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THE DIAGNOSIS AND TREATMENT OF TUBERCULOSIS IN FIVE RUSSIAN TB HOSPITALS: A BRIEF OVERVIEW

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I INTRODUCTION

This report describes the diagnosis and drug treatment of tuberculosis (TB) in five specialized Russian TB hospitals, and is based on a study conducted in April 1998

The US Agency for International Development (USAID) requested the study as a first step in developing a strategy to address the control of TB in Russia The study focused particularly on factors associated with the availability and appropriate use of the essential first-line TB drugs [1] The study also addressed the availability and use of second-line TB drugs [2] The Management Sciences for Health (MSH) Rational Pharmaceutical Management (RPM) Project was asked to conduct a rapid study of five TB hospitals in cities and *oblasts* (regions) where the RPM project had previously worked [3] The RPM Project had worked in Russia since 1993 in the area of pharmaceutical sector management, and had worked with local experts at all sites except Moscow Moscow was chosen because it has a Drug Information Center (DIC) and because of its proximity to RPM Moscow staff

A Background

In Russia, tuberculosis morbidity and mortality rates have risen sharply since the early 1990s It is estimated that between 1989 and 1995 TB mortality rates increased by nearly 90% In 1995, Russia had one of the highest tuberculosis case notification rates (57 8 per 100,000) in the region and the highest new smear positive rate (25 5 per 100,000), many times higher than other industrialized economies (Global Tuberculosis Control Annual Report 1997)

A few relatively inexpensive antibiotics control TB, but treatment usually requires a minimum of six months Clearly, the sine qua non of the successful treatment is the reliable availability of the indicated drugs However, some reports (Global Tuberculosis Control Annual Report 1997) indicate that shortages of pyrazinamide, rifampicin, and ethambutol are common in Russia Of particular concern is the fact that poor prescribing practices, drug shortages, and interruptions in drug supply may have augmented the development and spread of drug-resistant strains of the disease

B Objectives

The objectives of this report are to

1 Describe the prevailing diagnostic and treatment practices for TB in five selected TB hospitals
2 Identify some key factors influencing the effective drug treatment of TB at these sites
3 Identify potential areas for further investigation and intervention in order to improve the availability and use of drugs for the treatment of TB in Russia

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[1]The first-line TB drugs referred to in this document are isoniazid, rifampicin, pyrazinamide streptomycin, and ethambutol

[2]Second-line TB drugs include amikacin and fluoroquinolones

[3]Ryazan Oblast, Novgorod Oblast, Pskov Oblast and St Petersburg

C Methodology

The intent of this study was not to conduct a scientific assessment, but rather a targeted investigation of selected sites USAID/Moscow prepared a list of questions that were modified after discussion with RPM (Appendix A) RPM selected five TB facilities in Ryazan, Novgorod, Pskov, St Petersburg, and Moscow based on previous experience working in those areas Ryazan, Novgorod, and Pskov oblasts have been implementing the RPM project for several years These oblasts, St Petersburg, and Moscow have RPM-established DICs that have experience in conducting pharmaceutical assessments The DICs could also maintain communication via the Internet with RPM/Moscow, Washington-based RPM staff, and USAID/Moscow Another major factor in choosing the sites was the willingness of oblast health authorities and chief physicians of the TB facilities to participate in the study

The questions were sent to four of the sites by electronic mail in April 1998 In the fifth site, Moscow, RPM visited the TB facility and interviewed the deputy-chief physician The data were obtained from the TB facilities over a two-week period, collected, compiled, and sent to RPM The responses were then translated into English, and submitted to USAID/Moscow

The main limitation of this study is that, in the absence of a structured investigation tool, the detail of the data collected varied from hospital to hospital

II THE DIAGNOSIS OF PULMONARY TUBERCULOSIS

Initially, history, physical examination, and X-rays can provide a tentative diagnosis of TB The American Thoracic Society (ATS) and Centers for Disease Control (CDC) recommend that, once this diagnosis is made, a stained sputum smear be examined microscopically for the presence of acid-fast bacilli (AFB) This may provide the first bacteriological evidence of TB (specifically the mycobacterium *M tuberculosis*) However, sputum smear examination permits only the presumptive diagnosis of TB because the AFB in a smear may be mycobacteria other than that causing TB Additionally, many TB patients have negative smears Therefore, ATS/CDC further recommend that sputum culture examination be done on all specimens, regardless of AFB smear results

