CrossMark

REVIEW

The reliability of rifampicin resistance as a proxy for multidrug-resistant tuberculosis: a systematic review of studies from Iran

M. J. Nasiri[1] · S. Zamani[2] · A. Pormohammad[1] · M. M. Feizabadi[3,4] · H. R. Aslani[5] ·
M. Amin[6] · R. Halabian[7] · A. A. Imani Fooladi[7]

Abstract In Iran, patients showing rifampicin (RIF) resistance detected by the Xpert® MTB/RIF assay are considered as candidates for multidrug-resistant tuberculosis (MDR-TB) treatment. Despite the fact that RIF resistance has been used as a proxy for MDR-TB, little is known about the proportion of isoniazid (INH) resistance patterns in RIF-resistant TB. We systematically searched MEDLINE, Embase, and other databases up to March 2017 for studies addressing the proportion of INH resistance patterns in RIF-resistant TB in Iran. The data were pooled using a random effects model. Heterogeneity was assessed using Cochran's Q and I^2 statistics. A total of 11 articles met the eligibility criteria. Data analysis demonstrated that 33.3% of RIF-resistant isolates from new TB cases and 14.8% of RIF-resistant isolates from previously treated cases did not display resistance to INH. The relatively high proportion of INH susceptibility among isolates with RIF resistance indicated that RIF resistance may no longer predict MDR-TB in Iran. Therefore, the detection of RIF resistance by the Xpert MTB/RIF assay will require complementary detection of INH resistance by other drug susceptibility testing (DST) methods in order to establish the diagnosis of MDR-TB.

Introduction

Tuberculosis (TB) still remains a worldwide problem and ranks high alongside human immunodeficiency virus (HIV) as the leading cause of death from infectious diseases [1]. Drug-resistant strains of *Mycobacterium tuberculosis* have emerged as a major threat to global TB control programs [2, 3]. The World Health Organization (WHO) estimated that there were 480,000 new cases of multidrug-resistant tuberculosis (MDR-TB) in 2015, defined as strains that are resistant to at least isoniazid (INH) and rifampicin (RIF) [1]. MDR-TB arises due to the mismanagement of TB in patients with active infection [4, 5]. The management of MDR-TB should begin with the identification of cases. Although early diagnosis and proper treatment of the cases can intercept the development of MDR-TB, accurate diagnosis of drug-resistant cases remains a barrier to TB control [3, 5]. Conventional methods for detecting drug-resistant TB take weeks to months to produce results. During this time, patients may be inappropriately treated and drug-resistant strains may spread to the community [6]. Recently, the WHO endorsed the use of an automated rapid molecular assay, Xpert® MTB/RIF, for the detection of *M. tuberculosis* and RIF resistance [3, 7, 8]. Concomitant INH resistance is often communicated with RIF resistance [9]. In Iran, with increased prevalence of MDR-TB, some TB reference laboratories use Xpert MTB/RIF for the rapid diagnosis of TB and detection of drug-resistant TB. Based on the National Tuberculosis Control Program (NTP), patients

✉ A. A. Imani Fooladi
imanifouladi.a@gmail.com; imanifouladi.a@bmsu.ac.ir

1. Department of Microbiology, School of Medicine, Shahid Beheshti University of Medical Sciences, Tehran, Iran

2. Department of Microbiology, School of Medicine, Golestan University of Medical Sciences, Gorgan, Iran

3. Department of Microbiology, School of Medicine, Tehran University of Medical Sciences, Tehran, Iran

4. Thoracic Research Center, Imam Khomeini Hospital, Tehran University of Medical Sciences, Tehran, Iran

5. Department of Clinical Pharmacy, School of Pharmacy, Shahid Beheshti University of Medical Sciences, Tehran, Iran

6. Department of Drug and Food Control, and Pharmaceutical Quality Assurance Research Center, Faculty of Pharmacy, Tehran University of Medical Sciences, Tehran, Iran

7. Applied Microbiology Research Center, Baqiyatallah University of Medical Sciences, Tehran, Iran

detected as having RIF resistance on this assay are administered MDR-TB treatment. Despite the fact that RIF resistance has been used as "a surrogate marker" for MDR-TB, there is a growing concern for the increase of rifampicin monoresistance in Iran [10–12]. This implies that, if these patients were treated as having MDR-TB, a significant number would be treated incorrectly by excluding INH from the treatment regimen. In the present study, the extent of the INH resistance pattern in RIF-resistant TB is investigated. To our knowledge, this is the first report that investigates the INH resistance patterns in RIF-resistant cases.

