Tanaffos (2010) 9(3), 15-21

Spatial Distribution of Tuberculosis in Mazandaran Province–Iran: Spatiotemporal Modeling

Jamshid Yazdani Charati, Anoshirvan Kazemnegad
Biostatistics Department, Medical Science Faculty, Tarbiat Modares University, TEHRAN-IRAN.

ABSTRACT

Background: *Incidence of Tuberculosis (TB) in Golestan province is higher than its national incidence rate in Iran (about 13 in 100,000). Considering the proximity of Mazandaran to Golestan this survey was conducted to determine the high risk areas in Mazandaran province.*

Materials and Methods*: This was an observational, longitudinal, ecological study conducted during the years 1999 to 2008. Our understudy cases were 2,444 TB patients registered in the TB center of Mazandaran province. Collected data including patients' age, gender, type of disease and residential location were analyzed using descriptive statistical methods and Nested Poisson regression models.*

Results: *Of 2,444 registered patients, 1,283 (52.5%) were males and 1,161(47.5%) were females; among which, 61% were urban and 39% were rural residents. A total of 96.4% of them were Iranian. No significant difference was observed in TB incidence between the two genders, but incidence of TB in the cities of Tonekabon and Behshahr was 30% higher than the mean incidence rate of this province (P<0.05). Risk of contracting TB infection was 1.46 times greater in urban compared to rural areas (95% confidence interval=1.35-1.59).*

Conclusion: *No significant difference was detected between our study results and those of similar studies conducted in Gilan and Golestan provinces. Higher incidence of TB in Behshahr and Tonekabon compared to the mean incidence of the province is indicative of the spatial correlation of the disease. Lower incidence of TB in neighboring cities might be due to delayed detection of smear-positive pulmonary TB patients.* ***(Tanaffos 2010; 9(3): 15-21)***

Key words: *Tuberculosis, Spatiotemporal pattern, Incidence rate, Mazandaran province, Poisson regression*

INTRODUCTION

Tuberculosis has been among the most important causes of morbidity and mortality for many years. It still ranks 7th in the list of diseases responsible for 25% of preventable deaths in the world (1).

Correspondence to: Kazemnegad A
Address: Biostatistics Department, Medical Science Faculty, Tarbiat Modares University, Tehran-Iran.
Email address: Kazem_an@modares.ac.ir
Received: 1 March 2010
Accepted: 18 May 2010

TB infection is caused by various strains of mycobacteria including *Mycobacterium tuberculosis*, *Mycobacterium africanum* and *Mycobacterium bovis* and is manifested as pulmonary or extra-pulmonary tuberculosis. About 85% of TB cases are pulmonary while 15% are extra-pulmonary tuberculosis. Extra-pulmonary tuberculosis may involve the spinal cord, kidneys, skin, gastrointestinal tract, lymph nodes, genitourinary system and etc. However, pulmonary

