



Summary of findings

■ Multidrug-resistant tuberculosis (MDR-TB) is a major threat to public health in the Russian Federation. There are an estimated 7000 to 10 000 new MDR-TB cases each year, equivalent to 6-9% of all new cases.¹

■ The World Health Organization (WHO) and partner agencies have developed a strategy for the management of MDR-TB known as DOTS-Plus. Tomsk Oblast² was the first place where the DOTS-Plus strategy was introduced in the Russian Federation.

■ The DOTS-Plus programme in Tomsk Oblast substantially improved the treatment outcomes of MDR-TB patients. The cure rate after the introduction of DOTS-Plus was 76%, compared to 17% Pre-DOTS-Plus. The death rate fell from 64% to 4%.

■ The average cost per patient treated in the DOTS-Plus programme was US\$ 10 319 compared to US\$ 2281 before DOTS-Plus was introduced.

■ Treatment of MDR-TB cases using the DOTS-Plus strategy in Tomsk Oblast is a cost-effective health intervention. The cost per DALY (Disability-Adjusted Life Year) gained was US\$ 550, less than widely-used benchmarks (for example, average income per capita) that are used for assessing whether an intervention is cost-effective or not.

■ Major factors that affect the efficiency of DOTS-Plus are the availability of highly-concessionary drug prices through the Green Light Committee (GLC), provision of technical assistance, and use of social support to increase treatment adherence.

■ The findings in Tomsk Oblast are consistent with other economic evaluations of DOTS-Plus pilot projects: the cost per DALY gained by DOTS-Plus was US\$ 180 in the Philippines and US\$ 1100 in Estonia.

■ Expansion of DOTS-Plus is feasible through funding available to the national TB programme from the World Bank and the Global Fund to Fight AIDS, Tuberculosis and Malaria (GFATM), provided that the Russian Federation meets all international requirements for DOTS-Plus implementation.

¹ There is no reliable information (i.e. that conforms to WHO standards) available on MDR drug resistance country wide.

² An oblast is an administrative unit or region. There are 88 oblasts in total.

The feasibility and efficiency of controlling MDR-TB using the DOTS-Plus strategy in the Russian Federation

Multidrug-resistant tuberculosis (MDR-TB) is defined as tuberculosis (TB) that is resistant to at least isoniazid and rifampicin, the two principal first-line drugs used in combination chemotherapy. While TB strains can be naturally resistant to anti-TB drugs, MDR-TB is considered a human-induced phenomenon, resulting from the inappropriate management of cases by a TB control programme.

MDR-TB is a major challenge for TB control in the Russian Federation. It is estimated that 7000 to 10 000 (6-9%) new TB cases have MDR-TB, and that in total there are about 30 000 cases of MDR-TB [1]. According to the third Global Report on Anti-TB Drug Resistance produced by WHO and the International Union Against Tuberculosis and Lung Disease (IUATLD), Tomsk Oblast had one of the highest rates of MDR-TB in the world, with 14% of new cases and 44% of previously treated cases estimated to have MDR-TB in 2002 [2]. The treatment of MDR-TB with first and second-line drugs is a potentially life-saving intervention. Such treatment is a patient's last chance for cure, and can help to reduce the transmission of MDR-TB strains. However, the cost of treatment is high: drug costs alone for the 30 000 estimated cases of MDR-TB could amount to US\$ 70 million at highly-concessionary Green Light Committee (GLC) prices,³ and US\$ 452 million at market prices (see Table 1).

Table 1

Estimation of TB drug costs for treatment of MDR-TB cases, 2003 US dollars [1].

	Average cost per patient treated	Total costs - number of estimated incident MDR cases per year = 8000	Total costs - number of prevalent MDR cases = 30 000
GLC prices	US\$ 2 349	US\$ 18 792 000	US\$ 70 470 000
Market prices	US\$ 15 060	US\$ 120 480 000	US\$ 451 800 000

Currently, there is a general shortage of the second-line drugs needed for effective treatment of MDR-TB, and no external quality control for drug susceptibility testing [3]. In addition, rational use of second-line drugs requires effective management and appropriate laboratory capacity. Inappropriate use of second-line drugs can result in the creation of additional drug resistance (the so-called “amplifier effect” [2]), which leads to the loss of these drugs as effective therapies for active TB disease. As a result, the widespread use of second-line drugs by national TB programmes needs to be carefully controlled.

