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RESEARCH ARTICLE

Anti-Tuberculosis Therapy: International, State, and Regional Pharmaceutical Care Policy

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Abstract

Today, pulmonary tuberculosis is a disease, which potentially threatens the whole humanity. Therefore, prompt actions should be taken. Tuberculosis is still the main threat to the global community. In this article, we investigated anti-tuberculosis therapy in an international, state and regional perspective. We have studied the use of combined therapy in treating tuberculosis patients. Thus, combining several anti-tuberculosis drugs in chemotherapy is deemed effective nowadays. We evaluated the drug supply for tuberculosis patients in regions and found out that patients have to take medicines constantly at all stages of anti-tuberculosis therapy. When analyzing the outcomes of cases of treatment of patients with tuberculosis and methods of increasing its effectiveness, we showed that insufficient adherence to treatment, as well as its insufficient control, provide almost half (44.6%) of unfavorable outcomes. Thus, it is necessary to develop methods and methods to motivate patients to comply with the recommendations of doctors.

Keywords: *Tuberculosis, Tuberculosis infection, Tuberculosis morbidity, TB services, Primary course of chemotherapy.*

Introduction

Standard chemotherapy is a key principle of treating tuberculosis patients. Anti-tuberculosis drugs cause the death of Mycobacterium tuberculosis (M. tb). In the mid-1950s, it became known that M. tb stay in the human body in different metabolic states. Dormant mycobacteria reside inside cells or in acid environment (necrosis centres, lime), while active mycobacteria multiply extracellularly [1, 2].

Mycobacteria tuberculosis is divided into 4 conventional groups by mycobacteria metabolism and the way anti-tuberculosis drugs affect them. Group A is comprised of active M. tb that continue to grow and reside, for example, in the wall of a cavity, where the pH is neutral. Isoniazid, rifampicin, streptomycin, and other medications are good at killing them. Group B includes dormant, persistent, and spurting microorganisms that accidentally grow within a short period of time. They can only be killed with rifampicin. Bacilli present inside a cell or in areas of caseation fall into Group C; their growth is inhibited by the acid environment. They are effectively controlled by pyrazinamide.

Group D includes fully dormant mycobacteria. Medications have no effect on them. These M. tb usually die and seldom cause relapses [3]. Ineffective treatment of patients with tuberculosis is a cause of its high morbidity. At present, the Russian Federation is one of the countries with a high burden of tuberculosis and low treatment effectiveness [4, 5].In 2011, 53.9% of new cases of pulmonary tuberculosis (TB) (civilian

and prison patients) had successful chemotherapy. As for recurrent cases, this ratio was 41.5%, which is less than a half of the registered patients. According to calculations by K. Styblo, 75% of patients with sputum smear-positive tuberculosis should be cured to reduce tuberculosis morbidity quickly [6, 7]. The global goal of tuberculosis control is to cure 85% of new cases of sputum smear-positive pulmonary tuberculosis [8, 7]. Despite the fact that the definitions adopted in 2013 [9, 11] provide for the use of other methods of bacteriological confirmation of the diagnosis (including culture diagnostics), this task is still difficult.

The research is aimed at studying the use of anti-tuberculosis therapy in international, state and regional treatment policies. Research objectives: 1) to study the use of combined therapy for treating tuberculosis patients; 2) to evaluate the drug supply for tuberculosis patients in regions; 3) to analyse the treatment results in patients with tuberculosis and ways to make this treatment more effective.

Resources and Methods

We used the materials according to official data published on the website of Federal Service for Surveillance in Healthcare, World Health Organization. Epidemiological parameters are calculated for the mid-year population.

Results

Combined Therapy in Treating Tuberculosis Patients

The discovery of the first anti-tuberculosis medication, streptomycin (Sm), in 1944, then of PAS in 1949 and isoniazid (INH) in 1952 enabled doctors to use combined therapy in treating tuberculosis patients with three drugs for 24 months [12, 13]. The chemotherapy regimen consists of isoniazid, a unique drug of early bactericidal activity killing group-A active mycobacteria, rifampicin, a drug sterilising persistent intracellular group-B mycobacteria, and pyrazinamide, a drug sterilising group-C mycobacteria which reside in an acidic environment, areas of caseation, and lime [14].

Since the early 1970s, the International Union Against Tuberculosis and Lung Disease has recommended short-term six-month courses of chemotherapy (isoniazid, rifampicin, pyrazinamide for 2 months of intensive treatment and isoniazid, rifampicin for 4 months of the continuation phase) as the basis of national anti-tuberculosis measures; later, this regimen has become one of the 5 main components of the DOTS strategy (directly observational treatment short scheme chemotherapy) featuring streptomycin or ethambutol added in the intensive treatment phase. At present, the mycobacteria drug sensitivity is paid close attention during the treatment of tuberculosis patients in Eastern Europe. Multidrug resistance is the resistance of Mycobacterium tuberculosis to the combination of isoniazid and rifampicin, regardless of their resistance or resistance to other anti-tuberculosis drugs [15, 16].

Pyrazinamide is included in every MDR TB treatment regimen since there is no reliable drug sensitivity test; nevertheless, mycobacteria are very often resistant to this drug. As data on the effectiveness of the new generation of fluoruquinolones are accumulated, and new anti-TB drugs are developed, the chemotherapy regimen for MDR tuberculosis will decrease in duration [17, 18].

