Silent changes of tuberculosis in Iran (2005–2015): A joinpoint regression analysis

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ABSTRACT

Introduction and Aim: Tuberculosis (TB) poses a severe risk to public health through the world but excessively distresses low-income nations. The aim of this study is to analyze silent changes of TB in Iran (2005–2015): A joinpoint regression analysis. **Materials and Methods:** This is a trend study conducted on all patients ($n = 70$) that register in control disease center of Joibar (one of coastal cities and tourism destination in Northern Iran which was recognized as an independent town since 1998) during 2005–2015. The characteristics of patients imported to the SPSS 19 and variation in incidence rate of different forms of pulmonary TB (PTB) (PTB+ or PTB–) and extra-PTB (EPTB)/year was analyzed. Variation in incidence rate of TB for male and female groups and different age groups (0–14, 15–24, 25–34, 35–44, 45–54, 55–64, and above 65 years) was analyzed, variation in trend of this diseases for different groups was compared in intended years, and also, variation in incidence rate of TB was analyzed by Joinpoint Regression Software. **Results:** The total number of TB was 70 cases during 2005–2015. The mean age of patients was 42.31 ± 21.26 years and median age was 40 years. About 71.4% of patients were PTB (55.7% for with PTB+ and 15.7% with PTB–) and rest of them (28.4%) were EPTB. In regard to classification of cases, 97.1% of them were new cases, 1.45% of them were relapsed cases, and 1.45% of them imported cases. In addition, history of hospitalization due to TB was observed in 44.3%. **Conclusion:** Despite recent developments of governmental health-care system in Iran and proper access to it and considering this fact that identification of TB cases with passive surveillance is possible. Hence, developing certain programs for sensitization of the covered population is essential.

Keywords: Government, Iran, Northern of Iran, regression analysis, tuberculosis

Introduction

Tuberculosis (TB) poses a serious threat to public health throughout the world but disproportionately afflicts low-income nations.[1] Principal tendency of TB in the world introduces this disease to be one of the most important infectious diseases in the world. So that every year, 9 million people are afflicted to active TB and about 5.1 million people die of the disease.[2] TB is a prevalent and sometimes fatal infectious disease. This is caused by different types of mycobacterium, especially "*Mycobacterium tuberculosis*."[3] TB usually attacks the lungs, but it might affect other parts of the body too.[4] When individuals have active TB infection, they transfer the infection through coughing, sneezing, or their saliva. TB spreads out through air.[5] Most of such infections had not any symptom, but out of 10 latent infections, usually 1 infection will progress to turn into an active

disease. If TB is not treated, more than 50% of contaminated cases will die.[6] Almost 33 percent of global population are at TB risk. Every year, 9 million people experience active TB and 1.5–2 million people die because of this disease.[7] TB is the main cause of death due to one-factor infectious diseases (even more than HIV, malaria, and measles). In regard to global burden of disease, it has the tenth rank and it is predicted that TB may maintain its current status up to 2020 or rise to the seventh rank. More than 90% of TB-caused cases of fatality occur in developing counties. In such countries, 75% of cases belong to most active group age economically (15–54 years old). In these countries, adults with TB may not be able to work for 3–4 months averagely. Consequently, 20%–30% of annual income of their family may be lost. This is while their death will be equivalent with loss of 15 years of family income at once.[8] Evidently, apart from economic losses, TB will exert other indirect adverse effects on quality of life of patients or their family members.[9]

Currently, incidence rate of smear-positive pulmonary TB (PTB+) is the main index of TB status in Iran.[10] In terms of TB status, the reports of Ministry of Health reported that the incidence of TB has gone from 142 cases (per 100,000) in 1965 to 12.59 cases (per 100,000) in 2016. Among the provinces, Sistan va Baluchistan (Southeastern Iran) and Golestan (Northeastern Iran) reported highest level of incidence rate. The incidence rate of PTB in Mazandaran Province (Northern Iran, in adjacency to Golestan Province) was 12.39 cases (per 100,000) in 2016.[11]

One of the methods for detection of the disease is regression analysis of disease trend. In this method, independent variable is divided into certain intervals, and for each interval, a fitted distinct regression line and boundary between breakpoints will be determined.[12]

Review of trend, measures, and their variations helps health executives to evaluate and determine performance of health system for different periods. In addition, they could evaluate the extent to which programs of health executive and health facilities, human and financial resources, how much, helped them in achieving goals. It also determines that the changes in the incidence rate of diseases can be a useful tool for evaluating the efficiency and effectiveness of health control programs, measures employed, the performance of the health-care professionals and decision-making for health programing. Therefore, the aim of this study is to analyze trend of TB during 2005–2015 and determinants affecting it.

