Original research article

« Factors associated with Treatment Failure for Microscopy-positive Pulmonary Tuberculosis at the General Reference Hospital of Beni (DR Congo) (DR Congo) between 2010 and 2020: Case-control study »

ABSTRACT

Introduction: Failure to treat microscopy-positive pulmonary tuberculosis (MPT+) poses a risk to public health through the spread of infection and could be a gateway to anti-tuberculosis drug resistance. The objective of this study is to analyse the risk factors and characteristics of TB patients whose treatment failed between 2010 and 2020 at the General Referral Hospital of Beni in DR Congo.

Methods: This is a retrospective case-control study conducted from 1 January 2010 to 31 December 2020 at the CDTMR of the General Referral Hospital of Beni. The cases are patients treated for PMT+ and who had a therapeutic failure. Three controls for each case were selected among patients with PMT+ who were declared cured. Data analysis was performed using Epi-Info version 3.5.3 for Windows.

Results: 128 patients were included in the study. 32 patients were treatment failures. The mean age of cases and controls was 42 years (+/- 14), the M/F sex ratio was 31 and 2.4 in cases and controls respectively, urban residents accounted for 90.3% and 83.2% in cases and controls respectively. Bivariate analysis showed a significant association between treatment failure and weight loss at first control (OR=1.55), non-decrease in bacillary density at first control (OR=25.5) and treatment discontinuation (OR=20.5). After adjustment, weight loss of 1 kg (adjusted OR=1.92), no decrease in BAAR density (adjusted OR=8.30) and treatment discontinuation (adjusted OR=12.2) remained significantly associated with treatment failure.

Conclusion: Active surveillance should be instituted in TB patients with PMT+ who present at first check-up with weight loss, non-decrease in bacillary density on direct examination and/or a notion of treatment discontinuation.

Keywords: **Associated factors, Treatment failure, Pulmonary tuberculosis, Microscopy positive.**

List of abbreviations

- ANOVA: Analysis of Variance
- BK: Bacillus Koch
- BMI: Body Mass Index
- CDTMR: Centre for the Diagnosis of Tuberculosis and Respiratory Diseases
- DEDC: Directorate of Epidemiology and Disease Control
- DOTS: Directly Observed Treatment Short course

UNDER PEER REVIEW

- DRC: Democratic Republic of Congo
- EMRO: Eastern Mediterranean Regional Office
- ENSP: National School of Public Health
- ETM: Ethambutol
- GRH: General Reference Hospital
- INH: Isoniazid
- LAT: Lutte antituberculeuse
- MDG: Millennium Development Goals
- MHD: Medical Health Delegation
- NTCP: National Tuberculosis Control Programme
- OR: Odds Ratio
- ORa: Adjusted Odds Ratio
- PMT+: Microscopy positive pulmonary tuberculosis
- RHD: Regional Health Directorate
- RIF: Rifampicin
- STM: Streptomycin
- TAF: Tuberculosis in All Forms
- TB: Tuberculosis
- WHO: World Health Organization

1. INTRODUCTION

Tuberculosis is a disease caused by the tubercle bacillus Mycobacterium tuberculosis, which most commonly affects the lungs. It is transmitted through the expectoration of droplets of bronchial secretions by people with TB disease [1].

TB is a major global health problem. In 2011, the World Health Organization (WHO) estimated that there were 8.7 million new cases of TB, equivalent to 125 cases per 100,000 population, and 1.4 million people died of the disease. The burden of TB in children (under 15 years) in 2011 is estimated at 0.5 million cases and 64,000 deaths [2].

In 2006, WHO recommended the Stop TB Strategy to reduce the burden of TB in line with the global Millennium Development Goals (MDGs) set for 2015: to halt and reverse the increase in TB incidence by 2015 [3].

In the WHO TB report, TB treatment failure in the WHO regions as a whole in 2010 was 2% for new cases of PMTCT+ and 4% for retired cases; in the EMRO region, it is 1% and 3% respectively [2].

