

Role of Immigration in Tuberculosis Transmission to Iran: A Systematic Review

Abstract

Background: Today, because of increasing immigration and the prevalence of drug-resistant tuberculosis in Iran, identifying intra-community cases is necessary in the country. It will be possible through the use of molecular epidemiologic methods. In this inquiry, in order to determine the role of immigrants in the transmission of specific strains to Iran, the studies have been examined which had been conducted based on molecular epidemiologic methods among Iranians and non-Iranians people. **Methods:** All studies from 1997 to the end of March 2017 were examined in three databases of PubMed, Scopus, and Google Scholar and finally, 16 studies were selected. **Results:** The common clustering rate between Iranians and non-Iranians was determined to be 19.8, and the intra-community recent transmission rate was from 0% to 49% with average of 18.1%. The rate of multidrug-resistant tuberculosis (MDR-TB) was 12.5%, which was higher among immigrants, especially Afghans, and a significant number of the strains were Beijing. **Conclusions:** The studies have shown that migrants, especially Afghans, are more effective in transmitting specific strains of tuberculosis to migratory areas. To control tuberculosis, it is necessary to register of immigrant's health information, while enter to the country, so that, by doing appropriate diagnostic tests, the curing the patients, the transmission of tuberculosis to the country would be prevented.

Keywords: Immigration, Iran, molecular typing, tuberculosis

Introduction

Despite the great medical advances, tuberculosis (TB) is still one of the major health problems in the world, and nearly one-third of the world's population is infected with *Mycobacterium tuberculosis*,^[1] and according to the World Health Organization (WHO), nearly 10 million of new TB cases have been reported in the world in 2019, which about 465,000 cases of them have been multidrug-resistant tuberculosis (MDR-TB).^[2] Although some individuals would be afflicted with active disease after infection with this bacterium, but 90% of them remain asymptomatic.^[3] At present, the TB worldwide control program has two serious threats: one is the HIV epidemic^[4] and another is the prevalence of drug resistance, in particular MDR-TB.^[5] Therefore, the use of methods that could identify TB bacteria, especially MDR-TB, and stop its transmission will be effective in controlling this disease. Several factors,

such as traveling to contaminated areas,^[6] homelessness, HIV infection,^[4] migration,^[7] as well as strain type,^[8] are effective in the rapid transmission and spread of TB. Although TB is under control in Iran, but it has not been decreased yet, and immigrants are one of the most important factors of this problem. Immigration, besides causing the economic and social challenges, is an important and influential factor in the epidemiology of infectious diseases.^[9] An increase of immigration may have a significant impact on the pattern of TB transmission in countries.^[10] TB immigrants are normally people who move from countries where TB is indigenous to the affluent countries from the view point of facilities. Thus, migratory flows from developing countries with a high prevalence of TB are a source of concern for TB control,^[11] as some immigrants due to having a hidden infection^[12] on the one hand, and TB patients travelling to other countries such as Iran who called "health tourism"^[13] on the other hand, are effective in the transmission of TB; therefore, international travel and migrations will

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change the epidemiology of this disease.^[14] Iran has been faced a significant number of immigrants from the countries of Afghanistan and Iraq as a result of its geographical location and proximity, as well as people from Azerbaijan, referred to as Health Tourism, for the low-cost or free-of-charge TB treatment come to the provinces of the North-West of Iran. Regarding the lack of reduction of TB cases in the country, this study attempts to focus on the role of immigration in the transmission of TB in Iran, and help to make preventive decisions to reduce TB by identifying how migrants influence the transfer of TB to Iran.

Methods

Study selection

Because molecular typing methods can be used to study the genetic pattern of strains, the pathway of transmission, and examine of risk factors, therefore, in this study, those molecular epidemiological studies were included in the study which had used genotyping methods to examine the *M. tuberculosis* isolates. Their study included Iranian and non-Iranian individuals, focused on the transmission of TB between Iranians and migrants, with a sample size of more than 50 cases and identified the number of samples inside the cluster. Studies that had not performed genotyping or had selected specific cases and studies on nonhuman specimens were excluded. Meanwhile, studies that only had focused on TB prevalence and its detection were removed.

Literature search

All studies from 1997 to the end of March 2017 were examined in three databases of PubMed, Scopus, and Google Scholar. For search, the terms TB, transmission, immigration, and Iran were selected. English and Persian articles were intended.