Materials and Methods

This is a trend study conducted on all patients (*n* = 70) that register in control disease center of Joibar (one of coastal cities and tourism destination in Northern Iran which was recognized as an independent town since 1998) during 2005–2015. The data were collected by TB Register Software. The characteristics of patients imported to the SPSS Statistics for Windows Version 22.0 (IBM Corp., Armonk, NY) and variation in incidence rate of different forms of PTB (PTB+ or PTB−) and extra-PTB (EPTB)/year was analyzed. Variation in incidence rate of TB was analyzed by Joinpoint Regression Software. This software is one of the most applicable in piecewise regression which is used for estimation of regression variables, estimation of breakpoints, and drawing diagram of fitted regression lines. To estimate regression variables, least square method was used. In addition, variation in incidence rate of TB for male and female groups and different age groups (0–14, 15–24, 25–34, 35–44, 45–54, 55–64 and above 65 years) was analyzed, and variation in trend of this disease for different groups was compared in intended years. Average annual percent change was used for summarizing trend of TB and statistical yearbooks were used for statistical estimation of the population. Furthermore, comparison of changes in TB incidence rate in 1-year intervals during the study period was investigated.

Case definition

Smear PTB+ is diagnosed with at least two positive initial sputum smears for acid-fast bacilli (AFB) by direct microscopy or one positive smear for AFB by direct microscopy and culture positive or one positive smear for AFB by direct microscopy and radiographic abnormalities consistent with active TB as determined by a clinician. The laboratory keeps all positive and negative slides for external quality assurance. Quality assurance is performed regularly at the regional laboratory, and feedback is given to a reporting health facility. A previous study reported a high specificity and good agreement of sputum microscopy between peripheral and reference laboratories.

Smear PTB− is diagnosed when the patient is presented with symptoms suggestive of TB and has at least three initial smear examinations negative for AFB, no response to antibiotics, repeat smear-negative and radiological abnormalities consistent with PTB, as well as a clinician's decision.

EPTB is diagnosed by one culture-positive specimen from an extrapulmonary site or histopathological evidence from a biopsy, which is based on strong clinical evidence consistent with active EPTB by a clinician's decision. However, most health facilities diagnose the disease based on a clinician's decision because there are inadequate laboratory facilities for sputum culture or histopathology.[13]

Results

The total number of TB was 70 cases during 2005–2015. The mean age of patients was 42.31 ± 21.26 years and median age was 40 years. Nearly 71.4% of patients were PTB (55.7% for with PTB+ and 15.7% with PTB−) and rest of them (28.4%) were EPTB. In regard to classification of cases, 97.1% of them were new cases, 1.45% of them were relapsed cases, and 1.45% of them imported cases. In addition, history of hospitalization due to TB was observed in 44.3%. In analysis of variables, the significant factors those influencing TB infection (PTB+ and

EPTB) included: previous history (in last year) of incarceration and addiction ($P < 0.05$). Other demographic characteristics of TB cases are shown in Table 1.

Mean of TB incidence rate in this zone was 8.34 cases (per 100,000) for intended period. The incidence of PTB+, PTB−, and EPTB were 3.79, 1.46, and 7.6 cases (per 100,000), respectively.