In Morocco, the Ministry of Health considers tuberculosis control as a priority health intervention and it is organised within the framework of the National Tuberculosis Control Programme (PNLAT). In 1991, the PNLAT adopted, after its restructuring, the DOTS (Directly Observed Treatment Short-course) strategy and since 2006 the PNLAT has adopted the Stop TB Strategy 2006-2015 after having been able to reach the global objectives for 2005, namely the detection of 70% of contagious cases and the cure of 85% of detected cases [4].

Significant progress has been made in the fight against tuberculosis thanks to the efforts made by the Ministry of Health, in particular the free and decentralised services provided to tuberculosis patients. Thus, the detection rate has been maintained at over 95% and the therapeutic success rate at over 86% [5]. This has made it possible to reduce the incidence of microscopy-positive

UNDER PEER REVIEW

pulmonary tuberculosis (MPT+), which is the contagious form, by 32.5% in 15 years [5]. However, the rate of reduction does not meet the objective set by the NPAA, which aims to reduce the incidence of all forms of tuberculosis (FTT) by at least 6% per year from 2010 [6]. This can be explained by the emergence of resistant germs, therapeutic failures and relapses, which are three factors likely to increase the risk of the disease spreading to the surrounding population [7].

In 2011, nearly 27,000 new cases of tuberculosis were notified in Morocco, defining an incidence of 82 new cases per 100,000 inhabitants for FTT and 35 new cases per 100,000 inhabitants for PMT+ [5].

National Tuberculosis Control Programme (NTCP) data show that the average number of TB treatment failures recorded between 2007 and 2010 is 147 cases per year.

At the level of the Oriental region, the 2011 regional data from PNLAT show a failure rate of 1.9% (9/473) for new cases of MPT+, and 18.18% (4/22) for previously treated MPT+ [8].

In 2011, the incidence of TB in HGR BENI was 76.6 and 18.4 per 100,000 population for FTT and PMT+ respectively. Between 2001 and 2010, treatment failure ranged from 1% to 3% among MPT+ TB patients [8].

The aim of treatment for active TB is to achieve a permanent cure of the disease while avoiding the development of drug resistance and thus stopping the transmission of the infection. This is achieved by administering effective drugs for a sufficient period of time to treat all forms of TB [9].

Failure to treat TB poses a risk to public health through the development of drug-resistant TB, which is the end result of a number of different failures [10]. Globally, it is estimated that 3.7% of new cases and 20% of previously treated cases carry multidrug resistant bacilli [1], in Morocco the proportion of multidrug resistance among new never treated TB cases is 0.5% compared to 12% for previously treated cases [4].

Cases that have failed anti-tuberculosis treatment present a source of infection and can disseminate drug-resistant tuberculosis, which requires the use of second-line drugs that are more expensive and cause more serious side effects; the treatment regimens recommended by the WHO must be administered for a maximum of 2 years and the cure rates are lower (between 50% and 70%)

In the DRC two national studies (Ottmani S.E. et al [28] and Dooley et al [27]) on TB treatment failure only looked at re-treatment and in addition to treatment failure, they also looked at treatment discontinuation and relapse for TIP. Dooley showed that gender (ORa=2.29), presence of BAARs in sputum at month 3 (ORa=7.14) and hospitalisation were risk factors for treatment failure at initial treatment. The national study by Tachfouti N. et al [29] investigated the association between exposure to smoking and failure of antibacillary treatment for TIP and PET.

But no province-level study has investigated the risk factors associated with treatment failure for PMT+.

This study is in response to the needs of the regional health directorate to:

UNDER PEER REVIEW

- Contribute to the strengthening and/or implementation of measures to improve the prevention of treatment failure by identifying patients at risk of treatment failure and addressing the risk factors;

- Contribute to the promotion of rational use of anti-tuberculosis drugs through early identification of patients with drug resistance.

The main objective of this study was to analyse the risk factors and characteristics of people with TB whose treatment has failed.

The specific objectives were :

- to describe the epidemiological characteristics of MPT+ patients with treatment failure;
- to measure the degree of association between different factors and TB treatment failure;
- to formulate recommendations for improving the activities of the National Tuberculosis Control Programme.

2. METHODS

This was a retrospective case control study. The retrospective nature and the characteristics of the variables studied guided us towards a purely quantitative approach.

