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## PROGRAM SUZBIJANJA TUBERKULOZE U SRBIJI 2005-2015: REZULTATI I IZAZOVI

### TUBERCULOSIS CONTROL PROGRAMME IN SERBIA 2005-2015: RESULTS AND CHALLENGES

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#### SAŽETAK

Najznačajniji napredak u suzbijanju tuberkuloze (TB) širom sveta tokom poslednje dve decenije postignut je razvojem i primenom strategija Svetske zdravstvene organizacije. Nacionalni program prevencije i suzbijanja TB u Srbiji sprovodi se u okviru Programa zaštite stanovništva od zaraznih bolesti. Cilj programa je bio da se smanji incidencija i smrtnost od TB i dostignu stope incidencije TB od 14 na 100.000 u 2014. godini. Implementacija je dovela do postizanja cilja programa, smanjujući stopu incidencije TB sa 32/100.000 u 2005. na 13/100.000 u 2015. Ojačani su kapaciteti u sistemu zdravstvene zaštite za dijagnostiku i lečenje TB osetljive na antituberkulotske lekove prve linije, uspostavljen je organizovan sistem za dijagnostiku i lečenje rezistentnih oblika bolesti, poboljšana je dijagnostika i lečenje udružene infekcije TB i HIV-om, smanjeno je opterećenje bolešću u zatvorima, uspostavljeno je aktivno pronalaženje obolelih od TB u populacijama pod posebnim rizikom, poboljšan je epidemiološki nadzor nad TB i uspostavljen je nadzor nad kvalitetom stručnog rada. Međutim, prevencija i suzbijanje TB u Srbiji još uvek nije na nivou razvijenih zemalja u Evropskoj uniji. Potrebno je da i dalje ostane na listi javnozdravstvenih prioriteta zbog prisustva oblika bolesti otpornih na lekove, udružene infekcije TB i HIV-om, sve većeg broja migranata iz područja sa velikim opterećenjem TB i mogućeg preokreta epidemioloških kretanja u vreme socijalno-ekonomske krize.

**Ključne reči:** tuberkuloza, preventivni programi, incidencija, rezistencija na lekove

#### SUMMARY

The most significant progress in tuberculosis (TB) control worldwide over the last two decades has been achieved through the development and implementation of World Health Organization strategies. The National TB Prevention and Control Programme in Serbia has been implemented under the Programme for Population Protection from Infectious Diseases. The goal of the programme was to reduce the incidence and mortality of TB and to reach the TB incidence rate of 14 per 100,000 in 2014. The implementation has led to achievement of the programme objective, reducing the TB incidence rate from 32/100,000 in 2005 to 13/100,000 in 2015. Capacities of the health care system to diagnose and treat TB sensitive to first-line anti-tuberculosis drugs have been strengthened, an organized system of diagnosis and treatment of drug-resistant forms of the disease was established, and management of TB and HIV coinfection was improved. The burden of the disease in prisons has been reduced, the active detection of TB cases in populations at special risk has been established, the epidemiological surveillance of TB has been improved and the surveillance has been established over the quality of professional work. However, TB prevention and management in Serbia is not yet at the level of the developed countries in the European Union. It still needs to remain on the list of public health priorities due to the presence of drug-resistant forms of the disease, the combined TB and HIV infection, the increasing number of migrants from areas with high TB burden and possible reversal of epidemiological trends during the social-economic crisis.

**Keywords:** tuberculosis, prevention programmes, incidence, drug resistance

#### Introduction

The most significant progress in tuberculosis (TB) control worldwide over the

last two decades has been achieved due to the development and widespread implementation of the World Health Organization (WHO) strategies for TB control, which present a

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combination of technical and organizational components of diagnosis and treatment easily applicable in the population (1).

The implementation of the WHO's DOTS (Directly Observed Treatment Short Course) strategy from 1994 to 2005 strengthened the health sector and established basic conditions for diagnosis and treatment of TB, thereby contributing to reduction of TB transmission and preventing the development of resistant forms of the disease. Elements of this strategy represent the minimum necessary measures to control TB. WHO STOP TB strategy, implemented from 2006 to 2015, has contributed to the fight against drug-resistant TB, TB and HIV coinfection and promotion of research by strengthening the health system, expanding partnerships among all health care providers and organizations, civil society and the community (1,2).

