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Review Article

Prevalence of Tuberculosis among People Who Use Drugs in Iran: A Systematic Review and Meta-analysis

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Abstract

Background: Drug use, especially injecting drug use, is associated with a higher risk of tuberculosis (TB). This study aimed to systematically review the prevalence of TB among people who use drugs (PWUD) in Iran.

Methods: A systematic search was conducted in international and national databases. All studies that provided data on the prevalence of TB among PWUD based on screening tests and diagnosis from 1990 up to August 2019 were assessed. Meta-analysis was performed on the prevalence of active TB among people who inject drugs (PWID).

Findings: Overall, nine studies were included. The studies were carried out from 1994 to 2012 in seven out of the 31 provinces of Iran. Seven studies provided data on the prevalence of TB diagnosis among 1087 PWID. The pooled prevalence of TB diagnosis was 10.1% (95% CI: 4.5, 15.8) in studies carried out in hospitals and 0.54% (95% CI: 0.04, 1.04) in other settings.

Conclusion: The present review suggests an approximately 40 times higher prevalence of TB among PWID compared to the general population. However, most of the included studies were conducted on a subpopulation of drug users, and caution should be exercised when generalizing the findings.

Keywords: Prevalence, Drug users, Tuberculosis, Iran

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Introduction

For centuries, tuberculosis (TB) has been known as a major public health problem. With the introduction of preventive measures and effective treatment, the incidence of TB and associated deaths has declined drastically over the years. However, TB is still a top ten leading cause of death worldwide.[1,2] The World Health Organization (WHO) has estimated 10 million individuals are infected with TB (9.0-11.1 million) and the annual incidence is 133 (120-148) per 100 000 population. In Iran, it has been estimated that 11 (8.7-14) thousand were infected in 2017, with an annual incidence of 14 (11-18) per 100 000 population.[1]

During recent years, new cases of TB have been linked to undernourishment, human immunodeficiency virus (HIV) infection, diabetes, alcohol use, and cigarette smoking.[1] In addition, regular drug use, especially injecting drug use, puts individuals at a higher risk of TB infection. This risk has been shown to be independent of HIV infection.[3] People who use drugs (PWUD) are frequently considered socially deprived. They may face risk factors for TB acquisition like poverty, unstable housing, and overcrowded living situations. Medical conditions among PWUD usually have a worse prognosis and do not receive adequate treatment. A better understanding of the prevalence of TB among PWUD can promote early detection and treatment, and effectively fill this gap.[4] Opioid use and dependence are relatively high in Iran.[5,6] In the last decade, stimulant use and dependence have also appeared on the drug scene.[7-9] In recent years, health consequences, especially infectious diseases among PWUD have been a major public health concern.[10-13]

Several systematic reviews have been conducted on TB among inmates, HIV-positive inmates, people living with HIV, and those with alcohol use disorder in different countries around the world.[14-18] However, no systematic review was found on the prevalence of TB among PWUD and more specifically, among people who inject drugs (PWID), neither globally nor in Iran. This study aimed

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to collect the relevant data and provide an estimate of TB prevalence among Iranian PWUD and the subgroups using systematic review and meta-analysis.

Methods

Search strategy

This systematic review complied with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA).[19] The search strategy included three parts: (1) searching international (ISI Web of Science, PubMed, SCOPUS, and Embase) and national (Scientific Information Database - SID) databases for published documents, (2) hand-searching the reference lists of the retrieved papers, and (3) communicating with the relevant Iranian professionals to access unpublished studies.

Search terms were categorized into three groups: (1) the keywords related to Iran and its provinces and large cities, (2) the terms related to substance use and dependence, and (3) the terms related to tuberculosis as well as the MeSH terms of tuberculosis and Mycobacterium tuberculosis. Keywords were combined with the Boolean operator of "OR" within each group and "AND" between groups.

For the Iranian databases, a search was conducted using the Persian terms for tuberculosis. There were no restrictions on study design and language for the full texts. There was only a limitation for publication time from 1990 up to the time of the search in August 2019. The search strategy for the PubMed database is provided as an example in Supplementary file 1.

Screening

The retrieved documents were screened in two steps: first, the titles and abstracts were screened to exclude irrelevant studies and then, the full texts were assessed for eligibility. Both stages were conducted independently by two investigators. Studies were included if the target population consisted of Iranian participants with substance use or dependence and the study had provided prevalence of TB, either through biological testing i.e., positive tuberculin skin test (TST), positive sputum smear or culture, and findings suggesting TB infection in chest X-rays (CXR), or through clinical diagnosis.