³ The working group has made arrangements with the pharmaceutical industry to provide concessionally-priced, second-line anti-TB drugs to DOTS-Plus pilot projects meeting the standards outlined in the Guidelines for Establishing DOTS-Plus Pilot Projects for the Management of MDR-TB.



The World Health Organization (WHO) and partner agencies have developed a strategy for management of MDR-TB known as DOTS-Plus. This strategy is being evaluated in various countries, to assess whether it is feasible, effective, affordable and cost-effective. This brief reports the feasibility, treatment outcomes, cost and cost-effectiveness of DOTS-Plus in Tomsk Oblast [4]. In 2001, Tomsk Oblast became the first oblast to implement DOTS-Plus in the Russian Federation. To provide an international perspective, results are compared with those from economic evaluations carried out in the Philippines and Estonia.

The DOTS-Plus strategy

The DOTS-Plus strategy has five essential components, based on the fundamental principles of TB control. They are:

- sustained government commitment;
- accurate, timely diagnosis through quality-assured culture and drug susceptibility testing;
- appropriate treatment utilizing second-line drugs under strict supervision;
- an uninterrupted supply of quality-assured anti-TB drugs;
- a standardized recording and reporting system.

These five components are similar to the five essential components of a DOTS programme, thus facilitating the integration of both programmes. Moreover, the definition of DOTS-Plus allows for some flexibility, so that programme design and implementation can vary among countries and regions according to the local situation. Factors that affect the design of a DOTS-Plus programme include the magnitude and distribution of drug-resistant TB, the existing infrastructure, possibilities for case-finding, how patients are selected for treatment, drug-resistance patterns, available laboratory capacity, the resources available for directly-observed treatment over a long period of time, and the availability of human and financial resources.

Description of DOTS-Plus in Tomsk Oblast

The WHO-recommended DOTS strategy was implemented in Tomsk Oblast in 1994. Implementation of DOTS-Plus began in 2001. In January 2003 there were 609 MDR-TB patients in Tomsk Oblast. By March 2003, 338 patients had been enrolled in the DOTS-Plus programme and 65 patients

had successfully completed treatment [5]. The key approach of the programme is to administer five anti-TB drugs (first and second-line) to which a patient is still susceptible. During the intensive phase of treatment,⁴ Tomsk City residents are treated in a TB hospital or in a day stay hospital. During the continuation phase of treatment,⁵ patients are treated at either a day stay hospital or in the outpatient department of the TB dispensary. Outside Tomsk city, patients are also initially treated on an inpatient basis. For the continuation phase, patients are treated as outpatients, with supervision provided by district physicians or, in remote areas, by nurses at health outposts. Food parcels including protein supplements are provided to encourage compliance with treatment. The average duration of treatment is 18 months.

The cost, effectiveness and cost-effectiveness of DOTS-Plus in Tomsk was assessed using retrospective data for 100 new and chronic MDR-TB patients enrolled on DOTS-Plus between January 2001 and July 2002, and compared with the costs, effectiveness and cost-effectiveness of the treatment provided to a control group of 100 MDR-TB patients treated between July 1998 and July 1999, prior to DOTS-Plus implementation (hereafter the “Pre DOTS-Plus strategy”).

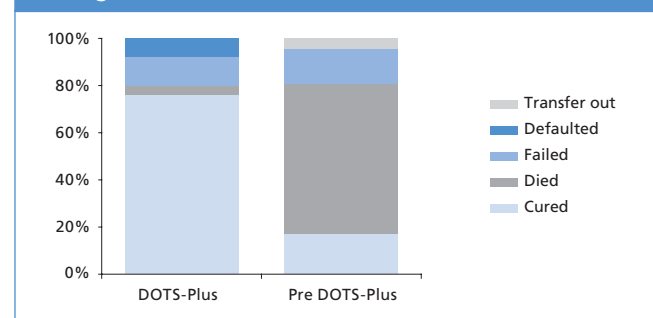
Results for DOTS-Plus in Tomsk Oblast

The cure rate was 76% for the DOTS-Plus strategy compared to 17% for the Pre DOTS-Plus strategy.

