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Research article

The trend of tuberculosis case notification and predictors of unsuccessful treatment outcomes in Samdrup Jongkhar district, Bhutan: A fourteen-year retrospective study

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ABSTRACT

Tuberculosis (TB) continues to be an important public health issue in Bhutan. This study aims to describe the trend of tuberculosis and investigate factors associated with a unsuccessful treatment outcome in Samdrup Jongkhar District in Bhutan.

A fourteen-year (2004–2017) case records in two TB centres of Dewathang and Samdrup Jongkhar Hospitals were reviewed and analyzed to examine trends in case notification and treatment outcomes. Univariable and multivariable logistic regression analysis was undertaken to identify covariates of unsuccessful TB treatment.

Of the total of 820 TB cases registered in surveillance record, 729 cases were analysed. Males made up 53.8% (397) of total cases and the median age was 29 years (range: 2–87 years). A gradual downward trend in TB case notification was noticed in the district with overall case notification rate of 139/100,000 during the study period. The annual treatment success rate was over 90% except for years 2013–2015 with overall treatment success rate for the study period at 93%. A re-treatment TB patient, sputum-positive at the second month of treatment and being of Indian nationality were significant correlates of unsuccessful treatment outcomes. The overall TB inclidence has declined and TB treatment success rate was above WHO recommended 90% in Samdrup Jongkhar District during the study period. A special attention should be paid to the poor treatment outcome predictors including re-treatment cases and failed sputum conversion at the second month of treatment.

1. Introduction

Tuberculosis (TB) is an infectious disease of major public health concern caused by the bacillus *Mycobacterium tuberculosis* complex that typically affects lungs (Pulmonary TB [PTB]) and other body parts known as extra-pulmonary TB (EPTB). According to the World Health Organization (WHO), TB is now the leading infectious disease killer in the world, having surpassed HIV, and is among the top 10 causes of death worldwide. It is estimated that 5–15% of the estimated 1.7 billion people infected with *M. tuberculosis* could develop active TB during their lifetime. In 2017, an estimated 10.4 million people suffered from TB with 1.3 million deaths, of which over 95% occurred in low and middle-income countries [1, 2]. The WHO South-East Asian Region (SEAR) accounted for up to 45% of new TB cases globally [3, 4] and is number one cause of disability-adjusted life years (DALYs) lost amongst 15–49 years [5]. The World Health Assembly in 2014 endorsed the 'End TB Strategy' aimed at ending the global TB epidemic by 2030 [2]. A similar regional level effort was initiated in SEAR to reduce TB deaths by 90% and TB incidence by 80% by 2030, compared to 2015 baseline [5, 6].

In Bhutan, TB continues to remain one of the leading public health problems despite a decrease in morbidity and mortality since the introduction of Directly Observed Treatment Short-course (DOTS) in 1997. Despite the significant reduction in incidence, the current challenge of the National TB Control Program (NTCP) lies to bridge the case detection gaps through early diagnosis and prompt initiation of treatment and improve the treatment outcomes as priority intervention [7]. In 2017, there were a total of 929 TB cases and 10 deaths in Bhutan [8]. More than 85% of TB cases in the country were reported by eight districts including

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Samdrup Jongkhar [9]. There is also high default rates among retreatment TB cases at 7% in Bhutan [10] which is a potential risk factor to develop into multidrug resistance [11, 12, 13]. The increasing MDR-TB has currently emerged as a major issue for the national TB program. The 2014 national TB surveillance data reported MDR-TB prevalence of 14% in Bhutan [14]. Therefore, the main aim of this study was to examine the trend of tuberculosis and treatment outcomes, and explore the factors associated with a poor TB treatment outcome in Samdrup Jongkhar District.

2. Materials and methods

2.1. Study area

This study was conducted in Samdrup Jongkhar District which is located in the south-eastern part of Bhutan and is one of the four major commercial towns in Bhutan with an open border with neighbouring India (Figure 1). It is administratively divided into 11 sub-districts (*Gewogs*) with a total population of 35,059 with 47.7% (16,750) women in 2017 [15]. There are 12 primary health centres and two hospitals providing health services to the population of the district. However, only Samdrup Jongkhar Hospital and Dewathang Hospital are designated TB treatment centre in the district with TB diagnosis and intensive treatment facilities [16].

