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Trend of Smear-positive Pulmonary Tuberculosis in Iran during 1995–2012: A Segmented Regression Model

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ABSTRACT

Background: Describing trend in tuberculosis (TB) over time can play an important role to assess the disease control strategies and predict the future morbidity and mortality. This study aimed to determine the incidence trend of smear-positive pulmonary tuberculosis (SPPT) in sub-age and sex groups during the years of 1995–2012.

Methods: This retrospective cohort study was performed in 2015 by using the dataset regarding National Statistics of SPPT reported by World Health Organization during 1995–2012. Annual percent changes (APCs) and average annual percent changes (AAPCs) were estimated to determine the summery statistics of trend using segmented regression model.

Results: During 1995–2012, there were 96,579 SPPT case notifications in Iran (male to female ratio: 0.99). There was only one change point in 1997 for SPPT incidence in subgroups of age and sex during 1995–2012. The AAPCs for both genders and also all three age groups had a significant descending trend during the time period ($P < 0.05$).

Conclusions: Our results showed a downward trend in the SPPT incidence. It seems that to achieve the set goals and high successful in TB control program especially reduction in SPPT, pay more attention to old age and males should be considered. In addition, improvement of clinical and medical care services and notification processes would be imperative.

Keywords: Annual percent change, Iran, segmented regression, tuberculosis

INTRODUCTION

Tuberculosis (TB) is the second most prevalent cause of infectious-related mortality right behind HIV/AIDS.[1,2] Despite effective treatment,[3] TB remains as one of the main public health problems around the world.[2,4]

The number of affected people with TB has been reached to 9.6 million in 2014, whereas in the same year, 1.5 million deceased from TB related complications.[1] More than 95% of TB cases and its mortality have occurred in low- and middle-income countries.

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Overall, decrease of mortality and occurrence of TB has become in all six World Health Organization (WHO) regions is in line with the millennium development goals. As a result, compared to year 2000, the proportion of 18% in TB cases and 47% in the mortality between 1990 and 2015 has decreased.[5,6]

Despite international attention to the disease and effective prevention and control programs, still expected success in reducing and controlling TB is not provided. The pandemic of HIV/AIDS is one of the main causes of increasing TB cases.[7] Poverty, population growth, migration, economic and social conditions, diabetes, and malnutrition are other related causes to lack of accepted indicators in the disease detection and successful treatment of TB.[8] In Iran, the disease incidence rate since 1964, from 142 cases per one hundred thousand has reached to 13.71 per one hundred thousand cases in 2013.[9] According to the WHO report in 2015, TB incidence is estimated 22 per hundred thousand people in Iran.[10] The reduction trend of TB incidence varies among various Provinces of Iran. It is expected that various patterns depend on the reduction of TB. Iran is partly surrounded by countries which are regarded among 22 high-burden countries for TB in Eastern Mediterranean Region, such as Afghanistan, Pakistan, and Iraq.[2] On the other hand, newly independent countries of Soviet Union on the North of Iran are facing the problem of multi-drug resistant TB which complicates TB control programs.[7]

Description of the disease trend over time can play an important role to assess the disease control strategies, health development index, predicting the future incidence, and prevalence and also in health planning. Although previous national[11,12] and international[13] reports on the TB incidence trend revealed a decline in the incidence, these studies were limited to the Persian language studies and were related to the past 5 years.[11,12] They also used the data from Iran's Ministry of Health and Medical Education. Therefore, this study, which used the data from the WHO, aimed to determine the incidence of smear-positive pulmonary tuberculosis (SPPT) by sub-age and sex groups in Iran during the years of 1995–2012. The results of the present study provide insights for decision makers to identify effective factors contributing on TB control programs, as well as comparisons of National TB Program (NTP) with WHO strategies.

METHODS

Study design and dataset

This retrospective cohort study was performed in 2015. Due to the notification legislation in almost all countries around the world, NTPs are mandated to monitor and notify TB cases as a routine practice.

The data of TB cases were reported to WHO annually. We used dataset regarding National Statistics of SPPT reported by WHO during 1995–2012. Directive of integration TB control program in the Public Health Network system was communicated to all provinces of the country in 1991. In 1995, according to the international recommendations, Directly Observed Treatment Short (DOTS) strategy for TB program was notified to all medical universities. Then with the introduction of DOTS II strategy in the world, TB control strategy in the country was adapted with this program. According to the NTP, a case of TB should has definite criteria including microscopic positive sputum-smear (at least two), microscopic positive sputum-smears along with culture positive sputum-smears, or microscopic sputum-smears along with pathologically active TB on chest X-ray.

Procedures

Segmented analysis was used because of nonconstant trend of TB over time period. The model assumption is that the change in trend would be constant within each time segment (e.g., change points) and varies between different time segments.