The death rate was 4% with the DOTS-Plus strategy and 64% for the Pre DOTS-Plus strategy (see Figure 1).

Figure 1

Treatment outcomes for DOTS-Plus and Pre DOTS-Plus strategies in Tomsk Oblast (%)



⁴The intensive phase of treatment lasts for six months if there are no positive cultures in the first, second and third months of treatment and improvements are visible on X-rays. In other cases, the intensive phase continues until cultures are negative for at least seven consecutive months.

⁵The continuation phase lasts for between 18 and 24 months, depending on the extent of lung damage. Injectable drugs are discontinued in the continuation phase.



The average cost per patient treated was US\$ 10 319 for DOTS-Plus and US\$ 2281 for Pre DOTS-Plus (see Table 2). Drug costs were much higher with the DOTS-Plus strategy (US\$ 3718 versus US\$ 603). With the DOTS-Plus programme, patients spent about twice as many days in inpatient facilities and made three times more visits to day-stay wards compared to the Pre DOTS-Plus strategy (239 versus 120 inpatient days and 358 versus 109 days in day stay wards respectively). New costs that were associated with DOTS-Plus included technical assistance to ensure effective implementation, programme and data management, training of staff, advocacy and research (these accounted for 21% of total costs). Nutritional support and food packages to encourage adherence were relatively small costs (1% of total costs).

Table 2

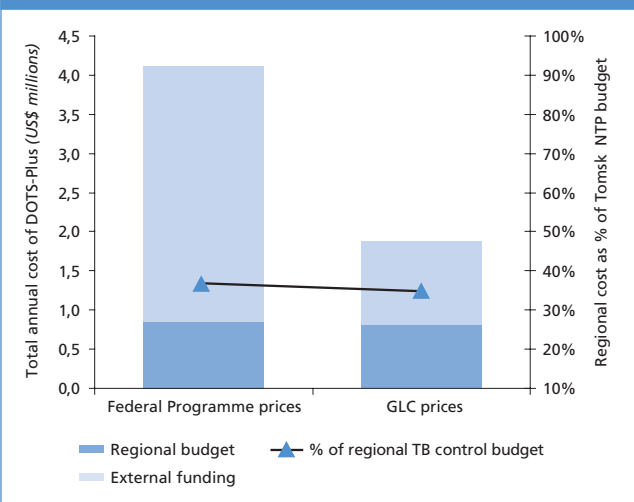
Average cost per patient treated for DOTS-Plus and Pre DOTS-Plus strategies, 2003 US dollars

Item	DOTS-Plus		Pre DOTS-Plus	
Drug costs	3718*	36%	603**	(26%)
Inpatient care at US\$ 9.3 per day	2224	22%	1113	(49%)
Day stay ward at US\$ 3.1 per day	1117	11%	341	(15%)
DOT visits (TB and GHC) at US\$ 1.4 per visit	772	7%	97	(4%)
DOTS-Plus programme and data management costs	416	4%	0	(0%)
DOTS-Plus technical assistance and supervision	370	4%	0	(0%)
DOTS-Plus training	302	3%	0	(0%)
DOTS-Plus advocacy	288	3%	0	(0%)
DOTS-Plus related research	272	3%	0	(0%)
DOTS-Plus laboratory support	200	2%	0	(0%)
X-rays at US\$ 2.6 each and CT scans at US\$ 93 each	168	2%	21	(1%)
DOTS-Plus nutritional support and food parcels	130	1%	0	(0%)
Cultures at US\$ 2.6 each	83	1%	22	(1%)
Visits by TB specialist at US\$ 2.1 per visit	27	0%	63	(3%)
Smears at US\$ 0.50 each	17	0%	4	(0%)
Specialists consultations at US\$ 2.1 per visit	15	0%	9	(0%)
DST (1st, 2nd) at US\$4.0 per test	11	0%	9	(0%)
Other DOTS-Plus related costs	189	2%	0	(0%)
Total	10 319	100%	2281	100%