In all adult patients who have X-ray evidence of TB, but 1) cannot produce sputum normally, or 2) have sputum that is negative for *M tuberculosis*, the ATS/CDC recommend attempting to obtain sputum by inhalation of hypertonic saline, or, if necessary, bronchoscopy If smear and culture results are negative, and no other diagnosis can be established, presumptive treatment for TB may be indicated In such adults, the major indicators of response to therapy are the chest radiograph and clinical evaluation

A positive sputum culture for *M tuberculosis* confirms a diagnosis of TB In many industrialized countries, the BACTEC radiometric system and rapid methods are used for species identification and give culture results within 10 to 14 days of specimen collection (Case Definitions for Infectious Conditions under Public Health Surveillance)

In the TB hospitals surveyed, the diagnosis of pulmonary TB is made by the methods outlined above

Sputum culture and the testing for sensitivity to anti-TB drugs are performed in central oblast laboratories for the Novgorod, Pskov, and Ryazan TB Hospitals St Petersburg and Moscow TB Hospitals send their samples to central city laboratories for testing The culture and sensitivity testing takes three months in all hospitals except Novgorod In Novgorod, technology was introduced in 1997 that allows sensitivity results to be obtained in one month The technique used in Novgorod was not identified in the study

The five TB hospitals surveyed diagnose TB using guidelines similar to those used internationally It is of some concern that results from sensitivity testing, which allow physicians to decide which drugs to use and the duration of therapy, are not available for three months in four of the five hospitals The implementation of rapid methods of sensitivity testing, such as the BACTEC system, should be considered for all TB hospitals

III THE PREVALENCE OF DRUG-RESISTANT TB

Data from the Ivanova Oblast, in "Global Surveillance For Antituberculosis-Drug Resistance" (Pablos-Mendez et al), show high levels of anti-TB drug resistance in that oblast Primary drug resistance (drug resistance in patients who have no history of prior exposure to TB drugs) to one anti-TB drug was 15 3 percent Primary resistance to more than one drug was 12 9 percent The prevalence of acquired drug resistance (resistance acquired in the course of TB treatment) to one drug was 45 5 percent and acquired resistance to more than one drug was 54 5 percent

Facilities were not asked for data on the prevalence of drug-resistant TB Data on drug resistance were only obtained from St Petersburg and Pskov St Petersburg TB Hospital reported that 10 to 15 percent of patients were resistant to one anti-TB drug Pskov TB Hospital reported that primary resistance was observed in 36 percent of patients and acquired drug resistance was observed in 54 percent of patients Thirty-four percent of all TB isolates were resistant to two or more drugs (Table 1)

Table 1 Drug Resistance in 485 Cultures of *M tuberculosis* at the Pskov Oblast TB Hospital

Resistance to	Number of Patients	Percentage (%)
Streptomycin	69	14 2
Rifampicin	18	3 7
"2 drugs"	67	13 8
"3 drugs"	70	14 4
"4 drugs"	41	8 4
Total number of resistant cultures	265	54 5

The data from this survey corroborate the data from the Ivanova Oblast (Global Tuberculosis Control Annual Report 1997, and Pablos-Mendez et al) The high prevalence of drug-resistant TB is a cause for concern since there is no consensus on treatment (as is discussed in Section IV) In addition, the morbidity and mortality rates are higher in patients with drug-resistant TB than in those with TB sensitive to anti-TB drugs Furthermore, patients with drug-resistant TB remain infectious longer and may act as reservoirs of drug-resistant tubercle bacilli

IV TREATMENT OF TUBERCULOSIS

A Treatment of Pulmonary Tuberculosis

The Advisory Council for the Elimination of Tuberculosis recommends that, because the administration of a single drug often leads to the development of a bacterial population resistant to that drug, effective regimens for the treatment of TB must contain multiple drugs to which the organisms are susceptible (Initial Therapy for Tuberculosis) When two or more drugs are used simultaneously, each helps prevent the emergence of tubercle bacilli resistant to the others However, when the in vitro susceptibility of a patient's isolate is not known, which is generally the case at the beginning of therapy, selecting two agents to which the patient's isolate is susceptible can be difficult Improper selection of drugs for the treatment of drug-resistant TB may subsequently result in the development of additional drug-resistant organisms

