

Treatment of Tuberculosis in South Kazakhstan: Clinical and Economical Aspects

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Key Words: tuberculosis; antibiotics; treatment costs; Kazakhstan.

Summary. *Background and Objective.* Since 1990, the tuberculosis incidence rate in Eastern Europe and post-Soviet republics has been increasing in many countries including Kazakhstan. This problem is particularly important in Kazakhstan regions with limited financial resources, among them – in South Kazakhstan province. The aim of this study was to investigate the main clinical and antibiotic-related economic aspects of tuberculosis treatment in South Kazakhstan province.

Material and Methods. In total, 502 patients participated in the study. They were hospitalized to the tuberculosis dispensary of Sayram district (South Kazakhstan province) in 2007–2013. Statistical analysis included logistic regression for better treatment outcomes and analysis of antibiotic treatment costs.

Results. Two-thirds of patients had infiltrative tuberculosis (67%). Positive treatment outcomes were determined in 85% of cases. The patients were mostly treated with cycloserine, protionamide, capreomycin, and ofloxacin. The majority of antibiotic costs were related to the treatment with capreomycin. In case of the positive results of the test for *Mycobacterium tuberculosis*, antibiotic expenses were almost 3 times greater than in case of negative test results ($P < 0.001$).

Conclusions. The majority of patients had extensively drug-resistant tuberculosis. The negative results of the test for *Mycobacterium tuberculosis* at discharge were not related to pretreatment factors. Antibiotic-related costs were significantly higher in case of the positive results of the test of *Mycobacterium tuberculosis*, but were not associated with gender, residence place, hospitalization recurrence, or main blood test results before treatment.

Introduction

Since 1990, the tuberculosis (TB) incidence rate in Eastern Europe and post-Soviet countries has been increasing and in 2008 reached a peak in Belarus, the Russian Federation, Ukraine, and Central Asian republics: Kazakhstan, Kyrgyzstan, Tajikistan, and Uzbekistan (1, 2). Although the rates have begun to decline in many of these countries, the problem of multidrug-resistant tuberculosis (MDR-TB) is still relevant. Of the 17 283 MDR-TB cases reported in 2004 worldwide, more than 60% (10 595) were from the European region, especially from Eastern Europe and the Baltic states: Estonia, Latvia, and Lithuania. Following the collapse of the Soviet Union in 1991, healthcare systems in post-Soviet countries experienced substantial reductions in financing, decline in population coverage, and huge increases in out-of-pocket payments (3).

Despite the considerable efforts of authorities and the improvement of healthcare in Kazakhstan, the extent of tuberculosis issue remains the same

and is becoming increasingly problematic. This is largely due to an increasing prevalence of MDR-TB that is a form of TB resistant to the main effective antibiotics (4, 5). This problem is particularly important in the regions of Kazakhstan with limited financial resources. Among them, there is South Kazakhstan province with a high incidence of tuberculosis, accompanied by a rapid increase in the number of cases with diagnosed TB resistant to main antibiotics used for TB treatment.

MDR-TB is tuberculosis that does not respond to at least isoniazid and rifampicin, the two most powerful anti-TB drugs. Extensively drug-resistant TB (XDR-TB) is a form of MDR-TB that responds to even fewer available medicines (6). MDR-TB attracted the attention of physicians in the late 1970s and the early 1980s. On the one hand, its fast and threatening spread throughout the world forced the search for new effective antibiotics and, on the other, the use of new strategies and forms of the treatment (1).

The treatment of patients with MDR-TB is much more expensive than the treatment of drug-sensitive TB. Many post-Soviet countries report the cases of XDR-TB, which is a severe form of MDR-TB be-

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cause of the resistance of the disease to most major second-line anti-TB drugs (7, 8).

Antibiotic resistance increases the costs of TB treatment. The longer duration of the disease and more complex regimens increase the costs of treatment and subsequently the financial losses of individual families and the whole society. According to the experts, the total burden of antibiotic resistance in the European Union is about 1.5 billion euros (9).

Kazakhstan has a high rate of TB and one of the highest rates of MDR-TB in the world (10). With the collapse of the Soviet Union and deteriorating economic situation in the 1990s, health funding deteriorated in all former Soviet Republics, including Kazakhstan. This initially led to a sharp increase in the TB infection rate in all regions of Kazakhstan. TB incidence peaked in Kazakhstan in 2004 (223/100 000 population) (5). Then, a better economic situation in the country allowed the government to improve the provision of healthcare. Authorities launched the National Tuberculosis Program and started to apply the Directly Observed Therapy Short Course (DOTS) (11, 12). Nevertheless, the number of patients with TB, resistant to multiple antibiotics, has increased. This may have happened due to an improved diagnosis and the expansion of health service coverage of the target population.