In this study, total TB incidence rate trend had no breakpoint and CI 95% (−2.4–26) had increased up to 10.9% which is statistically insignificant [Figure 1]. Due to TB incidence rate based on sex, annual percentage changes in men have increased 56.3% during 2005–2015. This increasing trend with a breakpoint (2005–2007) risen 6.551%, which was significant (at $\alpha = 0.05$), and then, during 2005–2015, 4.9% has increased [Figure 2]. Trend analysis of PTB incidence rate increased 18% during 2005–2015 (50% increase in 2005–2007 and 11.1% increase in 2007–2015 and significant association at $\alpha = 0.06$ [Figure 3]. The analysis of EPTB incidence rate observed a decreasing trend (annual change is −7.6%) which is insignificant at $\alpha = 0.05$ [Figure 4]. The PTB+ with changes 11/4% has been a decreasing trend and the trend of PTB− with changes 34/3% has been an increasing trend and their annual variation of trend was insignificant at level of $\alpha = 0.05$ [Figure 5]. In regard to incidence rate of TB in all age groups, highest variation trends

belonged to 75≤ years old and 45–54-year-old groups. The age groups of 25–34 and 55–64 years old had decreasing trend, but the incidence rate variation trend was insignificant for all age groups at level of 95%.

Discussion

This study presented that TB incidence rate increased during 2005–2015. However, the increase was not statistically significant. Based on reports of the Ministry of Health, total incidence rate of TB in Iran during this period has been decreased (1.17%), while in Mazandaran Province, it has increased 4% approximately.[11] A study conducted in Western Iran (Kurdistan Province) observed that incidence rate had decreasing trend during 2000–2012.[14] Another study on Iran showed a decreasing trend during 1998–2009.[12] Glaziou *et al.* reported decreasing trend of incidence, prevalence, and mortality rate of TB in the world during 1990–2015.[15] Based on CDC report of the United States during 1993–2010, the TB incidence rate had been decreasing trend.[16]

In this study, PTB (PTB+ and PTB−) incidence rate had a statistically significant increasing trend, during intended period. This trend, in Mazandaran province, is increasing, but it has been a decreasing in Iran.[11] Another survey in Iran pointed to a decreasing trend in incidence rate of PTB and EPTB during 1995–2012.[17] A study in Southern Tehran showed an increasing trend of PTB+ incidence during 2005–2012.[2] Noeske *et al.* accompanied a study in Cameron reported decreasing trend of PTB+ from 139 to 121 cases per 1000 people during 2006–2014.[18] In a study in Southern India, observed decrease in incidence rate of PTB+ during 1999–2008.[19]

In this study, the trend of TB incidence rate has a significant increasing in men, but in women, a decreasing trend is not statistically significant. In the world, this asymmetry is observed, for example, in Asia, men than women are less likely to infect

Table 1: Characteristics of study participants in Joibar 2005-2015

| Characteristics	n (%)	P		
		PTB positive	PTB negative	EPTB
Sex				
Male	38 (54.3)	0.17	0.98	0.075
Female	32 (45.7)			
Age category				
0-14	4 (5.7)	0.64	0.039	0.8
15-24	12 (17.1)			
25-34	17 (24.3)			
35-44	4 (5.7)			
45-54	9 (12.9)			
55-64	11 (15.7)			
65-74	8 (11.5)			
75+	5 (7.1)			
Job				
Stable job	26 (37.1)	0.8	0.7	0.67
Unstable job or unemployed	44 (62.9)			
Incarceration				
Yes	14 (20)	0.012	0.4	0.032
No	56 (80)			
Addiction				
Yes	19 (27.1)	0.001	0.26	0.006
No	51 (72.9)			
Habitancy				
Urban	36 (51.4)	0.6	0.67	0.9
Rural	34 (48.6)			

