Comparison of the effectiveness of WHO short-course chemotherapy and standard Russian antituberculous regimens in Tomsk, western Siberia

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Summary

Background There has been a resurgence of tuberculosis in Russia in the past decade. Traditional Russian services for treatment of tuberculosis are very different from those in the west. We aimed to compare the effects of WHO short-course chemotherapy with standard Russian antituberculous regimens.

Methods New tuberculosis patients aged 18 years or older were included in a trial and systematically allocated to traditional Russian tuberculosis treatments or WHO short-course chemotherapy in the two largest tuberculosis diagnostic and treatment centres of Tomsk Oblast, western Siberia. Standard WHO tuberculosis outcomes and rates of sputum conversion were used as primary outcomes. Analyses were by intention-to-treat.

Findings 646 new cases were enrolled into the trial, of which 356 patients were given Russian tuberculosis treatment (155 smear positive) and 290 were given WHO short-course chemotherapy (155 smear positive). There was no statistical difference between the proportion cured or completing treatment (63% for both groups [difference in proportion=0%, 95% CI –11 to 11%]); or dying (short-course chemotherapy, 8% *vs* Russian, 11% [difference in proportion=–3%, 95% CI –9 to 4%]). There was no statistical difference with respect to sputum conversion rate at 6 months (91% *vs* 85% [difference in proportion=6%, 95% CI –2 to 13%]). Overall, outcomes were worse among patients with multidrug resistant isolates than non-resistant isolates.

Interpretation WHO short-course chemotherapy treatment for tuberculosis can work well in Russia.

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See Commentary page 434

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Introduction

Tuberculosis is endemic in Russia, with notification rates rising from a low of 34 per 100 000 population in 1991 to 48 per 100 000 in 1994 and 76 per 100 000 in 1998.[1] This resurgence of tuberculosis has been linked to a general healthcare crisis that has its roots in declining health-service funding during the 1980s.[2] Then in the 1990s, the collapse of the Russian economy, with socioeconomic upheaval and massive public-sector debt, further compromised health-care provision. Life expectancy in Russia has deteriorated substantially, general health indicators are declining, and rates of a range of infectious diseases including diphtheria and sexually transmitted diseases are rising.[2]

Traditional Russian tuberculosis services are large vertical structures supported by an extensive network of tuberculosis hospitals and sanatoria. Patients with suspected tuberculosis are referred by doctors or community health workers from the general medical services. In 1993, there were more than 120 000 tuberculosis beds and around 100 000 doctors were employed.[3] The Russian system favours population screening through Mantoux testing and Mass Miniature Radiography. BCG revaccination is widespread. After diagnosis, each patient receives a unique cocktail of drugs that is devised by the clinician responsible for their care. Antibiotics are administered with various timings and routes (including intrabronchial and intracavernous). There are various complex and expensive non-specific (eg, hepatoprotectors) and pathogenetic (vibromassage, galvanisation, and ultraviolet irradiated blood transfusion) therapies. Surgery is done on around 10% of cases. Many of the interventions predate the chemotherapy era. Radiographical cavity closure is the principle definition of successful outcome. Treatment regimens generally last more than 12 months. These approaches[4–6] are quite different to those recommended by WHO,[7] which uses simple standardised regimens. Although the Russian regimens are more expensive and more difficult to supply and organise, the results of the two approaches have not been objectively compared—in part because there is no tradition in Russia of developing a western-style evidence base from controlled trials.

In 1994, MERLIN (Medical Emergency Relief International) became the first foreign organisation in Russia to work in tuberculosis control after the break up of the Soviet Union. A collaborative project was established in Tomsk Oblast (Region), Siberia, as the first attempt to encourage reform of tuberculosis control practices along the lines recommended by WHO. We wanted to determine the effectiveness of short-course chemotherapy in Russia and use this as an opportunity to introduce some western evidence-based practice into Russia.

Tomsk Oblast (area 312 000 km^2, population 968 000) lies on the western Siberian basin about 3000 km east of Moscow. About half the population lives in the city of Tomsk, and the remainder is scattered over a territory the size of Germany. Temperatures here might drop to –40°C in winter. In 1994, the notification rate for new cases of

tuberculosis in Tomsk was 61 per 100 000 population (mortality rate 22·4 per 100 000). In 1996, a detailed assessment showed that Tomsk Oblast had 1071 tuberculosis beds and 102 tuberculosis physicians (phthisiatrists).[8] The Tomsk collaborative project has promulgated each of the five elements of WHO's tuberculosis control strategy: the use of standardised drug regimens administered under close supervision, internationally consistent recording and reporting systems, passive case finding through smear microscopy, reliable drug supplies, and promotion of government commitment.[7] We report here results from the formal comparison of the effects of short-course chemotherapy and standard Russian antituberculous regimens.