Data extraction

The following data were extracted from the included studies: bibliometric characteristics, the year of study implementation, study location, recruitment setting (treatment centers, harm reduction services, prison, etc), sample size, sampling method, refusal rate, demographic characteristics of the participants, injecting or non-injecting drug use, method of biological testing of TB, test results, and finally the prevalence of TB among PWUD, and in subgroups of gender, injecting and non-injecting PWUD, and study setting. Two investigators extracted data independently, and discrepancies were checked with a third reviewer.

Quality assessment

To assess the quality of the included studies, some important criteria were defined using the most common tools (e.g., Newcastle-Ottawa Quality Assessment Scale)[20] and specialists' opinions. The quality of the studies was assessed using the following criteria:

1. Source of sampling is defined clearly
2. Sampling method is defined clearly
3. Refusal rate is less than 30% OR the characteristics of those who refused are described
4. Gender-specific data are provided
5. Results are presented separately for injecting and non-injecting PWUD
6. Definitions of injecting and non-injecting drug use are provided
7. Types of lab tests are explained
8. Year of study implementation is reported
9. Samples are not selected from the infectious diseases wards of hospitals

If the data on items 1, 4, 5, 7, and 8 were not reported in the document, we communicated with the authors to obtain the information. Even if the authors provided the missing data, still the item was considered unfulfilled for the document. The numerals of unfulfilled items were reported for each study.

Statistical analysis

Studies reported TB prevalence either based on screening tests (i.e., TST results or findings on CXR) or diagnostic measures (i.e., positive sputum smear or culture, or clinical diagnosis) for active TB. Considering the clinical significance of diagnostic measures to assess active TB, and since most of the studies (6 out of 9 studies) were conducted on PWID, only the pooled prevalence of active TB among PWID was estimated, and the forest plots among PWID were presented for two study settings (hospitals and other settings). The meta-analysis was conducted using random effects model to account for expected heterogeneity between studies. Heterogeneity was assessed using the I^2 statistic (I-squared variation in ES attributable to heterogeneity), describing the percentage of variation between studies.[21] If the I^2 value is more than 75%, the heterogeneity is deemed considerable.[22] Data analysis was conducted in Stata software v.14.2 using the "metaprop" command. Other findings, such as the results of screening tests and data on people who use drugs through non-injecting routes were presented descriptively.

Results

Study selection

A total of 896 documents were found through an initial

systematic search, of which 97 were duplicates (Figure 1). After screening the titles and abstracts, 29 studies were selected and the full texts of the articles were assessed. Of the remaining 29 studies, 20 did not meet the eligibility criteria, mainly because they did not provide any data on TB prevalence.

Study characteristics

A total of nine studies were included in this systematic review. Six studies were conducted only on PWID,[23-28] and one included both injecting and non-injecting PWUD.[29] Two studies were on PWUD without defining their route of drug administration.[30,31] Table 1 shows the characteristics of the nine studies. A total of 2033 drug-using participants were included and the sample size of the included studies was from 31 up to 561. The studies were conducted in seven out of the 31 provinces of Iran; three were from Fars, two from Khorasan Razavi, and one from Tehran, Kermanshah, Hamedan, and Sistan-Baluchestan provinces each (Figure 2). The settings of the studies were hospitals (n = 4), prison/correctional facilities (n = 3), and drug treatment centers (n = 2). The oldest study was carried out in 1994[31] and the latest in 2011-2012.[29] Different studies used different indicators for reporting the socio-demographic characteristics of the participants. However, the majority of studies on PWID reported that the participants had an average age of 34-38, more than half of them were unmarried, about half were unemployed, more than 60% had a history of imprisonment, and more than one-third of the participants were either illiterate or had primary education.

Assessment of the quality of the included studies showed that the number of unfulfilled criteria ranged from two to five, and six studies had more than two unfulfilled criteria out of the nine quality criteria (Table 1). None of the studies provided the definition for injecting drug use (e.g., lifetime or last 12 months).