PTB: Pulmonary tuberculosis; EPTB: Extra-PTB
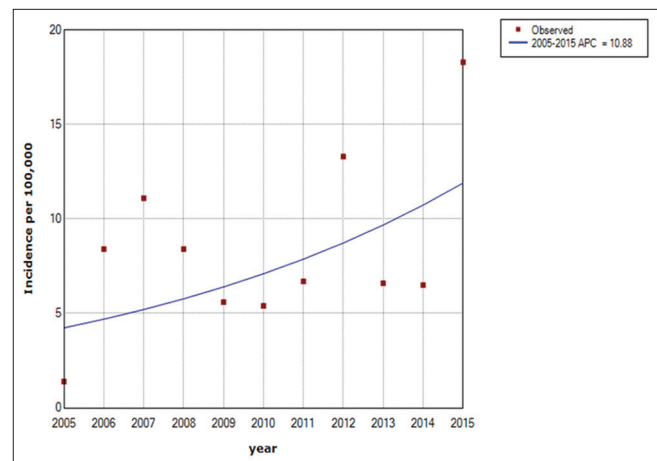
Figure 1: Tuberculosis trend analysis based on all incidence rate in Joibar: 2005–2015
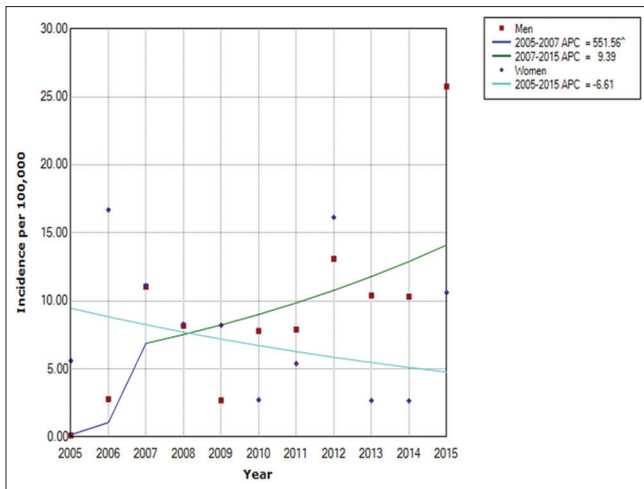
Figure 2: Tuberculosis trend analysis based on sex of incidence rate in Joibar: 2005–2015
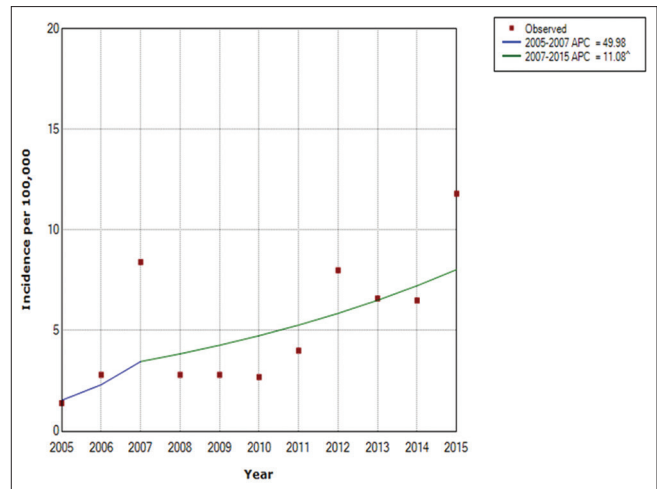

Figure 3: Tuberculosis trend analysis based on pulmonary tuberculosis incidence rate in Joibar: 2005–2015
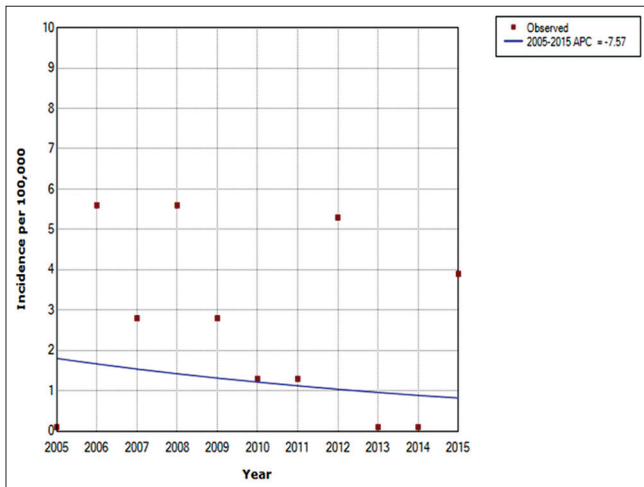