The study consisted of the exploitation of registers and medical records of patients with PMT+ who were admitted to the HGR BENI tuberculosis and respiratory diseases diagnostic centre (CDTMR). The study took place between 1 January 2010 and 31 December 2020.

The CDTMR is the basic unit for the implementation of the PNLAT, it ensures the management and follow-up of tuberculosis patients referred by the ESSBs, which represents an ideal location for this study.

The following were included in the study

- Cases: any patient undergoing treatment for MPT+ and whose bacteriological examination (direct examination or culture) remained positive throughout treatment until the fifth month or more, or became positive again at the same time frames after transient negativation.

- Controls: any patient undergoing treatment for MPT+ who was considered cured, i.e. had completed the treatment and had two negative bacteriological tests: one during the course of the treatment, and another during the last month of the treatment course.
  A "3 controls to 1 case" approach was chosen. Cases were selected exhaustively from the CDTMR and controls were matched for age (+/- 5 years), treatment regimen of the case and follow-up protocol; gender matching was not performed due to the high male dominance of our cases. Controls were selected from the CDTMR registers in the same time interval or treatment period as the cases.

Data were collected using a standardised data collection form (see appendix). The data to be collected included:

- Dependent variable: Treatment failure
- Independent variables: socio-demographic, clinical, biological data and risk factors (toxic habits);

UNDER PEER REVIEW

The date of onset of TB symptoms, the date of diagnosis of PMT+ and the date of initiation of antibacillary treatment were also collected to calculate the time to initiation of treatment and the duration of antibacillary treatment.

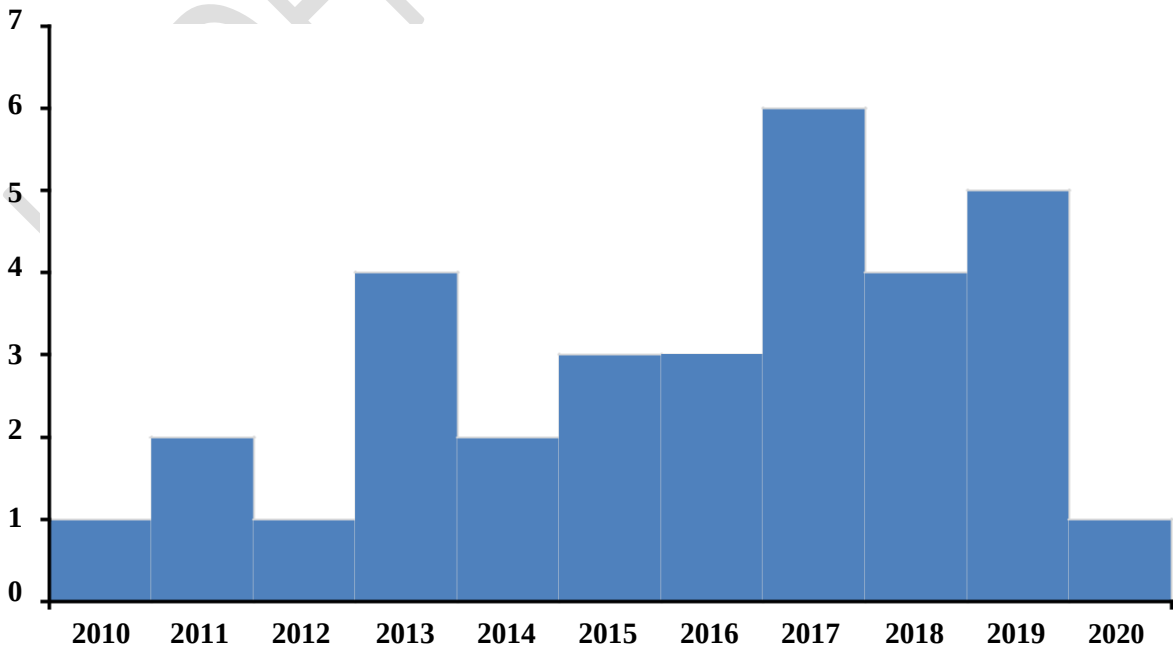
Data analysis was performed using Epi-Info version 3.5.3 for Windows. It focused on the general characteristics of the study population. Qualitative variables were expressed as percentages and quantitative variables as means. The chi-2 test was used to assess the statistical significance of the independent categorical variables, the parametric ANOVA test was used to compare the means of the independent quantitative variables. Multi-variate logistic regression analysis was used to assess the risks (OR) between treatment failure and the different independent factors and to build an explanatory model for the occurrence of treatment failure. Measures of association are calculated with 95% confidence intervals.