The aim of this study was to investigate the main clinical and antibiotic-related economic aspects of TB treatment in the province of South Kazakhstan. The study was targeted to investigate the general situation of TB in South Kazakhstan province and especially the prevalence of TB that is resistant to 2 or more antibiotics as well as antibiotic-related costs to treat these forms.

Material and Methods

The study was observational and used longitudinal data. In total, 502 patients participated in the study. The study subjects were patients hospitalized to the TB dispensary of Sayram district, South Kazakhstan province (oblast) from October 16, 2007, to February 27, 2013. The period was chosen based on the availability of data necessary for analysis. This dispensary is specialized in the treatment of MDR-TB and XDR-TB. The majority of the patients were undergoing the DOTS-plus course, category 4 (laboratory-approved MDR-TB or XDR-TB and negative TB treatment outcomes). Treatment was assigned on an individual basis taking into account drug resistance status, age, and body mass index. The total treatment duration of MDR-TB was 24 months, including intensive and supportive care of outpatients. The data for analysis were drawn from medical records and databases. Antibiotic resistance was determined based on bacteriological tests.

In the study sample, 65.5% were men. Before admission to the hospital, half of the patients were residing in urban areas, and another half, in rural areas (50.8% and 49.2%, respectively). The mean age of the patients was 38.3 years (SD, 12.9); body weight, 58.2 kg (SD, 11.97); and height, 167.6 cm (SD, 8.98). The majority (95%) of the patients were hospitalized for TB treatment for the first time. The overwhelming majority of the patients had undergone TB vaccination previously in their life, except up to 3% of the patients from families with a very poor socioeconomic status.

The statistical data analysis was conducted using the statistical SPSS package 19.0 for Windows. In descriptive analysis, categorical variables were described using numbers (n) and percentages; continuous variables, using mean (standard deviation). The comparison of subgroups was performed using the chi-square test. The prognostic potential of possible predictors was calculated using univariate binary logistic regression modeling. As the outcomes of interest, the negative results of the test for *Mycobacterium tuberculosis* at discharge (only for those with positive test results at admission), minor positive changes on x-rays, and general improvement were chosen. The sensitivity analysis for antibiotics-related costs was conducted as a univariate model for different factors. It compared the dichotomous subgroups of presumable pretreatment factors (gender, residence, hospitalization number, results of blood and microscopy tests at admission) and costs for those subgroups, including significance estimate for difference based on the Student *t* test and the Levene test for the equality of variances. The costs are presented in euros (205.89 tenge for 1 euro; February 3, 2013). The statistical significance level was set at 5%.

Results

Less than quarter (23.5%) of the patients had a contact with the illness previously; 4.2% of the patients underwent surgery. At admission to the hospital, 59.2% of the patients had the positive microscopic results of the test for *Mycobacterium tuberculosis*; at discharge, this percentage decreased to 11.8% ($P < 0.001$). Data on the extent of TB in the lungs were grouped based on the number of the affected lungs (one or two, irrespective of the number of affected lobes) and by affection of the lobes (only for cases with one affected lung). Analysis revealed that almost half of the patients had both lungs affected; more than one-third of the patients had one lobe affected (Fig. 1).

Two-thirds of the patients had infiltrative TB (67.3%); others were diagnosed with fibrous-cavernous (27.3%), disseminated (2.2%) or other type of TB (3.2%). The outcome of treatment was considered positive for 85.4% of the patients enrolled in the study. Minor positive x-ray dynamics was ob-

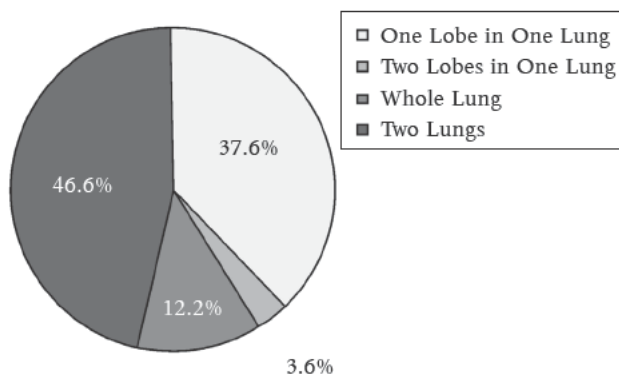


Fig. 1. The distribution of patients according to lung affection

served in almost half of all the patients (45.2%); others had either no (48.2%) or negative changes (6.6%).