Figure 4: Tuberculosis trend analysis based on extrapulmonary tuberculosis incidence rate in Joibar: 2005–2015
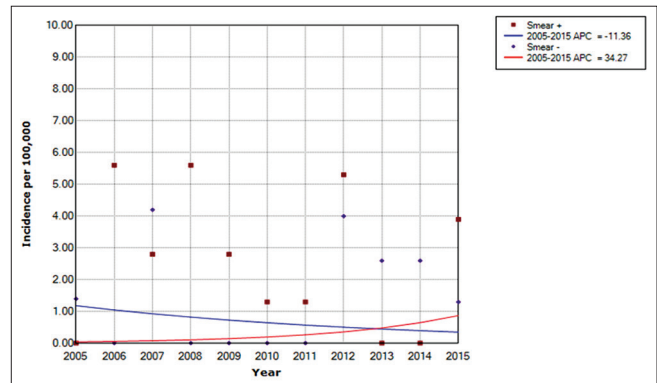

Figure 5: Tuberculosis trend analysis based on PTB+ and PTB- incidence rate in Joibar: 2005–2015

with TB.[20,21] Dangisso *et al.* reported a significant difference in incidence rate between the two sex groups.[22] The study in Khorasan Razavi Province (Eastern Iran) observed that incidence of TB among female is more than male.[23] In this annual report of European Centre for Disease Prevention and Control (ECDC) reported that incidence rate ratio of TB for male to female is 1.7%.[24]

In this study, the trends in TB incidence rate by age groups had a significant association. A study in Western Azerbaijan Province (North Western Iran) showed that the most of the TB cases were aged between 31 and 65 years old during 2001–2010.[25] Age groups of 18-40 and over 60 years old comprised the majority of patients with TB 39.0 and 31.5%, respectively in the health center of Babol County during the years 2009-2013.[26] The ECDC reported increased TB incidence rate in 25–40 years old up to 15.1% (per 100,000). A study in Australia found that highest TB incidence rate, mortality, and disability were observed in 65≤ years old.[27]

In this study, a significant association of PTB+ and EPTB incidence rate with a history of incarceration (at least 1 month during the past year) was observed. Because the inmates in many countries, as high-risk groups to emerging and re-emerging infectious diseases are known, TB cases are considered, as a health and medical problem in prison.[28] The prison risk factors include that overcrowding, malnutrition, high-risk behaviors, addiction, and HIV infection can be mentioned. The TB incidence rate in Iranian prisons is high. As well as, combination of TB and HIV in some cases is impaired the treatment process and caused an increase in the antibiotic resistance.[28] The prevalence of TB in world's prisons usually estimated to be 3–200 times compared to community.[29] A study conducted in Karachi (Pakistan) found that incidence rate of latent TB was about 48% and this issue was the significant association with education level, smoking, and duration of incarceration.[30] A study on the present prisoners of Mazandaran Province found that incidence rate of PTB+ among prisoners is 17.7 times higher than incidence rate of TB in the community.[31] Therefore, by attention to this issue, we need to get serious active surveillance TB in all prisons by the prison health personnel, an initial examination before entering the prisons, and suitable ventilation as a general principle is felt.

In this study, a significant association between TB (PTB+, EPTB) incidence rate and drug use was found. A study by Alavi *et al.* was found, intravenous drug abuse as a risk factor for TB infection in prisoners.[32] In other study, a significant association between drug use and TB infection was found.[33] Other studies in the world also had the same result.[34,35] Babamahmoodi *et al.* by study on clinical and laboratory of 212 TB infected cases found that drug use as a main factor in the incidence and one of the important clinical findings to assess and diagnosis of TB.[36]

According to the results of this study, the rate of case identification was low, and subsequently, the TB incidence rate has a different trend compared to trend in national and around the world, which of the reasons, it can be noted as follows:

1. This zone has getting started independently since 1998. Previously, the health-care system had been regarded by health experts as an out of reach center for offering optimal health care. Therefore, proper infrastructure of health care and means of identifying suspected cases were not available
2. Due to closeness of cities in Northern Iran, especially in this zone, many TB infected cases were diagnosed and treated in adjacent cities, and consequently, there was no register about them in this zone
3. Because of easy access of population to private health-care centers, they not refer to public health care center and then their excluded from Registration and care system. In other words, coordination and interaction between private and governmental health-care centers are very weak
4. In this study, 40% of TB+ cases were identified through hospitals. The system of identification and surveillance of suspected cases through governmental health care in TB case founding performed weakly.