The ATS/CDC recommend in a joint statement that the initial regimen for treating TB in areas where the prevalence of drug-resistant TB is more than four percent should include four drugs These are isoniazid, rifampicin, pyrazinamide, and either ethambutol or streptomycin (Treatment of Tuberculosis and Tuberculosis Infection in Adults and Children, 1994) The regimen can be adjusted when drug susceptibility results become available In areas where the rate of drug resistance is documented to be less than four percent, the CDC recommendation states that three drugs (isoniazid, rifampicin, and pyrazinamide) may be adequate for the initial regimen

WHO has also published standardized treatment guidelines for national TB programmes (see also Section VI and Appendix B) The treatment regimens in these guidelines are from six months to eight months' duration similar to the six to nine months recommended in the ATS/CDC guidelines

The Moscow TB Hospital reports that they follow WHO guidelines Inpatients are treated with isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol for two months They then have outpatient treatment with rifampicin and ethambutol for four months However, in the continuation phase, the Moscow TB Hospital uses ethambutol instead of isoniazid, 20 to 30 percent of patients in Moscow also receive sanatorium treatment for an unspecified period of time, and treatment duration ranges from nine to twelve months instead of six to nine months Thus the Moscow regimen in fact differs substantially from the WHO regimens

At the Ryazan TB Hospital, inpatients are treated with isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol for two months, followed by isoniazid, rifampicin, pyrazinamide, and ethambutol for another two months Outpatients are treated with isoniazid, pyrazinamide, and ethambutol for two months Thirty percent of patients are also treated in specialized TB sanatoriums with isoniazid and ethambutol for two months Ryazan TB Hospital reports that the duration of therapy is from eight to twelve months, depending on patient response

At the Novgorod TB Hospital, inpatient therapy is conducted with isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol for an average of three and a half months Outpatient therapy lasts four months and 30 percent of patients are treated in a sanatorium for an additional two months Novgorod reports that the total duration of therapy for pulmonary TB varies from twelve to eighteen months depending on the severity of the disease and patient response The drugs used in outpatient and sanatorium treatment are not described

At the Pskov TB Hospital inpatients are treated with tubazid (a Russian-made therapeutic equivalent of isoniazid), rifampicin, pyrazinamide, and streptomycin for six months This is followed by outpatient treatment with streptomycin for two to three months Patients are also treated in TB sanatoriums with tubazid, rifampicin, pyrazinamide, and streptomycin for six to eight months The total duration of therapy reported by Pskov is twelve to eighteen months, again depending on the severity of the disease and patient response

In St Petersburg inpatients receive tubazid, rifampicin, pyrazinamide, streptomycin, and ethambutol for four to six months Outpatient treatment is conducted with tubazid and pyrazinamide for two to four months Some patients receive sanatorium treatment with tubazid, rifampicin, pyrazinamide, and ethambutol for two months In addition, some patients considered at high risk for relapse receive chemoprophylaxis with ftivzide (another Russian-made therapeutic equivalent of isoniazid) two months a year over the course of two years St Petersburg reports that the total duration of treatment for pulmonary TB varies between twelve and thirty-six months

The survey found that, in most cases, internationally recognized drugs were used in the treatment of TB, although there were aspects of treatment that differed from internationally accepted norms For example, neither the WHO nor the CDC guidelines include treating patients in sanatoriums as part of their regimens In addition, the duration of therapy seen in these Russian hospitals is considerably longer than the ATS/CDC regimen (six to nine months), as well as the two WHO regimens (six to eight months)

B Treatment of Drug-Resistant TB

The CDC recommends that in managing patients whose organisms are resistant to one or more drugs, at least two drugs to which there is demonstrated susceptibility should be administered For patients who may have isolated isoniazid resistance, the recommended six-month regimen that includes a two-month period of isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol is effective Once isolated isoniazid resistance is documented, isoniazid should be discontinued and pyrazinamide continued for the entire six months of therapy Similarly, the nine-month regimen and other regimens should be adjusted once the results of the susceptibility tests become available, with appropriate changes made in the drugs used and the duration of therapy

Unfortunately, good data are not available on the relative effectiveness of the various treatment regimens and the necessary duration of treatment for patients with organisms resistant to both isoniazid and rifampicin Moreover, many such patients will have resistance to other first-line drugs (e g , ethambutol and streptomycin) when drug resistance is discovered Because of the poor outcome in such cases, it is preferable to give at least three different drugs to which the organism is susceptible This regimen should be continued at least until the sputum becomes negative, followed by at least 12 months of two-drug therapy Often, a total of 24 months of therapy is given empirically The role of new drug agents such as quinolone derivatives and amikacin in the treatment of multidrug-resistant disease has not been documented, although these drugs are commonly being used in such cases