The Stop TB strategy launched in 2006 consolidates the progress made and draws our attention to new threats to humanity: MDR TB and tuberculosis combined with HIV infection. On the basis of the new requirements for recommendations development by WHO and the GRADE approach (emerging consensus on grading the quality of evidence and the strength of recommendations), the fourth edition of the tuberculosis treatment guide dated 2010 and the third edition of MDR TB management guide were developed [19, 12].

WHO defined seven key aspects in developing recommendations on TB treatment: duration of rifampicin treatment courses; dose frequency; initial treatment regimen for a new case in countries with a high incidence of isoniazid resistance; treating HIV-infected patients; monitoring of sputum test results during the treatment; prolonging treatment courses; refresher courses of therapy [4, 20].

The overriding priority of the current public health policy is to build a system that ensures availability of medical care, improve

efficiency of healthcare services, the scope, types and quality of which should correspond to the morbidity rate, public demand, and the newest achievements of medicine and pharmaceutical care [4, 16].

The indicative basis of current state healthcare policy was established by the Decree of the President of the Russian Federation dated May 7, 2012 No. 598 [4, 21].In implementation of this decree, the government of Russia issued Order dated December 28, 2012 No. 2599-r [22, 12].“On approval of the state program of healthcare development” [17], which provided for reducing the tuberculosis mortality rate to 12.8 per 100,000 population in 2015, to 11.8-by 2018, and to 11.2-by 2020; reducing the tuberculosis morbidity rate to 56.12 in 2015 and to 35.0 by 2020; increasing access to periodic tuberculosis screening to 73.88% in 2015 and up to 81.08% in 2020; raising the contingents abacillation index to 52.5 in 2015 and 75.0 in 2020.

In future, some of these parameters were adjusted to the demand and capability of Russian healthcare by Decree of the government of Russia dated April 15, 2014 No. 294 “On approval of the Healthcare Development state program of the Russian Federation” [22, 23].Current indicative support provides for:

- Raising the TB screening coverage rate from 65.8% in 2013 to 72.5% by 2020;
- Reducing the tuberculosis morbidity rate from 63.0 per 100,000 population in 2013 to 61.6 per 100,000 population in 2020, and to 35.0-by 2020;
- Reducing the tuberculosis mortality rate from 11.3 in 2013 to 11.2 in 2020, and to 11.2 by 2020;
- Raising the contingents abacillation rate from 43.2 in 2013 to 46.2 in 2020.

From the perspective of the classification of state policy indicative support [16], the first two parameters (reducing the morbidity and mortality rates) are impact parameters showing the target positive effect of the implementation of state policy; these parameters are not discussed in this paper. The other two parameters are result parameters that are to be achieved in order to obtain the target values of the mortality and morbidity rates. In this paper, we explored the possibility of achieving these parameters.

Being a member of the International Union Against Tuberculosis and Lung Disease, the Russian Federation also takes part in the global Stop TB strategy, which is aimed at [20, 18]:

- Reducing the tuberculosis morbidity rate to 110 per 100,000 population by 2015, to 85-by 2020, to 55-by 2025, to 20-by 2030, to 10-by 2035, and to less than 1 case per 1 million population by 2050;
- Reducing the tuberculosis mortality rate to the half of the 1990 rate by 2015, by 35% of the 2015 rate by 2020, by 75% of the 2015 rate by 2025, by 90% of the 2015 rate by 2030, and by 95% of the 2015 rate by 2035;
- Reducing the tuberculosis prevalence number to the half of the 1990 rate (to 155 per 100,000 population) by 2015;
- Reducing the rate of mortality in tuberculosis patients from 15% anticipated in 2015 to 6.5% by 2020;
- Reaching the detection rate of contagious TB cases equal to at least 70%;
- Curing 85% of new cases of sputum smear-positive tuberculosis.

In this case, result parameters include: the tuberculosis mortality, detection rate of contagious TB cases, and curing 85% of new cases of sputum smear-positive tuberculosis.

While the first two parameters have already been reached in the Russian Federation, the problem of curing 85% of new cases of sputum smear-positive tuberculosis remains unsolved.

This problem is particularly important in light of the goals of the post-2015 global strategy for the tuberculosis prevention, treatment and control [19], which includes reducing the tuberculosis mortality and morbidity rates and nulling the number of the affected families bearing catastrophic tuberculosis-related costs by 2020, as well as:

- reducing the mortality rate to 6.5% by 2025;
- reaching the rate of successful treatment of at least 85%;

- testing 100% of patients for M. tuberculosis drug sensitivity to anti-mycobacterials and for HIV infection.

Drug Supply for Tuberculosis Patients in Regions

Later on in the paper, we analysed the treatment results in patients with tuberculosis and ways to make this treatment more effective. Chemotherapy regimens prescribed are specified in Table 1 (Khabarovsk region). The treatment results in new cases and tuberculosis relapses were achieved mainly through prescribing basic anti-mycobacterial drugs (further adjustment of the anti-mycobacterial combination is not ruled out if MDR TB is detected later). In other recurrent cases of recent years, the share of chemotherapy regimens featuring initially included reserve anti-mycobacterials has been growing in last years.

Table 1: Chemotherapy regimens prescribed in 2013–2015

Category of treatment cases	Chemotherapy regimen	Years of cohort registration		
		2013	2014	2015
New cases	I,III, IIA	91.4	90.7	91.2
	IIB, IV	8.6	9.3	8.8
Relapses	I,III, IIA	76.3	75.8	75.2
	IIB, IV	23.7	24.2	24.8
Other recurrent cases	I,III, IIA	29.6	28.6	26.5
	IIB, IV	70.4	71.4	73.5

When treating new and recurrent cases in prisons, even more regimens including basic anti-mycobacterial drugs were used (in 2015: 95.7 % for treating new cases and 87.2% for treating relapses). Reserve anti-mycobacterials were used mostly for treating patients who had an ineffective chemotherapy course [4].