Methods

Procedure

The study was a non-blinded clinical trial. All new patients referred to two large tuberculosis diagnostic and treatment centres within the Oblast (Tomsk and Seversk) with confirmed or suspected tuberculosis who were 18 years or older were eligible for inclusion in the study. Patients whose tuberculosis had relapsed, or were being retreated after interruption in therapy, or who remained or became again smear positive after completing a fully supervised retreatment regimen (chronic cases) were not included. The only withdrawal criterion was a change of diagnosis.

We systematically allocated patients into two groups by week of presentation between March, 1995, and June, 1996. Doctors admitting patients used desk calendars to indicate whether the admission fell into week A or B. Allocations were monitored on a weekly basis by two researchers (TVL and VTG). The first group received treatment according to the principles of Russian tuberculosis medicine.[4,6] The second group received directly observed short-course chemotherapy (DOTS). Differences in treatment between the two groups are summarised in table 1. All patients had two sputum microscopy and culture examinations.[9,10] Sputum microscopy for acid-fast bacilli was done with Ziehl-Neelsen staining of direct sputum smears. Cultures were set up on Finn-2, Papiescou, or Lowenstein-Jensen media and incubated at 37°C for up to 12 weeks. Sensitivity testing was done on Lowenstein-Jensen media with the absolute concentration method.[11] A chest radiograph was done at 2, 4, and 6 months. All patients were screened for HIV with ELISA (ECOlab, Moscow 142530, Russia).

Outcomes

Outcomes as defined in the original protocol were: (1) standard WHO tuberculosis outcomes—cured (patient who is smear-negative at, or 1 month before, the completion of treatment and on at least one previous occasion), treatment completed (patient who has completed treatment but without proof of cure), died (patient who dies for any reason during the course of treatment), defaulted (patient whose treatment is interrupted for 2 months or more), failed treatment (patient who remains or becomes again smear-positive at 5 months or later during treatment), transferred out (patient who is transferred to another reporting unit and for whom the treatment outcome is not known) for all patients at the end of treatment; and (2) sputum conversion at 6 months for smear-positive patients. Culture conversion and cavity closure at 2 and 6 months and side-effects to antibiotics were also recorded.

Ethical approval

As in much of the rest of Russia, there are no formal local ethical committees in Tomsk. Meetings between MERLIN and all the relevant local clinicians considered the potential risks and benefits of the trial and the treatment regimens and agreed that the trial should go ahead. Before admission to the study, all patients were informed about the trial regimens as well as being educated about tuberculosis and the importance of completing treatment.