The TB Control Programme in Serbia is implemented within the Programme of Population Protection against Infectious Diseases (3). It is being implemented by health care institutions and other health care service providers, government administration, civil society organizations and communities (4).

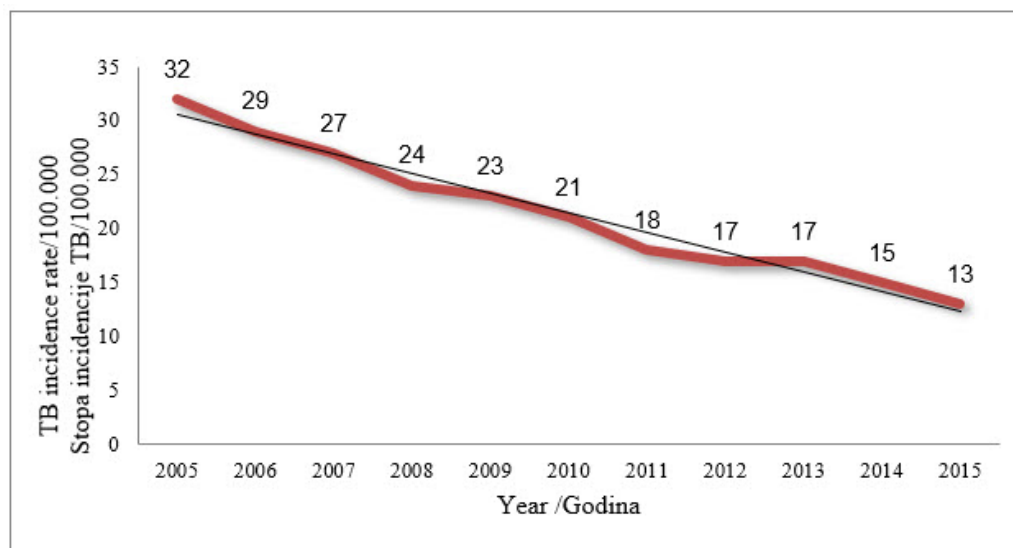
Since 2003, the Ministry of Health of the Republic of Serbia has declared TB control to be one of its public health priorities

and has begun implementing programmatic approach based on internationally effective strategies. From December 2004 to March 2015, National TB Control Programme in Serbia was supported by donations of the Global Fund to Fight AIDS, Tuberculosis and Malaria. The programme goal was to reduce the TB incidence and mortality by strengthening the implementation of the DOTS strategy, an increased level of interventions related to the management of multidrug-resistant tuberculosis (MDR TB) and TB/HIV coinfection programme activities, as well as by strengthening TB management in vulnerable populations, in order to reach TB incidence rate of 14 per 100,000 in 2014. The aim of this review was to examine whether the goals of the TB control programme in the Republic of Serbia were achieved.

### Key programme performance indicators

Tuberculosis Control Programme implementation led to overachievement of the programme goal, by reducing the TB incidence rate from 32/100,000 in 2005 to 13/100,000 in 2015 and placing Serbia among the countries with low TB burden in the WHO European Region (Figure 1).

Figure 1. Tuberculosis incidence rate, Republic of Serbia 2005-2015 / Grafikon 1. Stopa incidencije tuberkuloze, Republika Srbija 2005-2015.