Therefore, the trend and number of change points are as independent variables and are determined by segmented regression with at most three change points for the entire time period of 18 years (1995–2012). The number of change points is defined based on the time period.[14] The incidence rate of SPPT per 100000 by sex and age groups was considered as dependent variable.

Statistical analysis

We also estimated the annual percent changes (APCs), a way to measure trends of disease over time, and average annual percent changes (AAPCs), an index for trend and the interval of years, to determine the summery statistics of trend.

APC again assumes constant incidence rate within each time segment (change points). The annual constant change in the rate is linearly done based on natural log scale of the rate. The following regression model was used to estimate the APC:

Log (Ry) = $b_0 + b_{1y}$, where Log(Ry) is the natural log of the rate in year y. In addition, the APC from year y to year $(y + 1)$ is:

$$\left[\frac{R_{y+1}-R_y}{R_y}\right]\times 100 = \left[\frac{e^{b_0+b_1(y+1)}-e^{b_0+b_1(y)}}{e^{b_0+b_1(y)}}\right]\times 100$$

$$= \left(e^{b_1}-1\right)\times 100.$$

AAPC provides a summary measure of trend over fixed time intervals. It also uses a value as the average APCs over years and is valid even when the join-models indicates some changes. Estimation of AACP is based on a weighted average on ACPs from join-models, with

weights proportional to length of APC intervals. The following equation is used to estimate the AAPC:

$$\text{AAPC} = \left\{\exp\left(\frac{\sum w_i b_i}{\sum w_i}\right) - 1\right\} \times 100.$$

That $b_i s$ are the slope coefficients for each segment in the desired range of years, and the $w_i s$ are the length of each segment runs in the range of years.[15,16] Bayesian information criteria was used to select the number of change point and model selection.

Joinpoint software version 3.5.1 (National Cancer Institute, USA) was used to perform statistical analysis. A $P < 0.05$ considered as statistically significant level.

RESULTS

During 1995–2012, there were 96579 SPPT case notifications in Iran (male to female ratio: 0.99). Of them, 19.5% were 0–14 years, 70.9% were 15–65 years old, and the rest were over 60 years of age. Table 1 shows the incidence rate of SPPT by age groups and sex during 1995–2012.

Table 1: Incidence rate (per 100,000 populations) of smear-positive pulmonary tuberculosis by age groups, sex, and years of study in Iran

Year	Age groups (year)			Sex		Overall
	0-14	15-64	+65	Male	Female	
1995	1.50	21.62	64.73	14.70	16.38	15.54
1996	0.76	11.86	40.55	8.64	9.11	8.88
1997	0.64	10.93	41.92	8.52	8.48	8.50
1998	0.54	10.53	37.47	7.94	8.13	8.03
1999	0.35	9.56	40.42	7.46	7.85	7.66
2000	0.49	10.06	41.08	7.88	8.41	8.15
2001	0.66	9.92	41.46	7.95	8.56	8.25
2002	0.50	9.19	41.96	7.81	7.97	7.89
2003	0.52	8.41	42.17	7.59	7.45	7.52
2004	0.40	7.81	38.18	7.30	6.90	7.10
2005	0.30	7.00	36.61	6.88	6.21	6.54
2006	0.30	6.98	39.60	6.99	6.54	6.76
2007	0.27	6.58	38.94	6.63	6.43	6.53
2008	0.28	6.27	40.29	6.56	6.38	6.47
2009	0.32	6.72	42.25	6.97	7.14	7.06
2010	0.39	6.48	42.92	6.80	7.22	7.01
2011	0.28	6.83	44.56	7.43	7.34	7.39
2012	0.33	6.55	41.90	7.41	6.82	7.12

According to Table 2, there is only one change point in 1997 for SPPT incidence in subgroups of age and sex during 1995–2012. AAPC for both genders and also all three age groups have a negative sign that shows decreasing trend during these period of time ($P < 0.05$). AAPC of TB incidence for females (AAPC = −4.7) compared to men (AAPC = −3.9) was far more than zero. In age groups, the maximum decrease of estimated AAPC is attributed to age group 0–14 years (AAPC = −9.1) and the minimum value is attributed to age over 65 years (AAPC = −2).

However, according to last segment (1997–2012) which are shown in Table 3, there is a mild decreasing slope of incidence rate. As far as in age group over 65 years, this trend has been reversed (APC = 0.24). The results of APC and estimated trends for all SPPT incidences by sex and age groups are shown in Figures 1 and 2.

DISCUSSION

In the present study, the incidence trend of SPPT over an 18-year period (1995–2012) in Iran was evaluated which has been changed in this period.