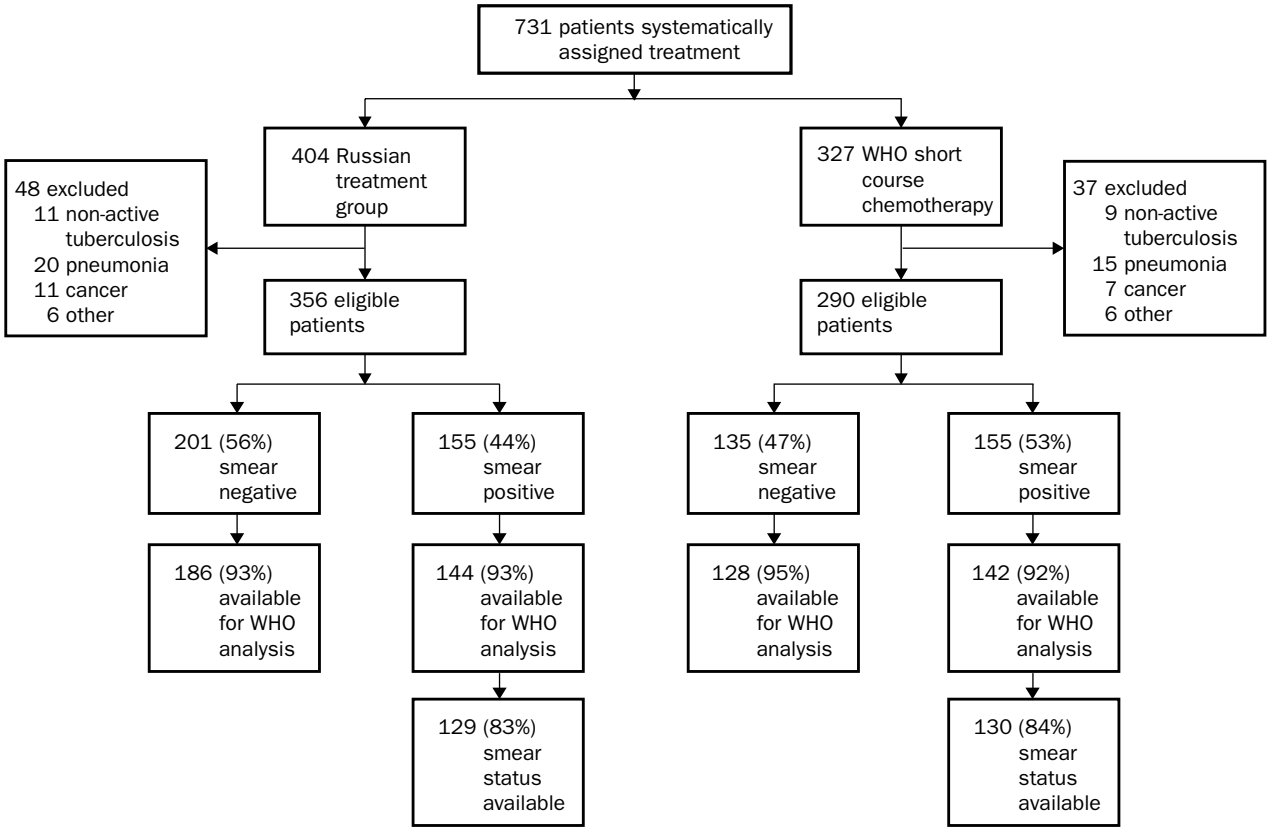
Statistical analyses

We calculated sample size assuming 80% power, with a significance level of $p<0·05$. We assumed that 50% of new patients were smear positive and that 6-month smear conversion rates for WHO short-course chemotherapy would reach 85%. We calculated that 636 eligible patients should be enrolled to enable a 10% difference between the two groups to be statistically significant. χ^2 tests with Yates' correction were done with Epi-Info (version 5.01). CIs were calculated by standard methods.[12] Smear conversion (in smear positive patients) and WHO outcomes (in all patients) were analysed on the basis of intention-to-treat. Where statistically significant differences between variables in the allocation groups were found we calculated adjusted relative risks by stratified analysis using Epi-Info. Because relative risks did not change after adjustment for potential confounders, crude results (differences) only have been presented.

	Regimen*	
	Russian	WHO short-course chemotherapy†
WHO treatment category		
I	3HR (Z, S, K or E)/7HR	2HRZ (E or S)/4HR
III	2–4HRS/2–4HR	2HRZ/4HR
Drug regimens		
Isoniazid	10 mg/kg (maximum 900 mg) intravenously, intramuscularly, or orally	5 mg/kg (maximum 300 mg) orally
Rifampicin	7 mg/kg (maximum 450 mg), orally	10 mg/kg (maximum 600 mg) orally
Pyrazinamide	30 mg/kg	30 mg/kg
Ethambutol	15 mg/kg	15 mg/kg
Streptomycin	15 mg/kg	15 mg/kg
Adjunctive therapy		
Artificial pneumothorax, galvanisation, autotransfusion of ultraviolet irradiated blood, intrabronchial instillation of antituberculosis drugs	Individually or in combination, at the discretion of clinician.	None

H=isoniazid, R=rifampicin, Z=pyrazinamide, E=ethambutol, S=streptomycin, K=kanamycin.[7] *A regimen consists of two phases. By convention, the number before a phase is the duration of that phase in months. †Under WHO's principles for tuberculosis treatment, each patient is allocated to treatment category I-IV. I and III refer to new patients. Category II and IV patients were not included in this study and refer to patients who have relapsed, who are chronic cases, and those retreated after an interruption in their treatment.[7]

Table 1: **Summary of treatments used**



Trial profile

Results

731 patients were recruited. 646 were eligible for inclusion into the study, and of these 310 (48%) were smear positive (figure). 356 patients (155 of whom were smear positive) were allocated into Russian treatments and 290 (155 smear positive) into WHO short-course chemotherapy. Similar proportions of patients were followed up in both groups. Of the 310 originally smear-positive patients, 6-month smear status was available for 259 (84%) and WHO outcome for 286 (92%). WHO outcomes were recorded in 314 (93%) smear-negative patients.