Methods

Literature search

We searched MEDLINE (via PubMed), Embase, Web of Science, and Iranian databases up to 31 March 2017. We used a combination of Medical Subject Headings (MeSH) and keywords, focusing on terms to describe the relevant populations (patients with drug-resistant TB). We also screened the bibliographies of included studies for relevant articles. We included only studies published in English or Persian.

Selection criteria

We included original articles on the prevalence of drug resistance of TB in Iran. The included studies shall provide drug resistance data of either new cases or retreated cases or both and use a standard method for drug susceptibility testing (DST) of *M. tuberculosis*. In order to minimize the potential bias caused by too small a sample size, articles with less than 100 subjects were excluded. Each article was reviewed by two researchers independently. In case of discrepancies, the opinion of a third researcher was sought. If the study was reported in duplicate, the most informative version of the study was included. Studies that did not report the number of cases with

Fig. 1 Flow chart of study selection for inclusion in the systematic review
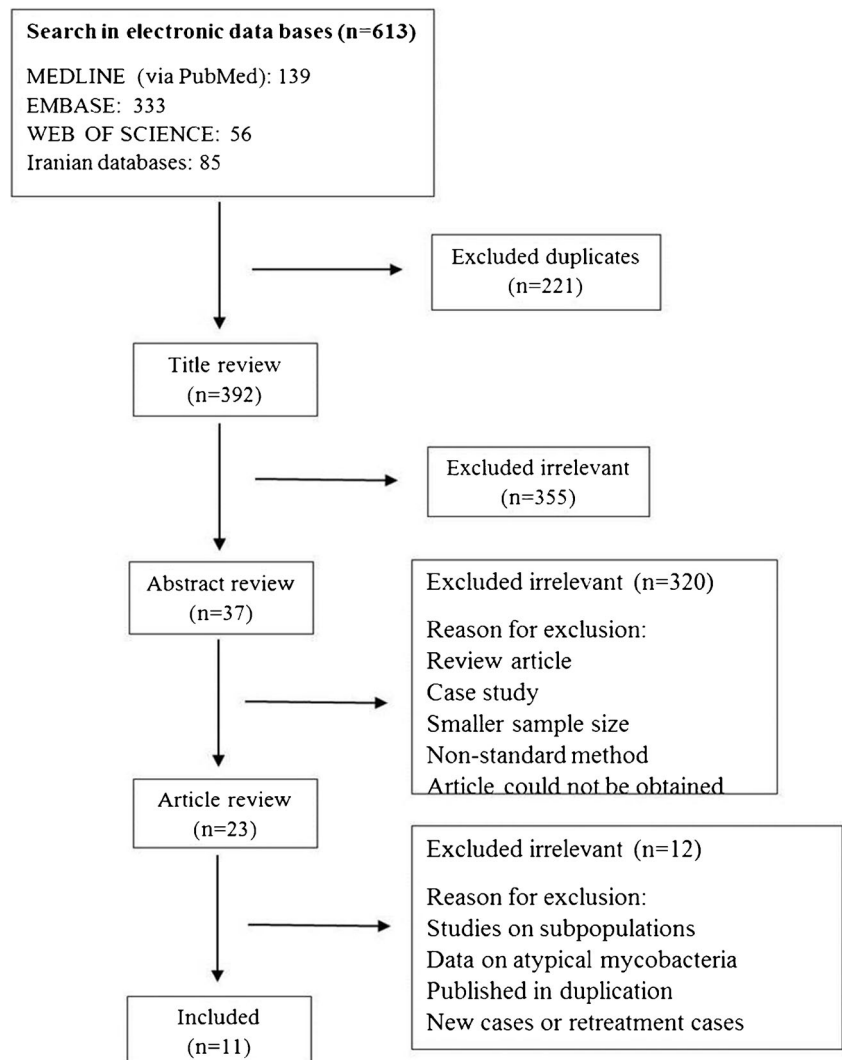

