Tropical Journal of Pharmaceutical Research August 2019; 18 (8): 1755-1762
ISSN: 1596-5996 (print); 1596-9827 (electronic)

Available online at http://www.tjpr.org
http://dx.doi.org/10.4314/tjpr.v18i8.27

Original Research Article

Outcome of interim multidrug-resistant tuberculosis treatment in Yemen

Ammar Ali Saleh Jaber*, Baharudin Ibrahim
Department of Clinical Pharmacy, School of Pharmaceutical Sciences, Universiti Sains Malaysia, Penang, Malaysia

For correspondence: **Email: amarali20142015@gmail.com; **Tel:** 0060-174673989*

Sent for review: 15 February 2019 *Revised accepted: 29 July 2019*

Abstract

Purpose: *To assess the interim therapy outcomes of patients with multidrug-resistant tuberculosis (MDR-TB) in Yemen.*
Methods: *This study was performed in four major tuberculosis (TB) centers in Yemen, namely, Alhodidah, Taiz, Sana'a, and Aden. Data were collected between January 1, 2014 and December 31, 2016, and consistent methods were adopted to obtain data from MDR-TB patients. The standardized WHO method of calculating and reporting the interim therapy outcomes patients enrolled in the study was applied, and the relation between dependent and independent variables was obtained by logistic regression.*
Results: *A total of 85 MDR-TB cases were reported between January 1, 2014 and December 31, 2016. Of these cases, 62 reported available interim results. Among the 62 MDR-TB cases, only 40 (64.5 %) were categorized into successful interim therapy outcome group. This study found a baseline weight ≤ 40 kg, comorbidity, and first-line drug (FLD) resistance (> 3) as risk factors influencing unsuccessful interim therapy outcomes.*
Conclusion: *This cohort study reports an alarmingly high rate of unsuccessful interim therapy outcomes among Yemeni MDR-TB patients. Enhancement of the clinical management of patients with a baseline weight ≤ 40 kg, comorbidity, and FLD resistance (>3) may improve TB therapy outcomes.*

Keywords: *Multidrug resistance, Khat, Tuberculosis, TB*

Tropical Journal of Pharmaceutical Research is indexed by Science Citation Index (SciSearch), Scopus, International Pharmaceutical Abstract, Chemical Abstracts, Embase, Index Copernicus, EBSCO, African Index Medicus, JournalSeek, Journal Citation Reports/Science Edition, Directory of Open Access Journals (DOAJ), African Journal Online, Bioline International, Open-J-Gate and Pharmacy Abstracts

INTRODUCTION

Multidrug-resistant tuberculosis (MDR-TB) is the main hindrance of the successful control of tuberculosis (TB). Controlling and curing MDR-TB are intricate processes; thus, obtaining positive therapy outcomes, even under ideal circumstances, is challenging. This issue could be partly attributed to the prolonged duration and high toxicity and cost of MDR-TB therapy [1,2]. Ineffective therapy outcomes may also occur due to a lack of evidence from previous clinical trials, insufficiency of (Secnd Line Drugs) SLD supplements, and relatively low number of professionals and laboratories [3,4]. The duration of MDR-TB therapy is usually 16−20 months but may be extended depending on the results. Most therapy results can only be obtained 2−3 years following initiation of MDR-TB therapy.

National Tuberculosis Program (NTP) managers, health workers, and administrators have demanded signs of therapy efficacy from registered MDR-TB patients [5]. Indeed, the WHO has developed different interim scales to monitor drug-resistant TB programs and implement proper and well-timed actions to control the disease [5]. Among these interim scales, a negative culture of sputum in the initial months of therapy is comprehensively utilized as a primary interim scale/indicator of non-infectiousness; it also allows tracking of the clinical development and efficacy of therapy [5,6].

A negative culture after 2 months of therapy indicates a successful therapy outcome in MDR-TB patients [7,8]. Conversely, patients with a positive culture at end of two months of therapy are likely to have an unsuccessful therapy outcome [9]. Lack of follow-up during the initial 6 months of therapy due to various reasons, such as symptom relief and adverse side effects [10], is valuable in evaluating adherence to MDR-TB therapy and reflects the overall NTP performance [5].