Note: * at GLC prices ** at federal prices
GHC = General Health Care; DST = Drug Susceptibility Test

Figure 2

Total annual costs (by sources of funding) and affordability (black line) of the DOTS-Plus programme for different drug cost scenarios in Tomsk Oblast (US\$ and % of Tomsk NTP budget), 2003 US\$

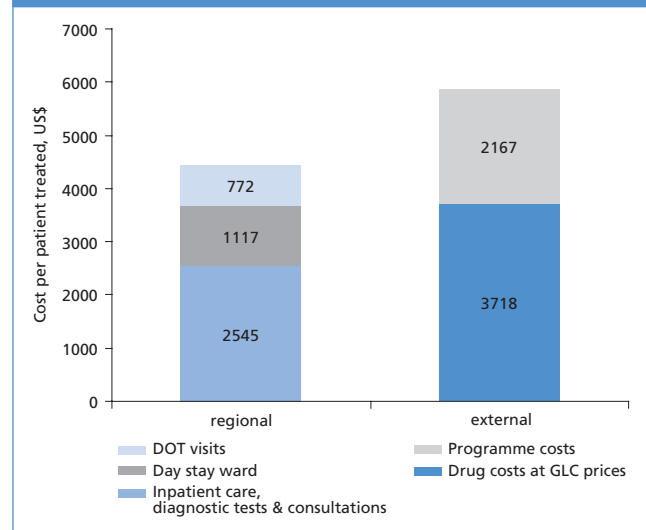


Access to drugs at GLC prices was crucial for ensuring that DOTS-Plus was affordable. The total annual costs of the DOTS-Plus programme in Tomsk Oblast for the estimated 274 patients that need treatment would double from around US\$ 2 million at GLC prices to over US\$ 4 million at federal programme prices (Figure 2).

DOTS-Plus implementation in Tomsk relied extensively on external funding (Figure 3).⁶ Drugs and other new

Figure 3

Average cost per patient treated in the DOTS-Plus programme by item and source of funding, GLC prices scenario, 2003 US\$

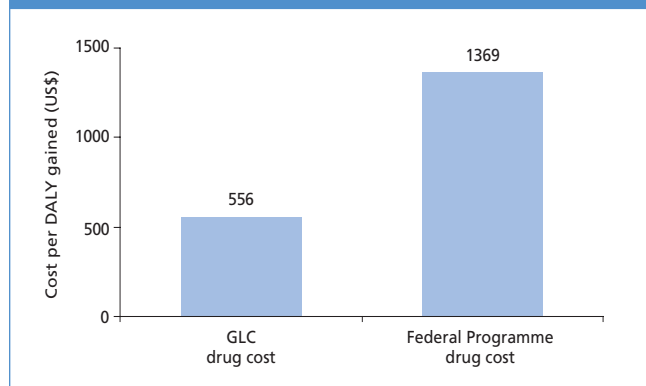


⁶ External sources means funding from both federal level and international agencies.



Figure 4

The cost-effectiveness of DOTS-Plus, alternative drug price scenarios in Tomsk Oblast (US\$)



costs associated with DOTS-Plus implementation (programme management and supervision, technical assistance, training, advocacy, research, laboratory support, nutritional support and food parcels) were high, at US\$ 5885 per patient, and funded entirely from external sources.

The cost-effectiveness of the DOTS-Plus strategy (i.e. the increase in total costs compared to the Pre DOTS-Plus strategy divided by the increased effectiveness compared to the Pre DOTS-Plus strategy) was estimated at US\$ 566 per DALY gained.⁷ This is almost equivalent to US\$ 566 per year of life saved, since most of the DALYs gained through curing TB are associated with prevented mortality. This is less than benchmarks that have been used to define whether an intervention is cost-effective or not. For example, two recently used benchmarks are per capita income (US\$ 2610 in the Russian Federation in 2003) and three times per capita income [6].