According to the results, the trend of SPPT through all ages and in males and females has significantly decreased in 1997 which these findings consistent with the results of other studies.[10,11,13] Another similar study conducted in Iran showed the decreasing trend in the incidence rate of TB after year 1992. This study indicated that one reason may be the successful implementation of TB programs in Iran.[11] Although the incidence trend of TB is declining nationally, but the results of province studies might be difference. A study conducted in Hamadan Province, Western Iran, to determine the epidemiological status of TB over a 7-year period, demonstrated that the incidence rate of all TB classifications has increased significantly during the study period.[17]

With regard to the implementation of the DOTS strategy in 1995 in Iran and also in many other countries around the world; therefore, it can be noted that by the implementation of this strategy, many patients with SPPT after a treatment period, they were completely

Table 2: Number and local of change points and average annual percent changes in smear-positive pulmonary tuberculosis incidence

	Sex		Age groups (year)		
	Male	Female	0-14	15-64	+65
Number of change points (year)	1 (1997)	1 (1997)	1 (1997)	1 (1997)	1 (1997)
AAPC TB incidence	−3.9* (−5.6, −2.2)	−4.7* (−7.4, −2)	−9.1* (−15.6, −2)	−6.4* (−9.6, −3)	−2* (−3.7, −0.3)
P	<0.05	<0.05	<0.05	<0.05	<0.05

*AAPC is significantly different from zero at α=0.05. AAPC=Average annual percent change, TB=Tuberculosis

Table 3: Annual percent changes in smear-positive pulmonary tuberculosis incidence in two change points by sex and age groups

Year	Sex		Age groups (year)		
	Male	Female	0-14	15-64	+65
1995-1997					
Slope	−2.9	−3.6	−0.043	−5	−10.8
P	<0.001	<0.001	0.005	<0.001	0.002
1997-2012					
Slope	−0.06	−0.09	−0.18	−0.24	0.24
P	0.02	0.024	0.006	<0.001	0.07

and successfully cured. Thus, we prevented from the spreading the disease to other individuals and its spread in the community and therefore a significant decline was found in the incidence trend of SPPT in Iran and other countries. So that after the implementation of global DOTS strategy as a direct measurement of TB intensity control to measure and identify smear-positive TB cases, the results of various studies have reported a significant decrease in the TB incidence. As a result, five countries have experienced more than 10% reduction in the TB incidence due to the implementation of DOTS strategy.[18] On the other hand, sharp decreasing trend in 1995–1997 years could be due to consequences of predisposing factors such as increased primary health cares, reducing of immigrants and the persistence of TB treatment in the country. Political and social changes in the neighboring countries, particularly Afghanistan (Afghan Civil War in 1992–1996) caused enormous Afghan refugees into Iran during the years of war in Afghanistan. Forasmuch as TB is closely associated with poverty, malnutrition, overcrowding and inadequate housing.[19] Therefore, immigrants and refugees are considered as the groups at higher risk of TB.[20] Some of high incidence rate of SPPT in 1995 can be attributed to this subject. In a study conducted in Italy, immigration and AIDS created two onward in the trend of TB in 1988 and 1996, respectively.[21]

According to the results in this study, the SPPT incidence rate at the beginning period of assessment was higher in women than men, but this trend, at the end of period, increased in men. Arsang *et al*.[12] in an investigation on TB epidemiology in Iran during 2001–2008 reported the decreasing incidence trend of TB among women and the increasing trend for both sexes over 65 years of age. However, studies conducted in Ethiopia[22] and Bhutan[23] showed that the incidence rate of SPPT in men were always more than women. The higher incidence rate of SPPT in women than in men can be attributed to several factors. For example, women are more sensitive about their health status and with onset of disease symptoms, they refer to health centers. Accordingly, early diagnosis

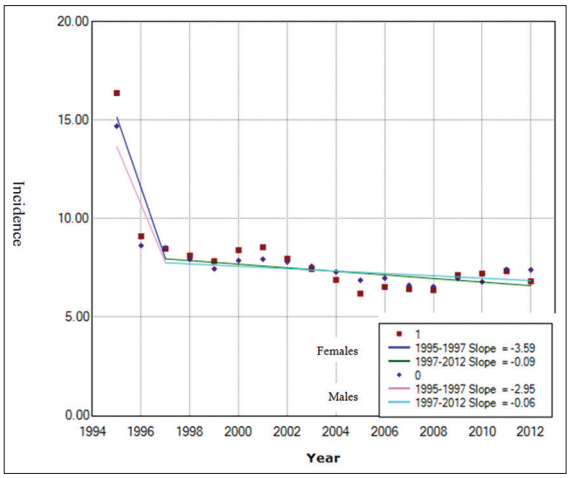

Figure 1: Trend and annual percent change smear-positive pulmonary tuberculosis incidence rate in Iran, by sex during 1995–2012

and treatment will be started among women. Gender differences due to health related outcome, as a possible another reason in this regard, has been reported.[24] On the other hand, the increasing of public awareness in terms of TB disease and improving health care services in our country could be important factors to increase the trend of identifying SPPT among men. Moreover, according to social and cultural conditions in which men have more outside occupation of the house than women and they are in the crowded places, they might be more likely exposed to *Mycobacterium tuberculosis*. Another reason about this finding should be considered that men are at a greater risk of HIV compared to women due to some high risk behaviors such as unsafe injection drug. HIV infection increases the risk of TB several more times[25] and then the increasing rate of SPPT in men is explainable compared to women.