Therefore, despite of recent developments of Iranian governmental health care system in and proper access to it and considering this fact that identification of TB cases with passive surveillance is possible. Hence, developing certain programs for sensitization of the covered population is needed (i.e., referring to the first level of access to health services, if you have suspicious symptoms of TB). Furthermore, improving motivation of staff that provide health services, especially in the first level of health care (to follow-up and care, seriously). Another point is that, training the peer groups (indigenous people of the same Zone) and enlist the executives supports that to strength inspiration of them. This maybe to have much impact on TB identifying and better surveillance.

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Conflicts of interest

There are no conflicts of interest.

References

1. Yazdani-Charati J, Siamian H, Kazemnejad A, Mohammad V. Spatial clustering of tuberculosis incidence in the North of Iran. Glob J Health Sci 2014;6:288-94.
2. Farzianpour F, Kooshad MA. Study of the status of tuberculosis control program based on the implementation of the directly observed treatment short-course strategy (dots). Mater Sociomed 2016;28:249-52.
3. World Health Organization. Tuberculosis. Fact sheet No. 104; 2017. Available from: http://www.who.int/tb/publications/factsheets/en. [Last updated on 27 Dec. 2017].
4. Bennett JE, Dolin R, Blaser MJ. Principles and Practice of Infectious Diseases. Philadelphia: Elsevier Health Sciences; 2014.
5. Huo HF, Zou MX. Modelling effects of treatment at home on tuberculosis transmission dynamics. Appl Math Model 2016;40:9474-84.
6. World Health Organization. WHO Treatment Guidelines for Drug-Resistant Tuberculosis; 2016. Available from: http://apps.who.int/iris/bitstre am/10665/250125/1/97892415 49639-eng.pdf. [Last updated on October 2016].
7. World Health Organization. Global Tuberculosis Control Surveillance, Planning, Financing; 2004. Available from: apps.who.int/iris/ bitstream/10665/42889/2/9241562641.pdf. [Last accessed on 27 Dec 2017].
8. Clark R. Treatment of tuberculosis: Guidelines for national programmes. Perspect Public Health 2010;130:240.
9. Goldberg A, Social CS. Contexts of Social Vulnerability and Health Risks: Tuberculosis in Bolivian Immigrants Who Work and Live in Clandestine Textile Workshops of Buenos Aires; 2016.
10. Mirhaghani L, Nasehi M. National Tuberculosis Program in Iran. Ministry of Health, Nashre Seda; 2002. p. 15-20.
11. CDC. TB_Situation in Iran Department of Tuberculosis and Leprosy Ministry of Health and medical education, Iran; 2016. Available from: http://tb-lep.behdasht.gov.ir/TB_Situation.aspx. [Last accessed on 2018 Jan 15].
12. Kazemnejad A, Arsang Jang S, Amani F, Omidi A. Global epidemic trend of tuberculosis during 1990-2010: Using segmented regression model. J Res Health Sci 2014;14:115-21.
13. Gebreegziabher SB, Yimer SA, Bjune GA. Tuberculosis case notification and treatment outcomes in West Gojjam Zone, Northwest Ethiopia: A five-year retrospective study. J Tuberc Res 2016;4:23.
14. Veisi N, Karimi M, Azadi NA, Rahmani K. Trend of TB incidence rate and its treatment success in Kurdistan, Iran from 2000 to 2012. Sci J Kurdistan Univ Med Sci 2015;20:1-9.
15. Glaziou P, Sismanidis C, Floyd K, Raviglione M. Global epidemiology of tuberculosis. Cold Spring Harb Perspect Med 2015;5:a017798.
16. Centers for Disease Control (CDC). A strategic plan for the elimination of tuberculosis in the United States. MMWR Morb Mortal Wkly Rep 1989;38:269-72.
17. Khazaei S, Soheilyzad M, Molaeipoor L, Khazaei Z, Rezaeian S, Khazaei S, *et al.* Trend of smear-positive pulmonary tuberculosis in Iran during 1995-2012:

A Segmented regression model. Int J Prev Med 2016;7:86.