TB prevalence

The pooled prevalence rates of active TB in PWID in the 272 participants recruited from hospitals and 815 participants from other settings (including methadone maintenance treatment centers, drop-in centers

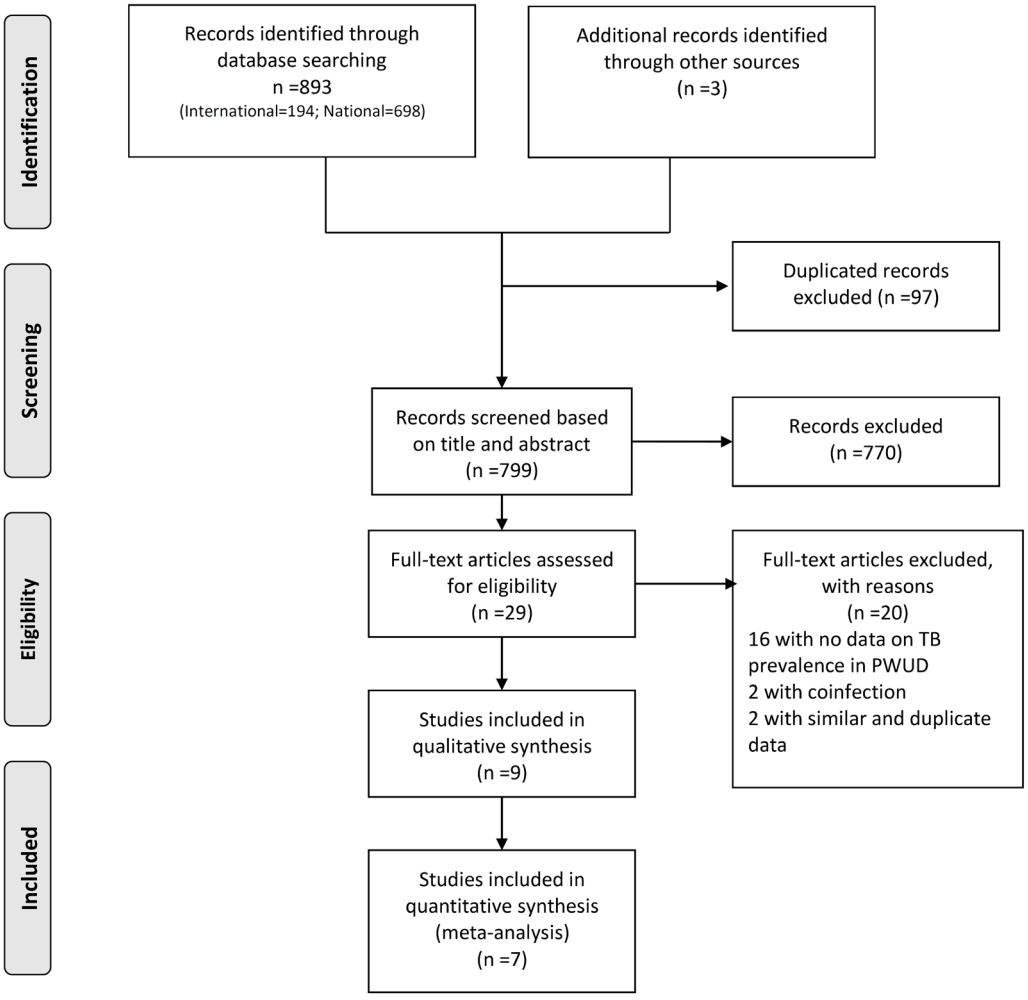

Figure 1. Flowchart diagram of search results

Table 1. Characteristics of the studies on TB prevalence in PWUD in the Iranian population