TB is much more important because it is the source of infection in the community. Routes of transmission include the inhalation of air when a TB patient coughs, sneezes or spits and use of infected dairy products (*Mycobacterium bovis*). The infectious dose of tuberculosis is very low and inhaling less than ten bacteria may cause an infection. A third of the world's populations are thought to be infected with *M. tuberculosis* (about 2 billion people). However, every person infected with TB bacilli is not necessarily sick. Body's immune system fights the disease. But if the immune system is compromised due to old age, use of immunosuppressive drugs or etc. about 5 to 10% of those with latent TB infection develop active tuberculosis at some point in their lives. An untreated TB patient can affect about 10 to 15 people annually. After the discovery of TB bacilli by Robert Koch, the German physician, and administration of BCG vaccination, incidence of TB was limited to a great extent. However, it is still considered a major cause of morbidity and mortality in low/moderate- income countries especially African countries (1-3). Due to the growing incidence of AIDS and MDR-TB, the World Health Organization in 1994 declared TB a "global emergency". According to a report by the WHO, only in 2007, 9,270,000 cases contracted TB worldwide (1,4-7). TB is the most important cause of death in AIDS patients and therefore it is still a health hazard. Every 10 seconds, a person dies as the result of TB infection. According to the WHO reports, 80% of TB patients live in 22 countries among which Afghanistan and Pakistan are Iran's eastern neighbors (2,8-10). Iran's northern neighbors, the Middle East countries also have MDR-TB cases. Iraq, our western neighbor has had an ascending incidence of TB due to the political issues and government change during the recent years (6,7,9-14). Therefore, TB is still considered a critical health priority in our country. According to a report by the Center for Disease Control affiliated to the Health Deputy of the Ministry of Health, there are about 10,000 new TB cases annually in our country half of which belonging to the age range of 15-45 which are considered occupationally active citizens. The national incidence of TB is 13 in 100,000 individuals. This rate is the highest in Sistan, Balouchestan and Golestan provinces. Since Mazandaran province neighbors Golestan province, this study aimed at epidemiologic evaluation of TB in Mazandaran province and detection of high risk areas. Our study results may be used by health authorities and strategy planners for designing and implementation of interventional TB control programs.

MATERIALS AND METHODS

This was an observational longitudinal ecological study conducted during 1999-2008 in Mazandaran province. The names and contact information of all patients presented to the medical centers affiliated to Mazandaran and Babol Universities of Medical Sciences were extracted from the TB registry (according to the rules and regulations of the ethics committees of Mazandaran University of Medical Sciences and Tehran Tarbiat Modarres University).

Patients suspected of having TB (who had TB signs and symptoms) were diagnosed according to the sputum smear test and pathological examinations by the physicians of the health centers or private clinics and were referred to TB registry centers for medical treatment. All the data regarding 2,444 TB patients who were suffering from various forms of TB were collected from 16 areas in Mazandaran province during 10 years. Age, sex, type of disease, time of diagnosis and residential location were evaluated. The mean age, male to female ratio, and urban to rural ratio were evaluated for each city for every understudy year. To evaluate the correlation between the above mentioned variables and incidence of TB both single variable and multivariable Nested Poisson Regression Models

were used (after applying the offset correction terms to city population). For single variable analysis P<0.01 and for multivariable analysis P<0.05 were considered significant. STATA Ver.10 software was used for data analysis.

RESULTS

Of 2,444 registered TB patients in this study, 1,283 (52.5%) were males and 1,161 (47.5%) were females. There were 61% urban and 39% rural residents. Also, 96.4% were Iranians and the remaining were Afghans. The mean age of male and female TB patients was 47.5±20 and 46.3±21.16 yrs, respectively. The 10-year incidence of TB in Mazandaran province was 10.69 in 100,000 individuals. The highest incidence rate belonged to Behshahr with 19.39 in 100,000 while the lowest rate belonged to Jooybar with 6.44 in 100,000. Also, incidence of TB in urban areas was 1.46 times greater than in the rural areas (95% confidence interval=1.1-35.59. P≤0.05).

For spatiotemporal modeling and evaluating the effect of variables like the mean age, location, male to female ratio and registration date on TB incidence, first single variable and then multivariable Nested Poisson regression analysis was used. As seen in Table 1, no significant difference was detected between the TB incidence rates based on different registration dates and the reference year (1999 was considered the reference year). For evaluation of the incidence rate based on the location, incidence of TB in Amol was considered the reference rate. TB incidence was 1.3 times the reference in Behshahr (95% CI=1.022-1.686, P≤0.033), 1.31 times the reference in Tonekabon (95% CI=1.020-1.688, P≤0.034) and 0.62 times the reference rate in Neka (95% CI=0.48, 0.81, P≤0.001).

As demonstrated in Tables 2 and 3, no significant difference was seen regarding male/female ratio or registration date (year) using multivariable Nested Poisson regression analysis.

Table 1. Single variable analysis (rates and 95% CI).