Data extraction

The collected data included the study time, the study period, the province or city, the number of examined samples, the genotyping method and the secondary typing method, MDR-TB strains, within cluster and unique samples, the size and number of clusters, the number of common clusters between Iranians and non-Iranians, and specific strains such as Beijing, and recent intra-community transmission. To calculate the common clustering rate, the number of common in-cluster samples divided into the total number of studied subjects and to calculate the TB ratio, which has resulted due to recent transmission between Iran and non-Iranians, the following formula has been used assuming that each cluster has an infectious resource in which the disease is activated and the rest have recently become infected. Minimum estimated rate of intra-community recent transmission was calculated by the following formula:^[15]

$$\frac{\text{number of common clustered patients} - \text{number of common clusters}}{\text{total number of patients}}$$

Isolates with unique patterns, non-cluster, and those that have the same genotyping pattern are classified as clustered. Therefore, a cluster consists of two or more isolates that have the same pattern^[16] and the common cluster contains clusters in which separated isolates from both Iranian and non-Iranian were inserted.

Results

Regarding including and excluding criteria from study, the information of 16 papers was finally analyzed [Figure 1], and the summary of important information is presented in Table 1.^[17-32] Methods used for genotyping include insertion sequence 6110-restriction fragment length polymorphism (IS6110-RFLP), spoligotyping, polymorphic GC-rich repetitive sequence-restriction fragment length polymorphism (PGRS-RFLP), mycobacterial interspersed repetitive unit-exact tandem repeat (MIRU-ETR), mycobacterial interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR), and direct repeat-restriction fragment length polymorphism (DR-RFLP). In eight studies, they used a secondary typing method, and eight