The organisation of drug supply for tuberculosis patients in Khabarovsk Krai is based on the cooperation of various structures calculating the demand, purchasing, delivering, prescribing, and dispensing anti-mycobacterials to certain patients (WHO PQP09001).

The problem of efficient use of medicines becomes particularly rampant in the context of persisting funding shortages. It can be solved through analysing the medications market at the territorial level, epidemiological parameters, in-depth study of the medical and pharmaceutical services in a certain region, and evaluating the efficiency of using anti-mycobacterials in certain medical institutions [4].

Having generalised the literature data and the results of our own research, we developed a model for optimizing the drug supply for tuberculosis patients in regions (Figure 1).

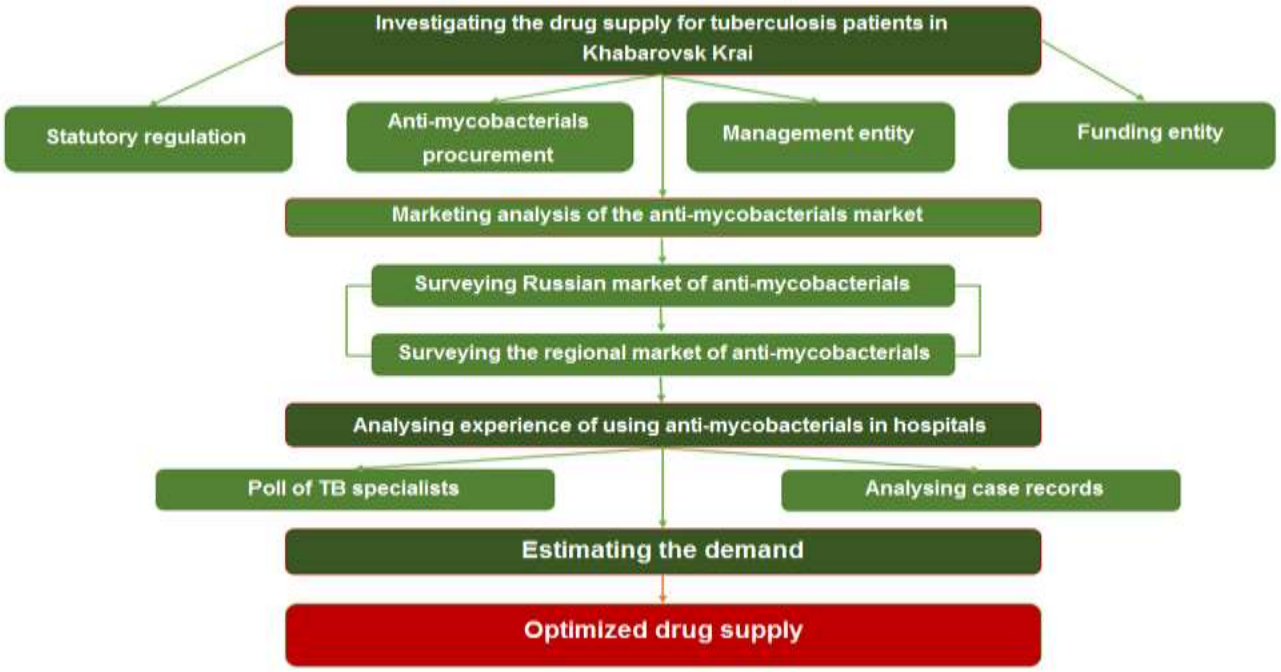

Figure 1: Model for optimizing the drug supply for tuberculosis patients in regions

Nowadays, projects and programmes launched by the state are being implemented, but they suffer from underinvestment. This problem is rampant in the regions as well. In order to make the therapy more effective and improve the quality of medical care, more medicines should be purchased at the expense of the regional budget [24, 26]. To work even more efficiently, the medical staff should be more aware of new effective anti-mycobacterials [6].The frequency analysis enabled us to identify the most frequently prescribed and switched anti-mycobacterials. Having identified the reasons for therapeutic substitution, we revealed not only drawbacks of the finance system, but also imperfection of the methodology of drug resistance detection and patients' treatment compliance (WHO PQP09001). Thus, following the research, we have developed methods to optimize the drug supply for tuberculosis patients in regions (see Figure 2).

