not tested and missing)	446 (11.2)	347 (11.5)	99 (10.3)	
HIV positive (%)				0.045
on ART[d]	464 (63.6)	284 (66.7)	180 (59.4)	
not on ART	265 (36.4)	142 (33.3)	123 (40.6)	
HIV type (%)[e]				0.458
HIV-1 infected	720 (98.8)	421 (98.8)	299 (98.7)	
HIV-2 infected	5 (0.7)	4 (0.9)	1 (0.3)	
HIV type unknown	4 (0.6)	1 (O.2)	3 (1.0)	

[c] retreatment regimen: tuberculosis treatment regimen with the addition of streptomycin and prolonged for 8 months (2HRZES/1HRZE/5HRE) [d] ART – antiretroviral therapy [e] HIV positive only. * the p-value refers to the major categories labeled with an asterisk. CHRS – "Centre Hospitalier Régional Spécialisé"

Percentages may not total 100 due to rounding.