Almost 90% of the patients had TB resistant to isoniazid, rifampicin, and streptomycin; almost half, to ethambutol. Resistance rates to all other analyzed antibiotics ranged from 0% to 1% (Fig. 2).

In our study, 86.9% of the patients had MDR-TB. Meanwhile, XDR-TB was highly prevalent among the subjects in our study (80.5%). In general, resistance to 13 antibiotics was tested, and 43.8% of the patients had resistance to 4 antibiotics; 38.0%, to 3 antibiotics; and 14.1%, to 2 antibiotics.

The study has also analyzed how the prescription of antibiotics (isoniazid, streptomycin, rifampicin, and ethambutol) matched with resistance to them. It was found that only ethambutol was more frequently prescribed for the patients without resistance, while isoniazid, streptomycin, and rifampicin were prescribed similarly to the patients with laboratory-approved resistance and without (Table 1). Regarding the actual treatment, the patients were mostly treated with cycloserine (90.8%), protiona-

mide (87.3%), capreomycin (66.9%), and ofloxacin (64.5%).

The regression analysis revealed that the negative results of the test of *Mycobacterium tuberculosis* could not be predicted with statistical significance using analyzed factors ($P > 0.05$, Table 2). Meanwhile, the patients with drugs side effects, high erythrocyte sedimentation rate, positive results of the test for *Mycobacterium tuberculosis* at admission, and other diseases were more likely to experience minor positive changes on x-rays ($P < 0.05$). A general improvement was observed more often among the patients who were hospitalized for the first time and among those with a normal erythrocyte sedimentation rate at admission compared with other study patients ($P < 0.05$).

The study also included pharmacoeconomic analysis, concerning exclusively antibiotic treatment costs (Table 3). It was found that more than half (58%) of all the antibiotic expenses were related to the treatment with capreomycin. Other drugs comprising the substantial part of the total costs of antibiotic treatment against TB were cycloserine (12%), levofloxacin (9%), and para-aminosalicylic acid (9%). All other antibiotics had a minor impact on total expenses – either due to low prices or to a small number of the patients treated with a certain antibiotic.

Table 1. Antibiotic Treatment and Antibiotic Resistance-Status in the Study Sample

Antibiotic	Actual Assignment of Antibiotics Among Subjects With Resistance	Actual Assignment of Antibiotic Among Subjects Without Resistance	P
Isoniazid	5.81	5.41	0.920
Streptomycin	0.89	1.82	0.515
Rifampicin	7.58	15.00	0.100
Ethambutol	10.29	28.19	<0.001

Values are percentages.

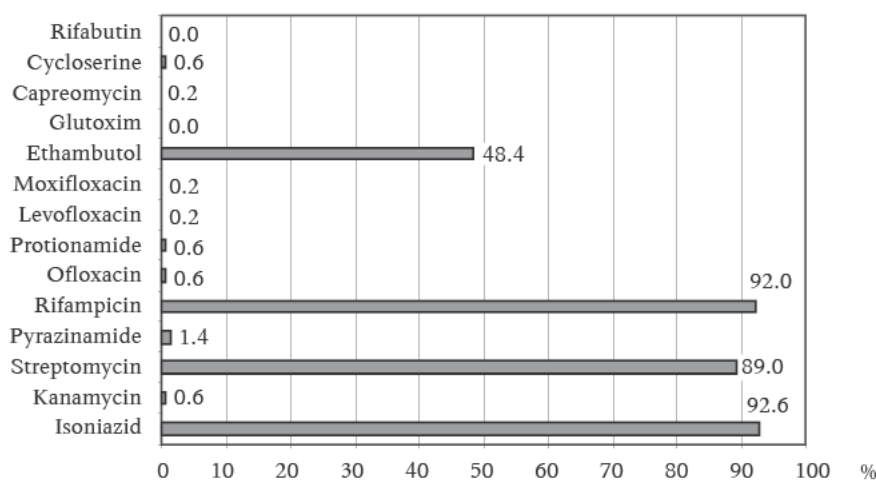


Fig. 2. Prevalence of antibiotic resistance before tuberculosis treatment

Table 2. Pretreatment Factors and Better Outcomes of Tuberculosis Treatment (Univariate Logistic Regression Analysis)