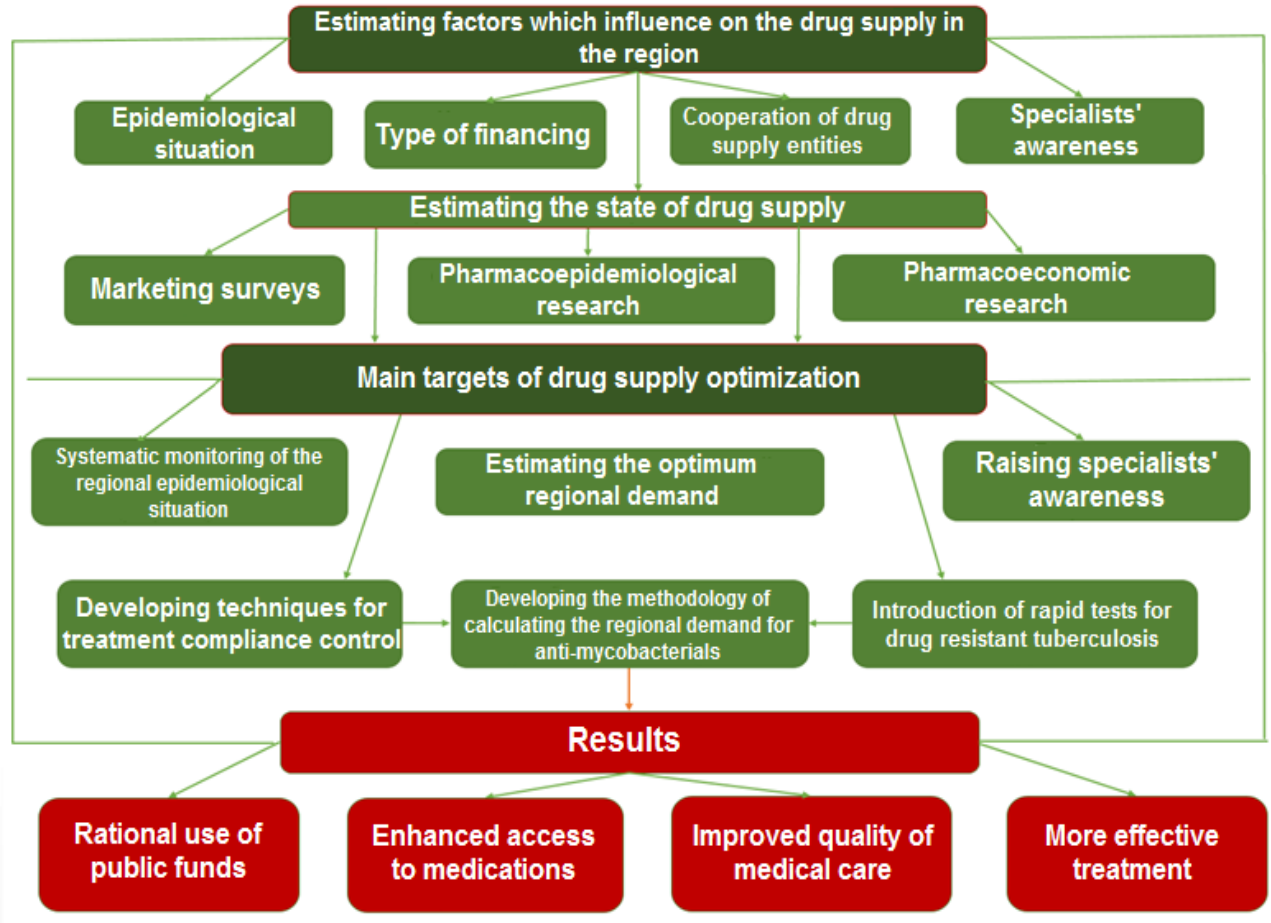

Figure 2: Strategy for optimizing the drug supply for tuberculosis patients in regions

Treatment Results in Patients with Tuberculosis and Ways to Make This Treatment More Effective

Analysing treatment results in patients with tuberculosis and ways to make this treatment more effective was the next step in our research. Chemotherapy regimens prescribed are specified in Table 1 and described above. When treating new and recurrent cases in prisons, even more regimens including basic anti-mycobacterial drugs were used (in 2015: 95.7 % for treating new cases and 87.2% for treating relapses). Reserve anti-mycobacterials were used mostly for treating patients who had an ineffective chemotherapy course. For the purposes of treatment regimen registration, new cases of sputum smear-positive tuberculosis are regarded as a standard indicative cohort selected for identifying the main problems which result in unsuccessful treatment of TB patients since this cohort is the most homogeneous and epidemically hazardous [6, 10]. The treatment effectiveness in this group of patients was selected for evaluation of the effectiveness of the Stop-TB strategy [27, 28, 20].At the moment, a little over half of the cases in the indicative group have successful treatment (Table 2).

Table 2: Chemotherapy results in new cases of sputum smear-positive tuberculosis registered in 2013–2015

Chemotherapy result	Years		
	2013	2014	2015
Successful chemotherapy	51.8	52.3	51.4
Unsuccessful chemotherapy	10.1	10.9	10.4
MDR TB detected	13.8	13.3	14.1
Died of tuberculosis	7.1	7.3	7.4
Died of other causes	5.1	4.4	4.6
Interrupted chemotherapy	7.8	7.6	7.3
Patient quitted	4.1	4.6	4.4

Positive treatment results in the indicative group are constantly reducing due to an increasing number of cases further diagnosed with MDR TB. In order to identify the main factors influencing the treatment results in the indicative cohort, we performed a factor analysis of treatment results in the regions and republics of Russia and highlighted the main components for patients registered in 2015 (Table 3). The choice of the cohort was conditioned by the normal distribution of treatment results (and, therefore, the suitability of the data for calculating the Pearson correlation coefficient which the factor analysis is based on) [28].