Risk factor	Rates	95% Confidence Interval		P-value
		Low	High	
Amol	1	1	1	Reference city
Babolsar	0.851263	0.666401	1.087407	NS
Behshahr	1.306151	1.022504	1.668483	0.033
Tonekabon	1.312213	1.020166	1.687865	0.034
Jooybar	0.837015	0.604241	1.159461	NS
Chaloos	0.767388	0.585505	1.005771	0.055
Ramsar	1.150647	0.900769	1.469841	NS
Sari	0.887442	0.677114	1.163103	NS
Savadkooh	0.940956	0.725438	1.2205	NS
Babol	1.078993	0.844676	1.378311	NS
Ghaemshahr	1.078649	0.778677	1.49418	NS
Galoogaah	1.133944	0.87426	1.470764	NS
Mahmoodabad	1.050127	0.822079	1.341437	NS
Neka	0.628757	0.48475	0.815546	0.00
Noor	0.829697	0.633046	1.087435	NS
Noshahr	0.957932	0.749905	1.223666	NS
Mean age	0.99855	0.992326	1.004812	NS
Male/female ratio	1.00005	0.999955	1.000144	NS

Table 2. Multivariable analysis (regression indices and confidence intervals for the variables except for the registration date)

Risk factor	Values	95% CI		P-value
		Low	High	
Male/female ratio	1.0001	0.999631	1.000568	NS
Mean age	0.994212	0.988594	0.999863	0.045
Babolsar	0.815389	0.676125	0.983337	0.033
Behshahr	1.290065	1.074087	1.549472	0.006
Tonekabon	1.316688	1.089639	1.591046	0.004
Jooybar	1.03689	0.782609	1.37379	NS
Chaloos	0.768301	0.622594	0.948107	0.014
Ramsar	1.119909	0.929082	1.349931	NS
Sari	1.145687	0.922708	1.422549	NS
Savadkooh	1.021937	0.830329	1.25776	NS
Babol	1.015916	0.817477	1.262524	NS
Ghaemshahr	1.159037	0.904351	1.48545	NS
Galoogaah	1.186548	0.943094	1.492849	NS
Mahmoodabad	1.026783	0.851171	1.238629	NS
Neka	0.764184	0.614767	0.949916	0.015
Noor	0.808192	0.649662	1.005407	0.056
Noshahr	0.952209	0.785952	1.153636	0.617

Table 3. Multivariable analysis (regression indices, and CI for the understudy year).

Risk factor	Values	95% CI		P-value
		Low	High	
2000	0.911866	0.72325	1.149673	NS
2001	1.024179	0.805949	1.301501	NS
2002	0.992521	0.793465	1.241515	NS
2003	0.920088	0.736576	1.14932	NS
2004	0.860651	0.68896	1.075128	NS
2005	0.873845	0.697542	1.09471	NS
2006	0.859395	0.68693	1.07516	NS
2007	0.827235	0.659908	1.036988	NS
2008	0.895588	0.718556	1.116234	NS

However, significant differences were found in the mean age (P=0.994, CI=0.988, 0.999, P≤0.045) and TB incidence rate in Babolsar which was 0.815 times the rate in Amol (CI=0.67-0.97,P≤0.033), Behshahr (1.29 times the rate in Amol, CI=1.07-1.54, P≤0.006), Tonekabon (1.31 times the incidence rate in Amol, CI=1.08-1.59, P≤0.004), Neka (0.76 times the rate in Amol, CI= 0.61-0.95, P≤0.015), and Noor (0.8 times the rate in Amol, CI=0.64-1, P≤0.05). No significant difference was detected in the TB incidence rates of other cities in this province in comparison with that of Amol.