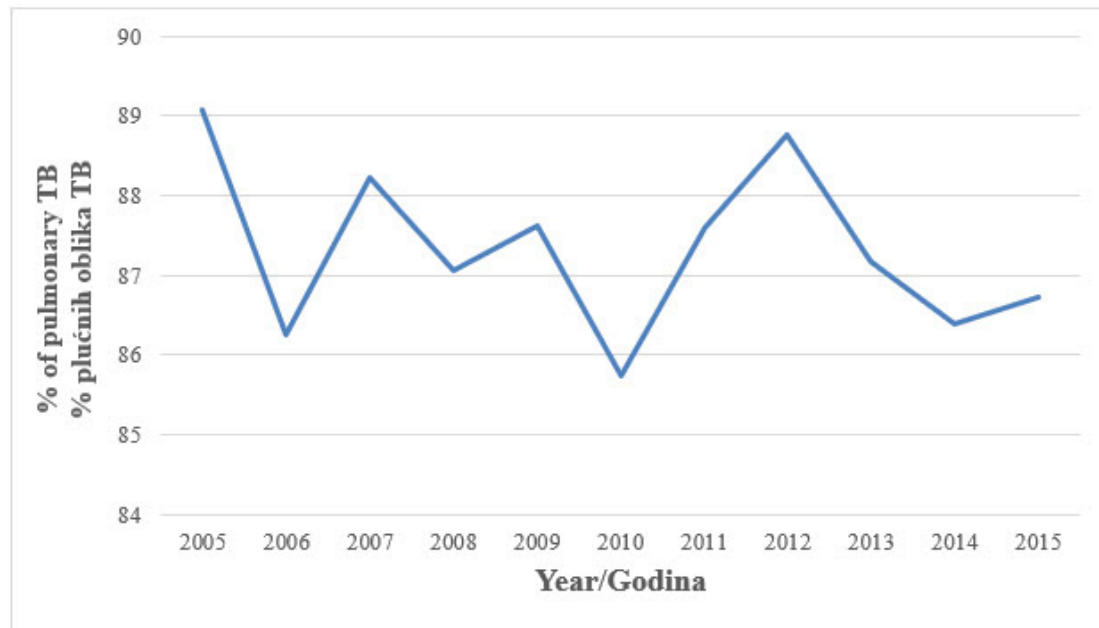


The number of TB patients decreased by 62%, from 2,378 registered in 2005 to 889 in 2015. Over the period of 11 years, there has been a constant gender ratio among patients, with male predominance (61%) over women (39%). The highest age-specific TB notification rate was in age group > 65

(24/100,000 in 2005 and 29/100,000 in 2015). The lowest age-specific TB notification rate was in age group 0-4 (2.3/100,000 in 2005 and 1.3/100,000 in 2015)

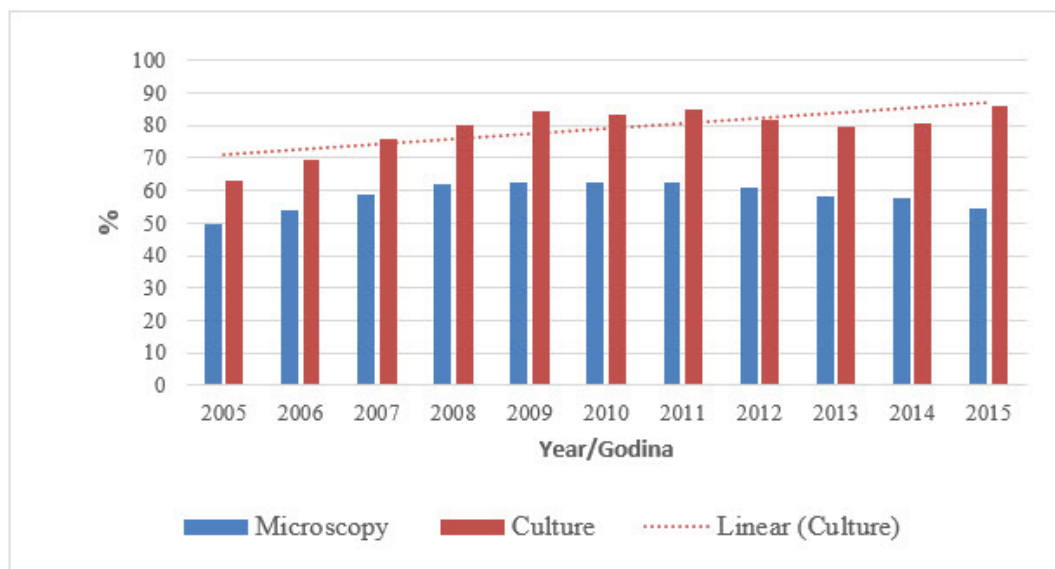
Pulmonary tuberculosis was diagnosed in 86-89% of cases, and the number has been declining over time (Figure 2).