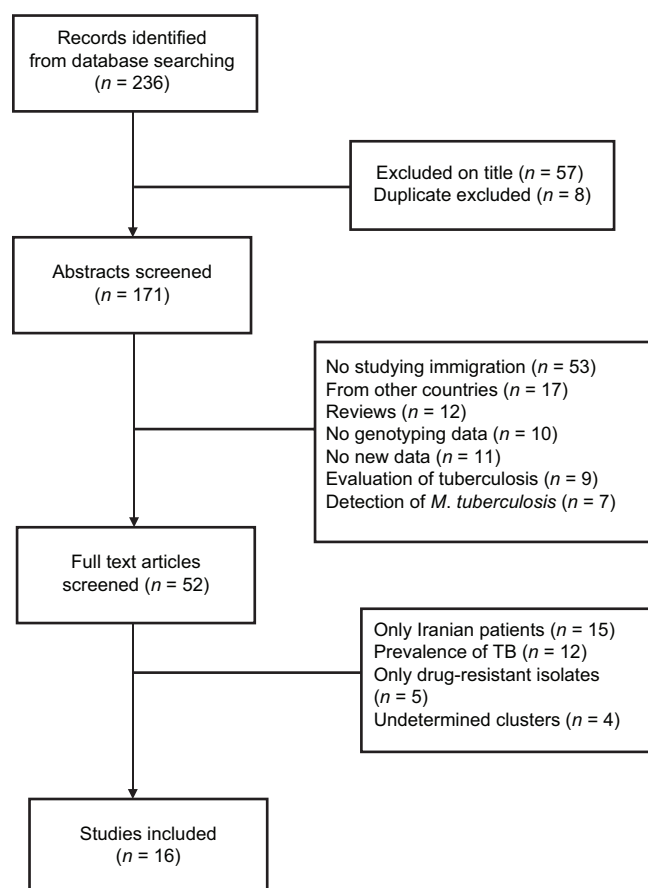


Figure 1: Flow diagram of literature review process

Table 1: Selected characteristics of included studies

Study region/duration (month)	Study subjects (Iranian-non-Iranian)	MDR/Beijing (%)	Genotyping method (primary/secondary)	Clustered isolates/ isolates with unique pattern	Cluster (no.)	RT* (%)	Clusters with shared isolates (Iranian and non-Iranian)	Isolated included in common clusters (Iranian-non-Iranian)	Common clustering rate (%)	Intra-community RT (%)
Tabriz ⁽¹⁷⁾ /12	119 (91-28)	NA	MIRU-VNTR/-	23/96	10	10.9	0	0	0	0
Tehran ⁽¹⁸⁾ /18	70 (60-10)	20/1.4	IS6110-RFLP/Spoligotyping	56/14	22	48.6	4	24 (18-6)	34.3	-
Markazi Province ⁽¹⁹⁾ /18	95 (88-7)	NA	IS6110-RFLP/PGRS-RFLP	75/20	28	49.5	-	-	-	-
Iran-21 Provinces ⁽²⁰⁾ /12	1242 (1172-70)	5.9/8.1	Spoligotyping/-	1165/77	10	93	-	-	-	-
Markazi Province ⁽²¹⁾ /12	57 (54-3)	NA	IS6110-RFLP/DR-RFLP	16/41	7	15.8	0	0	0	0
Markazi Province ⁽²²⁾ /6	53 (50-3)	NA	MIRU-ETR/-	13/40	4	17	1	2 (1-1)	3.8	1.9
Tehran ⁽²³⁾ /15	102 (73-29)	NA/15.7	Spoligotyping/-	77/25	10	65.7	5	55 (35-20)	53.9	49
Tehran ⁽²⁴⁾ /24	291 (231-60)	15.8/NA	IS6110-RFLP/Spoligotyping	60/231	25	12	5	13 (8-5)	4.5	2.7
Tehran ⁽²⁵⁾ /12	258 (199-59)	27.9/4.7	IS6110-RFLP/Spoligotyping	65/193	29	14	14	33 (18-15)	12.8	7.4
Mashhad ⁽²⁶⁾ /10	113 (109-4)	NA/7.1	Spoligotyping/-	69/44	17	46	1	8 (4-4)	7.1	6.2
East and West Azarbaijan Provinces ⁽²⁷⁾ /12	154 (152-2)	1.3/NA	IS6110-RFLP/MIRU-ETR	27/127	13	9.1	0	0	0	0
Tehran ⁽²⁸⁾ /60	1742 (1074-668)	15.1/5.3	Spoligotyping/-	1679/63	70	92.4	21	495	28.4	27.2
Tehran ⁽²⁹⁾ /12	195 (147-48)	12.8/9.2	Spoligotyping/-	109/86	9	51.3	3	45	23.1	21.5
East Azarbaijan Province ⁽³⁰⁾ /6	119 (105-14)	5.7/NA	IS6110-RFLP/-	38/81	12	21.8	1	3 (2-1)	2.5	1.7
Tehran ⁽³¹⁾ /18	120 (118-2)	19.2/NA	PGRS-RFLP/IS6110-RFLP	33/87	9	20	2	4 (2-2)	3.3	1.7
Tehran-Fars Provinces ⁽³²⁾ /12	62 (49-13)	6.3/10	IS6110-RFLP/Spoligotyping	12/50	6	9.7	1	2 (1-1)	3.2	1.6

*RT: Recent transmission

studies were without a secondary method. In the studies, of 4792 TB patients, 3772 people were Iranians and 1020 (21.3%) were non-Iranians. Non-Iranians included 968 Afghans, 49 Azerbaijanis, and 3 Iraqis. The most non-Iranians in the study in Tehran, the capital of Iran, were 38.3%.^[28] Of the antibiogrammed samples (4375 cases), 546 samples (12.5%) were MDR; the highest MDR in the study was related to Farnia *et al.*^[25] paper in Tehran, which was (27.9%) and the prevalence of the Beijing strain in the studies was determined to be 6.5%. The highest rate of Beijing's strain isolated by Torkman *et al.*^[23] in Tehran was (15.7%). The rate of common clustering between Iranians and non-Iranians was estimated to be 19.8% on average, which was the highest rate in the studies conducted by Torkman *et al.*^[23] in Tehran was 53.9% (55/102) and the highest rate of the recent intra-community in the study in Tehran was 49% [(55-5)/102] and the second highest rate of the recent intra-community transmission in Tehran in another study conducted by Velayati *et al.*^[20] was (27.2%) [(495-21)/1742]. In studies in which there were significant numbers of immigrants (non-Iranians) and strains in Beijing, the recent intra-community transmission rate has been higher.

Discussion

The use of molecular typing methods is essential for evaluation and improvement of TB control programs and determining the amount of recent transmission, especially intra-community transmission. Therefore, in this study to examine the role of migrants and therapeutic travelers in transferring TB to Iran, 16 studies have been evaluated in Iran based on the molecular typing methods. On the basis of these methods, the majority of TB cases were due to the recent transmission, and the recent transmission rate was variable from 9.1% in the study of Asgharzadeh *et al.*,^[27] to 93% in the study of Velayati *et al.*,^[20] and the intra-community recent transmission rate was determined from 0% to 49% and an average of 18.1%. The majority of intra-community transmission took place between Iranian and Afghan immigrants. The intra-community recent transmission rate was very different, as in Afagi *et al.*,^[17] Rafiee *et al.*,^[21] and Asgharzadeh *et al.*^[27] studies, the rate of intra-community was zero. In the studies of Rafiee *et al.*^[21] and Asgharzadeh *et al.*,^[27] the number of non-Iranians was very low, 3 and 2 cases, respectively; therefore, the intra-community probability would be very low and also they used two methods for typing. However, in the study of Afagi *et al.*,^[17] although Azerbaijanis represented 24% of the patients, there was no intra-community, and the inter-community transmission among the Azerbaijanis was $(\frac{5-2}{28} = 10.7\%)$ and among Tabriz people were $(\frac{18-8}{91} = 11\%)$. It seems, in contrast to the eastern provinces of Iran, Afghan immigrants have