First author (year of publication)	Study year	Province	Type of DU	Recruitment setting	Recruitment method	Sample size (M/F)	Age characteristics	Demographic characteristics	Study Quality*
Honarvar (2013)[29]	2011-12	Fars	PWID and non-injecting PWUD (Opioid users)	All MMT and DIC centers in several districts in Fars province	Convenience sampling	263 (226/37)	Range: 20-65 Mean: 37.4 (±8.3)	In PWID: Unmarried: 75.6% Low education**: 34.6% In NIDUs: Unmarried: 76.9% Low education: 42.1%	4, 6
Mamani (2013)[23]	2008-9	Hamedan	PWID	MMT centers in Hamedan	Convenience sampling	268 (240/28)	Range: 18-70 Mean: 34.5 (±8.2)	Unemployed: 51.1% Imprisonment: 83.6%	2, 6
Tavanaee Sani (2012)[24]	2007-8	Khorasan Razavi	PWID	Infectious ward of one hospital in Mashhad	Census	62 (60/2)	Mean: 34.3	Imprisonment: 83.5%	4, 6, 7, 9
Nazer (2016)[25]	2007	Kermanshah	PWID	A prison in Kermanshah	Census	350 (NK)	NK	NK	3, 4, 6
Asadi (2006)[26]	2002-3	Tehran	PWID	Infectious wards of three hospitals in Tehran	Census	126 (123/3)	Range: 18-54 Mean: 34	Imprisonment: 64.3%	4, 6, 7, 9
Sharifi-Mood (2006)[27]	2000-5	Sistan and Baluchestan	PWID	Infectious ward of one hospital in Zahedan	Census	31 (NK)	Range: 16-60 Mean: 35.7 (±14.7)	Unemployed: 45.2 Low education: 80.7%	4, 6, 7, 9
Sarvghad (2005)[28]	2002-3	Khorasan Razavi	PWID	Infectious ward of one hospital in Mashhad	NK	53 (50/3)	Age distribution: <30: 51%	Unmarried: 58.5% Low education: 41.1%	2, 4, 6, 7, 9
Askarian (2001)[30]	1997	Fars	PWUD (Never-imprisoned opioid addicts)	A correctional center in Shiraz	Convenience sampling	319 (NK)	Range: 18-50 Age distribution: <30: 31.0%	NK	2, 3, 4, 5, 6
Sadeghi Hassanabadi 1998)[31]	1994	Fars	PWUD (Opioid addicts)	A correctional center in Shiraz	Census	561 (561/0)	Range: 18-40	NK	2, 3, 5, 6, 8

DIC: Drop-in centers; DU: Drug user; MMT: Methadone maintenance treatment; NIDU: Non-injecting drug user; NK: Not known; PWID: People who inject drugs; PWUD: People who use drugs.
* Numerals of unfulfilled criteria, ** Low education: illiterate + Primary education.

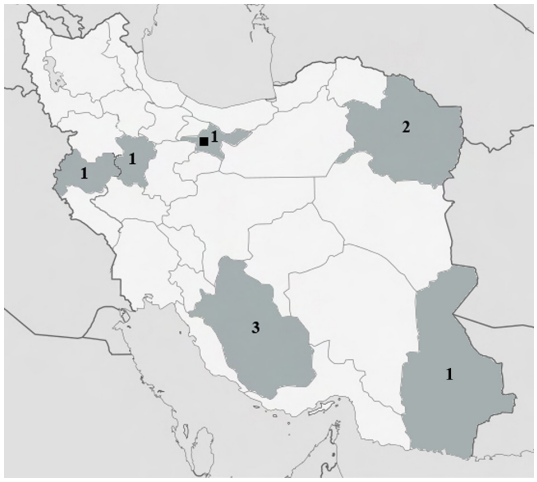

Figure 2. Distribution and number of TB prevalence studies on PWUD in Iran

providing harm reduction services, and prisons) were 10.1% (95% CI: 4.5 to 15.8) and 0.54% (95% CI: 0.04, 1.04), respectively (Figure 3). The studies with higher weight had the highest contribution in the polled estimation. Diagnosis of active TB was based on sputum smear and sputum culture in two out of the seven studies and based on clinical diagnosis in five studies.

Prevalence of positive TST and positive findings on CXR among PWID were reported in two studies and ranged from 5.4% to 18.3% and from 0.37 to 14.1, respectively. Positive sputum smear and sputum culture were reported in one study and their frequencies were 0.37 and 0.51, respectively (Table 2).

Two studies reported the prevalence of active TB in 328 male PWID as 0.42% and 0.53%, and only in one study, nine female PWID were assessed, none of whom had active TB. Only one of the studies on PWID reported TST prevalence according to gender, and it was 20.4% in male and zero in female participants (Table 2). Only, in one study[27] coinfection with HIV was assessed, and one out of the nine patients with active TB was found to be HIV positive.

A single study reported TB prevalence among non-injecting PWUD. Positive TST, CXR, and sputum culture among 57 participants were 3.9%, 10.9%, and 3.5%, respectively.[29] In this study, sputum culture was positive in 2.6% of males and 5.3% of females (Table 2).

Two relatively old studies were conducted on 880 PWUD, without mentioning the route of drug administration and reported a prevalence of 0.12% and 2.5% for active TB.[30,31] Three studies on PWUD - without mentioning the route of administration - reported a prevalence of 5.3%, 40.1%, and 66.7% for positive TST results (Table 2).