The eligible patients in each treatment group were compared for various sociodemographic factors and clinical indicators (table 2). Most patients were men (493, 76%), smokers (479, 74%), and classified as alcoholic (416, 64%). 140 (22%) were unemployed, 75 (12%) had chronic non-specific lung disease, 73 (12%) had been in contact with a patient with tuberculosis, and 42 (6%) were ex-prisoners. Significantly more patients were allocated to the Russian treatment group (n=404, 55%) than the WHO short-course chemotherapy group (327, 45%; p=0·0001). The Russian group had a statistically significant lower proportion of smear-positive patients (155 of 356, 44%) compared with the WHO short-course chemotherapy group (155 of 290, 53%; p=0·02).

There were statistically fewer unemployed patients in the Russian treatment group than in the WHO short-course chemotherapy group (64, 18%, *vs* 76, 26%; p=0·02). With respect to smear-positive patients, there were significantly more patients in the Russian treatment group who had been in contact with a case of tuberculosis than among the WHO treatment group (25, 16%, *vs* 13, 8%).

Table 3 shows the levels of resistance in culture positive patients, with 25 (4%) patients who were positive for

	All patients			Smear-positive patients		
	Russian regimen (n=356)	WHO short-course (n=290)	p	Russian regimen (n=155)	WHO short-course (n=155)	p
Male	274 (77%)	218 (75%)	0·59	121 (78%)	122 (79%)	0·89
Homeless	4 (1%)	3 (1%)	1	3 (2%)	3 (2%)	1
Ex-prisoners	24 (7%)	18 (6%)	0·78	12 (8%)	10 (6%)	0·82
Unemployed (includes pensioners & invalids)	64 (18%)	76 (26%)	0·01	31 (20%)	41 (26%)	0·23
Contacts	44 (12%)	31 (11%)	0·51	25 (16%)	13 (8%)	0·06
Drug addicts, substance misusers	2 (0%)	3 (1%)	0·66	1 (1%)	2 (1%)	1
HIV positive	0	0	..	0	0	..
Alcoholic	220 (62%)	196 (68%)	0·14	107 (69%)	117 (75%)	0·25
Smoker	260 (73%)	219 (76%)	0·47	122 (79%)	129 (83%)	0·38
WHO treatment category I	310 (87%)	250 (86%)	1	154 (99%)	154 (99%)	1
WHO treatment category III	46 (13%)	40 (14%)	1	1 (1%)	1 (1%)	..
Smear-positive	155 (44%)	155 (53%)	0·01	155 (100%)	155 (100%)	1
Culture-positive	252 (71%)	211 (73%)	0·58	134 (87%)	142 (92%)	1
Cavity-positive	224 (63%)	180 (62%)	0·82	128 (83%)	127 (82%)	1

*χ^2 with Yates' continuity correction. Data are number of patients (%).

Table 2: **Sociodemographic, clinical characteristics and WHO treatment categories among patients in the Tomsk trial**

	Russian regimen	WHO short-course
Isoniazid	55 (22%)	38 (18%)
Streptomycin	112 (44%)	82 (39%)
Rifampicin	25 (10%)	13 (6%)
Ethambutol	5 (2%)	3 (1%)
Pyrazinamide	4 (2%)	1 (<1%)
Streptomycin/isoniazid	24 (10%)	18 (9%)
Multidrug resistance*	19 (8%)	6 (3%)

*Resistance to rifampicin and isoniazid±other antimicrobial agents. Data are n (% resistant).

Table 3: **Antimicrobial resistance among isolates from 463 patients with culture positive *Mycobacterium tuberculosis***

	Smear-positive patients		Smear-negative patients*	
	Russian regimens (n=155)	WHO short-course (n=155)	Russian regimens (n=201)	WHO short-course (n=135)
Cure	86 (55%)	84 (54%)	NA	NA
Treatment completed	11 (7%)	13 (8%)	144 (72%)	107 (79%)
Died	17 (11%)	13 (8%)	14 (7%)	5 (4%)
Treatment failure	10 (6%)	8 (5%)	NA	NA
Default	16 (10%)	21 (14%)	16 (8%)	8 (6%)
Transfer	2 (1%)	5 (3%)	12 (6%)	8 (6%)
Uncoded	13 (8%)	11 (7%)	15 (7%)	7 (5%)

*Smear negative patients cannot be classified as either cured or treatment failure since these outcomes rely on the patient being initially smear positive.[7] Data are n (%).