Yemen has a low success rate for curing TB relative to the WHO's outcome standard of 90 % [11]. Because the mortality rate of TB is high in Yemen, the country's Ministry of Health has renewed its focus on disease control [12,13]. Approximately 1.6% of all recently reported MDR-TB cases are from newly diagnosed patients with TB; another 16% of these cases are from relapses [12]. However, Yemen appears to have no or limited capability to collaborate with international laboratories for second-line drug susceptibility testing (DST) [14,15]. Furthermore, no survey or study in Yemen has yet investigated the interim therapy outcomes of MDR-TB patients. Therefore, the purpose of the present work is to evaluate the risk factors associated with interim therapy outcomes of MDR-TB patients in the Yemeni cities of Alhodidah, Taiz, Sana'a, and Aden.

EXPERIMENTAL

Study location and ethical approval

This study was performed in four main TB centers in Yemen, namely, Alhodidah, Taiz, Sana'a, and Aden. These centers have a central laboratory for TB diagnosis, and all TB cases from other areas [13]. These centers are manned by 70 health workers comprising doctors, laboratory staff, and officers. The research was approved by National Committee of Health, Ministry of Health, Yemen (approval no. 1037 San-Yem), and carried out according to WHO consolidated guidelines on drug-resistance tuberculosis [16].

Study population

The current research is a retrospective cohort research. The duration of study is from January 1, 2014 to December 31, 2016. The inclusion criteria are all diagnosed with MDR-TB and initiated therapy following national TB control guidelines. Those patients who reported previous MDR-TB therapy, monoresistance, polyresistance, and extensive drug resistance tuberculosis (XDR-TB) were not include in our research. 85 MDR-TB were recorded in four cities. Ten patients were initially excluded; of these, two were under the age of 18 years, five exhibited polyresistance, and three declined participation in the study. Thirteen other patients were excluded because their interim therapy outcomes were unknown. Hence, a total of 62 MDR-TB with available interim therapy outcomes enrolled the study.

Bacteriology and DST

Based on Yemen's TB guidelines, suspected to MDR-TB were interviewed at outpatient area in TB centers to detect all possible MDR-TB risk factors. Then, all patients were enrolled to the study site for subsequent preliminary assessment. In the TB centers, two sputum samples were collected. The initial sample was taken during the time of diagnosis (spot time) and the second sample was collected early morning of the next day. The presence of acid-fast bacilli at the time of diagnosis was determined using direct smear microscopy via Ziehl–Neelsen staining. TST methods were applied to determine rifampicin resistance. A positive sample was subjected to direct sputum smear and culture examination. DST was also conducted using agar methods for FLDs. DST was performed at the start of therapy and repeated when necessary with a longer duration. AFTB and culture were performed monthly.

Data collection

The patients' hospital records were obtained to extract all sociodemographic data, including, age, sex, marital status, location, household size, smoking habits, chewing khat habits, literacy status, employment status, and monthly income. Other clinical and therapy reports were also obtained.

Finding and recording of interim therapy outcomes

Interim therapy outcomes were evaluated based on the well-defined measures stated in the WHO guidelines [5]. To assess the risk factors of unsuccessful interim therapy outcomes, the

interim indicators of DR-TB were divided in to 2 main categorized.

A negative culture after 6 months of therapy was classified as a successful outcome, while those who died, reported a positive culture and lost to follow up considered as unsuccessful.

Data management and analysis

The Statistical Package for the Social Sciences version 24 was performed in this study. The mean, median, and standard deviation of all continuous variables were obtained after measuring the normality of all variables via the Kolmogorov–Smirnov test [17]. Count and proportion (%) were used to define all categorical variables. The risk factors of interim therapy outcome were evaluated by using logistic regression analysis. All sociodemographic and clinical factors were considered independent factors, while unsuccessful interim outcomes were considered dependent factors. Significant findings were subjected to multiple logistic analysis to predict the final risk factor of interim therapy outcome. The model was evaluated by determining its chi-squared value, degree of freedom, and P-value. Pseudo R^2 was used to determine the extent of variance in the model. A P-value of < 0.05 was considered as significant result [17].