2.2. Study design and data collection

We undertook a retrospective analysis using secondary data of TB cases from two TB reporting centres in Samdrup Jongkhar District – Dewathang Military Hospital and Samdrup Jongkhar District Hospital. The data were extracted from TB registers of Dewathang Hospital and Samdrup Jongkhar District Hospital from 2004 to 2017. All variables included in this study were part of the routine TB surveillance data collected by the NCTP from TB treatment centres around the country. In Bhutan, TB sputum microscopy is only done in the hospitals while DOTS are provided by all the health centres. However, patients visit hospital in 5th and 8th month for sputum and blood test to monitor the effectiveness of treatment. All TB records are maintained in the TB centres in the hospitals. The National TB Treatment Guideline are used for TB diagnosis, treatment, case follow up and other interventions including health education. All clinical case and treatment outcome definitions used in this study were based on the National TB treatment guidelines adapted from WHO [7]. Any patients with symptoms of fever and cough lasting more than two weeks, haemoptysis, loss of weight, night sweats, chest pain, loss of appetite, and any person suggestive of TB are subjected to three sputum samples examination: one spot and two on the subsequent days. Patients with at least two positive smears or one positive smear with radiologic abnormalities consistent with pulmonary tuberculosis or sputum

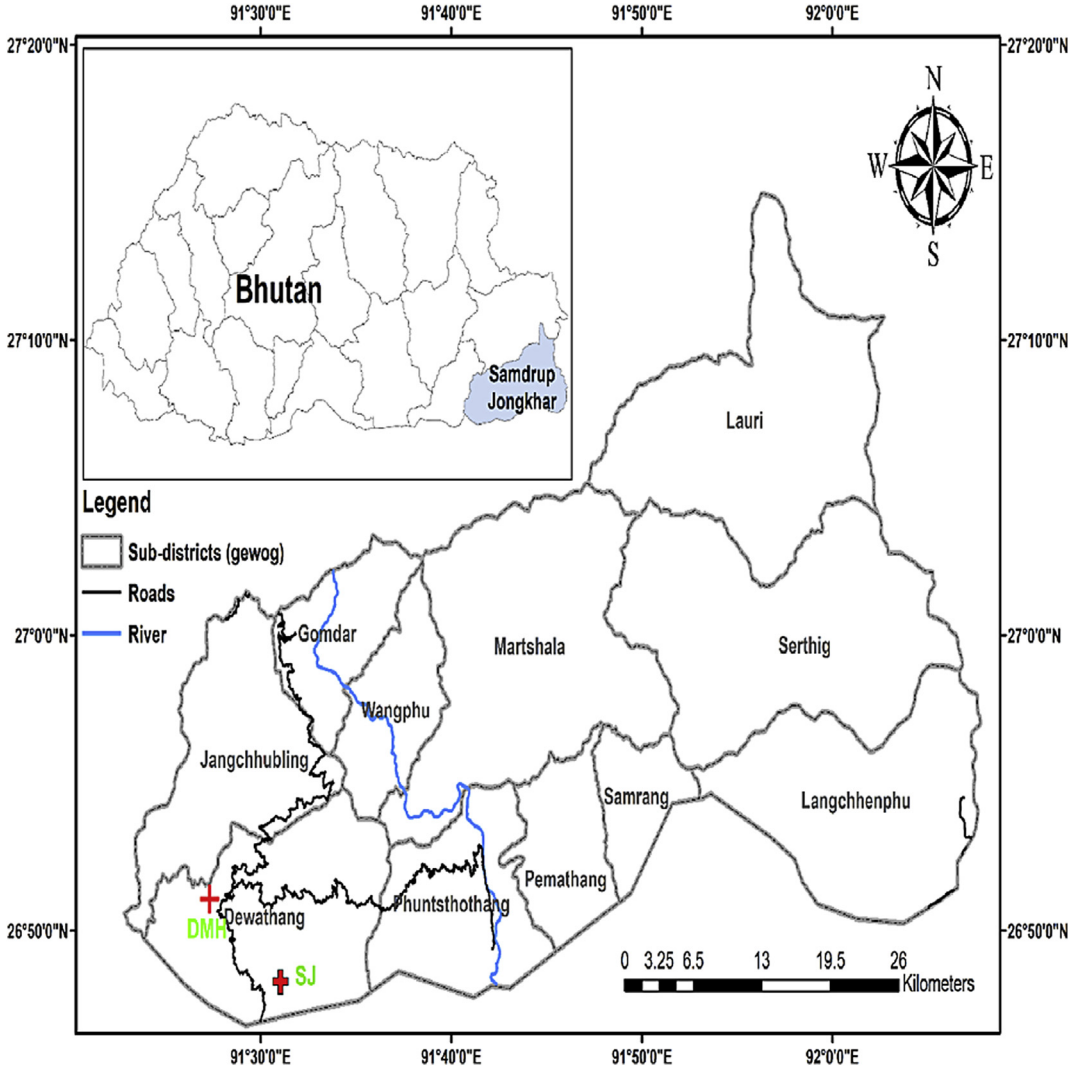

Figure 1. Map of Bhutan showing the study area in Samdrup Jongkhar district. (DMH- Dewathang Military Hospital, SJ- Samdrup Jongkhar).

culture positive were considered to have smear-positive PTB (SPPTB). Any patient having three consequent negative smears are given a course of antibiotic treatment and evaluated subsequently. These latter patients are considered to be smear-negative PTB (SNPTB) when they did not respond to the antibiotic course and chest X-ray are suggestive of PTB. The criteria for the diagnosis of EPTB are based on the clinical, radiological, or histological evidence suggestive of active TB in an extrapulmonary site. The variables extracted were: (i) date of registration of TB case, (ii) age, (iii) gender, (iv) current address at the time of diagnosis, (v) type of TB infection (new, relapse, default, treatment failure, transferred in), (vi) type of TB - SPPTB, SNPTB, and EPTB, (vii) treatment regimen, (viii) sputum conversion (2, 5, and 8 months), and (ix) treatment outcome (cured, completed treatment, defaulter, failure of treatment, died, or transferred out).