St Petersburg TB Hospital reports that if resistance to a drug is determined alternative drugs are used In Ryazan, if resistance is identified, treatment is modified based on sensitivity, and second-line drugs are used when they are available Novgorod also reports using alternative treatment if resistance is identified despite the fact that the only second-line drug listed by Novgorod is kanamycin At Moscow TB Hospital, the drug is withdrawn, or its dose is increased one and a half times if the patient is improving clinically, or, in 50 percent of the cases of drug-resistant TB, amikacin or fluoroquinolones are used

Ryazan, Moscow and Novgorod have adequate supplies of first-line drugs, which should allow them to treat most cases of drug-sensitive TB and TB resistant to one drug However, shortages of second-line drugs may make it difficult to effectively treat organisms that are resistant to two or more drugs

Pskov and St Petersburg both have a high prevalence of drug-resistant TB Pskov had steady supplies of only rifampicin and streptomycin St Petersburg only had steady supplies of ethambutol and tubazid (Table 3) Both Pskov and St Petersburg TB Hospitals use tubazid in their treatment regimens instead of isoniazid The intermittent supply of the some of the first-line drugs may be the reason that those two hospitals a have a high prevalence of drug-resistant TB

C Treatment of Side Effects

The only drugs recommended by the WHO for treating side effects of TB drugs are pyridoxine, used to decrease the neuropathy caused by isoniazid, and aspirin, for the arthralgia caused by pyrazinamide Gastrointestinal upset may be managed by giving the drugs at night (Treatment of Tuberculosis Guidelines for National Programmes) For major adverse drug reactions such as liver damage and some types of nerve damage, the drugs should be withdrawn and other drugs substituted (Appendix C)

The most common side effects of TB drugs noted by the five TB hospitals were gastrointestinal upset, liver damage, nerve damage, and allergic reactions Four out of five hospitals used significant numbers of drugs to treat the side effects (Table 2)

Table 2 Number of Drugs Reportedly Used in Surveyed TB Hospitals to Treat Side Effects

	Ryazan	Pskov	Novgorod	Moscow	St Petersburg
Number of Drugs Used	26	16	5	23	17

According to the responses from the TB hospitals, the main drug categories used to treat side effects include "hepatoprotectants," "pathogenetic," "desintoxication," "drugs for stimulating tissue metabolism," "resolving drugs," and "antioxidants " These drugs are listed in Appendix D by hospital It is not clear if the use of these drugs is rational, and this is an area for further study Their use may also increase cost and decrease patient adherence to the rigorous treatment regimen needed to effectively treat TB

D Criteria for Determining Treatment Efficacy

The response to anti-tuberculosis chemotherapy in patients with positive bacteriology (*M tuberculosis* identified in sputum) is best evaluated by repeated examinations of sputum It is desirable to run sputum examinations at least at monthly intervals until sputum is negative for AFB After two months of treatment with regimens containing both isoniazid and rifampicin, more than 85 percent of patients who have positive sputum cultures before treatment should convert to negative (Case Definitions for Infectious Conditions under Public Health Surveillance)

In at least three of the five TB hospitals, response is evaluated clinically, radiographically, and by confirming the absence of *M tuberculosis* in the sputum These criteria are the same as those recommended by the CDC It is unclear if sputum conversion is used at Novgorod, and if clinical evaluation is used at Pskov This uncertainty is probably due to variations in the details of the results obtained in the absence of a standardized questionnaire

V THE AVAILABILITY OF ANTI-TUBERCULOSIS DRUGS

A First-Line Anti-TB Drugs

Ryazan, Novgorod, and Moscow reported no shortages of first-line anti-TB drugs in the six- to twelve-month period prior to the survey Ryazan TB Hospital reported a four- to five-month stock of the five main TB drugs

In St Petersburg, one of the most effective drugs, rifampicin, was not available at the end of 1997 In addition, there were stock-outs of pyrazinamide and streptomycin (Table 3) In Pskov, there were eight-month shortages of isoniazid, ethambutol, and pyrazinamide As noted above, both Pskov and St Petersburg TB Hospitals use tubazid instead of isoniazid in their treatment regimens

Table 3 Availability of First-Line Anti-Tuberculosis Drugs During the Six to Twelve Months Prior to the Survey