Table 3: Results of the factor analysis of treatment results in patients with sputum smear-positive tuberculosis: the factors identified, their values above 1, and their components (load)

Chemotherapy result	Factor 1	Factor 2	Factor 3
Successful chemotherapy	**- 0.8**	- 0.4	0.0
Unsuccessful chemotherapy	**0.8**	- 0.3	- 0.4
MDR TB detected	-0.2	**0.9**	- 0.1
Died of tuberculosis	0.5	0.1	0.2
Died of other causes	- 0.2	0.2	**0.9**
Interrupted chemotherapy	0.7	0.0	0.2
Patient quitted	0.1	- 0.5	0.3

Note: the treatment results highly correlated with the factors (r>0.7) are put in bold

The most significant factor accounting for 30.3% of the total variance includes the "successful chemotherapy" result and is inversely correlated with the "unsuccessful chemotherapy" and "interrupted chemotherapy" results. The results highly correlated with this factor enabled us to regard it as a factor of poor treatment compliance: both the interruption of chemotherapy and poor treatment effectiveness are most often associated with skipping anti-mycobacterial medication doses or early termination of treatment. The second factor is determined by the "MDR TB detected" result and therefore called the MDR factor. It is weakly correlated with the "successful chemotherapy" result (r=-0.4). The main component of the third factor, the "died of other causes" result, is not correlated with the "successful chemotherapy" result (r=0.0). Thus, the main problem denting the chemotherapy results in the indicative cohort is poor compliance with controlled treatment. The tuberculosis mortality in patients taking the first chemotherapy course is actually similar to that in patients being observed for the first year since it reveals flaws in early detection of the disease [29, 34, 4].The "patient quitted" result is also associated with treatment evasion. The causes of treatment failures are shown in the diagram (Fig. 3).

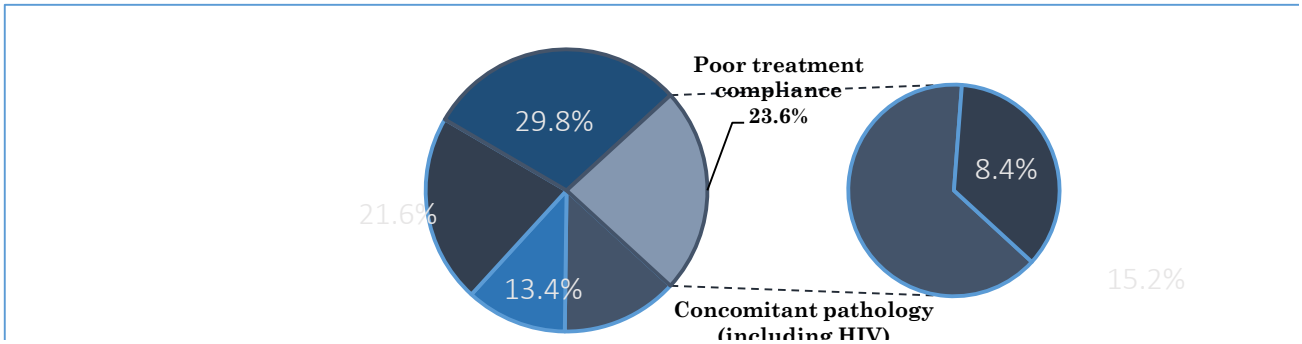

Figure 3: Causes of chemotherapy failures in new cases of sputum smear-positive tuberculosis registered in 2015

Poor treatment compliance and its poor control are the causes of almost a half (44.6%) of treatment failures. Each of the other causes (including the MDR TB diagnoses) is less significant than the specified ones. To further verify the causes of treatment failures and identify the stage at which treatment failures occur, we analysed forms 10-TB for patients registered in 2012. Deaths of new tuberculosis cases from any causes within the first 3 months of therapy account for 53.2% of the total number of deaths recorded at the end of treatment.

It means that some patients died of tuberculosis after three months of treatment, which may be associated with the termination of treatment. 38.2% of patients interrupted their therapy before 3 months of therapy passed given that the "interrupted chemotherapy" diagnosis is made 2 months after the last dose of anti-mycobacterials: in fact, before the first month of therapy ends. The patients who quitted the treatment within the first 3 months comprise 31.3% of all quitting patients. Therefore, patients should be motivated to continue the therapy right after its start.The treatment results in the indicative group of new prison patients are shown in Table 5.

Successful chemotherapy features in less than a half of cases. The decreased number of "unsuccessful chemotherapy" results is connected to the separation of MDR TB patients from the total number of patients since they were to be reregistered for chemotherapy regimen IV. In 2012, the tuberculosis mortality rate was 2.0%, which is significantly lower than that in civilian patients-6.9%.

It is connected to both continuous work on early TB detection and mandatory verification of the cause of death. The continuous increase in the number of patients with pulmonary tuberculosis who died of other causes may be related to an increase in the number of patients with tuberculosis and HIV infection. The dynamics of chemotherapy results in all new cases of pulmonary tuberculosis is shown in the diagram (Fig. 4).