18. Noeske J, Nana Yakam A, Abena Foe JL. Epidemiology of tuberculosis in Cameroon as mirrored in notification data, 2006-2014. Int J Tuberc Lung Dis 2016;20:1489-94.

19. Subramani R, Gomathy S, Lakshmi M, Swaminathan S. Trend in the incidence of smear-positive tuberculosis in a district in South India after DOTS implementation. Int J Tuberc Lung Dis 2016;20:1022-6.

20. Dogar OF, Shah SK, Chughtai AA, Qadeer E. Gender disparity in tuberculosis cases in Eastern and Western Provinces of Pakistan. BMC Infect Dis 2012;12:244.

21. World Health Organization. Global Tuberculosis Report 2013. Switzerland: World Health Organization; 2013.

22. Dangisso MH, Datiko DG, Lindtjørn B. Trends of tuberculosis case notification and treatment outcomes in the Sidama Zone, Southern Ethiopia: Ten-year retrospective trend analysis in urban-rural settings. PLoS One 2014;9:e114225.

23. Arab Borzou Z, Afzal Aghaei M, Esmaeli H, Samiei A, Jamali J, Mohammadzadelari S. Evaluating related factors with sputum smear negation at the end of the second month of tuberculosis treatment. Med J Mashhad Univ Med Sci 2016; 10:547-54.

24. ECDC. Tuberculosis Surveillance and Monitoring in Europe 2015. European Centre for Disease Prevention Control: ECDC Stockholm; 2015.

25. Rahimi Foroushani A, Farzianpour F, Tavana A, Rasouli J, Hosseini S. The 10-year trend of TB rate in West Azerbaijan Province, Iran from 2001 to 2010. Iran J Public Health 2014;43:778-86.

26. Ghaffari-Fam S, Hosseini SR, Heydari H, Vaseghi-Amiri R, Daemi A, Nikbakht HA. Epidemiological patterns of Tuberculosis disease in the Babol, Iran. J Anal Res Clin Med 2015;3:164-9.

27. Negin J, Abimbola S, Marais BJ. Tuberculosis among older adults – Time to take notice. Int J Infect Dis 2015;32:135-7.

28. Hosseini MJ, Morovvati S, Ghadiani MH, Ranjbar R, Farnia M. Epidemiology of tuberculosis (TB) in the Iran prisons in the first 6 months of 2004. Sci J Forensic 2004;13:7-10.

29. Maher D, Grzemska M, Coninx R, Reyes H. Guidelines for the Control of Tuberculosis in Prisons. World Health Organization; 1998.

30. Hussain H, Akhtar S, Nanan D. Prevalence of and risk factors associated with mycobacterium tuberculosis infection in prisoners, North West Frontier Province, Pakistan. Int J Epidemiol 2003;32:794-9.

31. Moosazadeh M, Amiresmaili M, Parsaei M, Ahmadi M, Jalahi H. Prevalence of tuberculosis among the prisoners of Mazandaran Province-2008: A short report. JRUMS 2012; 4; 309-16.

32. Alavi SM, Ahamadi F, Zargari N. The main risk factors of pulmonary TB patients in Razi hospital 2000-2006. J Gorgan Univ Med Sci 2012;14:106-11.

33. Eufrásio R, Alcobia M, Correia L. Pulmonary tuberculosis epidemiology in Coimbra's District (2000-2011): Information is essential to understand high risk groups. Rev Port Pneumol (2006) 2016;22:245-7.

34. Narasimhan P, Wood J, Macintyre CR, Mathai D. Risk factors for tuberculosis. Pulm Med 2013;2013:828939.

35. Shaler CR, Horvath CN, McCormick S, Jeyanathan M, Khera A, Zganiacz A, *et al.* Continuous and discontinuous cigarette smoke exposure differentially affects protective Th1 immunity against pulmonary tuberculosis. PLoS One 2013;8:e59185.

36. Babamahmoodi F, Alikhani A, Yazdani Charati J, Ghovvati A, Ahangarkani F, Delavarian L, *et al.* Clinical epidemiology and paraclinical findings in tuberculosis patients in North of Iran. Biomed Res Int 2015;2015:381572.