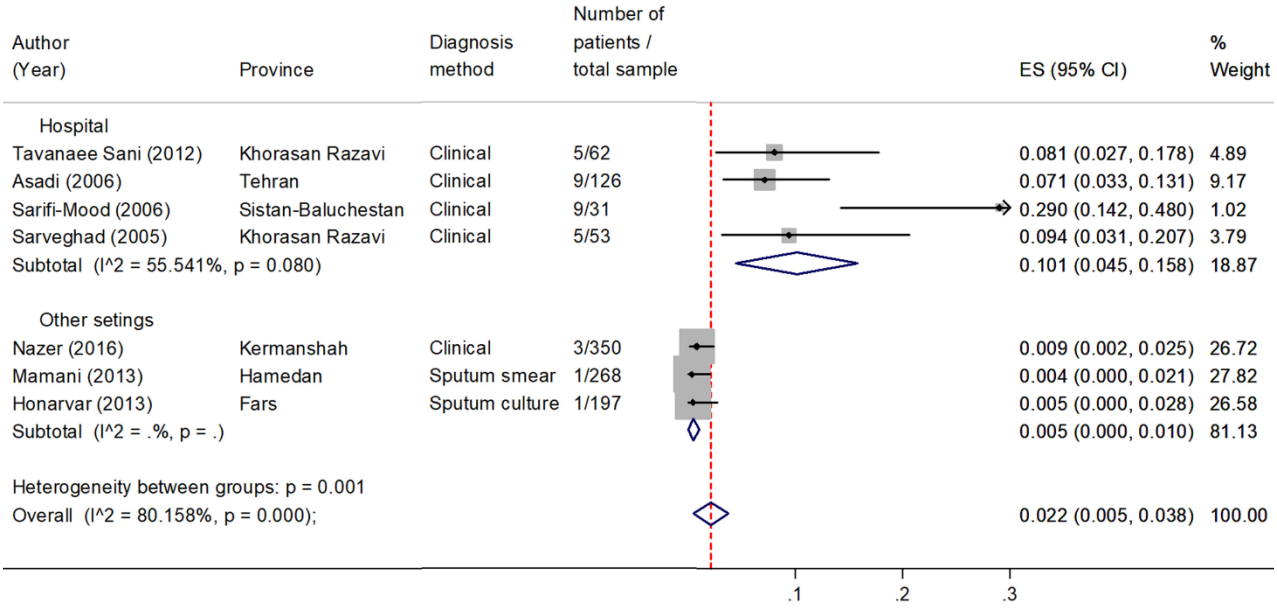

Figure 3. Meta-analysis of prevalence of TB diagnosis in PWID by setting

Discussion

In this study, nearly three decades of research on the prevalence of TB among PWUD in Iran were reviewed. The results of this review on active TB among PWID revealed a pooled prevalence of 10.1% in hospital settings and 0.54% in other settings, such as drug treatment centers and prisons. Compared to other settings, studies conducted in hospitals reported significantly higher rates of TB. All hospital-based studies were carried out in the infectious wards and this might explain the higher reported rates. The samples from other settings can be better considered as representatives for PWID. According to the national data, the prevalence of TB in Iran was estimated as 14 in 100 000 in the general population, in 2017.[1] The results of the present review suggested an approximately 40 times higher prevalence of TB among PWID than in the general population.

In the included studies, the highest prevalence of TB among PWID in the hospitals was in Zahedan (29%), the southeast of Iran.[27] Zahedan is a city in Sistan and Baluchestan Province. This province is among the least developed parts of the country[32] and is close to the neighboring countries of Pakistan and Afghanistan, with a high rate of TB.[1,33] A systematic review also reported a 29% TB prevalence among Afghan immigrants in Iran.[34] With the implementation of the national TB control and care program, a decreasing trend of TB was noted in Sistan and Baluchestan from 2006 to 2016.[35] However, the pattern and trend of TB infection among PWUD of the province remain unclear due to the scarcity of the studies.