Anonymity and confidentiality were respected for all personal data collected, the first and last names of cases and controls will not be entered, and data coding is ensured at the time of collection and entry by assigning the LAT number as a patient identifier.

The investigator was required to respect professional secrecy and the regulatory provisions of Dahir n° 1-09-15 of 22 safar 1430 (18 February 2009) published in the official bulletin N° 5714 of 7 rabii premier 1430 (5-3-2009) and promulgating law n° 09-08 relating to the protection of individuals with regard to the processing of personal data.

3. RESULTS

A total of 128 patients with microscopy-positive pulmonary TB were included in this study between 2010 and 2020, the number of cases failing TB treatment was 32 cases with an average number of cases recorded per year of 3 and a peak of 6 cases recorded in 2017 (Figure 1)



UNDER PEER REVIEW

Figure 1: Evolution of the number of cases of therapeutic failure per year at the CDTMR of the General Referebce Hospital of Beni between 2010 and 2020.

Description of cases and controls:

The variables describing the socio-demographic and clinical characteristics of the cases and controls are represented in Tables 1 and 2.

Socio-demographic characteristics:

The mean age of the cases was 42 years +/- 14, the youngest was 23 years and the oldest 70 years. For the controls the mean age was 41 +/- 14 years with a minimum age of 19 years and a maximum age of 75 years. The age range between 19 and 39 years represented 50% of all cases and controls. The cases were predominantly male with an M/F sex ratio.

The M/F sex ratio for controls was 2.4.

Patients residing in urban areas represented 90.3% and 83.2% of cases and controls respectively. Patients from health facilities located more than 6 km from the CDTMR represented 16.1% of cases and 18.7% of controls. Respectively 35.5% and 14.9% of cases and controls were attached to the Malepe and Kasanga health facilities.

Marital status was characterised by 48.4% of married cases and 50.5% of married witnesses. The average number of children per couple among cases and witnesses was 2 +/- 2. The average number of people living in the same household was 6 +/- 3 for cases and controls.

A permanent salary was reported by 10.3% of cases and 11.6% of controls. Basic medical coverage was reported by 3.2% of cases and 7.4% of controls.

Table 1: Socio-demographic characteristics of cases and controls

Variables	Case	Control
	Frequency (%)	
Age groups		
[19-29]	8 (25.0)	25(26.0)
] 29-39]	8 (25.0)	23(24.0)
] 39-49]	4 (12.5)	12(12.5)
] 49-59]	8 (25.0)	26(27.1)
> 59	4 (12.5)	10(10.4)
Gender		
Male	31(96.9)	68(70.8)
Female	1(3.1)	28(29.2)

UNDER PEER REVIEW

Background		
Suburban	2 (6.5)	17(18.1)
Urban	28 (90.3)	76(80.9)
Rural	1(3.2)	1(1.1)
Distance between home FS and CDTMR		
> 3 Km	5 (16.1)	18(19.6)
≤ 3 Km	26 (83.9)	74(80.4)
Marital Status		
Married	15 (48.4)	48(50.5)
Unmarried	16 (51.6)	47(49.5)
Permanent wage		
Yes	3 (10.3)	11(12.0)
No	26 (89.7)	81(88.0)
Health care coverage		
Oui	1(3.2)	7 (7.4)
Non	30 (96.8)	88(92.6)
	Average (+/- SD)	
Number of children per couple	2 (2)	2 (2)
Number of people living in the same household	6 (3)	6 (3)

Clinical characteristics :

Variations in mean weights during follow-up of cases and controls are shown in Figure 2.