Table 4: **WHO treatment outcomes**

multidrug resistant strains. There was no statistically significant difference between the two groups with respect to resistance status.

For smear-positive patients, treatment success (cure or treatment completion) was 63% in both groups (table 4). Death rates were marginally higher in the smear-positive Russian treatment group (17, 11%, *vs* 13, 8%). Of the 30 deaths in smear-positive patients, six patients died in the first 2 weeks. One patient had multidrug-resistant tuberculosis. 13 deaths were recorded as non-tuberculosis related deaths. Among 18 treatment failures, three (17%) were patients with multidrug-resistant tuberculosis, 16 (89%) were alcoholics, and two (11%) were ex-prisoners. 37 patients defaulted: one (3%) had multidrug-resistant tuberculosis, 29 (78%) were alcoholic, and four (11%) were ex-prisoners. For smear-negative patients, success (defined as treatment completion) was marginally higher in the WHO group (107, 79%, *vs* 144, 72%) whereas death rates were slightly raised in the Russian group (14, 7%, *vs* 5, 4%).

Table 5 shows that smear conversion rates at 6 months were not statistically different between the two groups at 6 months (short-course chemotherapy, 91% *vs* Russian, 85% [difference in proportions=6%, 95%, CI –2 to 13%]). This difference remained when smear conversion rates were adjusted for contact status.

Table 5 shows that 6-month culture conversion rates for short-course chemotherapy (95%) were significantly better than for Russian regimens (81% [difference in proportion=14%, 95% CI 8–20%]; p=0·0001). Statistical significance remained when culture conversion rates were adjusted for smear and employment status. Cavity-closure rates were marginally higher in the Russian treatment group at 2 months and in the WHO short-course chemotherapy group at 6 months. Overall, outcomes were worse among patients with multidrug resistant isolates than non-resistant isolates (culture conversion 9 of 20, 40%, *vs* 324 of 376, 86%; p<0·0001, and smear conversion 8 of 12, 67%, *vs* 220 of 247, 89%; p=0·04).

Less than 10% of patients had a severe adverse reaction to antituberculous medication: the most common drug necessitating withdrawal was pyrazinamide (18 of 646, 3%). There was no statistical difference in the rate of drug reactions between the two groups. Adverse reactions to adjunctive therapy were not formally recorded, but during retrospective discussions none were reported.

Discussion

The trial and its results are important as one of the first steps to building a strong and locally applicable evidence base for Russian medical care. Russian clinicians have distinct approaches to clinical and public health practice compared with the west. They are also working in a very different social and organisational context, which affects the diseases they see and the ways they deal with them. We used the trial to introduce new therapeutic and methodological ideas such as the use of comparative groups, statistical significance, and randomisation. One of the major successes of the trial was the way that methodological shortcomings were used as positive learning opportunities. As the Russian health system is currently being bombarded with advice and recommendations from external experts, many of whom have very limited knowledge of the local conditions (and previous successes), it is vital that local staff can develop their own ways of understanding and choosing between the various options.

Short-course chemotherapy regimens achieved just under 80% smear conversion rates at 2 months and 90% smear conversion at 6 months in the Tomsk patients. This result suggests that directly observed short-course chemotherapy can be applied successfully to Russian tuberculosis patients, within the Russian health service. Significantly higher 6-month culture conversion rates, and trends to higher smear conversion rates, with slightly higher WHO success rates and lower overall death rates in smear-negative patients, might even suggest that directly observed short-course chemotherapy regimens are more effective than traditional Russian treatments. Anecdotally, there have been suggestions that as the Tomsk tuberculosis specialists started to see the rapid results from WHO treatments they began to use short-course chemotherapy-type regimens in patients allocated to the Russian treatment group. Study design did not preclude this practice because any treatment deemed appropriate by the tuberculosis specialists was permissible in this group and the analysis was based on intention-to-treat. The effect of this change in allocated

	WHO short-course chemotherapy	Russian regimen	Difference in proportion	95% CI (%)	p
Smear conversion among smear-positive patients					
2 months	111 (78%) of 143	101 (73%) of 139	5%	–5 to 15	0·33
6 months	118 (91%) of 130	110 (85%) of 129	6%	–2 to 13	0·17
Culture conversion among culture-positive patients					
2 months	117 (61%) of 191	125 (57%) of 219	4%	–5 to 14	0·39
6 months	160 (95%) of 169	173 (81%) of 214	14%	8 to 20	0·0001
Cavity closure for all patients					
2 months	44 (26%) of 169	58 (29%) of 200	–3%	–12 to 6	0·53
6 months	97 (63%) of 154	114 (61%) of 186	2%	–9 to 12	0·75