Search in electronic data bases (n=613)

MEDLINE (via PubMed): 139
EMBASE: 333
WEB OF SCIENCE: 56
Iranian databases: 85

→ Excluded duplicates (n=221)

Title review (n=392)

→ Excluded irrelevant (n=355)

Abstract review (n=37)

→ Excluded irrelevant (n=320)

Reason for exclusion:
Review article
Case study
Smaller sample size
Non-standard method
Article could not be obtained

Article review (n=23)

→ Excluded irrelevant (n=12)

Reason for exclusion:
Studies on subpopulations
Data on atypical mycobacteria
Published in duplication
New cases or retreatment cases

Included (n=11)

Table 1 Characteristics of the included studies

Study	Study time	Province	Mean age	Males	No. of patients	Diagnostic test	New cases				Retreatment cases			
							No. of cases	RIF	RIF+INH	RIF-INH	No. of cases	RIF	RIF+INH	RIF-INH
Mansoori et al. [15]	1996–2000	Tehran	37	231	231	Proportion method	187	45	19	26	44	32	21	11
Bahrmand et al. [16]	1998–1999	Tehran	–	288	563	Proportion method	563	24	23	1	–	–	–	–
Shamaei et al.[17]	2000–2003	Tehran	45.4	317	548	Proportion method	363	14	10	4	185	105	96	9
Namaei et al. [18]	2001–2002	Mashhad	56.6	55	105	Proportion method	105	1	1	0	–	–	–	–
Mirsaeidi et al. [19]	2003–2004	Tehran	48	102	264	Proportion method	196	11	5	6	68	41	38	3
Marjani et al. [20]	2003–2008	Tehran	38	271	554	Proportion method	508	23	10	13	46	4	2	2
Livani et al. [21]	2009–2010	Golestan	54	81	148	Bactec MGIT	89	4	4	0	59	1	1	0
Nasiri et al. [22]	2010–2012	Tehran	45	–	252	Proportion method	252	12	11	1	–	–	–	–
Mohajeri et al. [23]	2011–2012	Kermanshah	–	64	112	Proportion method	112	16	16	0	–	–	–	–
Farazi et al. [24]	2011–2012	Arak	52	56	115	Proportion method	103	5	4	1	12	6	5	1
Tavanaee Sani et al. [25]	2012–2013	Mashhad	53	45	100	Proportion method	74	1	1	0	26	6	3	3

RIF: RIF-resistant isolates; RIF+INH: RIF-resistant isolates which are simultaneously resistant to INH; RIF-INH: RIF-resistant isolates which are susceptible to INH; MGIT: Mycobacteria Growth Indicator Tube (RIF: rifampicin, INH: isoniazid)

active TB, the patterns of drug resistance, or studies on subpopulations such as studies conducted on immigrants, or HIV-positive cases, were excluded.

Data extraction

Data were extracted into a pre-designed structured Microsoft Excel® form by one reviewer and appraised for accuracy by a second reviewer. The extracted data included characteristics of the target population, settings, study designs, methods, and results.

Quality assessment

The included studies were appraised for quality using a quality assessment checklist designed by the Joanna Briggs Institute [13].

Data analysis

Data analyses were performed using Comprehensive Meta-Analysis version 2.2 (Biostat, Englewood, NJ, USA) [14]. Generally, we used fixed or random effects models, depending on statistical heterogeneity between studies, to calculate summary estimates. Statistical heterogeneity was quantified by Cochran's Q and I^2 statistics. To check for publication bias, we generated a funnel plot and used Egger's test ($p < 0.05$ was considered indicative of statistically significant publication bias and funnel plot asymmetry also suggested bias in the meta-analysis).