The results of this study suggest that the SPPT incidence rate in 0–14 and 15–64 year age groups have downturn trend. In the age group over 65 years, the rate has significantly decreased in the first point of period (1995–1997) but in the end of that (1997–2012) had upward trend. This finding is homogenous with findings of Saudis studies,[26,27] but does not consistent with the results of studies which conducted in Zambia[28] and Butane.[23] To explain these findings, we should consider variety of factors including age-related diseases (e.g., malignancy and diabetes), poor nutrition, immunosuppression, chronic renal failure, that is the increasing result of TB risk in older people.[29]

This study had some limitations. Because of lack of access to data, changes in trend of some indices of SPPT (such as; treatment success rate, case detection rate, failure in treatment rate, SPPT mortality rate) and also by separate provinces were not assessed. Another limitation of the study is failure to examine the effect

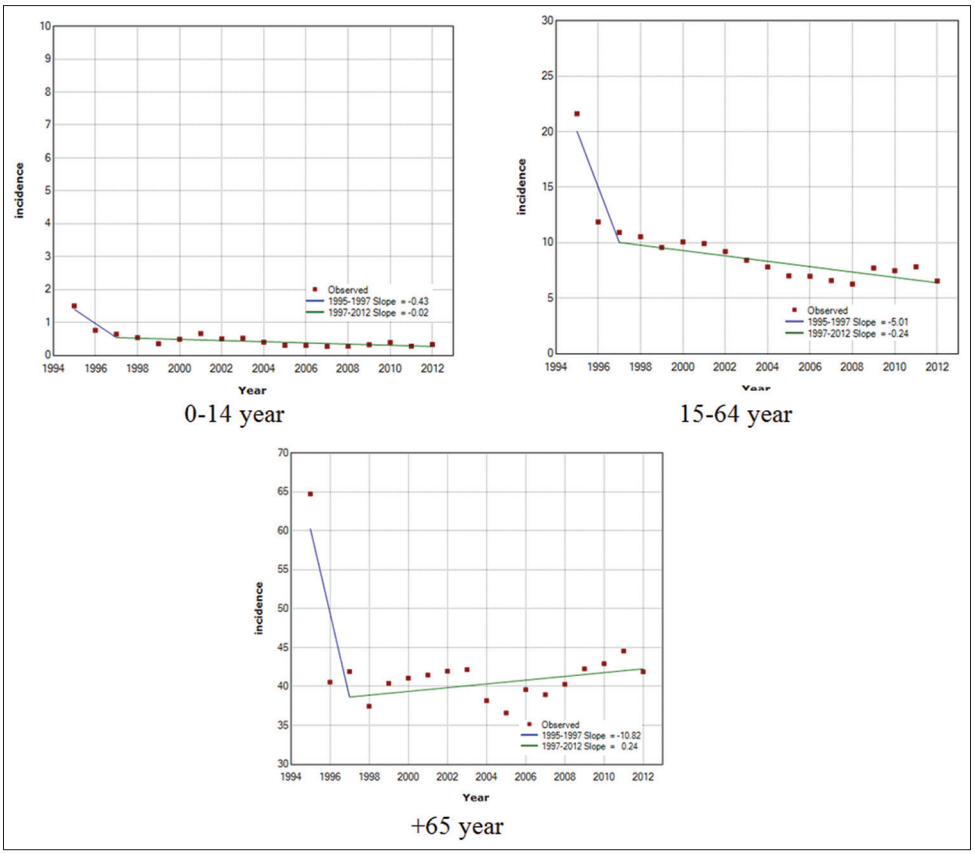

Figure 2: Trend and annual percent change of smear-positive pulmonary tuberculosis incidence rate in Iran, by age groups during 1995–2012

of related factors on the TB incidence such as HIV co-infection, ethnic groups, geographical regions, and individual's socioeconomic status. It is recommended that these issues can be considered in future studies. The third limitation is the under reporting of the cases because of passive surveillance system for TB control program, especially in small cities.

CONCLUSIONS

According to the results of this study, a downward trend in the SPPT incidence was seen after the implementation of DOTS strategy and the results might be due to the success of the strategy. Accordingly, the program should continue with more sensitivity and accuracy in the country. It seems that to achieve the set goals and high successful in TB control program, especially reduction in SPPT, pay more attention to old age and males should be considered. In addition, improvement of clinical and medical care services and notification processes would be imperative.

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Conflicts of interest
There are no conflicts of interest.

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