Table 5: **Smear, culture, and cavity conversion rates**

treatment will have reduced the possibility of showing a significant difference between the two groups, although it certainly does not detract at all from the conclusion that short-course chemotherapy can work in Russia. Unfortunately, the frequency and complexity of treatment change in the Russian group means that an exact log of treatment regimens was not recorded in this group.

There are two major methodological points of concern: bias resulting from non-random allocation and loss to follow-up. Bias is always possible when patients are allocated systematically, rather than randomly, as in this trial. With multiple risk groups and multiple disease characteristics compared, it is statistically unlikely that there would not be some significant difference between the two groups. Nevertheless, some of the differences (different proportions allocated to the two groups and different proportions smear positive) are so fundamental that they should not be ignored. Smear-positive patients were equally likely to be allocated to either group, but smear-negative patients were more likely to be allocated to the Russian treatment group in the first 8 months. There was no linear trend in the monthly proportion of patients allocated to either group during the entire trial or any seasonal variation, and review of trial entry dates showed that misallocation was not an issue. The stratified analysis suggested that smear status, unemployment, and contact status did not introduce bias. The difficulties in drawing firm conclusions from the non-randomised data were an important learning point for Russian staff, as they considered potential confounders.

The other major potential methodological problem was loss to follow-up. Although similar proportions of patients in the two groups were followed up there is still potential for bias. We modelled the missing microbiological data— first assuming that all missing cases remained smear and culture positive and then considering the result if all cases showed a successful treatment response with smear and culture conversion. These extreme scenarios did not affect the presence or absence of significance in the results. Back-calculations indicate that our final sample sizes would only have been able to identify a 10–15% difference in smear-conversion rates between the two groups. Perhaps the most important lesson from the loss to follow-up is related to the potential clinical effects.

There are high levels of resistance, particularly multidrug-resistance, in Russia,[13] and this study has underlined the poor outcomes among patients with multidrug-resistant disease. Pilot multidrug-resistant tuberculosis projects are being set up in Tomsk and other areas of Russia to identify effective treatment regimens for such patients.[14] Future research should concentrate on preventing patients acquiring resistance, while developing locally effective ways of keeping in contact with patients.[15]

Because only new patients were recruited, the trial did not address the important problem of the large number of previously or partly treated patients being cared for in the Russian tuberculosis system (often called chronics locally, these patients do not correspond exactly to the WHO definition of a chronic patient). 35 additional patients who previously received other treatment presented again during the course of the trial reported here. Although they had not received a standard course of WHO chemotherapy, they were offered WHO category II regimens, and their 6-month smear conversion rates exceeded 80%.

The trial did not systematically gather data on patient preferences for, or perceptions of, the two regimens. Although the clinicians responsible for daily care of the patients noted no obvious trends, this information would be useful to include in future research.

These results are important to the international community as the global threat of tuberculosis and multidrug resistant-tuberculosis worsens. More immediately the results are of importance to Russian policy makers who are currently negotiating a loan with the World Bank for US$90 million to control tuberculosis by means of the WHO strategy, initially with short-course chemotherapy. The trial has provided the framework for a health economics assessment, which has shown that substantial savings can be generated by moving from traditional Russian tuberculosis control to the more ambulatory WHO approach (B Jacobs, personal communication).

WHO standard methods mean that drug purchasing is simplified and cheaper, adherence can be easily assessed, and regimens can be easily implemented. With these advantages, and (at least) treatment equivalence, further work is needed to disseminate the principles of WHO's approach to tuberculosis control in Russia.

Contributors

The protocol for this trial was drawn up by C Mawer, T V Lyagoshina, and N V Ignatenko. V T Golubchikova and T V Lyagoshina locally coordinated the study; C Mawer, N V Ignatenko, and D F Wares coordinated the project in Tomsk. Statistical analyses were done by C Mawer and N Banatvala who also act as guarantors. All investigators contributed to the interpretation of the data. C Mawer, N V Ignatenko, and N Banatvala wrote the initial paper. N Banatvala was the London-based MERLIN medical adviser for the Tomsk Project.

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