2.3. Definitions of treatment outcomes as per national TB guidelines

Treatment success: The sum of cured and treatment completed cases.

Cured: A PTB patient with bacteriologically confirmed TB at the beginning of treatment and becomes smear- or culture-negative in the last month of treatment and on at least one previous occasion.

Treatment completed: A TB patient who completed treatment without evidence of failure BUT has 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 failure: A TB patient whose sputum smear or culture is positive during treatment at month 5 or later.

Died: A TB patient who dies from any reason before starting or during the course of treatment.

Lost to follow-up: A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.

2.4. Data analysis

The data were entered into Microsoft Excel (Microsoft Corp, Redmond, WA, USA) by the trained health workers at the two hospitals under the supervision of the investigators. Two independent investigators cross-checked the data to ensure the quality and validity of the data. Data were analyzed using STATA version 14 (Stata Corporation, College Station, TX, USA) software. TB records of the transferred in patients from other districts were excluded from the final analysis because they were not included in the district population. Descriptive analysis was performed by calculating frequencies and percentages of variables of interest to investigate distribution and pattern of TB related variables. The district population estimate for the years 2004–2017 was obtained from National Statistical Bureau [17]. Annual Case notification rates (CNR) of TB cases was computed from annual number of TB cases divided by district population estimate and expressed as per 100,000. The percent of successful treatment outcomes were calculated to examine trend in treatment outcomes. The treatment outcomes were categorized into: (a) "unsuccessful = 1" which included records with treatment failure, died, lost to follow

Table 1. General characteristics of TB patients and successful TB outcome (2004–2017).

