

ORIGINAL ARTICLES

Surveillance report

TUBERCULOSIS CONTROL IN LATVIA: INTEGRATED DOTS AND DOTS-PLUS PROGRAMMES

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From 1991 until the end of 1998, the number of patients with tuberculosis in Latvia increased 2.5 times with a simultaneous increase of drug resistant and multidrug resistant tuberculosis (MDR-TB).

Descriptive analysis of different TB programme services, activities and strategies including Directly Observed Therapy Short-course (DOTS) for tuberculosis and treatment of MDR-TB, were performed. Data from the state tuberculosis registry, drug resistance surveillance, and the national MDR-TB database were used. The state-funded national tuberculosis control programme (NTAP, Nacionala Tuberkulozes Apkarosanas Programma), based on WHO recommended DOTS strategy, was introduced in Latvia in 1996. The NTAP includes TB control in prisons. Treatment of MDR-TB using second line drugs was started in 1997. Cure rates for TB patients increased from 59.5% in 1996 to 77.5% in 2003. Between 1996 and 2003, more than 200 patients began MDR-TB treatment each year, and the cure rate was between 66% and 73%. Numbers of MDR-TB patients were reduced by more than half during this period. Treatment results including MDR-TB reached the WHO target, with cure rates 85% of newly diagnosed patients. These results demonstrate that MDR-TB treatment and management using the individualised treatment approach can be effectively provided within the overall TB programme on a national scale, to successfully treat a large number of MDR-TB patients.

Rapid diagnostic methods combined with early intensified case finding, isolation and infection control measures could decrease transmission of TB and MDR-TB in hospitals and in the community. Highly important that MDR-TB management follows WHO recommendations in order to stop creating drug resistance to first and to second line drugs.

Euro Surveill 2006;11(3): 29-33

Published online March 2006

Key words: DOTS, Latvia, MDR-TB, tuberculosis**Introduction**

Latvia has a population of 2.4 million people. Since independence from the former Soviet Union in 1991, Latvia has experienced an increase in tuberculosis (TB) morbidity and mortality together with the appearance of drug resistant and multidrug resistant tuberculosis (MDR-TB). Socioeconomic disruption, increasing poverty, unemployment, homelessness, substance abuse, increasing alcoholism and more recently, intravenous drug use have been the main factors.

In 1991, incidence of TB was 29 cases per 100 000 population [1], increasing to 74 cases per 100 000 in 1998 and then declining to reach 59 per 100 000 in 2004.

In 1998, the incidence of TB in prisons was alarmingly high, at 37 times higher than the national incidence, with outbreaks in several prisons leading to incidence 100 times higher than national incidence. Following the implementation of a strong TB control policy in the prison system, TB incidence declined rapidly.

Lack of first line antiTB drugs, and low quality and misuse of these drugs in the early 1990s are the most important factors for the development of TB drug resistance and MDR. Overcrowded hospitals, prisons and other mass gathering settings with bad environmental conditions, and lack of ventilation and other infection control measures have all contributed to the ongoing transmission of MDR Mycobacterium tuberculosis strains to healthcare workers, other patients and prisoners [2].

Health system reform including TB control services started in early nineties. Government support received for development and implementation of International standards in TB control.

The first global antiTB drug resistance survey performed by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Diseases (IUATLD) from 1994 to 1996 [3] surveyed 35 countries, and found that Latvia had the highest level of MDR-TB, with 14.4% (1 in 7) newly diagnosed infectious TB cases without prior history of TB treatment being diagnosed as MDR-TB [4-6].

Technical and financial assistance were given by several organizations (WHO for development and implementation of new international standards; the Nordic countries within the project No-TB Baltic for development of Directly Observed Therapy (DOT) as a standard of ambulatory care integrated with general services; CDC (Centre for Disease Control and Prevention, Atlanta), / United States Agency of International Development (USAID) supported two fold projects: 1/ to develop a Centre of Excellence for MDR-TB treatment and management, 2/ to establish self-sustainable International Training Centre.

The aim of the study is to demonstrate the implementation and effectiveness of the National Tuberculosis Control Programme in Latvia.

Methods

Descriptive analysis of different TB programme services, activities and strategies including Directly Observed Therapy Short-course (DOTS) for TB and treatment of MDR-TB, were performed. Data from the state tuberculosis registry, drug resistance surveillance, and the MDR-TB database were used. MDR-TB is defined as in vitro resistance to at least isoniazid and rifampin- the two most potent antiTB drugs used for TB treatment.