Figure 2. Trends of proportions of pulmonary TB among total number of notified TB cases, Republic of Serbia 2005-2015 / Grafikon 2. Kretanje plućnih oblika TB u ukupnom broju prijavljenih slučajeva TB, Republika Srbija 2005-2015.



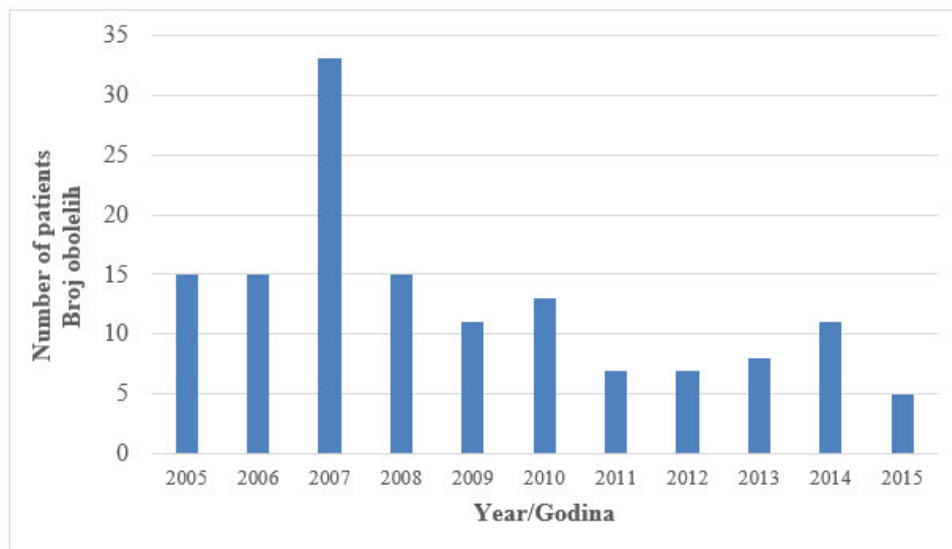
Total bacteriological confirmation among all cases ranged from 63% in 2005 to 75% in 2015 (Figure 3). Among extrapulmonary localisations, pleural (41-46%) and extrathoracic lymph nodes TB (22-23%) were most often registered.

Figure 3. Trends of proportions of bacteriological confirmation of pulmonary tuberculosis (by microscopy or by culture), Republic of Serbia 2005-2015 / Grafikon 3. Kretanje bakteriološke potvrđenosti plućne TB (mikroskopijom i kulturom), Republika Srbija 2005-2015.



Between 2005 and 2015, a total of 140 patients with multidrug-resistant tuberculosis were registered (Figure 4), accounting for 0.5 - 1.5% of the total annual number of registered tuberculosis patients.

Figure 4. Number of registered multi-drug resistant (MDR) TB patients in the Republic of Serbia 2005-2015 / Grafikon 4. Broj registrovanih obolelih od multirezistentne (MDR) TB, Republika Srbija 2005-2015.



Data on HIV status of TB patients have been available in the Republic of Serbia since 2010. The coverage of HIV testing among TB patients is very low, ranging from 1% in 2010 to 11% in 2015. The number of patients with the combined infection with TB and HIV in the same period ranged from 0.6% of the total

annual registered number of TB patients in 2005 to 1.0% in 2015.

Treatment success rate over the last eleven years remains stable (Table 1), although TB mortality rate for all forms of TB was twice reduced, from 1.91 per 100,000 in 2005 to 0.89 per 100,000 in 2015.

Table 1. Outcome indicators of TB control programme, Republic of Serbia, 2005 to 2015 / Tabela 1. Ishodni pokazatelji programa kontrole TB, Republika Srbija 2005-2015.