Policy recommendations

1. The DOTS Plus strategy is a cost-effective health care intervention that can contain the spread of MDR-TB and save lives. It may also save substantial governmental resources spent on sick leave, unemployment and rehabilitation care.
2. A drug resistance survey is urgently needed to assess the MDR problem country-wide and to inform the development of a national plan and budget for DOTS-Plus expansion.
3. Based on the cost-effectiveness results from Tomsk Oblast and given the additional financial resources available for implementation of DOTS-Plus

⁷Disability Adjusted Life Year (DALY).

The cost-effectiveness of DOTS-Plus pilot projects in the Philippines, Estonia and the Russian Federation

Increasing numbers of middle and low-income countries are implementing DOTS-Plus projects or programmes that use second-line drugs to treat patients with MDR-TB. However, evidence about their feasibility, effectiveness, cost and cost-effectiveness is limited. Using similar standardized study methods we evaluated the effectiveness, cost and cost-effectiveness of DOTS-Plus projects or programmes established at Makati Medical Center in Manila, the Philippines in 1999, in Tomsk Oblast, the Russian Federation in 2001, and in Estonia in 2001. Patients were treated with individualized regimens tailored to their drug susceptibility pattern. Total costs (in year 2003 US dollars) and effects (DALYs gained) were estimated as the additional (incremental) costs and effects compared with a situation in which DOTS-Plus is not implemented.

The cure rates achieved when DOTS-Plus was implemented were around 60-75% in all settings, much higher than the cure rates achieved Pre DOTS-Plus. The average cost per patient treated using the DOTS-Plus strategy was much higher compared with the situation Pre DOTS-Plus. From the health system perspective, the average cost per patient treated varied from US\$ 3400 in the Philippines to US\$ 10 000 in the Russian Federation. In all settings where DOTS-Plus was implemented, anti-TB drugs were the largest single cost item, followed by inpatient care (Estonia and the Russian Federation) and programme management activities such as technical assistance, training, advocacy and research (Russian Federation and the Philippines). The cost per DALY gained by the DOTS-Plus strategy varied from around US\$ 180 in the Philippines to US\$ 550 in the Russian Federation to US\$ 1100 in Estonia.

These international data provide evidence that DOTS-Plus programmes for MDR-TB using individualized regimens can be feasible, effective and cost-effective in low and middle-income countries.



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programmes during the next five years, the following recommendations can be made:

- develop MDR-TB guidelines for diagnosis and treatment based on international standards;
 - establish centres of excellence for treatment of MDR-TB;
 - implement a "Training of trainers" programme to facilitate rapid nationwide coverage of DOTS-Plus;
 - introduce social support to encourage adherence to treatment;
 - strengthen laboratory services so that they can provide high-quality culture and drug susceptibility testing services;
 - build capacity for MDR-TB treatment at regional level through renovation of capital equipment and improvement of infection control.
4. Purchase second-line drugs from the GLC at concessionary prices to ensure the affordability and efficiency of DOTS-Plus programmes.
 5. Federal TB research institutes and centres of excellence should be used to provide technical assistance to DOTS-Plus programmes implemented at oblast level, with a limited amount of external and international support.

Comment

Funding from the World Bank (US\$ 100 million for five years) and the Russian Government (US\$ 35 million) is available to partially address the MDR-TB problem. A Global Fund to fight Aids, Tuberculosis and Malaria (GFATM) grant (US\$ 91 million over five years) includes US\$ 31 million for strengthening national capacity to manage MDR-TB cases and for treatment of 8000 MDR-TB patients in the next three

Table 3

Total GFATM grant 2005 for Objective 2 to increase early detection and improve treatment rates for MDR-TB in US dollars [1].

Main Activities	US\$
Establishment of five centres of excellence in the civilian sector	1 375 450
Establishment of eight centres of excellence in the penitentiary sector	1 294 720
Second line drugs	17 614 400
Infectious control	8 655 500
Laboratory services	1 500 000
Training	586 500
Total	31 026 570

years (see Table 3). This GFATM funding will be made available on condition that the Russian Federation meets international requirements for DOTS-Plus programme implementation [1].

References

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