Consent to participate and confidentiality issues

The study did not involve human samples such as blood sample, urine, tissue and the like, but patient cards and registries were reviewed for data collection. Consent form for participation was designed by the investigators and approved by the ethical committee of the college. Ethical approval for this study was also obtained from the National Committee of Health (Ministry of Health-Sana'a/Yemen) and the NTCP. In addition, a collaboration letter was obtained from the TB centres by the NTCP. Confidentiality of the data was prioritised during the data collection period, i.e., the names and registration numbers of the patients were not mentioned in the datasheet. Consent forms were provided and signed by all TB patients before the study began.

RESULTS

Sociodemographic and other features of MDR-TB patients

Among the 62 patients with MDR-TB, the majority (n = 36, 58.1.3 %) were ≤ 45 years of age. The patients residing in urban areas found to be greater (n = 42, 67.7 %) than that residing in rural areas. Approximately 24.2 % (15) and 4.8 % (3) of the patients reported abnormal bilirubin and creatinine levels, respectively. Eighteen (30.1%) patients had one or more comorbidities, and 59 were HIV negative. Among the patients, only 28 (35 %) previously used streptomycin and only 7 (8.8 %) had used SLDs. Table 1 and Table 2 illustrate the sociodemographic and clinical findings, respectively.

Table 1: Socio-demographic and baseline characteristics (n = 62)

Clinical characteristics	Patient, n (%)
Governance	
Alhodidah	11 (17.7)
Taiz	11 (17.7)
Sana'a	13 (21)
Aden	27 (43.5)
Gender	
Male	42 (67.7)
Female	20 (32.3)
Age group (years)	
≤ 45	36 (58.1)
> 45	26 (41.9)
Marital status	
Married	48 (77.4)
Unmarried	14 (22.6)
Location	
Rural	20 (32.3)
Urban	42 (67.7)
Household size	
≤ 7	19 (30.6)
>7	43 (69.4)
Smoking habit	
Non-smoker	19 (30.6)
Smoker	43 (69.4)
Chewing khat[€]	
No	7 (11.3)
Yes	55 (88.7)
Literacy status	
Illiterate	36 (58.1)
Literate	26 (41.9)
Employment status	
Employed	21 (33.9)
Unemployed	41 (66.1)
Monthly income (Rial[¥]***)***	
≤ 10,000	41 (66.1)
>10,000	21 (33.9)
Baseline weight (kg)	
≤ 40	35 (56.6)
> 40	27 (43.5)

Note: Khat: is a flowering and shurb plant grows in Africa region and Yemen. [¥] rial USD 1.0 is equivalent to 420 rial

Table 2: Clinical characteristics of MDR-TB patients (n = 62)

Clinical characteristics	Patients, n (%)
Creatinine level	
Normal	59 (95.2)
Above normal	3 (4.8)
Hb[¥] level	
Normal	29 (46.8)
Below normal	33 (53.2)
WBCs[α] level	
Normal	47 (75.8)
Above normal	15 (24.2)
Bilirubin level	
Normal	58 (93.5)
Above normal	4 (6.5)
Comorbidity	
No	44 (70.9)
Yes	18 (30.1)
Type of comorbidity (n = 18)	
Diabetic Mellitus	6 (9.7)
Hepatitis	3 (4.8)
Hypertension	5 (8.1)
COPD[μ]	1 (1.6)
HIV[±]	3 (4.8)

[€] *Normal ranges: Hb = Male > 12 g/dl, Female > 11.5 g/dl; WBCs = > 12,000/ mm3; Creatinine = Male < 1.2 mg/dl, Female < .9 mg/dl; Bilirubin = ≤ 1 mg/dl; [¥]Hb: hemoglobin; [α]WBCs = white blood cells; [μ]COPD: chronic obstructive pulmonary disease;[±] HIV: human immunodeficiency virus

Drug resistance patterns

The drug resistance patterns of the patients are presented in Table 3. Among 62 patients, 21 had no available data. Thus, 41 patients were recorded to be resistant to FLDs. All MDR-TB patients were resistant to 2−5 MDR drugs, particularly isoniazid and rifampicin. Only 10 patients (16%) were resistant to pyrazinamide (Z). Seven (11.3%) patients were resistant to four FLDs, while approximately 9.7% (n = 6) of the patients were resistant to all five FLDs. Nearly 50% of the MDR-TB reported to be resistant to streptomycin (Table 3).