	Ryazan	Pskov	Novgorod	Moscow	St Petersburg
Isoniazid	Yes	N/A*	Yes	Yes	N/A*
Rifampicin	Yes	Yes	Yes	Yes	Stock-out at end of 1997
Ethambutol	Yes	Shortage for 8 months	Yes	Yes	Yes
Pyrazinamide	Yes	Shortage for 8 months	Yes	Yes	Stock-outs last 6-12 months
Streptomycin	Yes	Yes	Yes	Yes	Procurement problems during last 6-12 months

N/A represents data not available

* Tubazid, a Russian-manufactured therapeutic equivalent of isoniazid, is used instead of isoniazid

Availability problems in St etersburg and Pskov were reportedly caused by "financial problems," although it is not clear exactly what is meant by this Specific questions about the procurement of anti-TB drugs were beyond the scope of this survey

The lack of availability of first-line drugs at two hospitals is cause for concern Rifampicin and pyrazinamide are important components of any anti-TB drug regimen, and their absence, together with the absence of streptomycin in St Petersburg, could severely compromise treatment Using fewer than four drugs, or intermittent use of TB drugs, could lead to treatment failure and/or the development of multidrug-resistant TB (MDRTB) The fact that there is a 10 to 15 percent prevalence of drug-resistant TB at St Petersburg TB Hospital may be partially attributable to an intermittent drug supply

There is also cause for concern in Pskov, where the documented level of TB drug resistance (36 percent primary resistance and 54 percent acquired resistance) is greater than that of St Petersburg Indeed, as in St Petersburg, the shortages of isoniazid, ethambutol, and pyrazinamide may have contributed to the current high levels of antimicrobial resistance

B Second-Line Anti-TB Drugs

All five TB hospitals experienced difficulties with the availability of second-line drugs Ryazan encountered procurement problems with ethionamide prothionamide lomefloxacin and ofloxacin during the 6 to 12 months prior to the study These problems were not described by the hospitals Moscow TB Hospital stocked amikacin and fluoroquinolones, but reported that they lack experience with these drugs and that they are expensive Novgorod, Pskov, and St Petersburg TB Hospitals either did not stock second-line drugs or attributed shortages to their high cost

The serious nature of an inconsistent supply of first-line drugs at some of the hospitals, and of second-line drugs at all of the hospitals, cannot be too heavily underscored The lack of first-line drugs could result in sub-optimal patient treatment and the development of drug-resistant TB In addition, in patients with adverse reactions or resistance to first-line drugs, the lack of second-line drugs could cause or fail to control drug-resistant TB

VI COST INFORMATION

A Procurement Cost

The reported costs of the five first-line anti-TB drugs were compared with the prices charged by the International Dispensary Association (IDA) Although first-line anti-TB drugs are manufactured in Russia, rifampicin, isoniazid, ethambutol, pyrazinamide, and streptomycin are all more expensive than the IDA prices at all the TB hospitals studied The marked variation in the reported unit costs of the five first-line drugs is shown in Table 4

Table 4 Unit Costs of First-Line Anti-TB Drugs[1]

Drug	Ryazan	Pskov	Novgorod	Moscow	St Petersburg	IDA[2] Price
Isoniazid 300 mg tablet	0 0242	N/A	0 0225	0 032	N/A	0 0088
Rifampicin 150 mg tablet	0 1452	N/A	0 1290	0 1750	0 0814	0 0348
Ethambutol 400 mg tablet	0 0403	N/A	0 0451	0 0699	0 0742	0 0265
Pyrazinamide 400 mg tablet	0 0581	0 0709	0 0741	0 0839	0 0548	0 0307
Streptomycin 1 gram vial	0 4838	0 3225	0 2516	0 2096	0 1612	0 1014

[1]Costs listed include shipping costs (20% in the case of the IDA prices)
[2] Source March 1998 Price Indicator
N/A represents data not available

Some of the key points from the table above are

- Isoniazid in Ryazan was approximately three times the IDA price
- Rifampicin was twice as expensive in Moscow as in St Petersburg, and varied from twice the IDA price in St Petersburg to five times the IDA price in Moscow
- The price of ethambutol in Moscow and St Petersburg was almost twice the cost in Ryazan and Novgorod, and was three times the IDA price
- Pyrazinamide in Pskov, Moscow, and Novgorod was approximately one and a half times the price in Ryazan and St Petersburg, and more than twice the IDA price
- Streptomycin varied from one and a half times the IDA price in St Petersburg to approximately five times the IDA price in Ryazan