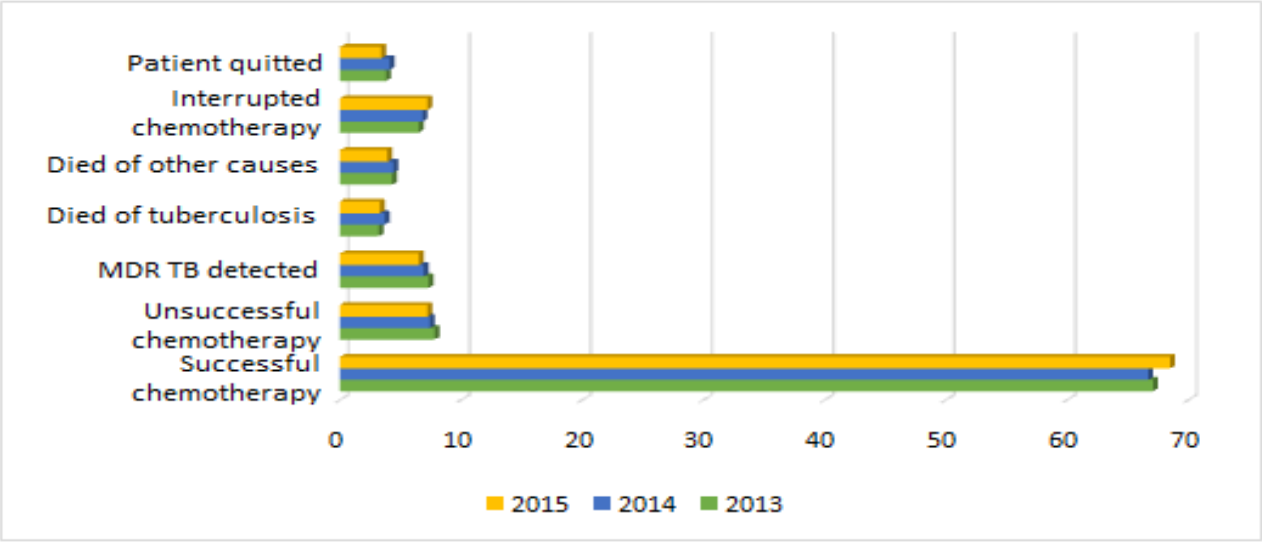

Figure 4: Chemotherapy results in all new cases of pulmonary tuberculosis: civilian patients registered in 2013-2015

Along with the increased number of patients further diagnosed with MDR TB, the attention should be paid to a reduced number of patients who interrupted their chemotherapy courses: they were excluded from the cohort at earlier research stages.The factor analysis revealed the main components which account for the larger portion of variance in all the values (Table 4).

The "successful chemotherapy" result rate is highly correlated with that of the "interrupted chemotherapy" outcome. Other factors are not correlated with the "successful chemotherapy" result. It means that poor treatment compliance leads to early termination of therapy, which is the main cause of its poor effectiveness.

Table 4: Results of the factor analysis of chemotherapy results in all new cases registered in 2015

Chemotherapy result	Factor 1	Factor 2	Factor 3	Factor 4
Successful chemotherapy	**-0.95**	0.04	0.79	-0.05
Unsuccessful chemotherapy	0.46	0.64	0.21	-0.34
MDR TB detected	0.09	**-0.93**	0.14	-1.11
Died of tuberculosis	0.49	-0.07	-0.63	-0.16
Died of other causes	-0.06	0.06	**-0.88**	0.05
Interrupted chemotherapy	0.81	0.14	0.04	0.21
Patient quitted	0.12	0.02	0.02	**0.97**

Different effectiveness of chemotherapy in new cases with or without formal signs of active tuberculosis is explained by the treatment failure risk, the analysis of which is presented in Table 5.

Table 5: Relative risk of chemotherapy failures in tuberculosis patients with or without formal signs of active tuberculosis

Chemotherapy result		Positive result of		Destructive changes
		Microscopy test	Inoculation test	
Unsuccessful chemotherapy	RR; p	1.8; p<0.01	1.6; p<0.01	3.0; p<0.01
	Number Needed to Get Result	20.6	28.8	6.6
MDR TB detected	RR; p	3.5; p<0.01	22.2; p<0.01	–
	Number Needed to Get Result	10.9	7.1	–
Died of tuberculosis	RR; p	3.8; p<0.01	1.9; p<0.01	4.7; p<0.01
	Number Needed to Get Result	18.5	40.8	17.6
Died of other causes	RR; p	1.4; p<0.01	1.2; p<0.01	1.1; 0.05<p<0.01
	Number Needed to Get Result	65.9	133.0	308.6
Interrupted chemotherapy	RR; p	1.1; p<0.01	1.1; p<0.01	1.3; p<0.01
	Number Needed to Get Result	151.3	118.6	54.5
Patient quitted	RR; p	1.0; p>0.1	0.9; p<0.01	1.1; p<0.01
	Number Needed to Get Result	3108.6	151.6	162.3
Any treatment failure	RR; p	1.8; p<0.01	1.9; p<0.01	2.0; p<0.01
	Number Needed to Get Result	4.3	4.5	4.6

As can be seen in the analysis results, new cases with sputum smear-positive tuberculosis and destructive changes had the least successful chemotherapy. New cases with a positive culture test result were less likely to die of tuberculosis; nevertheless, they were exposed to a higher risk of MDR TB (RR=1.13; p<0.01) and a lower risk of "unsuccessful chemotherapy" (RR=0.75; p<0.01) as compared to the indicative group. The detection rate of MDR TB in patients with negative or unrecorded inoculation test results was 0.7%

The risk of MDR TB in patients with a positive microscopy test results became 3.5 times higher. The rate of mortality in patients with pulmonary tuberculosis was several times higher if destructive changes or a positive result of sputum microscopy test were present. This effect was observed in every 18-19 patients. Comparison of patient groups with TL with positive and negative culture test results showed that the risk of death became 1.9 times as high. The risk of an ineffective course in the presence of a positive inoculation or microscopy test result became 1.6 and 1.8 times as high respectively.

Discussion

On average, tuberculosis control depends on the effectiveness of anti-tuberculosis

measures taken in each individual region or republic of the Russian Federation. Implementing programmes and projects, including those realised in Khabarovsk Krai only, helps to raise more funds for drug supply. We think that the quality of medical care will improve, anti-tuberculosis drugs will be more accessible to all patients, and public funds will be used rationally if the strategies described in the paper are put into practice.