Side effects during the first 2 months of treatment

Nineteen patients (30.6%) suffered from one or more adverse events, such as gastrointestinal disturbance, psychiatric disorders, and hearing troubles, during therapy. The incidence of side and lethal effects was rare. Nephrotoxicity and hepatotoxicity were reported in only one and two patients with MDR-TB, respectively (Table 4).

Table 3: First-line drug (FLD) resistance (n = 62)

Variable	Patients, n (%)
Resistance to TB[€] first-line drugs	
Resistance to HR	15 (24.2)
Resistance to HRE	4 (6.5)
Resistance to HRES	5 (8.1)
Resistance to HRESZ	6 (9.7)
Resistance to HRS	7 (11.3)
Resistance to HRZ	2 (3.2)
Resistance to HRZS	1 (1.6)
Resistance to HRZE	1 (1.6)
Result unavailable	21 (33.9)
Numbers	
Resistance to 2	15 (24.2)
Resistance to 3	13 (21)
Resistance to 4	7 (11.3)
Resistance to 5	6 (9.7)
Result unavailable	21 (33.9)

H: Isoniazid; R; Rifampicin; E: Ethambutol; S: Streptomycin; Z: Pyrazinamide

Table 4: Side effects related to DR-TB in the intensive phase (n = 19)

Adverse event	Patient[#], n (%[α])
Gastrointestinal effect	8 (12.9)
Arthralgia	3 (4.8)
Psychiatric disorder	6 (9.7)
Hearing disturbance	5 (8.1)
Renal toxicity	1 (1.6)
Peripheral neuropathy	1 (1.6)
Hepatotoxicity	2 (3.2)
Dermatological reaction	1 (1.6)
Hematological reaction	2 (3.2)
Others	7 (11.3)

[#] Drug-resistant patients with more than one adverse reaction; [α] 19 DR-TB patients

Interim therapy outcomes

The percentages of successful and unsuccessful outcomes of patients with MDR-TB are listed in Table 5. Among the 62 resistance cases under interim therapy course, over 50 % (n = 40, 64.5%) revealed a successful interim therapy outcome. Among those with unsuccessful interim therapy outcomes (n = 22; 35.5%), 4 (6.4%) patients died

Table 5: Interim therapy outcomes of MDR-TB patients (n = 62)

Therapy outcome	n (%)	Total, n (%)
Successful		
Negative culture by six months	40 (64.5)	40 (64.5)
Unsuccessful		
Died by six months	4 (6.4)	22 (35.5)
Lost to follow-up end of six months	5 (8.1)	
Positive outcome culture at six months	13 (20.9)	

Table 6: Final interim therapy outcome

Variable	Treatment outcome on time of analysis (n,%)					Total
	Still under treatment	***Died***	***Cured***	***Transfer out***	***Lost to follow-up***	
Successful interim outcome, n(%)	28 (70)	2 (5)	5 (12.5)	4 (10)	1 (2.5)	40
Unsuccessful interim outcome, n(%)	5 (22.7)	11 (50)	0 (0)	4 (18.2)	2 (9.1)	22
Total, n(%)	33 (53.2)	13 (21)	5 (8.1)	8 (12.9)	3 (4.8)	62

Table 7: Predictors of unsuccessful interim treatment outcome: Univariate logistic regression

Variable	Treatment outcome		B	SE	*P*-value	(OR) 95%CI
	Unsuccessful *(n = 22)*	***Successful*** *(n = 40)*				
Gender						
Male	17	25				1
Female	5	15	1.183	0.948	0.212	0.306 (0.048-1.964)
Smoking habit						
No	7	12				1
Yes	15	28	0.530	1.373	0.540	1.698 (0.312-9.239)
Chewing khat[#]						
No	4	3				1
Yes	18	37	1.348	1.373	0.326	0.260 (0.018-3.833)
Baseline body wt (kg)						
≤ 40	17	18				1
> 40	5	22	1.968	0.924	**0.033**	0.140 (0.023-0.855)
Comorbidity						
No	19	25				1
Yes	3	15	4.335	1.649	**0.009**	0.013 (0.001-0.322)
Number of FLD[®] ***resistance***						
≤ 3	13	36				1
> 3	9	4	2.128	0.891	**0.017**	8.395 (1.465-48.10)

P < 0.05 in bold; Ref reference group; OR: odds ratio; CI: confidence interval; [#]khat: a shrub plant that grows in parts of East Africa and Yemen. [®]FLD: first-line drug

during the 6-month period of treatment, 5 (8.1%) were lost to follow-up, and 13 (20.9%) tested positive after 6 months of therapy.