not resided in the North West of Iran because of distant and different languages of the Azeri language, and the non-Iranians who have been referred for diagnosis and treatment were from the Republic of Azerbaijan who have common language with people from northwest of Iran and have come to Tabriz for therapeutic tourism to provide medical services at a very low or free cost to treat TB patients, as they have not stayed for a long time in Tabriz to have close contact with different people and also the sample size was low (119 cases); therefore, it did not conclude all samples; as a result, the size of existing clusters was small (2-4 members) and there has not been common cluster between Azerbaijanis and Tabrizis.^[17] Therefore, there has not been intra-community. Of course, in another study conducted in this region, intra-community was observed to be 1.7%.^[30] Thus, it is necessary to monitor the movement of Azerbaijani TB patients to the northwestern region of Iran. In most studies reviewed, there was an intra-community,^[18,22-26,28-32] and in this study the majority of non-Iranians were Afghans. Because of the political situation and insecurity in the neighboring country, Afghanistan, immigration to Iran and through Iran to European countries is higher. A significant number of Afghan immigrants to Europe are being returned, and a significant number of them are residing in Iran. Meanwhile, there is much immigration within the country, which is marginalized in big cities such as Tehran, Mashhad, and Qom. Tehran is a metropolis, so Afghan refugees can get jobs, and the cities of Mashhad and Qom have led the Afghans to settle there because of pilgrimage and crowding. Immigrants have an impact on the epidemiology of TB in populations, as in advanced countries, the majority of recent transmission occur among immigrant groups or their children.^[11,12] Considering that Afghan immigrants, like other immigrants, have malnutrition, high stress, low education and lack of knowledge about the disease, population density in their residents, deprivation of living facilities and health services, and they are from low social groups and economic levels and generally because of illegally entering, they live secretly, so they have low incomes and also return some of their low income to the country of origin; therefore, there is a possibility of reactivation of the bacteria present in their bodies from their country, as well as there is a high possibility of getting infection from other roommates and colleagues. Of course, some Afghans may have entered Iran with active TB and the contamination would occur during travel to the country of origin, so they can become a person who can transfer the bacteria in the living room to the roommates or other people who are in constant and close contact with them or can get a new infection of them, therefore the inter-community can occur between Afghans and the intra-community between Iranians and Afghans, but it should be noted that, the risk factors for being afflicted with TB between immigrants and indigenous people of Iran can be different, therefore, despite the treatment of TB of

immigrants is free of charge like indigenous people of Iran, because they are not controlled by health services, so the diagnosis of TB in these people is delayed, eventually they will have the opportunity to infect other people.

The average common clustering rate among Iranians and non-Iranians in these studies was 19.8%, with the highest common cluster (53.9%) in Torkman *et al.*'s^[23] study in Tehran, the capital of Iran and next 28.4% in Velayati *et al.*'s^[28] study have also been observed in Tehran. In conducted studies, the maximum number of common clusters among Iranians and non-Iranians was 21, and the largest common cluster among Iranians and non-Iranians was 251 in the Iranian capital, separated from 152 Iranians and 99 Afghans and separated from the East African Indian 3 (EAI3 family).^[28] Factors associated with the strain and various factors, such as study duration, local TB incidence, and sampling fraction,^[33] have role in size and number of the clusters, and the size of the clusters is usually large in young adults, men, and city residents.^[34] In Torkman *et al.*'s^[23] study in Tehran as the Beijing strains that have more transferable power^[35] are more than the rest of the study, so the common clustering rate was the highest. In Velayati *et al.*'s^[28] study in Tehran because the duration of the study (60 months), the number of samples (1742) was higher, the number of males and young adults was higher among Iranians and non-Iranians, and there were

a significant number of Afghans $\left(\frac{668}{1742} = \%38/3\right)$; as a result, contact with other people was increased and caused increasing the social mixing among Iranians and non-Iranians; therefore, the number of common within the cluster isolates as well as the size of the largest common cluster has increased. It should be noted that the presence of a common cluster does not always indicate a definitive epidemiological link, so that in cases where two people who had never any contact with each other and were completely in the separated geographic regions, the bacteria isolated from them had the same pattern and were placed in the same cluster.^[36] This indicates that some strains were more prevalent in a particular region, so they could lead to mistakes in epidemiologic communications and indicate more recent transmission rates, especially when only the spoligotyping method is used which has a low distinction power.^[37] Therefore, it would cause increasing of the clustering and the recent transmission rate is estimated further. As in conducted spoligotyping studies, despite enough time and the number of suitable samples, the rate of clustering and recent transmission had been increased.^[20,23,28] Thus, to use molecular typing and the examine of TB transmission, it is preferable to use methods with high distinction power such as MIRU-ETR, IS6110-RFLP, or to use a secondary method with spoligotyping.