Results

From the records identified from the MEDLINE, Embase, Web of Science, and Iranian databases (Fig. 1), 11 studies published from different regions of Iran were included in this study (Table 1) [15–25]. In all included studies, the standard proportional method was employed for DST, except one that used BACTEC MGIT. The WHO/International Union Against Tuberculosis and Lung Disease (IUATLD) guidelines were used for direct microscopy, culture, and drug susceptibility testing. According to the data from included studies, all clinical isolates of TB were cultured from patients with active TB. There was no information about the preventive medication, especially with INH in those with latent TB infection (LTBI).

As shown in Table 2, of the 2552 tested isolates from new cases, 156 (5.5%) were resistant to RIF. About a third (33.3%) of RIF-resistant isolates from new cases were INH susceptible. Of the 440 tested isolates from previously treated cases, 195 (36.0%) displayed resistance to RIF, with 14.8% susceptibility to INH (Table 2).

Table 2 Isoniazid (INH) resistance patterns given resistance to rifampicin (RIF)

Subgroups	No. of patients	Isolates with any resistance to RIF			Isolates resistant to RIF	
		%	n/N	I²(%)	Susceptible to INH (% of any RIF resistance)	Resistant to INH (% of any RIF resistance)
New cases	11	5.5	156/2552	90	52 (33.3)	104 (66.7)
Retreatment cases	7	36.0	195/440	88	29 (14.8)	166 (85.2)

n/N: Isolates with any resistance to RIF/total tested; I² : heterogeneity test

A Forest plot for the meta-analysis of any RIF-resistant TB is shown in Fig. 2. As shown in Table 2 and Fig. 3, no evidence of publication bias was observed ($p = 0.2$ for Egger weighted regression analysis).
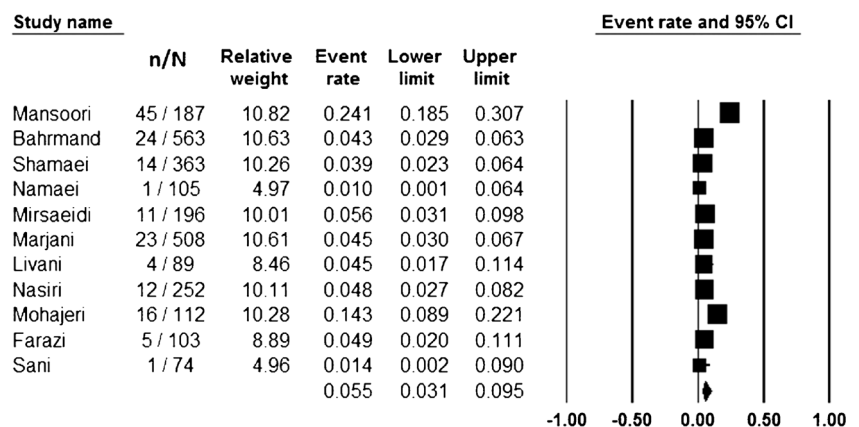
Discussion

In Iran, patients detected as having RIF resistance detected by the Xpert MTB/RIF assay are given MDR-TB treatment without knowing the patterns of INH resistance. Therefore, a significant number of patients would be accidentally rejected INH. According to our findings, RIF resistance is not accompanied by INH resistance in 33.3% of new cases and 14.8% of retreatment cases in Iran. These data showed that a considerable proportion of RIF-resistant isolates were susceptible to INH. According to the results of our study, the noncompliance for frequency of resistance against RIF and INH decreased from 30.3% in new cases to 14.8% in retreatment cases. One possible reason behind this observation could be the prior long-term TB therapy in retreatment cases, which can increase the risk of drug resistance [26]. Espinal et al. [26] indicated that drug-resistant TB was significantly associated with prior treatment periods of >12 months and >6 months, respectively, compared with a treatment period of 3 months or less.