Global data on the epidemiology of TB indicate a high prevalence among PWID. The rate of positive TST ranges from 12 to 39% in North America, 17 to 52% in Europe, and just above 60% in Mexico. There is also a wide variation (from 0.5 to 66%) in the reported active cases of TB among PWID, depending on the study population and testing method.[4,36,37] The limited data provided in the included studies showed a very high rate of unemployment and imprisonment among PWID. In addition, several other studies from Iran have shown that poverty and homelessness are quite common among this group.[10,38] Homelessness, poverty, history of imprisonment, malnourishment, smoking, and alcoholism were mentioned as risk factors for TB in some studies. Prisoners are at high risk for TB infection and PWID experience higher incarceration rates. The rates of TB in prisons can be more than 50 times higher than among people outside prisons. The prison environment, being associated with overcrowding, poor nutrition, and inadequate access to health services might be the reason for this greater risk.[4,37,39] Due to the high rate of HIV infection among Iranian PWID,[11] there is also a possibility of reactivation of TB in addition to the primary TB infection among HIV-infected PWID.

Most of the reviewed studies were conducted on PWID. Due to the scarcity of data, the risk of TB infection attributable to non-injecting drug use could not be estimated. The only included study was on a small sample of non-injecting PWUD which reported a relatively high prevalence of TB. Globally, most of the evidence linking TB to drug use comes from studies on PWID.[4] Nevertheless, an increased risk for TB has been reported for those who smoke opium as well.[40] Since smoking opium is the most common way of using drugs in Iran,[41,42] more research is required to understand the associated risks.

According to this review, the evidence on HIV and TB coinfection among PWID is very limited and this area

Table 2. Results of studies on TB prevalence in PWUD in the Iranian population

Fist author (year of publication)	Study year	Recruitment setting	Province	Biologic data and TB definition	TST Positive: Cases/ total (%)	Chest X-Ray Positive: Cases/total (%)	Sputum smear Positive: Cases/ total (%)	Sputum culture Positive: Cases/ total (%)	Clinical diagnosis of active TB: Cases/total (%)
PWID									
Honarvar (2013)[29]	2011-12	MMT and DIC centers	Fars	TST ≥ 10; Abnormal chest X-ray; Sputum culture for all with pulmonary TB-related symptoms	T: 10/184 (5.4)	T: 24/170 (14.1)	-	T: 1/197 (0.51) M: 1/188 (0.53) F: 0/9 (0.0)	-
Mamani (2013)[23]	2008-9	MMT center	Hamedan	TST ≥ 5 (for HIV+) and ≥ 10 (for HIV); Chest X-ray for TB; Sputum smear positive	T: 49/268 (18.3) M: 49/240 (20.4) F: 0/28 (0.0)	T: 1/268 (0.37) M: 1/240 (0.42)	T: 1/268 (0.37) M: 1/240 (0.42)	-	-
Tavanaee Sani (2012)[24]	2007-8	Hospital	Khorasan Razavi	Pulmonary TB and Non-pulmonary TB	-	-	-	-	T: 5/62 (8.1) and 1/62 (1.6)
Nazer (2016)[25]	2007	Prison	Kermanshah	Total score of signs and symptoms and sputum smear positive or sputum culture positive	-	-	-	-	T: 3/350 (0.90)
Asadi (2006)[26]	2002-3	Hospital	Tehran	Pulmonary TB	-	-	-	-	T: 9/126 (7.1)
Sharifi-Mood B. (2006)[27]	2000-5	Hospital	Sistan and Baluchestan	No definition	-	-	-	-	T: 9/31 (29.03)
Sarvghad (2005)[28]	2002-3	Hospital	Khorasan Razavi	No definition	-	-	-	-	T: 5/53 (9.4)
PWUD									
Honarvar (2013)[29]	2011-12	MMT and DIC centers	Fars	TST ≥ 10; Abnormal chest X-ray; Sputum culture for all with pulmonary TB-related symptoms	T: 2/51 (3.9)	T: 5/46 (10.9)	-	T: 2/57 (3.5) M: 1/38 (2.6) F: 1/19 (5.3)	-
Drug user									
Honarvar (2013)[29]	2011-12	MMT and DIC centers	Fars	TST ≥ 10; Abnormal chest X-ray; Sputum culture for all with pulmonary TB-related symptoms	T: 13/244 (5.3)	T: 29/223 (13.0)	-	T: 3/254 (1.2)	-
Askarian (2001)[30]	1997	Correctional center	Fars	TST ≥ 10; Positive chest X-ray for pulmonary TB; Sputum culture	T: 128/319 (40.1)	T: 8/128 (6.3)	-	T: 4/319 (0.12)	-
Sadeghi Hassanabadi (1998)[31]	1994	Correctional center	Fars	TST ≥ 10; Active pulmonary TB (TST, chest X-ray, pulmonary symptoms, smear or culture positive)	T: 374/561 (66.7)	-	-	-	T: 14/561 (2.5)