In general, the highest unit costs for anti-TB drugs (apart from streptomycin) were found at the Moscow TB Hospital The lowest unit prices for rifampicin, pyrazinamide, and streptomycin were found at the St Petersburg TB Hospital

To illustrate the implications of what appear to be high procurement prices in Moscow, the costs of two different WHO treatment regimens have been calculated using UNICEF and local prices As shown in Table 5, when Moscow unit prices are compared to UNICEF prices, the cost of Regimen 1 is four times greater and the cost of Regimen 2 is more than twice as great

Table 5 Cost of Treating TB in Moscow Using WHO Guidelines with UNICEF and Moscow Unit Prices

REGIMEN	Initial Phase	Continuation Phase	Total cost
WHO Regimen 1 UNICEF Prices	2[a] ERHZ[b]	4 RH	**$34 70**
WHO Regimen 1 Moscow Prices	2 ERHZ	4 RH	**$138 00**
WHO Regimen 2 UNICEF Prices	2 SRHZ	4 R3[c] H3	**$39 20**
WHO Regimen 2 Moscow Prices	2 SRHZ	4 R3 H3	**$92 98**

a) The number preceding the first letter indicates the duration in months of the phase of treatment (initial and continuation)
b) The drugs utilized in WHO regimens are conventionally represented by the letters H = isoniazid, R = rifampicin S = streptomycin Z = pyrazinamide E = ethambutol
c) The number following the letter represents the number of weekly doses if the regimen is intermittent

B Treatment Cost

The cost of treating a patient for non-resistant pulmonary TB with destruction of lung tissue reported by the five TB hospitals varied widely,as shown in Table 6

Table 6 Cost of Treatment of Destructive Non-Resistant Pulmonary TB in 5 TB Hospitals (US$)

	Ryazan	Pskov	Novgorod	Moscow	St Petersburg
Total Cost of Anti-TB Treatment, per Case	$2,430	$1,170 (inpatient)	$859	$333 –$500	$142

One factor that helps explain the variation in reported costs is that Ryazan took into consideration the cost of hospitalization as well as the cost of drug treatment when calculating treatment costs Pskov also considered inpatient costs The difference in the methods that the hospitals used to determine the cost of treating pulmonary TB is a limitation of the study

The prices for anti-TB drugs provided by the Ryazan TB Hospital were used to calculate the drug cost of the treatment of TB using two WHO treatment regimens These were compared with the treatment regimen used in Ryazan (without the cost of sanatorium treatment as the drugs used in sanatorium treatment were not provided in the survey) The two WHO regimens were chosen as examples of different but equally effective regimens, which could be used in areas with a greater than four percent drug-resistance to isoniazid

As shown in Table 7, the Ryazan regimen is more than twice as expensive as WHO Regimen 1 and also more expensive than WHO Regimen 2

Table 7 Cost of Treatment of TB in Ryazan Compared to Cost of Treatment Using WHO Guidelines

Regimen	Initial Phase	Continuation Phase	Total Cost US$
WHO Regimen 1	2 [a]ERHZ [b]	4 RH	**48 69**
WHO Regimen 2	2 SRHZ	4 R3 H3[c]	**85 47**
Ryazan Regimen	2 SRHE3 Z3 +2 RHE3 Z3	4H3 E3 Z3	**113 70**

a) The number preceding the first letter indicates the duration in months of the phase of treatment (initial and continuation)
b) The drugs utilized in WHO regimens are conventionally represented by the letters H = isoniazid, R = rifampicin, S = streptomycin, Z = pyrazinamide E = ethambutol
c) The number following the letter represents the number of weekly doses if the regimen is intermittent

Since the Ryazan treatment schedule may also include two months of sanatorium treatment with two unspecified drugs, and because the duration of treatment is usually nine to twelve months, the cost of drug treatment in Ryazan is significantly greater than shown

In addition to the differences in the unit prices of the first-line anti-TB drugs, there is a significant disparity between the costs reported for the treatment of side effects, ranging from US$55 in St Petersburg, to US$123 80 in Novgorod, to US$390 in Pskov

The results of this survey indicate the need for further study of both procurement practices for TB drugs and the financial implications of employing various treatment regimens

VII KEY FINDINGS

The key findings of the study of the five TB Hospitals are as follows

- Most of the treatment regimens described last between twelve and eighteen months The average treatment duration in the studied oblasts is long in comparison with the accepted international regimens, which last six to nine months