Characteristics			Treatment success	
	Total	%	Total	%
Gender				
Female	337	46.2	314	46.2
Male	392	53.8	365	53.8
Age				
<14	63	8.7	61	9
15-24	209	28.7	198	29.2
25-34	194	26.7	178	26.3
35-44	102	14.0	98	14.5
45-64	112	15.4	100	14.8
>65	48	6.6	43	6.3
Patient type				
New	643	88.2	609	89.7
Relapse	63	8.6	52	7.7
Default	8	1.1	8	1.2
Failure	5	0.7	2	0.3
Others	10	1.4	8	1.2
TB type				
EPTB	229	31.4	217	32.0
PTB	500	68.6	462	68.0
SPPTB	365	73.2	334	72.5
SNPTB	134	26.9	127	27.6
Nationality				
Bhutanese	706	96.8	660	97.2
Indian	23	3.2	19	2.8
Treatment outcomes				
Completed	353	48.7	355	52.3
Cured	323	44.5	324	47.7
Failure	22	3.0	0	0
Defaulted	3	0.4	0	0
Died	14	1.9	0	0
Unknown	10	1.4	0	0

EPTB- Extra-Pulmonary Tuberculosis; PTB- Pulmonary Tuberculosis; SPPTB – Smear positive PTB; SNPTB – Smear negative PTB; NA – Data Not available.

up, or unknown treatment outcomes and (b) "successful treatment = 0" if it was recorded as cured or treatment completed. Backward conditional multivariable logistic regression was performed to explore the predictors of unsucessful treatment outcomes after controlling for confounders. Variables with $P < 0.2$ on bivariable analysis were included in the multiple logistic regression model. Levels of significance were set at 5% ($P < 0.05$) for the full model. Unadjusted and adjusted odds ratio (OR) were computed to identify and quantify the strength of association.

2.5. Ethical issues

The study was approved by the Bhutan Research Ethics Board of Health (REBH) through approval number (REBH/Approval/2018/071) and permission to use these data was granted by the Ministry of Health of Bhutan (Ref: CI/(9)/2018-19/1654). Patient privacy and confidentiality were ensured by not including identifier details like name and hospital registration number into the data extraction form.

3. Results

3.1. Characteristics of TB patients

Of the total 820 TB cases recorded in TB surveillance registers, 729 TB patients were included in the final analysis after excluding 91 transfer in cases from other districts. Over half of the TB cases (53.8%, 392/729) were males and the median age was 29 years (range 2–87 years). The prevalence of TB was highest in the age group of 15–34 years (55.4%, 403/728), and children under 14 years made up 8.7% (63/728) of the total cases. The commonest patient types were new cases at (88.2%, 643/729). Majority (68.6%, 500/729) were PTB of whom almost two-thirds (73%, 365/500) were SPPTB. The proportion of EPTB to PTB was not significantly different between males and females. Male TB patients had 53.8% (365/679) treatment success rate while new TB cases accounted for 89.7% (609/679) of treatment success outcomes. The unsuccessful treatment outcomes was recorded in 6.9% (49/725) of the TB patient for the study period (Table 1).

3.2. Trend in TB case notification and treatment outcomes

The annual TB case notification rate for all forms declined from 180/100,000 in 2004 to 111/100,000 in 2017 with overall annual CNR of 139/100,000 for the study period. The maximum CNR was 186/100,000 in 2009, followed by downward trend reaching to lowest of 88/100,000 in 2015. The case notification rate of new TB cases showed similar trend (Figure 2). In terms of treatment outcomes, treatment success rate improved from 93% in 2004 to 100% in 2007. Thereafter, the treatment success rate fluctuated downward between 86 to 96% but overall fourteen-year treatment success rate of TB patient was maintained at 93% (679/729) (Figure 3).

3.3. Determinants of unsuccessful treatment outcomes

In the univariate analysis, re-treatment TB cases compared to new cases, positive sputum at two months and being of a Indian national were factors associated with a unsuccessful treatment outcome. The multiple logistic regression analysis demonstrated same set of factors as significant predictors associated with unsuccessful TB treatment outcomes; a positive smear in the second month (AOR:22.174; CI: 8.002–61.44), re-treatment TB cases compared to new cases (AOR:2.708; CI: 1.041–7.040) and the nationality of TB patient being Indian (AOR:4.076; CI: 1.062–15.627) (Table 2).