RIF resistance is considered as a proxy for MDR-TB, as a large proportion of RIF-resistant strains have INH resistance as well. Then, the detection of MDR-TB would be sufficient with a single test that detects RIF resistance [27, 28]. In areas

with low RIF mono-resistant TB but high MDR prevalence, this correlation is particularly applicable. However, in countries with increasing rates of RIF monoresistance, this correlation may be questionable and not always applicable. In Iran, during 2010–2011, Velayati et al. [10] reported a high prevalence of RIF mono-resistant TB among pulmonary TB patients. The increasing rates of RIF mono-resistant TB have also been reported from different regions of the world [28–31]. Rufai et al. [32], from India, a high TB burden country, reported that 22% of TB isolates were RIF mono-resistant [32]. Likewise, another investigation from this region observed a high percentage of RIF monoresistance [33]. These high rates of RIF mono-resistant TB in studies from India may suggest that methodologies relying on RIF resistance as a marker to detect MDR-TB are not likely to be successful. Rufai et al. [32] have also indicated that the Xpert MTB/RIF assay can give false-negative and false-positive RIF resistance results. They show that relying only on the Xpert MTB/RIF results may be a disastrous step for TB control programs. False-negative results of RIF resistance can keep patients unnecessarily on anti-TB chemotherapy for a long duration, thus leaving the patients inappropriately treated. This can lead to the amplification and spread of MDR-TB [32]. Unlike studies from India, much lower RIF monoresistance levels were reported from Pakistan and Turkey [34, 35]. According to Ayaz et al. [34], the low rates of RIF monoresistance would support the use of RIF as a marker for MDR-TB in the Pakistani population. In the current study, it is important to note that we did not specifically address the reliability of RIF resistance

Fig. 2 Forest plot of the meta-analysis on any rifampicin (RIF) resistance in new cases

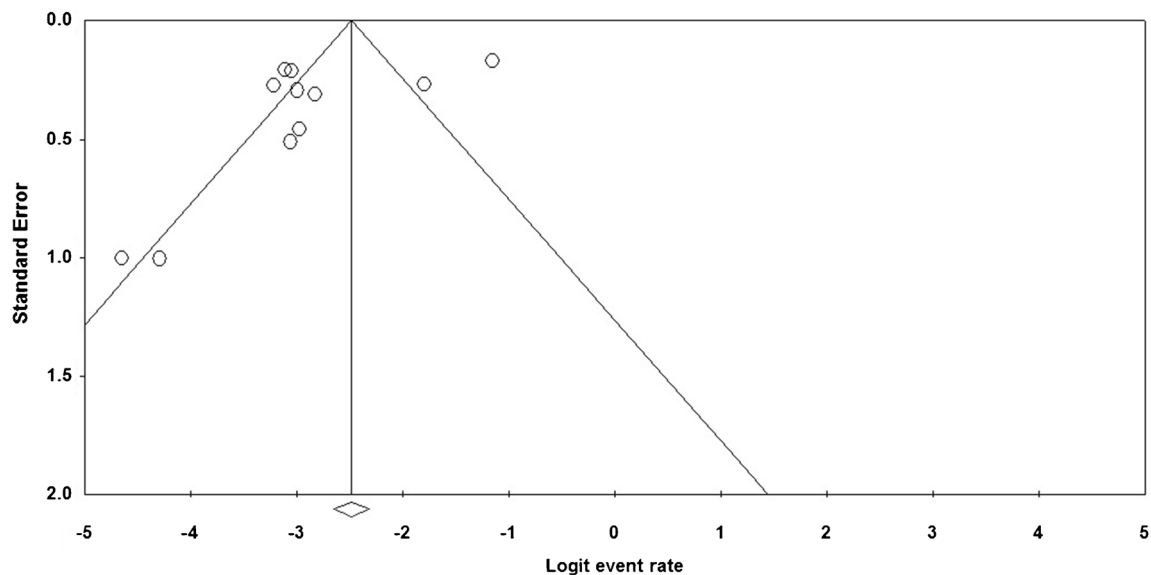| Study name	n/N	Relative weight	Event rate	Lower limit	Upper limit
Mansoori	45 / 187	10.82	0.241	0.185	0.307
Bahrmand	24 / 563	10.63	0.043	0.029	0.063
Shamaei	14 / 363	10.26	0.039	0.023	0.064
Namaei	1 / 105	4.97	0.010	0.001	0.064
Mirsaeidi	11 / 196	10.01	0.056	0.031	0.098
Marjani	23 / 508	10.61	0.045	0.030	0.067
Livani	4 / 89	8.46	0.045	0.017	0.114
Nasiri	12 / 252	10.11	0.048	0.027	0.082
Mohajeri	16 / 112	10.28	0.143	0.089	0.221
Farazi	5 / 103	8.89	0.049	0.020	0.111
Sani	1 / 74	4.96	0.014	0.002	0.090
			0.055	0.031	0.095