Treatment effectiveness, which has increased due to the implemented measures, will help to reduce the morbidity and multidrug resistance rates in the region, as well as public expenditures on treatment of tuberculosis patients. Ineffective treatment of patients with tuberculosis is a cause of its high morbidity. At present, the Russian Federation is one of the countries with a high burden of tuberculosis and low treatment effectiveness [35].Our research demonstrates that poor treatment compliance and its poor control are the causes of almost a half (44.6%) of treatment failures. Each of the other causes (including the MDR TB diagnoses) is less significant than the specified ones. Thus, the causes of poor compliance with controlled treatment should be influenced first in order to make treatment of new cases of sputum smear-positive tuberculosis more effective.

Conclusion

In view of this, to succeed in curing TB patients, we should establish an integrated system of evaluation of treatment results in TB patients, find out the causes of giving up and terminating drug therapy, test and implement methods and techniques of motivating patients to comply with doctors' recommendations, and provide continuous drug supply at all stages of anti-tuberculosis therapy.

References

1. Avdentova V B (2012) Kogortny analiz okonchatelnykh rezultatov lecheniya bolnykh tuberkulezom legkikh [Cohort Analysis of the Final Treatment Results in Patients with Pulmonary Tuberculosis] / Avdentova V. B. [et al.] // Russian Journal of Infection and Immunity, 2 (1-2): 16 (in Russian).
2. Mahamed D et al (2017) Intracellular growth of Mycobacterium tuberculosis after macrophage cell death leads to serial killing of host cells //E life, 6: e22028.
3. Hoa NB, Nhung NV, Khanh PH, Hai NV, Quyen BT (2015) Adverse events in the treatment of MDR-TB patients within and outside the NTP in Pham Ngoc Thach hospital, Ho Chi Minh City, Vietnam. BMC Research Notes, 8: 809-815.
4. Sterlikov S A, Testov V V, Vasilieva I A (2016) Treatment results of patients with multiple and extensive drug resistance registered in 2012 in the Russian Federation and in the world // Tuberculosis and Lung Diseases, 94 (1): 22-27. (in Russian)
5. Palmieri F (2002) Pulmonary tuberculosis in HIV-infected patients presenting with normal chest radiograph and negative sputum smear / F. Palmieri [et al.] Infection, 30 (2): 68-74.
6. Styblo K (1991) Tuberculosis can be controlled with exsisting technologies: evidence. Paris: Tuberculosis Surveillance Research Unit Progress: report / K. Styblo, R. Bumgarner // Intern. UN. Against Tuberc. Lung Dis., 2: 60-72.
7. Frontiers M S (2001) Revised international definitions in tuberculosis control: comments from the Aral Sea Area tuberculosis programme // Int J Tuberc Lung Dis., 5 (11): 1071-1076.
8. Global tuberculosis report (2013) [Electronic source] // WHO. – 289. Available at: http://www.resisttb.org/wp-content/uploads/2013/11/Global-TBReport-2013.pdf.
9. Definitions and reporting framework for tuberculosis (2013) revision [Electronic source] / WHO. – WHO/HTM/TB/2013.2. – Available at: http://www.tbinfo.ch/fileadmin/user_upload/tbinfo.ch/Publikationen/definition_of_tb_case.pdf
10. Shaw JB (1954) Infectivity of pulmonary tuberculosis in relation to sputum status / J.B. Shaw, N. Wynn-Williams // Amer. Rev. Resp. Dis., 69 (5): 724-732.

11. Behr MA (1999) Transmission of Mycobacterium tuberculosis from patients smear negative for acid fast bacilli / M.A. Behr, S.A. Warren, H. Salamon, P.C. Hopewell, A. Ponce de Leon, C.L. Daley, P.M. Small // Lancet., 353 (6): 444-449.

12. Sterlikov S A (2014) Problema borby s lekarstvenno-ustoychivym tuberkulezom v Rossiyskoy Federatsii [The Issue of Drug-Resistant Tuberculosis Control in the Russian Federation] / Sterlikov S.A. // Public Health and Life Environment, 6 (255): 21-23. (In Russian).

13. Borisov S E (2015) Smertnost bolnykh tuberkulezom v Rossiyskoy Federatsii [Mortality in Patients with Tuberculosis in the Russian Federation] / Borisov S.E. [et al.] // Tuberkulez v Rossiyskoy Federatsii 2012/2013/2014 gg. Analiticheskiy obzor statisticheskikh pokazateley v Rossiyskoy Federatsii i v mire [Tuberculosis in the Russian Federation, 2012/2013/2014. Analytical Review of Statistical Indicators in the Russian Federation and in the World]. – Moscow, 75-93. (In Russian).

14. Migliori G (2007) Clinical and operational value of the extensively drug-resistant tuberculosis definition / G. Migliori [et al.] // Eur. Respir. J., 30: 623-626.

15. Belilovsky E M (2015) Zabolevaemost tuberkulezom v Rossiyskoy Federatsii [Tuberculosis Incidence in the Russian Federation] / Belilovsky E. M. [et al.] // Tuberkulez v Rossiyskoy Federatsii 2012/2013/2014 gg. Analiticheskiy obzor statisticheskikh pokazateley v Rossiyskoy Federatsii i v mire [Tuberculosis in the Russian Federation, 2012/2013/2014. Analytical Review of Statistical Indicators in the Russian Federation and in the World]. – Moscow, 29-74 (in Russian).

16. Shilova M V (2014) Tuberkulez v Rossii v 2012-2013 godu [Tuberculosis in Russia in 2012-2013] / Shilova M.V. -Moscow: Promobyuro [Promotional Bureau], 244. (in Russian)

17. Filinyuk O V, Felker I G, Yanova G V, Buinova L N, Kolokolova O V (2014) Risk Factors for Ineffective Chemotherapy in Patients with Multidrug-Resistant Tuberculosis // Tuberculosis and Lung Diseases, 1: 20-26. (in Russian).