4. Discussion

According to the WHO, assessment of key program indicators and identifying risk factors affecting TB patient treatment outcomes are essential to monitor the performance of any TB program [18]. This study using surveillance TB data in Samdrup Jongkhar District showed a gradual downward trend of annual TB case notification rates with overall fourteen-year annual incidence of 139/100,000 from 2004-2017. The prevalence of TB was highest in the age group of 15–34 years (55%). The treatment success rate varied between 86-100% with an overall treatment success rate of over 90%. The highest and lowest treatment success were reported in 2007 and 2015, respectively. The significant covariates

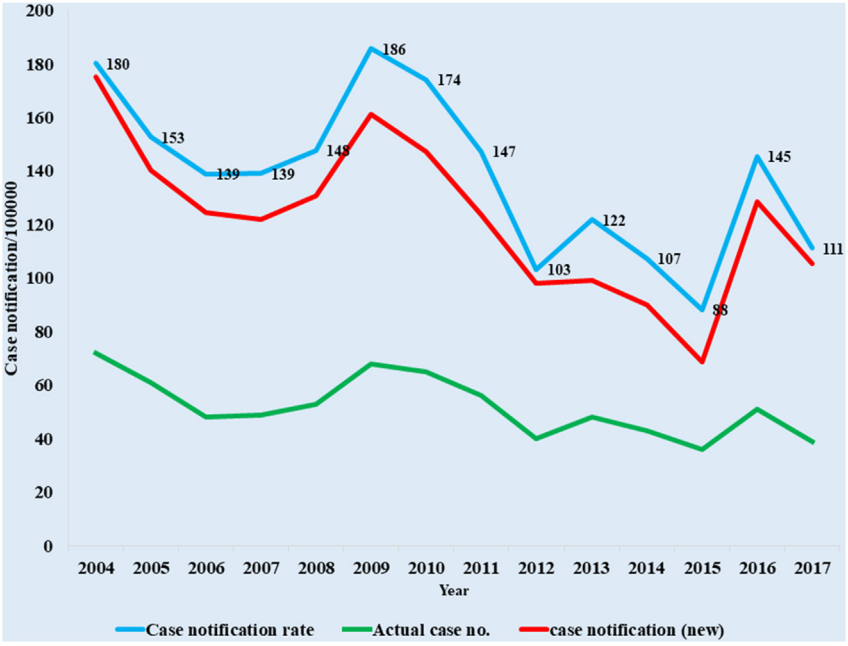

Figure 2. The trend of TB notification rate from 2004 to 2017.