Fig. 3 Funnel plot of the meta-analysis on any rifampicin (RIF) resistance in new cases

detected by molecular tests as a proxy for MDR-TB. However, RIF resistance may no longer predict MDR-TB in a significant number of patients in Iran. Thus, we suggest that each country carries out evaluation work, to prepare guidelines for the use of the Xpert MTB/RIF at the national level. Furthermore, the detection of RIF resistance by Xpert MTB/RIF will need to be complemented by the diagnosis of INH resistance by other DST methods in order to establish the diagnosis of MDR-TB. According to the WHO guidelines for the management of drug-resistant TB, "if isoniazid susceptibility cannot be ascertained, the addition of isoniazid to the regimen may be considered" [36].

Our systematic review had some limitations. First, we could not analyze the effect of factors such as previous preventive medication on drug susceptibility status, because of the limited information obtained from the studied articles. Patients with LTBI who received preventive therapy, especially with INH, are at higher risk for acquiring anti-TB drug resistance compared to those who did not [37]. Second, although in all included studies WHO guidelines were used for drug susceptibility testing, our findings should be interpreted in the context of the variability in study quality. Finally, as with any systematic review, limitations associated with publication bias should be considered.

In conclusion, due to the high proportion of INH susceptibility among isolates with RIF resistance, RIF resistance may no longer predict MDR-TB in a significant number of cases in Iran. Therefore, Xpert MTB/RIF results must always be confirmed by DST in order to establish the diagnosis of MDR-TB. INH should also be included in the treatment regimen at least until INH resistance is proven.

Compliance with ethical standards

Conflict of interest None declared.

Ethical approval The manuscript is a systematic review, so ethical approval was not required for the study.

References

1. World Health Organization (WHO) (2016) Global tuberculosis report 2016
2. Raviglione MC, Uplekar MW (2006) WHO's new Stop TB Strategy. Lancet 367(9514):952–955
3. Daley CL, Caminero JA (2013) Management of multidrug resistant tuberculosis. Semin Respir Crit Care Med 34(1):44–59
4. Zignol M, Hosseini MS, Wright A, Lambregts-van Weezenbeek C, Nunn P, Watt CJ, Williams BG, Dye C (2006) Global incidence of multidrug-resistant tuberculosis. J Infect Dis 194(4):479–485
5. Lynch JB (2013) Multidrug-resistant tuberculosis. Med Clin North Am 97(4):553–579
6. Van Rie A, Page-Shipp L, Scott L, Sanne I, Stevens W (2010) Xpert® MTB/RIF for point-of-care diagnosis of TB in high-HIV burden, resource-limited countries: hype or hope? Expert Rev Mol Diagn 10(7):937–946
7. Boehme CC, Nabeta P, Hillemann D, Nicol MP, Shenai S, Krapp F, Allen J, Tahirli R, Blakemore R, Rustomjee R, Milovic A, Jones M, O'Brien SM, Persing DH, Ruesch-Gerdes S, Gotuzzo E, Rodrigues C, Alland D, Perkins MD (2010) Rapid molecular detection of tuberculosis and rifampin resistance. N Engl J Med 363(11): 1005–1015
8. Hillemann D, Rüsch-Gerdes S, Richter E (2007) Evaluation of the GenoType MTBDRplus assay for rifampin and isoniazid susceptibility testing of Mycobacterium tuberculosis strains and clinical specimens. J Clin Microbiol 45(8):2635–2640
9. Kurbatova EV, Cavanaugh JS, Shah NS, Wright A, Kim H, Metchock B, Van Deun A, Barrera L, Boulahbal F, Richter E, Martín-Casabona N, Arias F, Zemanova I, Drobniewski F, Santos Silva A, Coulter C, Lumb R, Cegielski JP (2012) Rifampicin-resistant Mycobacterium tuberculosis: susceptibility to isoniazid