Indicator / Pokazatelj	2005	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Treatment success rate of new smear-positive TB cases (%) / Stopa uspeha lečenja novih sputum pozitivnih slučajeva TB (%)	82	83	85	85	86	86	84	82	79	80	83
Treatment success rate of laboratory confirmed MDR TB (%) * / Stopa uspeha lečenja laboratorijski potvrđenih slučajeva MDR TB *	-	-	-	-	55	76	71	57	75	89	80

TB-tuberkuloza; MDR-multirezistentna; \*There are no MDR TB treatment outcome data for years 2005-2008 since organised MDR TB treatment in Serbia started in 2009/ Nema podataka o ishodima lečenja MDR TB u periodu 2005-2008. godine, jer je organizovano lečenje MDR TB u Srbiji počelo 2009. godine.

## TB Prevention

The WHO recommends immunization with the Bacillus Calmette-Guérin (BCG) vaccine in countries with moderate and high incidence of pulmonary TB for infants to reduce the incidence of tuberculous meningitis and miliary tuberculosis in the first year of life. There is no evidence that BCG vaccination has an impact on TB incidence or control of the diseases in a future life (5). In the observed period, coverage of BCG vaccination ranged from 95-99%, representing very good vaccination coverage (6).

TB prevention is also performed by preventive treatment of latent TB infection – chemoprophylaxis, that includes administration of anti-TB medicines to persons at significant risk for tuberculosis (people living with HIV, adult and child HIV negative contacts, patients receiving anti-TNF therapy, patients on dialysis, those in process of preparation for transplantation and with silicosis) (7). Latent TB infection (LTBI) diagnosis and control in Serbia is a challenge, given the fact there is no organized data collection of diagnosed LTBI or on the administration of chemoprophylaxis, since the National Law on Population Protection against Infectious Diseases prescribes reporting active TB only (4).

### Early detection of TB patients and coverage by the first line anti-TB drugs susceptibility testing

Early detection of patients and rapid initiation of treatment are the most effective measures to prevent the TB spread and ensure treatment success (1). In the last 11 years, the proportion of sputum smear-positive pulmonary forms of the disease has increased from 50% to 60% (6,8). This is the indicator of the capacity of the programme for early TB detection. The value of the indicator should not exceed 45%. This data indicates that patients are detected at a later stage of the disease when the likelihood of the occurrence of severe forms with a worse prognosis is greater. Furthermore, the likelihood of disease spread due to the prolonged period before treatment initiation is higher (9). This may indicate reduced access and availability of TB care in our country. From 2011-2013, within the reform of the health care system in Serbia, decentralization and status transformation of health care facilities and services were carried out. Previous “pillars” of TB control

in Serbia, the so-called anti-TB dispensaries, have not been designated any more as special organizational units where the patients have direct access to the services. Instead, they have been associated with other specialized consultative services at the primary health care level or with the pulmonology departments of general hospitals. Moreover, in 2008, as a part of the patient centred approach in health care, the concept of “chosen doctor” was introduced. The overall health of the patients, including early detection of TB has been under their responsibility. Direct access to TB services is thus disabled, except in Belgrade and Nis, where the Municipality institutes for TB and lung diseases still exist at the primary level of health care.

In the same period, the coverage by drug susceptibility testing for first-line anti-TB drugs increased 8-fold, with a peak value of 94% in 2014. There is no possibility of *M. tuberculosis* resistance to second-line anti-tuberculosis drugs (8).

### Treatment of TB patients with support for the treatment of patients with drug-resistant TB

Tuberculosis treatment is being implemented through the use of standardized regimens in accordance with the national TB guidelines (10), and the treatment of resistant forms in accordance with the WHO guidelines for the treatment of drug-resistant TB with the individualized regimens based on drug resistance profile of the causative agent (11). Medicines for the treatment of extensively resistant forms of the disease are still not available in Serbia.