Throughout the duration of the analysis, 28 among the 40 patients with successful therapy outcomes remained under therapy and had a negative culture status. Among the remaining 12 patients with final therapy outcome status, 5 were declared cured, 2 died, 4 were transferred, and 1 was lost to follow-up. 22 patients reported as with unsuccessful outcomes, 5 remained under therapy and 17 were involved in the final therapy outcome. Among the 17 unsuccessful patients, 11 died, 2 were lost to follow up, and 4 were transferred to other centers (Table 6).

Predictors of unsuccessful outcomes

Univariate logistic regression revealed that baseline body weight (≤40 kg, p = 0.033, OR = 3.667), comorbidity (yes, p = 0.009, OR = 0.013), and FLD resistance (>3, p = 0.017, OR = 8.395) were statistically significantly related to unsuccessful interim therapy outcomes (Table 7). Multivariate logistic regression was conducted, and comorbidity and FLD resistance (>3) were observed to be risk factors of unsuccessful interim therapy outcomes (Table 8).

DISCUSSION

This work was designed to evaluate the risk factors associated with the interim therapy outcome of MDR-TB patients in the Yemeni cities of Alhodidah, Taiz, Sana'a, and Aden. Sixty-two MDR-TB patients reported therapy outcomes. The results clearly did not achieve the therapy success rate suggested by various TB amelioration programs, such as the TB Policy (75%) and the TB plan (90%) [17]. Such findings are consistent with earlier studies [18-20] reporting high death

Table 8: Risk factors of unsuccessful therapy outcomes: Multivariate logistic regression

Variable	B	SE	*P*-value	AOR	95%CI
Baseline weight ≤ 40 kg	1.217	0.694	0.079	0.296	0.076-1.153
Comorbidity	2.523	1.195	**0.035**	0.080	0.08-0.834
Number of FLD® resistance (>3)	1.910	0.778	**0.014**	6.754	1.471-31.004

P < 0.05 in bold; [α]I.P: intensive phase; AOR: adjusted odds ratio; CI: confidence interval; [®]FLD: first-line drug

cases and unsuccessful outcomes. These results are disturbing, given the provision of free TB therapy, a constant and reliable supply of medicines, health training, therapy administered by pharmacist and physicians, official residence visits by health workers, and weekly examinations by health workers at the nearest TB centers. In cases where patients' therapy default exceeded 4 weeks, patient monitoring was also conducted.

The related literature attributes the sub-optimal lost-to-follow-up rate to several reasons, including toxicity of therapy, poor TB knowledge, rural residence, high illiteracy, medical history of anti-TB therapy, poor care, and unhappiness with the behavior of healthcare employees and health facilities [2,21,22]. Consequently, strengthening Yemen's TB program by implementing suitable training of therapy supporters and encouraging patients to report to TB patient tracing facilities could result in decline the lost-to-follow-up rate of MDR-TB patients in Yemen.

The high death rate (21%) found in this study is analogous to previous reports in India and Russia [2,3], although some studies have reported lower mortality rates [18,19]. A study performed in Bulgaria reported a high mortality rate of 38% [23]. The high mortality rates observed in the present study may be attributed to the masking of death rates by the high lost-to-follow-up rate of patients. Higher mortality rates may also be attributed to the delayed diagnosis of TB or therapy initiation, low levels of education, significant number of earlier TB incidents, history of comorbid conditions, inadequate bacteriologic response, and poor therapy [23]. Consequently, novel steps for suitable MDR-TB discovery and control must be executed in the study area.

A negative culture after the second month of MDR-TB therapy commonly accepted an indicator of reduced TB; it is also applied to forecast current TB progress, efficacy, and eventual success of therapy. In this study, sputum culture positivity and negativity were respectively associated with unsuccessful and successful interim therapy outcomes following 2 months of MDR-TB therapy, consistent with contemporary studies [24]. Several studies reported successful therapy outcome for this obtained negative culture end of two month of treatment [8]. A similar study in Hong Kong reported a negative culture of 100% and 52.3% end of the two month of treatment as markers of success and failure, respectively [8]. A study in the Dominican Republic reported the successful therapy of patients with a negative culture end of two months of treatment [9]. Thus, the present study also supports the notion that a negative sputum culture may be a main indicator of successful interim therapy and help TB therapy coordinators to detect patients of high risk of unfavorable outcome.