At diagnosis, the mean weight of the cases was 58.4 kg +/- 6.7 and 57 kg +/- 11.3 for the controls. At the first control, cases lost an average of 0.73 kg +/- 4.1 and controls gained an average of 2.14 kg +/- 2.1.

At the second check, the cases gained an average of 0.66 kg +/- 2.63 kg between the first and second check and lost an average of 0.66 kg +/- 5.86 kg between the diagnosis and the second check. The controls gained 1.28 kg +/- 3.81 between the first and second check and 3.42 kg +/- 4.18 between diagnosis and the second check.

At the third check, cases lost an average of 0.46 kg +/- 2.1 kg between the second and third check and 0.53 kg +/- 7.34 kg between diagnosis and the third check. The controls gained an average of 2.07 kg +/- 3.22 kg between the second and third check and 5.5 kg +/- 4.81 kg between the diagnosis and the third check.

Kg

63

62

61

60

Case

Control

UNDER PEER REVIEW

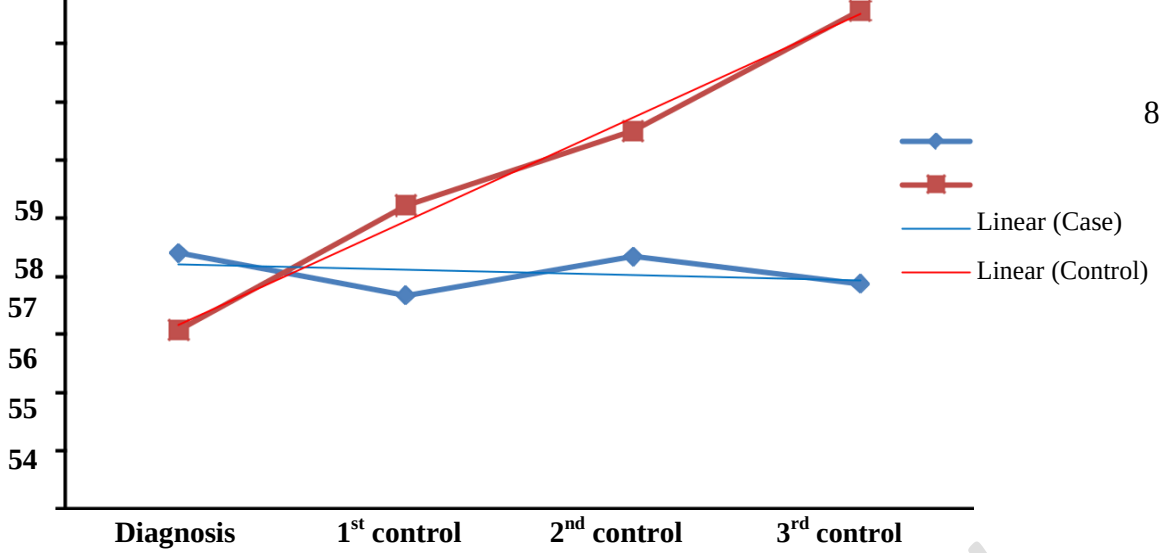


Figure 2: Evolution of the average weights of cases and controls during the follow-up.

It was noted that on direct examination of sputum samples, the presence of between 1 and 10 BAARs in 1 field (3+) represented 35.5% in the cases and 17.7% in the controls. The presence of 1-10 BAARs in 10 fields (2+) was 32.3% in cases and 31.3% in controls. The presence of 1-10 BAARs in 100 fields (1+) was 32.3% and 51% in cases and controls respectively.

The presence of a chronic disease was present in 32.3% of cases and 25% of controls. Diabetes was present in (17)50% of patients and silicosis in (10)29.4% of patients. The notion of tuberculosis infection was noted in 9.4% of cases and controls. Hospitalization was reported in 81.3% of cases and 71.7% of controls. The number of cases having abandoned their anti-tuberculosis treatment was 13, representing 40.6% of the cases. Three controls discontinued treatment, representing 3.2% of controls.

The average time to start TB treatment was 45 days +/- 37 for cases and 50 days +/- 47 for controls. The average duration of treatment was 14 months +/- 9 in cases and 7 months +/- 1 in controls.