There have been no reported interruptions in the supply of first and second-line anti-TB drugs for the treatment of all forms of TB in previous years. Procurement of second-line anti-TB was performed from 2009 to 2013 within the Ministry of Health’s Tuberculosis Control Project from the funds donated by the Global Fund to fight AIDS, TB, and malaria. From 2014, the National Health Insurance Fund has undertaken the obligation of centralized procurement of drugs according to the newly developed legislation (12).

Support to 46 MDR TB patients throughout Serbia was provided within the project of the Ministry of Health until March 2015, in order to increase their compliance with the therapeutic regimen and to help them complete the prolonged treatment lasting up to 2 years (8).

## Epidemiological surveillance of tuberculosis

According to National legislation (13), systematic collection of TB data is mandatory as a part of continuous routine surveillance of TB and is the basis for evidence-based assessment of TB programme performance. TB data have been collected in the last 11 years in two ways:

- By common notification form for data collection of all infectious diseases cases (basic data)

- By supplementary notification form where the detailed case-based TB data are collected in line with the WHO TB reporting form, developed in 2004 within the Global Fund TB project.

TB case definitions are clearly listed in the guidelines for TB doctors as a part of routine TB training in the country and are consistent with WHO guidelines (10,14). The first categorization of TB cases is usually performed at the time of completing the TB notification form, by a physician who diagnosed TB, based on medical investigations and medical records. Data from the TB notification form are further validated at the regional level by epidemiologists and pulmonologists before being entered into case-based electronic data collection system. The third data quality checks are usually performed at the central (national) level by automatic checks for duplicates, missing records and consistency during the process of data clean-up before data analysis, since central level receive copies of all case-based TB notification forms. The reliability of the data can be considered to be satisfactory.

## Epidemiological investigation and contact tracing

The coverage by examinations and contact tracing in the observed period decreased from 90% in 2005-2007 to 86% in 2015. The number of TB patients identified by contract tracing is decreasing as well, from 20-30 in the period from 2005-2010 to 12 in 2015, most likely due to the abolishment of TB dispensaries (8). In order to mitigate the consequences of organizational transitions within the healthcare system and to maintain the level of TB prevention in the population, there is a need for improvement in epidemiological investigation of TB cases and an increased coverage of contact tracing by priority groups based on the characteristics of the index case and the level of exposure,

by the competent services within the network of the public health facilities in line with the legislation (4).

## TB control in vulnerable populations

Due to implementation of the Global Fund grant programme from 2005 to 2015, active TB detection has been performed among prisoners, people living with HIV (PLHIV), users of opioid substitution therapy (OST), soup kitchen users, sex workers and injecting drug users. Interventions among prisoners, PLHIV and OST users have been performed by health service, while the interventions in other vulnerable populations have been provided by the Red Cross of Serbia and other civil society organizations. In prisoners, PLHIV, and users of substitution therapy, over 95% of persons with TB symptoms have been covered by medical examinations. Active TB screening among prisoners has been performed by chest-X ray examination while among other populations by symptom-based questionnaire. Interventions among prisoners and soup kitchen users did not turn to be cost-effective since they covered a population above 20,000 and detected only up to 10 TB patients (8).

This high level of interventions stabilised TB burden among previously listed population groups. On the other hand, the level of active interventions among migrant populations has been very low. Serbia is one of the transit countries for migrants heading to the European Union (EU). The number of arrivals that reaches 2,500 - 3,000 persons per day puts severe pressure on the existing reception capacities of the country. The majority of the refugees come from Syria (67%), Iraq (15%) and Afghanistan (7%), countries significantly more affected with TB and MDR-TB than Serbia (15). The immigration has been identified as a significant factor for increased prevalence of TB and MDR-TB in European countries (16). Therefore, efforts should be made to increase TB case detection among migrant populations, with special emphasis on those from countries with dominant MDR-TB strains (17).