This research further promotes the reliability of using sputum cultures to evaluate therapy effectiveness. Gastrointestinal disturbance, psychiatric disorders, hearing disturbances, hepatotoxicity, and nephrotoxicity are adverse events related to MDR-TB therapy; these effects can be managed by reducing the FLD dosage [11]. The results imply that introducing therapy with low doses of FLDs to prevent nephrotoxicity could lead to unsuccessful interim therapy outcomes. Affected patients may require comprehensive and major changes to their therapy that may, in turn, complicate therapy and hinder adherence to MDR-TB treatment. Therefore, monitoring the administration of therapeutic drugs can provide physicians with opportunities to exclusively manage individual patients' MDR-TB therapy.

A significant and distinctive outcome of this study is the positive association of baseline weight (≤40 kg), comorbidity, and resistance to several FLDs (>4) with unsuccessful interim therapy outcomes. From the clinical perspective, additional studies are essential to confirm this positive association. From the health-system perspective, Yemen lacks clinical hospital pharmacists [25]; thus improvements in dose−frequency procedures and studies on the role of clinical pharmacists in modifying anti-TB drug therapies, particularly among patients with a history of renal dysfunction, are necessary. This study can be considered an intervention. Reasons for loss to follow-up also require additional investigation to elucidate the failure of the follow-up system given the high level of support given to participants [10].

Limitations of the study

Although this study was conducted using a

comprehensive and consistent method obtained from the WHO, several limitations still exist. First, the outcomes of this study do not represent the outcomes of the whole of Yemen because the population was obtained from only the cities of Alhodidah, Taiz, Sana'a, and Aden. Second, some data on patient notification were missing because of the retrospective nature of the study. Hence, incorporating results from baseline lung cavitation, which was previously considered the main predictor of unsuccessful therapy outcomes in MDR-TB patients, was difficult [2,23].

CONCLUSION

The current cohort study found an alarmingly a high unfavorable outcome in Yemeni patients despite the free therapy provided to them and the great effort exerted by health workers in TB centers to enhance the adherence of these patients to MDR-TB therapy. Improving the clinical control of patients associated with a baseline weight ≤ 40 kg, comorbidity, and FLD resistance (>3) may enhance TB therapy outcomes. Future studies should focus on the relation of other factors, such as serum creatinine level and adherence to therapy, to unsuccessful interim therapy outcomes in MDR-TB.

DECLARATIONS

Conflict of interest

No conflict of interest is associated with this work.

Contribution of authors

We declare that this work was done by the authors named in this article and all liabilities pertaining to claims relating to the content of this article will be borne by the authors.