DIC: Drop-in centers; F: Female; M: Male; MMT: Methadone maintenance treatment; T: Total; TB: Tuberculosis; TST: Tuberculin skin tests; PWID: People who inject drugs; PWUD: People who use drugs.

needs more attention from researchers. Another review from Iran showed a 14.6% prevalence of HIV among current PWID.[11] Two studies from Iran on PWUD living with HIV reported a TB prevalence of 9.7% and 32.1%.[43,44] Studies from other countries showed that PWID living with HIV have a two- to six-fold increased risk of TB compared to those who are not injecting drugs.[45] TB is a top cause of hospitalization and mortality among people living with HIV.[4] HIV and TB coinfection is associated with several challenges, such as the difficulty of diagnosing TB, challenges of drug treatment, and problems related to adherence.[46]

With the restart of the national TB control programs in 1996, the incidence of TB has decreased steadily and considerably.[47] In addition to the TB-specific control programs, several other factors might have influenced this achievement, such as improvements in general health literacy and practice, sanitation, and primary and specialized health care.[48] However, TB control in PWUD, and more specifically in PWID, seems to be a

neglected area. It has been recommended that TB-specific services i.e., screenings linked to standardized treatment protocols, should be integrated into the general health and harm reduction packages and should be provided along with HIV and hepatitis prevention, treatment, and care services. Other important harm reduction services that are also effective in TB control are high coverage of opioid agonist treatment, needle syringe programs as well as targeted information, education, and communication. Since the prison environment is the main risk factor for TB, promoting primary and secondary prevention strategies for prisoners throughout incarceration and on release is also important. Availability of treatment for substance use disorders, harm reduction strategies, and TB screening and treatment in prisons are of utmost importance.[1,36,39]

The present review showed there is a limited number of high-quality studies on TB among PWUD. Compared to HIV, HCV, and HBV among PWUD, this topic could be considered a neglected area in Iran. No national or large multi-site study was detected and the included studies represented only a few geographical areas. Due to the lack of repeated surveys over different years, it was not possible to provide any information on the changes in the TB prevalence over the course of time. The included studies did not provide any definition for injecting drug use, and it was not clear if PWID were those with a lifetime experience of injecting drugs or were currently injecting. Moreover, the data on gender differences were not sufficient and the research on non-injecting PWUD was very limited. Finally, some of the studies did not provide their definition for active TB.

In Iran, the production of the Bacillus Calmette-Guérin (BCG) vaccine was initiated in 1947. Four years later, Iran had a vaccination plan and started high coverage of vaccination of infants in the country[49] which was extended annually. Therefore, relying on TST, which might be positive after vaccination, is not an appropriate way for TB screening or diagnosis of latent TB. Although TST results among PWUD were included in this review, we did not conduct meta-analysis nor concluded on the results of TST as latent TB diagnosis in this review.

Conclusion

Considering the paucity of data on TB among PWUD, it was necessary to conduct a systematic review in this area. Although too many studies could not be included, this meta-analysis revealed an elevated rate of TB infection in PWID (0.54%), which as expected, was much higher than the rate of TB in the general population. The present study could be considered a cornerstone in increasing our understanding of TB infection among drug users. The results of this study could be utilized by both policymakers and researchers. However, it must be reminded that most of the included studies in this review were carried out on a subpopulation of drug users, and generalization of the data should be carried out with caution.

Authors' Contribution

Conceptualization: Hosein Rafiemanesh, Behrang Shadloo, Masoumeh Amin-Esmaeili, Jaleh Gholami, Afarin Rahimi-Movaghar.
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Software: Hosein Rafiemanesh, Jaleh Gholami.
Supervision: Afarin Rahimi-Movaghar.
Validation: Hosein Rafiemanesh, Afarin Rahimi-Movaghar.
Visualization: Hosein Rafiemanesh, Yekta Rahimi.
Writing–original draft: Hosein Rafiemanesh, Behrang Shadloo, Yekta Rahimi, Afarin Rahimi-Movaghar.
Writing–review & editing: Hosein Rafiemanesh, Behrang Shadloo, Masoumeh Amin-Esmaeili, Yekta Rahimi, Jaleh Gholami, Afarin Rahimi-Movaghar.

Competing Interests

None.

Ethical Approval

Not applicable.

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Supplementary File

Supplementary file 1. Sample for PubMed search strategy and results.

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