DISCUSSION

The 10-year incidence rate for detected TB cases was 10.69 in Mazandaran province which was smaller than the national incidence rate (13.4/ 100,000 in the year 2008), eastern neighbor Golestan province TB incidence rate (44.8) and western neighbor Gilan province incidence rate (15.7). After Sistan and Balouchestan, Golestan province had the highest incidence rate for TB in the country (15). The mean age of patients was 47 years and no significant difference was found in this regard between both sexes. No significant difference was found in the mean age of patients in Mazandaran province and that of neighboring provinces (Golestan and Gilan). However, mean age of patients in our study was significantly different than that of a study conducted in Ardebil (16-18). The mean age of patients in Ardebil was 5 years younger than that of Mazandaran patients (P≤0.05) which is indicative of different age pattern of disease in different areas. In comparison with some other studies, an age pattern similar to that of Mazandaran province was observed among European countries (3). Increased mean age of patients is indicative of improved health care and successful TB control programs implemented by the Ministry of Health especially during the last 15 years. However, about 75.7% of understudy patients were under the age of 65 who comprise the economically active part of the society and it results in economical problems because a TB patient cannot work for at least 3-4 months and this rate is in accord with other studies (19,20). About 50% decrease in the incidence of TB in rural areas shows a more efficient health care service and better economical status in the rural areas compared to the cities and urban areas. Our results in this regard were not in agreement with those of a study conducted in Sistan and Balouchestan province which might be due to different environmental conditions, dust and sand storms all year long and different economical status of Sistan and Balouchestan (21). Role of environmental conditions in the development of TB has well been understood. In the past, TB patients would be taken to places with lots of sunshine and fresh air. Also, numerous studies have been conducted on the effect of dust on the development of TB and have demonstrated that incidence of disease is significantly higher among those exposed to dust. This is among the main reasons why incidence of TB is higher in desert areas compared to the other parts of the country. Ecological changes during the recent years have resulted in the development of increased dusty conditions in other areas of the country which might be considered as a probable cause for the increasing incidence of TB (22,23).

Tables 1, 2 and 3 demonstrate the single and multivariable analyses of the effect of different variables on the incidence of TB. Incidence of TB in Amol was almost similar to the mean incidence of TB in Mazandaran province. Therefore, this rate was considered the reference incidence rate and the year 1999 was considered the reference year. TB incidence in Behshahr and Tonekabon was about 30% higher than the mean incidence of Mazandaran province. These rates were higher than the national mean incidence of TB as well. This is indicative of the spatial correlation of TB dissemination since these cities are adjacent to Golestan and Gilan provinces, respectively. Lower incidence of TB in these cities in comparison to the adjacent areas in the above mentioned provinces might be due to the failure in detection of TB patients especially those with smear positive pulmonary tuberculosis because they are the source of TB dissemination. Incidence of TB in Neka, Noor and Chaloos was significantly lower than the mean incidence of TB in Mazandaran province. However, if we focus on various districts of these cities, down town area of Neka city is also considered a high risk area. On the other hand, HezarJarib is a mountain top area in Neka which has a lower incidence of TB due to its favorable weather, clean air and healthy nutrition of its inhabitants and therefore, the mean incidence rate of TB for Neka decreases. In the other 2 cities mentioned above, incidence of TB was homogenous in different city districts. Incidence of TB in other cities of Mazandaran province especially those located in the central area of this province showed no significant difference with that of Amol. For a better assessment, authors divided the mazandaran province into eastern, western and central areas. The eastern and western areas have a higher incidence of TB as the result of neighboring Golestan and Gilan provinces. Table 2 indicates the significant correlation of the mean age of patients with the incidence of TB in each city. Considering the incidence rate <1, we can conclude that incidence of TB decreases by increased mean age. The reason may be the improved financial status of families which per se results in improved quality of nutrition and consequently a stronger immune system. A study performed in Ahwaz evaluated the effect of vitamin D3 deficiency on the development of TB and found a significant correlation in this regard. The role of nutrition in body defense against infectious diseases has well been understood and cannot be ignored (24). As seen in Table 3, no significant difference was found in the incidence of TB among the study years. One reason may be the increased case detection rate. However, by using descriptive statistical analysis, an insignificant decrease is seen in TB incidence rate which can be due to appropriate interventions such as BCG (Bacillus Calmette-Guerin) vaccination of children and implementation of DOTS (Directly Observed Treatment, Short course chemotherapy) strategy in treatment of patients. A big problem against treatment and eradication of chronic infectious diseases like TB is that the medical staff are not familiar with the signs and symptoms of disease which results in delayed diagnosis. This is especially important in smear positive pulmonary tuberculosis patients because they are the main source of disease dissemination. If a smear positive pulmonary tuberculosis patient is not detected and treated in time, he/she can infect 15 individuals per year. According to the reports by the Ministry of Health, the national case detection rate in Iran is about 61%; and there is still a 9% gap to reach the goal of 70% formulated by the WHO. A compromised immune system can result in the development of disease. An intact immune system attacks the microorganisms. However, in case of breached or compromised immunity as in AIDS,