Of the 16 studies, there have been Beijing strains in eight studies [Table 1]. The Beijing strain has not been reported in Eastern and Western Azarbaijan and Markazi

provinces.^[17,19,21,22,27,30,38] The strain of Beijing was first reported by Doroudchi *et al.*^[32] in Iran. In total, in studies of a significant number of Afghans, the Beijing strain was higher,^[23,28,29,32] so it seems that the Beijing strain has been likely transmitted to Iran through the Afghans.^[18,29] The strain of Beijing in the people of Afghanistan is of circulating strains, so that in the eastern provinces of Iran and in cities such as Qom and Tehran, where more Afghans live, there are more Beijing strains.^[39] This strain is rapidly expanding and has a higher pathogenicity^[8] and a significant number of MDR strains have Beijing genotype.^[35] As vaccination of TB cannot prevent the infection with Beijing strain,^[40] so in the event of a lack of diagnosis and treatment of patients infected with the strain, in the future, being infected at lower ages, probably could be increased. It seems that not decreasing of TB in Iran is likely to be due to increasing of Beijing strains especially MDR strains. However, the increase of the number of HIV infected people in the country also plays a roll. So, in order to control TB, in particular to prevent the transmission of drug-resistant TB, breaking this transmission chain is necessary. Therefore, the Beijing strains should be identified through dedicated methods such as polymerase chain reaction (PCR)^[41] and spoligotyping^[42] in immigrants referring to health centers, especially in the eastern provinces of Iran, which are the place of entry of Afghan immigrants so that they could be treated properly.

Of antibiogramed samples, 12.5% were MDR. In studies with higher rates of migrants, the percentage of resistance was also higher. In a study by Farnia *et al.*^[25] in Tehran of 72 MDRs, 38 cases were isolated of Afghan patients, namely 63.3% (38/60) isolated strains were from Afghan MDR. In Velayati *et al.*'s^[28] study in Tehran and Ramezanzadeh *et al.*,^[29] MDR-TB rates were higher among immigrants than Iranians, and a significant number of resistant drug strains were Beijing.^[29,32] It seems that MDR-TB cases are more common among Afghans than Iranians in regions of Iran where migrants, especially Afghans, live. It is not always like this. Regarding that, a significant number of patients, especially cases of MDR-TB, are immigrants and they influence on distribution of certain strains in Iran, so to reduce TB in Iran, it is necessary to reduce of TB transmission in origin countries. It is also necessary to provide conditions in which, after the arrival of immigrants to Iran, their hidden TB would not become active and this is possible by improving migrant's living condition and according to the economic problems in the country it is hard to this country to handle the problem lonely, so financial aids from international organizations such as WHO is necessary.

The following limitations have been observed in the examined studies:

1. Different methods of genotyping have been used in these studies, which they had different power of distinction. Considering that the distinction power of the

typing technique is effective on the recent transmission rate, in studies that only used the spoligotyping method it seems that the recent transmissions has been falsely observed further

2. In some studies, the results were not complete due to the lack of testing for drug sensitivity and the failure to identify strains of Beijing
3. Studies were conducted on positive culture samples; therefore, cases such as children TB in which samples were prepared hardly for cultivation were excluded
4. In some studies, the samples were low and did not include all TB cases
5. In some provinces where immigration has taken place, the relevant studies have not been carried out.

It is suggested that in order to reduce the number of TB in Iran, immigrant's health information be recorded upon admission, which be accompanied by suitable diagnostic tests for TB and also be benefit from the health services provided to Iranians.

Conclusions

Regarding the arrival of foreign migrants from neighboring countries to Iran, that one of their main motivations is the pursuit of occupation and the treatment of their illness, including TB, because of being free, therefore, exploitation the molecular epidemiological studies has made it possible to assessment and impact of immigrants on the country's TB and has improved our understanding of the role of immigrants in the transmission of specific strains to Iran, so that the obtained information can help to control of TB in Iran and even in neighboring countries.

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Conflicts of interest

There are no conflicts of interest.

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