Of the ten antibacillary drug susceptibility tests performed in the cases, five were susceptible and the other five were drug resistant. Three tests showed BK strains resistant to one drug: isoniazid (INH), the other two to three drugs: INH + streptomycin (STM) + ethambutol (ETM) and rifampicin (RIF) + STM + INH.

Treatment side effects were reported in two cases and three controls.

For toxic habits, smoking was reported in one case. Smoking in addition to alcohol consumption was reported in one control.

Table 2: Clinical characteristics of cases and controls

Variables	**Cases**	**Control**
	Frequency (%)	
Chronic diseases		
Yes	10(32.3)	24(25)
No	21(67.7)	72(75)
Notion of tuberculosis contagion		
Yes	3(9.4)	9(9.4)
No	29(90.6)	87(90.6)

UNDER PEER REVIEW

BK density at diagnosis		
1 to 10 in 100 fields (1+)	10(32.3)	49(51)
1 to 10 in 10 fields (2+)	10(32.3)	30(31.3)
1 to 10 in 1 field (3+)	11(35.5)	17(17.7)
Hospitalization		
Yes	26(81.3)	66(71.7)
No	6(18.8)	26(28.3)
Discontinuation of treatment		
Yes	13(40.6)	3(3.2)
No	19(59.4)	90(96.8)
		Average (+/- SD)
Weight at diagnosis	59 (9)	58(11)
Weight at 1st check-up	57.1 (10)	61.4(11.5)
Weight at 2nd check-up	58 (9.6)	64.1(11.3)
Weight at 3rd check-up	58 (9)	62.6(14)
Time to start treatment in days	45 (37)	50(47)
Duration of treatment in months	14 (9)	7(1)

Bivariate analysis:

Table 2 presents measures of the degrees of association between socio-demographic and clinical characteristics of cases and controls and TB treatment failure.

A statistically significant association was shown between treatment failure and gender, treatment discontinuation, difference in BAAR density between treatment initiation and first control, difference in weight between weight at first, second and third control and initial weight and duration of treatment.

Tuberculosis patients who had a notion of discontinuing their anti-tuberculosis treatment were 20.5 times more likely (p-value = 0.000) to become a case of treatment failure than tuberculosis patients with regular treatment follow-up.

The absence of a decrease in BAAR density between the start of treatment and the first control was 25.5 times (p-value = 0.000) more likely to result in treatment failure than a decrease in bacillary density.

At the first control, a 1 kg decrease in initial weight increased the risk of TB treatment failure by 1.55 times, at the second control the risk increased by 1.26 times and at the third control the risk increased by 1.2 times.

The other variables had no statistically significant association with treatment failure.

Multivariate analysis:

Multivariate analysis by logistic regression allowed us to adjust the degree of association between treatment failure and weight variation at the first check while adjusting for the other variables.

UNDER PEER REVIEW

The final model retained is presented in Table 3. It was shown that discontinuation of treatment (ORa=12.2) and no decrease in bacillary density at first check (ORa=8.30) were associated with treatment failure. Weight gain of 1 kg (ORa=0.52) was a protective factor against treatment failure. A significant interaction was found between the difference in weight and the Change in bacillary density at baseline.

Table 3 : Adjusted risk factors for treatment failure

Variables	Ajusted OR	IC	Coefficient	P-value
Discontinuing treatment (yes)	**12.02**	1.30 – 113.43	2.47	**0.030**
Difference in weight at 1st check (Kg)	**0.52**	0.40 – 0.72	-0.65	**0.000**
Variation in bacillary density at 1st check (no decrease)	**8.30**	1.75 – 39.20	2.11	**0.010**
Difference in weight and variation in bacillary density at 1st check	**2.13**	1.40 – 3.26	0.76	**0.000**
Constant	*	*	-1.26	**0.001**

4. DISCUSSION

This study shows, after adjustment for potential confounding factors, that the main factors significantly associated with TB treatment failure in microscopy-positive pulmonary TB were: treatment discontinuation, weight loss and non-decrease in bacillary density.