- Testing of sensitivity to anti-TB drugs takes three months at all hospitals except Novgorod TB Hospital This time frame is very long, since recent technology can provide sensitivity results in 10 to 14 days

- There is a high incidence of drug-resistant TB in two of five hospitals Pskov TB Hospital reported that 36 percent of patients showed primary drug resistance and 54 percent acquired resistance in the course of therapy

- Twenty to thirty percent of TB patients at these five hospitals were also treated in TB sanatoriums, a practice that is not included in internationally accepted guidelines

- The use of a large number of drugs of questionable efficacy to treat side effects is a deviation from international norms, and may increase morbidity, decrease patient adherence, and increase treatment costs

- There are shortages of first-line anti-TB drugs in two of the five hospitals Pskov TB Hospital experienced shortages of ethambutol and pyrazinamide St Petersburg TB Hospital reported shortages of rifampicin, pyrazinamide, and streptomycin

- All hospitals reported shortages of second-line anti-TB drugs

- Despite the fact that first-line anti-TB drugs are manufactured in Russia, reported purchase prices were higher than the IDA prices for anti-TB drugs

- The cost of the TB drug treatment regimens in the Ryazan TB Hospital is higher than the cost of WHO-recommended treatment regimens, when calculated using Ryazan purchase prices

VIII POTENTIAL AREAS FOR FURTHER INVESTIGATION

The findings of this preliminary study indicate several problems with the diagnosis and treatment of TB in russian hospitals that warrant further investigation These include

- Evaluation of the current treatment regimens for TB in comparison to internationally accepted norms
- The feasibility of implementing more rapid methods of sensitivity testing, such as the BACTEC or a similar method, in all TB hospitals
- An assessment of the procurement and distribution of anti-TB drugs in Russia in order to determine why some TB hospitals are experiencing shortages of first-line TB drugs
- Further study of the use of drugs of questionable efficacy to treat side effects
- The findings on procurement prices indicate that TB drugs could possibly be purchased at lower prices

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APPENDICES

Appendix A Questions Asked of TB Hospitals

1 What methods are used to diagnose TB?

2 What are the common adverse drug reactions and what drugs are used to treat them?

3 What is the cost of the drugs used to treat side effects?

4 How is resistance determined? What are the methods used? What changes in therapy are made if drug resistance is found?

5 How is the efficacy of treatment monitored?

6 What is the duration of inpatient and outpatient treatment courses?

7 What drugs and what regimens are used in treating active pulmonary TB? List each drug, dosage form, dosage, frequency of administration, and length of treatment

8 What is the average unit cost of each drug?

9 Have there been any problems with the anti-TB drug supply over the last 6-12 months? If so, which drugs and what were the problems encountered?

10 What additional drugs are used in the case of multidrug-resistant TB? What drug regimen is used and what is the average cost of the regimen?

11 List any other drugs used as adjunctive therapy (e g , vitamins, hepatoprotectors, etc)

Appendix B Examples of WHO Recommended TB Treatment Regimens, with Costs

	Initial Phase [A] [B]	Cost (US$)	Continuation Phase [A] [B]	Cost [C] (US$)	Total (US$)
1	2 ERHZ	19 30	4 RH	15 40	34 70
2	2 SRHZ	32 60 [d]	4 R3 H3	6 60	39 20
3	2 E3 R3 H3 Z3	9 50	6 TH	2 00	11 50
4	2 S3 R3 H3 Z3	14 20 [d]	6 EH	11 20	25 40
5	2 RHZ	14 50	6 TH	2 00	16 50
6	2 R3 H3 Z3	7 00	6 EH	11 20	18 20
7	2 SERHZ/1 ERHZ	46 40 [d]	5 ERH	27 20	76 30
8	2 SERHZ/1 E3 R3 H3 Z3	27 20	5 E3 R3 H3	14 60	41 80

Adapted from WHO, Treatment of Tuberculosis Guidelines for National Programmes

[a] The following letters conventionally represent the drugs utilized in these regimens
H = isoniazid, R = rifampicin, S = streptomycin, Z = pyrazinamide, T = thioacetazone, E = ethambutol

[b] The number preceding the first letter indicates the duration in months of the phase of treatment (initial and continuation), the number that follows the letter represents the number of weekly doses if the regimen is intermittent

[c] Refers to the approximate drug cost of treatment for adults of more than 50 kg weight, calculated on the basis of UNICEF 1996 price list, including a handling charge of 6%