Factor		Negative Results of <i>Mycobacterium tuberculosis</i> Test at Discharge		Minor Positive Change on X-rays		General Improvement	
		OR (95% CI)	P	OR (95% CI)	P	OR (95% CI)	P
HIV test	Negative			1.00		1.00	
	Positive	NA		6.17 (0.72–53.21)	0.098	0.86 (0.10–7.43)	0.887
Rhesus factor	Negative	1.00		1.00		1.00	
	Positive	1.10 (0.23–5.35)	0.902	0.72 (0.26–2.00)	0.523	0.41 (0.05–3.16)	0.391
Drug side effects	No	1.00		1.00		1.00	
	Yes	0.98 (0.38–2.52)	0.972	1.80 (1.02–3.17)	0.043	1.17 (0.51–2.70)	0.714
Gender	Female	1.00		1.00		1.00	
	Male	1.32 (0.72–2.43)	0.366	1.12 (0.77–1.63)	0.542	0.63 (0.36–1.10)	0.103
Residence	Urban	1.00		1.00		1.00	
	Rural	0.62 (0.34–1.12)	0.112	0.71 (0.50–1.01)	0.055	1.06 (0.64–1.73)	0.831
Hospitalization	First	1.00		1.00		1.00	
	Recurrent	1.14 (0.24–5.37)	0.866	0.95 (0.42–2.13)	0.900	0.23 (0.10–0.53)	0.001
Surgery	Yes	1.00		1.00		1.00	
	No	1.00 (0.21–4.75)	0.996	0.74 (0.31–1.78)	0.506	1.00 (0.29–3.48)	0.997
Erythrocyte sedimentation rate at admission	≤15 mm/h	1.00		1.00		1.00	
	>15 mm/h	0.81 (0.43–1.50)	0.499	1.64 (1.15–2.35)	0.006	0.54 (0.33–0.89)	0.016
Leukocytosis at admission	≤9×10 ⁹ /L	1.00		1.00		1.00	
	>9×10 ⁹ /L	0.86 (0.45–1.64)	0.643	1.22 (0.79–1.87)	0.372	0.73 (0.41–1.29)	0.281
Lymphocytosis at admission	≤40%	1.00		1.00		1.00	
	>40%	0.86 (0.33–2.22)	0.752	0.70 (0.37–1.33)	0.272	1.06 (0.43–2.61)	0.896
<i>Mycobacterium tuberculosis</i> at admission	Positive	NA		1.00		1.00	
	Negative			0.43 (0.30–0.62)	<0.001	1.39 (0.83–2.34)	0.213
Other diseases	No	1.00		1.00		1.00	
	Yes	1.20 (0.64–2.22)	0.573	1.69 (1.15–2.47)	0.007	1.58 (0.88–2.82)	0.123
Isoniazid resistance	No	1.00		1.00		1.00	
	Yes	0.38 (0.09–1.65)	0.196	0.97 (0.49–1.90)	0.926	1.40 (0.59–3.32)	0.445
Streptomycin resistance	No	1.00		1.00		1.00	
	Yes	0.91 (0.33–2.50)	0.852	1.27 (0.72–2.25)	0.411	1.02 (0.46–2.25)	0.967
Rifampicin resistance	No	1.00		1.00		1.00	
	Yes	1.24 (0.44–3.51)	0.679	1.41 (0.73–2.75)	0.308	1.79 (0.82–3.94)	0.147
Ethambutol resistance	No	1.00		1.00		1.00	
	Yes	0.65 (0.36–1.16)	0.145	0.97 (0.68–1.38)	0.874	1.34 (0.81–2.22)	0.250

NA, not applicable.

The sensitivity analysis of antibiotic-related costs revealed that only microscopy of *Mycobacterium tuberculosis* at admission among the analyzed pretreatment factors was related to significantly different antibiotic costs (Table 4). In case of the positive results of the microscopy test for *Mycobacterium tuberculosis*, the antibiotic expenses were almost 3 times greater than in cases of negative test results ($P<0.001$). Even though it was observed that being a female, living in rural areas, being hospitalized for the first time, and having unfavorable results of blood testing were associated with higher antibiotic costs, no significant differences were documented ($P>0.05$).

Discussion

The National Tuberculosis Program has reported large differences in the incidence of TB and diagno-

sis of new cases of the disease across the regions of Kazakhstan. An increase in the prevalence of MDR-TB in South Kazakhstan province appears to be particularly menacing (11).