18. Kapadia Vishakha K, Tripathi Sanjay B (2013) Analysis of 63 Patients of MDR-TB on DOTS Plus regimen: An LG Hospital, TB Unit. Ahmedabad Experience. Gujarat Medical J., 68: 52-57.

19. Frolova O P (2007) Organisatsiya protivotuberkuleznoy pomoshchi bolnym VICh-infektsiey: posobie dlya vrachey [Advancing TB Services to HIV-Infected Patients: a Guide for Doctors] / ed. by Frolova O. P. [et al.].-Moscow -Tver: Triada [Tver: Triad], 120. (in Russian)

20. Bloss E, Kuksa L, Holtz TH, Riekstina V, Skripconoka V, Kammerer S, Leimane V (2010) Adverse events related to multidrug-resistant tuberculosis treatment, Latvia, 2000-2004. Int. J. Tuberc. Lung Dis., 14 (3): 275-278.

21. Nelson LJ (2003) Global epidemiology of childhood / L.J. Nelson [ET al.] // Tuberculosis and Lung Disease, 8: 636-647.

22. Gelmanova I E, Zemlyanaya N A, Khon L V, Kruk E A, Mishustin S P, Yanova G V (2016) Treatment Costs Evaluation for Drug Susceptible and Drug Resistant Tuberculosis Patients in the Units of Tomsk Regional TB Services // Tuberculosis and Lung Diseases, 94 (3): 20-27. (In Russian).

23. Gandhi NR (2006) Extensively drug-resistant tuberculosis as a cause of death in patients co-infected with tuberculosis in a rural area of South Africa / N.R. Gandhi [et al.] // Lancet., 368: 1575-1580.

24. Zignol M (2006) Global incidence of multidrug-resistant tuberculosis / M. Zignol [et al.] // J. Infect. Dis., 194 (4): 479-485.

25. Neeta PN, Prashanth NG, Ramaprasad T, Gangadhar Goud, Sameena ARB (2016) A study on outcome of standardized treatment in multi-drug resistance tuberculosis patients. Int. J. Community Med. Public Health, 3 (1): 257-263.

26. Zhang Y, W u S, Xia Y, Wang N, Zhou L, Wang J, Fang R, Sun F, Chen M, Zhan S (2017) Adverse events associated with treatment of multidrug-resistant tuberculosis in China: An ambispective cohort study // Medical Science Monitor: International Medical Journal of Experimental and Clinical Research, 23: 2348-2356.

27. The Global Plan to Stop TB 2006-2015 [Electronic source]. – Geneva, 2006. – WHO/HTM/STB/2006.35 – Available at:

http://www.stoptb.org/assets/documents/global/plan/GP_P1_S1.pdf

28. Assefzadeh M (2009) Tuberculosis case-finding and treatment in the central prison of Qazvin province, Islamic Republic of Iran / M. Assefzadeh, R.G. Barghi, Sh.S. Shahidi ShS // East Mediterr Health J., 15 (2): 258-263.
29. Hasker E (2008) Default from tuberculosis treatment in Tashkent, Uzbekistan; who are these defaulters and why do they default? // E. Hasker, M. Khodjikhanov, S. Usarova, U. Asamidinov, U. Yuldashova, M. J van der Werf, G. Uzakova, O. Veen // BMC Infect. Dis., 8: 97-97.
30. Ruddy M et al (2005) Rates of drug resistance and risk factor analysis in civilian and prison patients with tuberculosis in Samara Region, Russia //Thorax, 60(2): 130-135.
31. Guideline on Submission of Documentation for Prequalification of Multisource (generic) Finished Pharmaceutical Products approved by Stringent Regulatory Authorities / Document WHO PQP09001 [Electronic source]. – Available at: http://apps.who.int/prequal/info_applicants/Guidelines/PQProcGenericSRA_July2011.pdf7
32. Coninx R (1999) First-line tuberculosis therapy and drug-resistant Mycobacterium Tuberculosis in prisons / R. Coninx., C. Mathieu, M. Debacker, F. Mirzoev, A. Ismaelov, R. de Haller, D.R. Meddings // Lancet., 353: 969-973.
33. Marco A (1988) Predictor of adherence to tuberculosis treatment in a supervised therapy programme for prisoners before and after release. Study Group of Adherence to Tuberculosis Treatment of Prisoners / A. Marco, J.A. Cayla, M. Serra, R. Pedro, C. Sanrama, R. Guerrero, N. Ribot // Europ. Resp. J., 12 (4): 967-971.
34. Minisi T (2013) Factors associated with pulmonary tuberculosis outcomes among inmates in Potchefstroom Prison. / T. Minisi, J. Tumo, I. Govender // South Afr. J. Epidemiol. Infect., 28 (2): 96-101.
35. Global tuberculosis report WHO (2016) Tuberculosis and Lung Diseases, 96: 3.
36. Unahalekhaka, A (2014) Status of nosocomial tuberculosis transmission prevention in hospitals in Thailand / A. Unahalekhaka, S. Lueang-a-papong, J. Chitreecheur // Am J Infect Control, 42 (3): 340-343.
37. Uplekar M, Weil D, Lonnroth K, Jaramillo E, Lienhardt C, Dias H M, Gilpin C (2015) WHO's new end TB strategy // Lancet., 385: 1799-1801.