and other anti-tuberculosis drugs. Int J Tuberc Lung Dis 16(3):355–357

10. Velayati AA, Farnia P, Mozafari M, Sheikholeslami MF, Karahrudi MA, Tabarsi P, Hoffner S (2014) High prevalence of rifampin-monoresistant tuberculosis: a retrospective analysis among Iranian pulmonary tuberculosis patients. Am J Trop Med Hyg 90(1):99–105

11. Nasiri MJ, Dabiri H, Darban-Sarokhalil D, Rezadehbashi M, Zamani S (2014) Prevalence of drug-resistant tuberculosis in Iran: systematic review and meta-analysis. Am J Infect Control 42(11):1212–1218

12. Nasiri MJ, Chirani AS, Amin M, Halabian R, Fooladi AAI (2016) Isoniazid-resistant tuberculosis in Iran: a systematic review. Tuberculosis (Edinb) 98:104–109

13. Munn Z, Moola S, Lisy K, Riitano D (2014) The Joanna Briggs Institute Reviewers' Manual 2014. The systematic review of prevalence and incidence data. The Joanna Briggs Institute, Adelaide

14. Nasiri MJ, Dabiri H, Darban-Sarokhalil D, Shahraki AH (2015) Prevalence of non-tuberculosis mycobacterial infections among tuberculosis suspects in Iran: systematic review and meta-analysis. PLoS One 10(6):e0129073

15. Mansoori S, Mirabolhasani Z, Farnia P, Velayati A (2003) The pattern of drug resistance among newly diagnosed and old cases of pulmonary tuberculosis in NRITLD. Arch Iranian Med 6(4):255–260

16. Bahrmand AR, Velayati AA, Bakayev VV (2000) Treatment monitoring and prevalence of drug resistance in tuberculosis patients in Tehran. Int J Tuberc Lung Dis 4(6):544–549

17. Shamaei M, Marjani M, Chitsaz E, Kazempour M, Esmaeili M, Farnia P, Tabarsi P, Amiri MV, Mirsaeidi M, Mansouri D, Masjedi MR, Velayati AA (2009) First-line anti-tuberculosis drug resistance patterns and trends at the national TB referral center in Iran—eight years of surveillance. Int J Infect Dis 13(5):e236–e240

18. Namaei MH, Sadeghian A, Naderinasab M, Ziaee M (2006) Prevalence of primary drug resistant Mycobacterium tuberculosis in Mashhad, Iran. Indian J Med Res 124(1):77–80

19. Mirsaeidi MS, Tabarsi P, Farnia P, Ebrahimi G, Morris MW, Masjedi MR, Velayati AA, Mansouri D (2007) Trends of drug resistant Mycobacterium tuberculosis in a tertiary tuberculosis center in Iran. Saudi Med J 28(4):544–550

20. Marjani M, Baghaei P, Tabarsi P, Shamaei M, Mansouri D, Masjedi MR, Velayati A (2012) Drug resistance pattern and outcome of treatment in recurrent episodes of tuberculosis. East Mediterr Health J 18(9):957–961

21. Livani S, Mirinargesi M, Nemati-Shoja E, Rafiei S, Taziki M, Tabarraei A, Ghaemi E (2011) Prevalence of multidrug resistant Mycobacterium tuberculosis by mycobacteria growth indicator tube in Golestan province, north of Iran (in Persian). Med Lab J 5(2):7–14

22. Nasiri MJ, Rezaei F, Zamani S, Darban-Sarokhalil D, Fooladi AAI, Shojaei H, Feizabadi MM (2014) Drug resistance pattern of Mycobacterium tuberculosis isolates from patients of five provinces of Iran. Asian Pac J Trop Med 7(3):193–196

23. Mohajeri P, Norozi B, Atashi S, Farahani A (2014) Anti tuberculosis drug resistance in west of Iran. J Glob Infect Dis 6(3):114–117