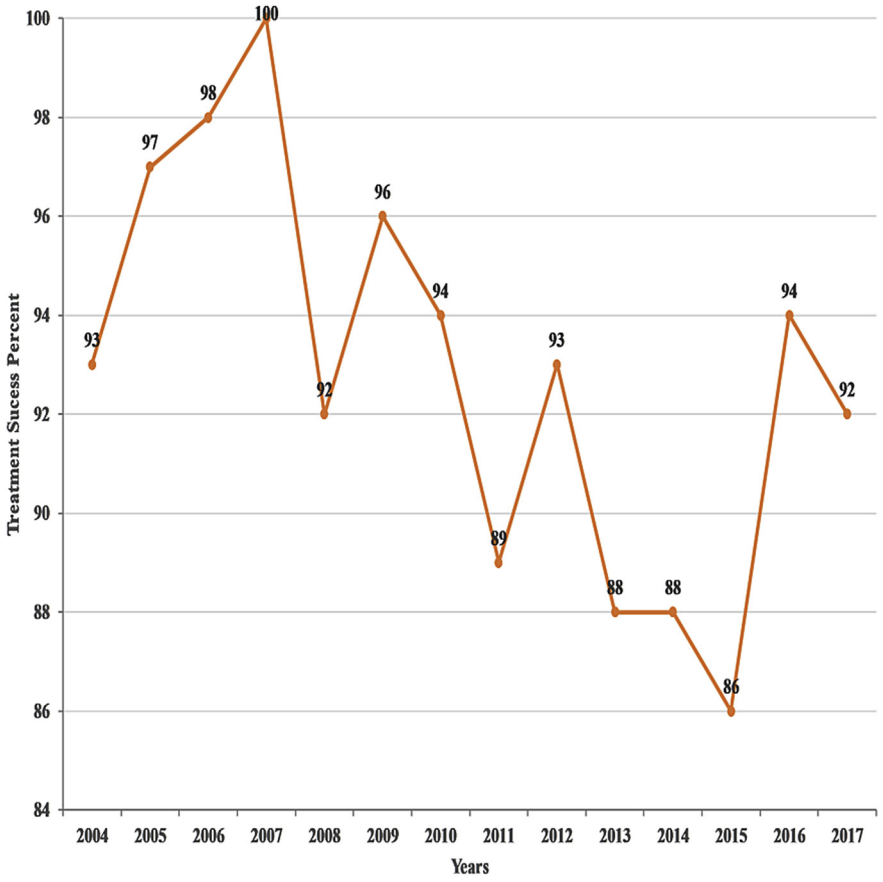

Figure 3. The trend of annual TB treatment success rate from 2004 to 2017.

Table 2. Logistic regression analysis with factors associated with unsuccessful TB treatment outcomes.

Characteristics	COR	CI	P value	AOR	CI	P value
Sex						
Female	1.00					
Male	1.051	0.587–1.884	0.865			
Age category						
25-34	1.00			1.00		
<14	0.364	0.082–1.632	0.187	0.507	0.103–2.500	0.404
15-24	0.571	0.252–1.290	0.178	0.818	0.308–2.173	0.688
35-44	0.454	0.148–1.396	0.168	0.219	0.044–1.097	0.065
45-64	1.335	0.607–2.934	0.472	0.909	0.321–2.565	0.856
>65	1.294	0.449–3.726	0.633	1.327	0.384–4.513	0.662
Patient type						
New	1.00					
Re-treatment	4.010	2.077–7.741	0.000	2.708	1.041–7.040	0.041
TB type						
EPTB	1.00					
PTB	1.437	0.735–2.812	0.289	3.062	0.884–10.603	0.077
SMT						
Negative	1.00			1.00		
Positive	25.303	9.428–67.912	0.000	22.174	8.002–61.441	0.000
NA	5.780	2.228–14.995	0.000	16.446	4.274–63.280	0.000
Nationality						
Bhutanese	1.00			1.00		
Indian	3.249	1.055–10.005	0.04	4.076	1.062–15.627	0.040

Note: COR-crude odds ratio; AOR-adjusted crude odds ratio; CI- confidence interval; SMT- Second month smear test; NA- Not Available (data).

for a unsuccessful treatment outcome were sputum non-conversion at second month, re-treatment TB patient and being of a foreign nationality.

The decreasing trend in TB case notification rate noticed in this study is in concordance with the general trend of TB notification rates recorded in the country during the study period. The case notification rate of all forms of TB has declined from 211/100,000 in 2000 to 143/100,000 population in 2014 in Bhutan [7, 19]. Some of the plausible reason cited for this steady reduction in TB incidence include the effective implementation of the TB DOTS program in the country [19, 20] and improved case detection capacity, laboratory services and treatment strategy for TB diagnosis in the health facilities which are carried out in all districts in Bhutan. These program initiative was supported by the Global Fund to Fight AIDS, Tuberculosis and Malaria (GF) Round 4 grant to strengthen the laboratory services for TB program services in health facilities. The continued advocacy on TB in the communities by the NTCP and district health workers has also played role in improved early case detection and early seeking of treatment [21].