This study demonstrates the severity of the problem: the prevalence of MDR-TB among the study patients was 87%. Meanwhile, XDR-TB also was highly prevalent among our study subjects (80%). This proportion is significantly different from the average statistics in the country. This phenomenon must have objective reasons. One of them could be a possible labor force migration from other countries. In recent years, Kazakhstan has become an important destination for seasonal workers from Uzbekistan. In a context of high TB incidence, TB treatment is provided free for all residents in Kazakhstan; however, migrants rarely access these services (6).

Table 3. Total Antibiotic-Related Costs of Tuberculosis Treatment

Antibiotic	Costs per Treated Patient, Euros	Total Costs	
		Euros	%
Amikacin	35.06	4383	1.0
Amoxicillin	25.05	250	0.1
Capreomycin	788.91	265 074	57.9
Clarithromycin	146.73	587	0.1
Cycloserine	117.47	53 564	11.7
Ethambutol	4.20	412	0.1
Isoniazid	1.01	36	0.0
Kanamycin	7.24	94	0.0
Levofloxacin	196.23	41 797	9.1
Moxifloxacin	108.46	1085	0.2
Ofloxacin	32.92	11 026	2.4
Para-aminosalicylic acid	133.33	40 400	8.8
Para-aminosalicylic acid 3%	144.92	29 418	6.4
Protonamide	12.87	5635	1.2
Pyrazinamide	8.05	3003	0.7
Rifampicin	5.77	237	0.1
Streptomycin	91.50	457	0.1
Total	911.27	457 457	100

The strains resistant to isoniazid and rifampicin were among the strains of *Mycobacterium tuberculosis* isolated from TB patients in different regions of Kazakhstan (10). The costs of treatment of these patients are markedly increased. Thus, the replacement of only 2 major antibiotics (isoniazid and rifampicin) based on resistance to them greatly increases the costs of treatment.

A literature review has identified several global risk factors for TB (10). Individual risks include age, gender, smoking, alcoholism, diabetes, HIV status, marital status, ethnicity, homelessness, incarceration, drug use, and migrant status (10, 13–18). In our study, the regression analysis revealed that the negative results of the test for *Mycobacterium tuberculosis* at discharge could not be predicted by analyzed factors. Treatment success was documented in 85% of the patients enrolled in this study. A similar study conducted in the former Soviet countries reported similar percentages: a success rate of 87%

in Nagorno-Karabakh, Azerbaijan, and 61% in Kemerovo prison, Russia (19).

Our study was among the first ones that evaluated the clinical and economical aspects of TB in Kazakhstan. It was performed in a high-risk province of South Kazakhstan, showing the effects of socioeconomic changes on TB resistance in the post-Soviet country 2 decades following the collapse of the Soviet Union. The findings revealed the most common patterns of antibiotic treatment, treatment outcomes and antibiotic resistance including costs for antibiotic drugs. However, the study is limited as it estimated only antibiotic-related costs and did not account for other treatment costs such as social costs. This gives a potential for the future TB management at regional or national levels. Using the current data as a baseline, the implementation of monitoring systems could enable the evaluation of success of health programs targeted at TB control. Therefore, our study can serve as one of the first steps toward evidence-based decision-making in the management of TB in Kazakhstan.

Conclusions

The majority (80%) of patients at the TB dispensary had extensively drug-resistant tuberculosis, especially resistant to streptomycin, rifampicin, and isoniazid (about 90% of patients). The prevalence of *Mycobacterium tuberculosis* infection following the treatment at the tuberculosis dispensary essentially decreased from 59% at admission to 12% at discharge. Based on the study results, the negative results of the test for *Mycobacterium tuberculosis* at discharge was not related to pretreatment factors. Antibiotic-related costs were significantly higher in case of the positive results of the test for *Mycobacterium tuberculosis* but were not related to gender, residence place, hospitalization recurrence, or main blood test results before treatment.

Statement of Conflict of Interest

The authors state no conflict of interest.