[d] Includes the cost of water and disposable syringes for injections

Appendix C Symptom-Based Approach to Adverse Effects of TB Drugs

Side Effects	Drug(s) Probably Responsible	Management
Minor		**Continue anti-TB drugs, check drug dosage**
Anorexia, nausea, abdominal pain	Rifampicin	Give drugs last thing at night
Joint pains	Pyrazinamide	Aspirin
Burning sensation in the feet	Isoniazid	Pyridoxine 100 mg daily
Orange/red urine	Rifampicin	Reassurance
Major		**Stop responsible drug(s)**
Itching of skin, skin rash	Streptomycin	Stop anti-TB drug
Deafness (no wax on auroscopy)	Streptomycin	Stop streptomycin, use ethambutol
Dizziness (vertigo and nystagmus)	Streptomycin	Stop streptomycin, use ethambutol
Jaundice (other causes excluded)	Most anti-TB drugs	Stop anti-TB drugs
Vomiting and confusion Suspect drug-induced acute liver failure	Suspect most anti-TB drugs	Stop anti-TB drugs Urgent liver function tests and prothrombin time
Visual impairment (other causes excluded)	Ethambutol	Stop ethambutol
Shock, purpura, acute renal failure	Rifampicin	Stop rifampicin

Source WHO, Treatment of Tuberculosis Guidelines for National Programmes

Appendix D 1 Drugs Used to Treat Side Effects at Moscow TB Hospital

Category	Drug
Central Nervous System	Pyridoxine
	Thiamine
	Glutamic acid
	Piracetam
Cardiovascular System	"Hypotensive drugs"
Hepatotoxicity "Hepatoprotectants"	Silibinin
	Essential phospholipids and multivitamins
	Silymarin
	Flumecinol
	Methionine
Allergic Reactions	Clemastine fumarate
	Mebhydrolin
	Diphenhydramine hydrochloride
	Promethazine hydrochloride
	Chlorpromazine hydrochloride
Gastrointestinal System	Vicalin
	Magnesium and aluminum hydroxides
	Metoclopramide
"Desintoxication Therapy"	Dextrose
	Polyvinylpyrolidone
"Stimulating Tissue Metabolism"	Extract aloes
	Suspension placentae
	Levamisole
	Sodium nucleinate
	Methylthiouracil
	Tuberculin
"Resolving Drugs"	Hyaluronidase
"Antioxidants"	Vitamin E
	Sodium thiosulfate

Appendix D 2 Drugs Used to Treat Side Effects at St Petersburg TB Hospital

Category	Drug
Gastrointestinal	Magnesium and aluminum hydroxides
	Vicalin
	"Enzymes"
Hepatotoxicity	Sodium thiosulfate 30%
	Polyvinylpyrolidone
	Essential phospholipids and multivitamins
	Potassium orotate
	Essential phospholipids
	Silibinin
Vestibular and Ototoxic Disturbances	Polyvinylpyrolidone
	Cinnarizine
Allergic Reactions	Diphenhydramine hydrochloride 1%
	Diphenhydramine hydrochloride
	Promethazine hydrochloride 2 5%
	Aminocaproic acid 5%
	Prednisolone

Appendix D 3 Drugs Used to Treat Side Effects at Ryazan TB Hospital

Drug
Ascorbinic acid
Calcium gluconate
Calcium chloride
Calcium gluconate
Triamcinolone
Prednisolone
Hydrocortisone
Dexamethasone
Dextran
Inosine
Inosine 2%
Fencarol
Essentiale (essential lipids, multivitamins)
Colibacterin
Bactisubtil
Biphidumbacterin
Thiamine 5%
Pyridoxine 5%
Dextrose 40%
Dextrose 5%
NaCl 0 9%
NaCl 0 9%
Piroxicam
Polyvinylpyrolidone

Appendix D 4 Drugs Used to Treat Side Effects at Pskov TB Hospital

Drug
Glutamic acid
Metoclopramide
Allahol (bile, garlic extract, activated coal)
Mezym-forte (pancreatin, amylase, lipase, proteases)
Silymarin
Diphenhydramine
Thiamine
Pyridoxine
Ascorbic acid
Inosine
Sodium thiosulfate
Aminophylline
Essential phospholipids and multivitamins
Essential phospholipids

Appendix D 5 Drugs Used to Treat Side Effects at Novgorod TB Hospital

Drug
Pyridoxine
Chlorpromazine hydrochloride
Prednisolone
Essential lipids, multivitamins
Sodium thiosulfate