## Quality control of professional work

The plan of regular external quality control of healthcare institutions is created by the Institute of Public Health of Serbia, while financial resources are provided from the budget of the Republic of Serbia based on the annual work plan. According to the existing

legislation (18,19), the quality of professional work is supervised at the level of the institution as a whole, and not in relation to the disease programme. In the period 2006-2014, external quality control of professional work was carried out in each pulmonology service and microbiology laboratory performing TB diagnostics at the district level, based on the internationally recognized strategies. It contributed to the implementation of the unique professional doctrine and continuity in the quality of all segments of professional work (8). As part of our country's international cooperation with the European Centre for Disease Control in Stockholm, the quality control of the National Reference Laboratory (NRL) for TB is carried out annually. In the observed period, the results showed 100% agreement with the findings of the European Centre (8).

### **Continuous medical education for health care professionals**

Education and training are essential for sustainable TB control programmes (1). The training should not only be limited to health professionals; it is also important to extend it to all partners in programme implementation, the decision-makers who have an impact on health education plans, as well as the public. These groups need to be aware of the existence of TB and its elimination as a public health problem and to understand the interventions required to achieve that (2).

The Ministry of Health of the Republic of Serbia and the Medical Schools are responsible for comprehensive training in the field of TB at undergraduate and postgraduate level of education of health care providers, as well as for their continuous education during their TB-related practice. They are also responsible for the continuous health resource planning and profiling in order to ensure the appropriate numbers of health care professionals, with adequate knowledge, skills and motivation to provide services to persons in need in a timely manner.

In the context of the reform of the health care system and discontinuation of the specialization in pneumophysiology, the need for continuous development of human resources at the primary health care level is increasing (20).

### **Development of professional guidelines**

In addition to staffing, facilities and equipment, the pillars of the implementation of health programmes are continuous development and revision of strategic framework documents and professional guidelines. Resource allocation within the health sector budget depends on the strategic interventions, while the quality of services depends on the guidelines. The revisions should be based on the results of continuous monitoring and evaluation of the programme, the definition of priority activities and interventions for the next period, and in compliance with the latest internationally agreed recommendations and proven successful practices.

In the period 2005-2015, during the implementation of the Ministry of Health project, 11 publications were issued (8).

### **Research and innovations**

The continuous research is needed to ensure evidence-based decision-making, the introduction of new diagnostic methods, medicines, vaccines and effective programme implementation (2). Due to financial shortcomings in our country, the limited funds are allocated for that purpose.

To increase allocations for TB research, awareness of all key stakeholders (scientists, public health professionals, programme managers, financial partners, decision-makers and civil society representatives) needs to be strengthened on the importance of implementing tuberculosis research at the local and national level or to contribute to global TB research through inclusion in international research. From 2006 to 2014, four researches were performed within the national TB programme, all financed from the Global Fund donation (8).

### **Conclusion**

During the observed 11 years period, the burden of TB in Serbia has significantly decreased due to the implementation of the National TB Control programme based on WHO DOTS and STOP TB strategy. Capacities in the health care system for diagnostics and treatment of drug-susceptible TB were strengthened, organized system for the diagnosis and treatment of drug-resistant forms of diseases was established, management of TB and HIV coinfection was

improved, good disease control in prisons was established, active TB case finding for populations at special risk and epidemiological surveillance of TB was improved and quality control of professional work was established.

Good disease control is the result of more than a decade of well-coordinated programmatic measures but also of the good basic capacities of the anti-tuberculosis health service built in the Republic of Serbia since the early 1920s.

The comprehensive task of TB elimination as a public health problem requires further expansion of the scope of preventive, diagnostic and therapeutic interventions. In practical terms, the continuous progress in control of this disease beyond 2015 requires more intensive activities within and outside the TB programme, both inside and outside the health sector. From 2012 to 2014, the recent WHO End TB Strategy was developed for the period 2016-2035, with the aim of contributing to the elimination of tuberculosis as a public health problem, reaching the Global Millennium Development Goals beyond 2015 and Sustainable Development Goals.

However, TB control in Serbia is still not at the level of the developed countries in the European Union. It is necessary to keep it on the list of public health priorities due to the presence of drug-resistant forms of the disease, coinfection with TB and HIV, increasing number of migrants from the high TB burden areas and possible reversal of epidemiological trends due to the social-economic crisis.

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