The curve of the evolution of the mean weights of the cases and controls shows a slight decrease in weight in the cases against a strong increase in weight in the controls. This change in weight was statistically significant. Using the change in weight or body mass index (BMI), similar studies show the same finding [11;12;13;15], while in another study the overall mean weight of cases and controls respectively increases in a progressive manner but the increase in controls is greater [15].

Even if TB is associated with malnutrition [16] the persistence of general clinical signs (weight loss) during treatment, should suspect treatment failure before the expected completion date of treatment [17].

These findings could have a significant impact on public health. Weight assessment could be an easy, cheap and useful form of predicting the outcome of TB treatment. Weight loss at first check-up can be considered a poor prognostic sign for a favourable outcome of TB treatment and may prevent early case failures [12;15].

In our study, failure to decrease bacillary density at first check was a risk factor for treatment failure. Studies show that persistence of sputum positivity on direct examination after two months of antibacillary treatment is a factor associated with treatment failure [13;15;18;19;20;21].

UNDER PEER REVIEW

Bacteriological control of sputum is the only means of declaring the cure of patients treated for microscopy-positive pulmonary tuberculosis. Under conditions of limited resources (culture and drug susceptibility testing), direct sputum examination at the end of the first phase of treatment is the critical discriminator of "high" and "low" risk patients for treatment failure. [18] Patients with positive sputum smears after 2 months of treatment may not respond well to treatment due to infection with drug-resistant Mycobacterium tuberculosis, one of the main risk factors for non-curement [20].

Although positive sputum microscopy at the end of the second month is an unspecific test for early identification of failures, [22] sputum microscopy is a low-cost test that can be used by TB control programmes to identify and manage people at risk early [13].

Discontinuation of TB treatment is a common cause of treatment failure; [13;17;23;27] The association between TB treatment discontinuation and treatment failure is found in other studies; [11;24] Indeed, it is contrary to human nature to take drugs for long periods of time after the symptoms of the disease have disappeared, especially if the side effects of treatment are more unpleasant than the disease itself [25].

Some studies have noted the association between TB treatment failure and male gender [26;27], but gender is considered primarily a risk factor for treatment discontinuation [26;27].

The sample size was insufficient as evidenced by the wide confidence intervals (1 case of failure was female and treatment discontinuation was in 3 controls) which does not allow for precision in assessing the degree of association.

In our study, delay in treatment was not associated with treatment failure, but in some studies a delay of more than 60 days was significantly associated with treatment failure. For TB patients on category II treatment, a delay of more than 3 weeks is significantly associated with treatment failure [31]. Thus the delay in starting treatment allows the disease to progress to a more severe clinical phase in which cure becomes more difficult [30].

This study was limited by its retrospective design, socio-demographic and clinical variables were extracted from routine medical examinations during patient follow-up and several risk factors were not checked.

Similarly, behavioural characteristics were absent (tobacco, alcohol), which may be explained by the widespread use of chemma snuff in Oujda and the conservative nature of the population.

CONCLUSION

The results of this study showed that there is a significant association between TB treatment failure and weight loss, non-decrease in bacillary density at first check and treatment discontinuation.

The validity of these results needs to be verified by prospective studies.

Failure of TB treatment may be suspected at the first visit, which requires special attention for patients who present to the CDTMR at the first visit and whose clinical examination reveals weight loss with a similar direct bacillary count to that at diagnosis.

These results suggest that measures can be applied from the first check-up at the end of the second month, in order to avoid failure:

UNDER PEER REVIEW

- To initiate active follow-up of at-risk patients through home visits;
- To Search for drug resistance and introduce GenExpert resistance testing;
    - Assess adherence to treatment;
    - Involve the family and community in the management of patients;

- Involve social workers in case investigations;
- Facilitate a support network to maintain a permanent link between patients and health staff;
- Establish a climate of trust with all patients based on an appreciation of the patient's needs and mutual respect between the patient and the health care providers;
- Establish, in consultation with the patient, family and community, acceptable measures for assessing and encouraging good adherence to treatment.

CONSENT AND ETHICAL APPROVAL

As per international standard or university standard guideline written and informed respondents' consent and ethical approval has been collected and preserved by the authors.

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UNDER PEER REVIEW

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