Open Access

REFERENCES

1. *Diel R, Vandeputte J, De Vries G, Stillo J, Wanlin M, Nienhaus A. Costs of tuberculosis disease in the European Union: A systematic analysis and cost calculation. Eur Respir J. 2014; 43(2): 554–65.*
2. *Ahmad N, Javaid A, Basit A, Afridi AK, Khan MA, Ahmad I. Management and treatment outcomes of MDR-TB: Results from a setting with high rates of drug resistance. Int J Tuberc Lung Dis. 2015; 19(9): 1109–1114.*
3. *Abubakar I, Zignol M, Falzon D, Raviglione M, Ditiu L, Masham S, et al. Drug-resistant tuberculosis: Time for visionary political leadership. Lancet Infect Dis. 2013; 13(6): 529–539.*
4. *Wells WA, Ge CF, Patel N, Oh T, Gardiner E, Kimerling ME. Size and usage patterns of private TB drug markets in the high burden countries. PLoS One. 2011; 6(5): 1-10.*
5. *World Health Organization. Companion handbook to the WHO guidelines for the porgrammatic management of drug-resistance tuberculosis. World Health Organization. 2014. 464 p.*
6. *Basit A, Ahmad N, Khan AH, Javaid A, Syed Sulaiman SA, Afridi AK, et al. Predictors of two months culture conversion in multidrug-resistant tuberculosis: Findings from a retrospective cohort study. PLoS One. 2014; 9(4): 5–10.*
7. *Kurbatova E V., Cegielski JP, Lienhardt C, Akksilp R, Bayona J, Becerra MC, et al. Sputum culture conversion as a prognostic marker for end-of-treatment outcome in patients with multidrug-resistant tuberculosis: A secondary analysis of data from two observational cohort studies. Lancet Respir Med. 2015; 3(3): 201–209.*
8. *Yew WW, Chan CK, Chau CH, Tam CM, Leung CC, Wong PC, et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. Chest. 2000; 117(3): 744–751.*
9. *Rodriguez M, Monedero I, Caminero JA, Encarnación M, Dominguez Y, Acosta I, et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013; 17(4): 520–525.*
10. *Javaid A, Shaheen Z, Shafqat M, Khan AH, Ahmad N. Risk factors for high death and loss-to-follow-up rates among patients with multidrug-resistant tuberculosis at a programmatic management unit. Am J Infect Control. 2017; 45(2): 190–193.*
11. *World Health Organization. Global tuberculosis report 2016. 2016.*
12. *Programme NTC. Guideline on management of drug resistance-TB Yemen. 2012. 1–62 p.*
13. *WHO. Treatment of tuberculosis guidelines. 2010. 1–56 p.*
14. *Saleh Jaber AA, Khan AH, Syed Sulaiman SA, Jaber AAS, Khan AH, Sulaiman SAS. Evaluating of tuberculosis defaulters in Yemen from the perspective of*

health care service. J Pharm Heal Serv Res. 2018; 10(1): 1–12.

15. *Al-Shamiry AA, Al-Haddad AM, Al-Shamahy HA. Co-existing diseases of patients with pulmonary tuberculosis in Yemen. J Trop Nephro-Urology. 2011; 10(6): 46–57.*
16. *WHO. Consolidated guidelines on drug-resistance tuberculosis treatment. 2016; pp 1-104.*
17. *Pallant J. Spss Survival Manual. 2013. 102 p.*
18. *WHO Treatment Guidelines for Drug-Resistant Tuberculosis, 2016. World Health Organization; 2016*
19. *Floyd K, D P, Jaramillo E, Lönnroth K, Weil D, Sc M. MDR Tuberculosis — Critical Steps for Prevention and Control. October. 2010; 6(2): 1050-1058.*
20. *Tang S, Tan S, Yao L, Li F, Li L, Guo X, et al. Risk factors for poor treatment outcomes in patients with MDR-TB and XDR-TB in China: Retrospective multi-center investigation. PLoS One. 2013; 8(12): 1–8.*
21. *Cox HS, Kalon S, Allamuratova S, Sizaire V, Tigay ZN, Rüsch-Gerdes S. Multidrug-resistant tuberculosis treatment outcomes in Karakalpakstan, Uzbekistan: Treatment complexity and XDR-TB amongst treatment failures. PLoS One. 2007; 2(11): 1-9.*
22. *Tupasi TE, Marie A, Garfin CG, Kurbatova E V, Mangan JM, Orillaza-chi R, et al. Factors Associated with Loss to Follow-up during Treatment for Multidrug-Resistant Tuberculosis, the Philippines, 2012–2014. 2016; 22(3): 2012–2014.*
23. *Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009; 9(3): 153–161.*
24. *Franke MF, Appleton SC, Bayona J, Arteaga F, Palacios E, Llaro K, et al. Risk Factors and Mortality Associated with Default from Multidrug-Resistant Tuberculosis Treatment. Clin Infect Dis. 2008; 46(12): 1844–1851.*
25. *Singla R, Osman MM, Khan N, Al-Sharif N, Al-Sayegh MO, Shaikh MA. Factors predicting persistent sputum smear positivity among pulmonary tuberculosis patients 2 months after treatment. Int J Tuberc lung Dis. 2003; 7(1): 58–64.*
26. *Jaber AAS, Khan AH, Sulaiman SAS. Evaluating treatment outcomes and durations among cases of smear-positive pulmonary tuberculosis in Yemen: a prospective follow-up study. J Pharm Policy Pract. 2017; 10(1): 36-46.*