diabetes, acute renal diseases, silicosis, head and neck neoplasms, long-term use of immuno-suppressive drugs and alcohol consumption, the immune system is defeated and the infectious disease occurs (25). Therefore, more attention should be paid to above mentioned conditions especially AIDS which has resulted in the emergence of new TB cases in many countries. All TB patients should be evaluated for HIV and AIDS. In this study, 89.2% of TB patients detected in Mazandaran province in the year 2008 were not evaluated for HIV. Only 25 TB cases were examined in this regard out of which 3 were HIV positive. A higher percentage of HIV positive patients would be detected if all TB patients had been examined. Clearly, underlying conditions should be taken care of first in order for us to control TB and people should be educated regarding the routes of transmission for these conditions through the media. Also, laboratories and pathology departments should be well equipped in order to achieve more efficient diagnoses and treatment of patients.

CONCLUSION

Extensive efforts and efficient actions are required in order to achieve the most important goals of the century which are to reduce TB prevalence and related deaths by 50% till the year 2015 in comparison to the year 1990 and eradication of TB by the year 2050 (decreasing the incidence of disease to less than 1 in a million)(1).

These efforts should include better case detection, familiarizing the personnel and medical staff with the signs and symptoms of TB, and equipping the laboratories for more efficient, rapid diagnoses. An important action that can be undertaken in the elderly for prevention and early diagnosis of TB is the regular examination and follow up of diabetic and AIDS patients as well as those with acute renal diseases and head and neck neoplasms for detection and treatment of those with passive tuberculosis.

Acknowledgement

The authors would like to thank all the fellow coworkers in the Center for Disease Control affiliated to the Health Deputy of Mazandaran University of Medical Sciences and Health Services who cooperated sincerely in the conduction of this research project.

REFERENCES

1. WHO. World Health Organization Global tuberculosis control surveillance, planning, financing. WHO 2006 [cited Jul 18]; Available from: http://www. who.int/ tb/ publications/global_report/2004/en/index.html
2. Tuberculosis (TB) Diagnosis. National Institute of Allergy and Infectious Diseases 2008 [cited 2008 Dec. 20]; Available from: http://www3.niaid.nih.gov/topics/tuberculosis/ Understanding/diagnosis.htm
3. WHO. Global Tuberculosis Control - Surveillance, Planning, Financing. WHO Report 2009
4. Maartens G, Wilkinson RJ. Tuberculosis. ***Lancet*** 2007; 370 (9604): 2030- 43.
5. Bass JB Jr, Farer LS, Hopewell PC, O'Brien R, Jacobs RF, Ruben F, et al. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society and The Centers for Disease Control and Prevention. ***Am J Respir Crit Care Med*** 1994;149 (5): 1359- 74.
6. Gutierrez MG, Master SS, Singh SB, Taylor GA, Colombo MI, Deretic V. Autophagy is a defense mechanism inhibiting BCG and Mycobacterium tuberculosis survival in infected macrophages. ***Cell*** 2004; 119 (6): 753- 66.
7. Wieland CW, Florquin S, Chan ED, Leemans JC, Weijer S, Verbon A, et al. Pulmonary Mycobacterium tuberculosis infection in leptin-deficient ob/ob mice. ***Int Immunol*** 2005; 17 (11): 1399- 408.
8. Diagnosis of Tuberculosis Disease. Centers for Disease Control and Prevention. 2008 [cited Dec. 20; Available from:http://www.cdc.gov/tb/pubs/tbfactsheets/diagnosis.htm.