Table 4. Antibiotic Treatment Costs of Tuberculosis: Sensitivity Analysis

Factor		Mean Costs, Euros	<i>t</i>	<i>P</i>
Gender	Female	1222 (4013)	2.002	0.141
	Male	748 (720)		
Place of residence	Urban	782 (703)	-1.149	0.251
	Rural	1045 (3537)		
Number of hospitalization	First	935 (2594)	0.426	0.364
	Recurrent	463 (375)		
Erythrocyte sedimentation rate at admission	≤15 mm/h	860 (3254)	-0.505	0.614
	>15 mm/h	975 (1133)		
Leukocytosis at admission	≤9×10 ⁹ /L	873 (2607)	-0.660	0.510
	>9×10 ⁹ /L	1056 (2236)		
Lymphocytosis at admission	≤40%	912 (2641)	0.014	0.989
	>40%	906 (657)		
Results of <i>Mycobacterium tuberculosis</i> test at admission	Positive	1239 (3224)	4.213	<0.001
	Negative	436 (530)		

References

1. World Health Organization. Global tuberculosis control – surveillance, planning, financing. WHO Report 2008. Geneva; 2006. WHO/HTM/TB/2008.393.
2. Dye C, Watt CJ, Bleed DM, Hosseini M, Raviglione MC. Evolution of tuberculosis control and prospects for reducing tuberculosis incidence, prevalence, and deaths globally. *JAMA* 2005;293:2767-75.
3. Balabanova D, McKee M, Pomerleau J, Rose R, Haerpfer C. Health service utilization in the former Soviet Union: evidence from eight countries. *Health Serv Res* 2004;39:1927-50.
4. Kim SJ. Drug-susceptibility testing in tuberculosis: methods and reliability of results. *Euro Respir J* 2005;25:564-9.
5. Sataeva LG. Tuberculosis morbidity in the Republic of Kazakhstan under new economic conditions. *Probl Tuberk Bolezn Legk* 2009;(2):29-32.
6. World Health Organization. What is multidrug-resistant tuberculosis and how do we control it? Available from: URL: <http://www.who.int/features/qa/79/en/>
7. Aziz MA. Epidemiology of antituberculosis drugs resistance (the Global Project on Anti-tuberculosis Drug Resistance Surveillance): an updated analysis. *Lancet (North American edition)* 2006;368(9553):2142-54.
8. Espinal MA, Laszlo A, Simonsen L, Boulahbal F, Kim SJ, Reniero A, et al. Global trends in antituberculosis drugs. *N Engl J Med* 2001;344(17):1294-303.
9. World Health Organization. Anti-tuberculosis drug resistance in the world: fourth global report. WHO Report. Geneva; 2008. WHO/HTM/TB/2008.394.
10. Terlikbayeva A, Hermosilla S, Galea S, Schluger N, Yegeubaeva S, Abildayev T, et al. Tuberculosis in Kazakhstan: analysis of risk determinants in national surveillance data. *BMC Infect Dis* 2012;12:262.
11. World Health Organization. Global Health Observatory Data Repository: country statistics Kazakhstan, retrieved October 29, 2011.
12. Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. *Int J Tuberc Lung Dis* 2005;9:640-5.
13. Coker R, McKee M, Atun R, Dimitrova B, Dodonova E, Kuznetsov S, et al. Risk factors for pulmonary tuberculosis in Russia: case-control study. *BMJ* 2006;332:85-7.
14. de Alencar Ximenes RA, de Fátima Pessoa Militão de Albuquerque M, Souza WV, Montarroyos UR, Diniz GT, Luna CF, et al. Is it better to be rich in a poor area or poor in a rich area? A multilevel analysis of a case-control study of social determinants of tuberculosis. *Int J Epidemiol* 2009;38:1285-96.
15. Dye C, Lönnroth K, Jaramillo E, Williams BG, Raviglione M. Trends in tuberculosis incidence and their determinants in 134 countries. *Bull World Health Organ* 2009;87:683-91.
16. Goldhaber-Fiebert JD, Jeon CY, Cohen T, Murrar MB. Diabetes mellitus and tuberculosis in countries with high tuberculosis burdens: individual risks and social determinants. *Int J Epidemiol* 2011;40:417-28.
17. Kim S, Crittenden KS. Risk factors for tuberculosis among inmates: a retrospective analysis. *Public Health Nurs* 2005; 22:108-18.
18. Kolappan C, Gopi PG, Subramani R, Narayanan PR. Selected biological and behavioural risk factors associated with pulmonary tuberculosis. *Int J Tuberc Lung Dis* 2007; 11:999-1003.
19. Bonnet M, Sizaire V, Kebede Y, Janin A, Doshetov D, Arzumaniyan A, et al. Does one size fit all? Drug resistance and standard treatments: results of six tuberculosis programmes in former Soviet countries. *Int J Tuberc Lung Dis* 2005;9:1147-54.

Received 23 May 2013, accepted 30 July 2013