The mean treatment success rate of above WHO recommended cutoff of 90% (93%) in the study district is comparable to national [22, 23] and other countries in the region including Bangladesh (94%), Nepal (91%), Sri Lanka (85%), Pakistan (93%) [24] and Ethiopia (92.5%) [25]. This is in line with the recommended target of the End TB Strategy set by the WHO [2, 18]. Other studies reported factors such as being an HIV-negative and non-alcohol drinkers as significant determinants of successful TB outcome [26, 27, 28]. However, these factors were not captured in the national TB recording system. The high treatment success rate in this study could be again attributed to the successful implementation of the DOTS program [29] and strengthening of district level TB diagnostic and treatment capacities by NTCP. Fourteen (1.9%) TB related deaths recorded in this study is comparatively lower than other countries of Asia and Africa [30, 31, 32]. The overall lower mortality rates may be due to early detection and treatment intervention provided by the government in Bhutan. There was an inverse relationship between age and the treatment outcome. Old age is associated with poor treatment outcome. This is consistent with other studies where TB patients with younger age groups are associated with better outcome compared to older age groups who were associated with high mortality [33, 34, 35, 36, 37]. This could be due to the presence of various co-morbid illness, decreasing health and immunity at old age. However, a study in Denmark showed that age was not an associated factor for TB outcome [38]. This could be due to the difference in the definition of the unsuccessful outcome since the above-mentioned study excluded TB death from an unsuccessful outcome.

Our analysis of the potential predictors of unsuccessful TB treatment outcome demonstrated sputum non-conversion in the second month to be significant which have been previously reported [39, 40]. A sputum positive at two months indicates that TB treatment is not working against *M. tuberculosis* [41] which could be used as an important predictor of unsuccessful treatment outcome by the NCTP [42, 43]. However, sputum non-conversion at the second month may not necessarily indicate an unfavourable outcome due to low sensitivity and low specificity of sputum microscopy to detect failure [44, 45]. This also may result from the false-positive results due to the inability of microscopist to differentiate dead and live bacilli which is possible only through mycobacterial culture. Mycobacterial culture facilities are not readily available in most hospitals in Bhutan.

An unsuccessful treatment outcomes in re-treatment TB patients (relapse and failures) compared to new cases has been previously reported from studies conducted in countries in Asia [46, 47, 48] and Africa [49]. The poor treatment outcomes in re-treatment cases may be explained by the higher likelihood of treatment default and MDR-TB in this category of patients. A drug resistance survey conducted by the national TB reference laboratory in 2010 reported 35% MDR-TB rates among re-treatment cases compared to 5% among new cases in Bhutan [50]. On the other hand, a more favourable treatment outcomes in Bhutanese patients as compared to Indian national could be attributed to their migration and follow up challenges because there are a significant number of Indians who reside temporarily and work in Bhutan. It has been shown in the past that foreign-born patients stood at higher risk for default and unfavourable treatment outcomes [48]. It is plausible that Indian nationals would seek treatment in Samdrup Jongkhar and later travel back to their place of origin for continuing treatment. Therefore, the outcome of TB remains unknown for this group of patients.

There are a number of limitations to our study. First, there was no way to ascertain the quality of data which might be subjected to inaccuracies and incompleteness of register and treatment card. Second, other important unmeasured variables such as occupation, socioeconomic status, type of residence, educational level, distance from the health centres and co-infection with HIV and co-morbidities were not available. Third, some of the findings of this study may not necessarily reflect national trends because the study was based on the patients diagnosed and treated in two hospitals in Samdrup Jongkhar Districts. Lastly, the predictors of unsuccessful treatment outcome reported in our study could be independently associated with drug-resistant TB. However, this could not be investigated in our analysis as drug susceptibility testing data was not available. Therefore, the potential for these factors being confounders for the true causative exposure (i.e., drug resistance) cannot be excluded.

5. Conclusion

The overall incidence of TB has declined over the study period in Samdrup Jongkhar District. The treatment success rate (cured or treatment completed) during the study period was 93%. However, re-treatment cases and patients failing a sputum conversion at the second month and PTB warrants special attention because it is associated with poor treatment outcome. In the context of increasing challenges posed by increasing emergence of MDR-TB in the country, it is also critical that comprehensive surveillance for drug resistance among TB cases diagnosed is further strengthened. It is recommended to undertake a similar study using national data to identify possible covariates of unsuccessful treatment outcome at the national level.

Declarations

Author contribution statement

Tshokey and Kuenzang: Conceived and designed the experiments; Analyzed and interpreted the data; Wrote the paper.

Kinley Penjor and Kinley Wangdi: Conceived and designed the experiments; Performed the experiments; Analyzed and interpreted the data; Wrote the paper.

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Data availability statement

Data will be made available on request.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

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