24. Farazi A, Sofian M, Zarrinfar N, Katebi F, Hoseini SD, Keshavarz R (2013) Drug resistance pattern and associated risk factors of tuberculosis patients in the central province of Iran. Caspian J Intern Med 4(4):785–789

25. Tavanaee Sani A, Shakiba A, Salehi M, Bahrami Taghanaki HR, Ayati Fard SF, Ghazvini K (2015) Epidemiological characterization of drug resistance among Mycobacterium tuberculosis isolated from patients in northeast of Iran during 2012–2013. Biomed Res Int 2015:747085

26. Espinal MA, Laserson K, Camacho M, Fusheng Z, Kim SJ, Tlali RE, Smith I, Suarez P, Antunes ML, George AG, Martin-Casabona N, Simelane P, Weyer K, Binkin N, Raviglione MC (2001) Determinants of drug-resistant tuberculosis: analysis of 11 countries. Int J Tuberc Lung Dis 5(10):887–893

27. Caws M, Duy PM, Tho DQ, Lan NTN, Hoa DV, Farrar J (2006) Mutations prevalent among rifampin- and isoniazid-resistant Mycobacterium tuberculosis isolates from a hospital in Vietnam. J Clin Microbiol 44(7):2333–2337

28. Coovadia YM, Mahomed S, Pillay M, Werner L, Mlisana K (2013) Rifampicin mono-resistance in Mycobacterium tuberculosis in KwaZulu-Natal, South Africa: a significant phenomenon in a high prevalence TB-HIV region. PLoS One 8(11):e77712

29. Mukinda FK, Theron D, van der Spuy GD, Jacobson KR, Roscher M, Streicher EM, Musekiwa A, Coetzee GJ, Victor TC, Marais BJ, Nachega JB, Warren RM, Schaaf HS (2012) Rise in rifampicin-monoresistant tuberculosis in Western Cape, South Africa. Int J Tuberc Lung Dis 16(2):196–202

30. Sanders M, Van Deun A, Ntakirutimana D, Masabo JP, Rukundo J, Rigouts L, Fissette K, Portaelst F (2006) Rifampicin mono-resistant Mycobacterium tuberculosis in Bujumbura, Burundi: results of a drug resistance survey. Int J Tuberc Lung Dis 10(2):178–183

31. Traore H, Fissette K, Bastian I, Devleeschouwer M, Portaels F (2000) Detection of rifampicin resistance in Mycobacterium tuberculosis isolates from diverse countries by a commercial line probe assay as an initial indicator of multidrug resistance [technical note]. Int J Tuberc Lung Dis 4(5):481–484

32. Rufai SB, Kumar P, Singh A, Prajapati S, Balooni V, Singh S (2014) Comparison of Xpert MTB/RIF with line probe assay for detection of rifampin-monoresistant Mycobacterium tuberculosis. J Clin Microbiol 52(6):1846–1852

33. Kumar P, Balooni V, Sharma BK, Kapil V, Sachdeva KS, Singh S (2014) High degree of multi-drug resistance and hetero-resistance in pulmonary TB patients from Punjab state of India. Tuberculosis (Edinb) 94(1):73–80

34. Ayaz A, Hasan Z, Jafri S, Inayat R, Mangi R, Channa AA, Malik FR, Ali A, Rafiq Y, Hasan R (2012) Characterizing Mycobacterium tuberculosis isolates from Karachi, Pakistan: drug resistance and genotypes. Int J Infect Dis 16(4):e303–e309

35. Zeka AN, Tasbakan S, Cavusoglu C (2011) Evaluation of the GeneXpert MTB/RIF assay for rapid diagnosis of tuberculosis and detection of rifampin resistance in pulmonary and extrapulmonary specimens. J Clin Microbiol 49(12):4138–4141

36. World Health Organization (WHO) (2014) Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis

37. Ai J-W, Ruan Q-L, Liu Q-H, Zhang W-H (2016) Updates on the risk factors for latent tuberculosis reactivation and their managements. Emerg Microbes Infect 5(2):e10