9. Harries AD. Integration of operational research into National Tuberculosis Control Programmes. ***Tuberculosis (Edinb)*** 2003; 83 (1-3): 143- 7.
10. Porter JD. Geographical information systems (GIS) and the tuberculosis DOTS strategy. ***Trop Med Int Health*** 1999; 4 (10): 631- 3.
11. Haas DW. Mycobacterial diseases. In: Mandell GL, Bennett JE, Dolin R, editors. Mandell, Douglas, Bennett's principles and practice of infectious diseases. Vol 4, 5th ed. Philadelphia: Churchill Livingstone; 2000, pp. 2576-607.
12. Riley LW. Microbiology and pathogenesis of tuberculosis. [cited 2008 Dec. 22]; Available from: http://www.uptodate.com/home/index.html
13. Vassler JH. Mycobacterium tuberculosis and other non-tuberculosis mycobacterium. In: Mahon CR, Manuselis G, editors. Textbook of diagnostic microbiology. 2nd ed. Philadelphia: W.B .Saunders 2000:692-5.
14. WHO 1997. Treatment of Tuberculosis. Guideline for national programs.
15. Health Ministry of Iran. General Report of Tuberculosis. 1388 [cited; Available from: http://www.cdc.hbi.ir/Iran_global_tb_map.html
16. Amani F, et al. Epidemiologic survey of Tuberculosis Disease in Ardebil, between 2002 and 2005 Medical survey. ***Journal of Ardebil Medical Science University*** 2007; 7 (3): 236- 41.
17. Rafiee S, et al. Smear positive pulmonary tuberculosis in Golestan province 18th national congress on tuberculosis . Sanandaj-Iran 2007.
18. Resaii A, et al. Tuberculosis epidemiology in Gillan. 18th National Congress on Tuberculosis. Sanandaj-Iran 2007.
19. M'Boussa J, Yokolo D, Pereira B, Ebata-Mongo S. Flare- up of TB due to war in Congo. The International Journal of Tuberculosis and Lung Disease 2002; 6 (6) : 475-478(4).
20. Blumberg HM. Treatment of latent tuberculosis infection: back to the beginning. ***Clin Infect Dis*** 2004; 39 (12): 1772-5.
21. Khazaei HA, Rezaei N, Bagheri GR, Dankoub MA, Shahryari K, Tahai A, et al. Epidemiology of tuberculosis in the Southeastern Iran. ***Eur J Epidemiol*** 2005; 20 (10): 879-83.
22. Taguchi O, Saitoh Y, Saitoh K, Fuyuki T, Shida H, Mishina M, et al. Mixed dust fibrosis and tuberculosis in comparison with silicosis and macular pneumoconiosis. ***Am J Ind Med*** 2000; 37 (3): 260- 4.
23. Kim YM, Kim M, Kim SK, Park K, Jin SH, Lee US, et al. Mycobacterial infections in coal workers' pneumoconiosis patients in South Korea. ***Scand J Infect Dis*** 2009; 41 (9): 656- 62.
24. Baraz pordanjani SML, et al. A Study on Relationship Between Tuberculosis And Vitamin D3 Deficiency Among Hospitalized Patients. ***Scientific J of Ilam Med University*** 2008; 16 (2): 2- 16.
25. Pezzella AT, Fang W. Surgical aspects of thoracic tuberculosis: a contemporary review--part 1. ***Curr Probl Surg*** 2008; 45 (10): 675- 758.