TB control in Latvia

The National Tuberculosis Control Programme (NTAP) of Latvia is operated by the Ministry of Health. The State Agency for Tuberculosis and Lung Diseases (TPSVA, Tuberkulozes un Plausu slimību Valsts Agentūra) has primary responsibility for prevention and control

State Agency for Tuberculosis and Lung Diseases, Latvia

TB through development and implementation of the TB control programme core components activities throughout the country (<http://www.tuberculosis.lv>). The first NTAP was implemented in 1996. It was based on WHO guidelines for TB control of DOT short course and DOTS strategy - combining the five following elements: sustained political commitment; case detection through quality assured bacteriology laboratory; standardised short-course chemotherapy to all cases of TB under proper case-management conditions including DOT and patient support; uninterrupted supply of quality certified TB drugs; and a reporting and recording system allowing assessment of TB treatment and programme performance (<http://www.who.int/gtb/dots/whatisdots.htm>).

All five DOTS programme components were introduced and adopted nationwide to address the increasing TB epidemic. Penitentiary system TB control began in 1996 and was fully integrated into the NTAP in 1997. All TB control activities were applied simultaneously to the prison and civil sectors.

MDR TB was already a problem in Latvia and the number of diagnosed patients increased dramatically since 1994. Although DOT short course can cure almost 90% of new smear positive cases sensitive to antiTB drugs, the treatment success of MDR-TB cases is much lower. Untreated, these patients contribute to the spread of MDR-TB in hospitals, in the community and in prisons, to healthcare workers and to other patients.

NTAP initiated MDR-TB patients' treatment, based on individualised case management, in 1997 and implemented it in prisons a year later. MDR-TB management was built into the existing DOTS programme. Existing recourses for TB control were reallocated, facilities for MDR-TB treatment and management established, and staff trained.

In 1999 WHO and its partners launched a strategy for managing MDR-TB called DOTS-Plus, allowing access to second line drugs for countries with MDR-TB and well implemented DOTS strategy. Latvia was one of the pilot projects to evaluate a feasibility of using second line drugs in limited resource settings.

Results

Government commitment

The NTAP is state-funded. All patients diagnosed with TB or MDR-TB are treated free of charge.

Inpatient treatment is provided by nine TB hospitals in Latvia, including one TB ward within the penal system. The total number of beds was 2010 in 1991, 1380 in 1998 and 1150 in 2004. Specialised facilities are established to treat MDR-TB patients including facilities for prisoners and psychiatric patients.

TABLE 1

Social background of TB patients in 2002 (n=1540) and 2003 (n=1481), Latvia

	2002		2003	
	Number	%	Number	%
TB in prisons	162	10.52	95	6.41
Born in other country	98	6.36	75	5.06
Unemployed	742	48.18	693	46.79
Alcoholics	466	30.26	445	30.05
Contact with TB	321	20.84	350	23.63
Drug users	13	0.84	39	2.63
HIV infected	21	1.36	34	2.30
Ex-prisoners	111	7.21	117	7.90
Homeless	92	5.97	87	5.87

State health reform is continuing with a transition to more ambulatory-based health care, including for TB. In all 26 districts, TB control is under the general health services. On district level, TB specialists are responsible for TB control including MDR-TB and closely collaborate with the primary healthcare services, sharing responsibility for case finding and for providing treatment under direct observation during the ambulatory phase of treatment.

TB case detection

TB case detection is based on bacteriological examination of symptomatic patients who attend primary healthcare services. Active case finding is performed to detect secondary cases during contact investigation and active screening of high risk populations (such as prison inmates, homeless people, soup kitchen attendants, harm reduction programme participants) [TABLE 1].

In all patients, TB diagnosis is based on bacteriological examination. Three consecutive sputum smears, two cultures and one drug susceptibility test to first line drugs are performed before the initiation of TB treatment. For all mycobacterium strains confirmed as MDR-TB, a drug susceptibility testing for second-line antiTB drugs is performed.

Laboratory diagnostic services

Laboratory network with three levels provide diagnostic services for country (smears, cultures and DST). The central bacteriology laboratory (CBAK LAB, Centrala Bakteriologiska Laboratorija) is part of the TPSVA. It provides all diagnostic services and, serves as the national reference laboratory for TB and collaborates with the Swedish Institute for Infectious Disease Control (Smittskyddsinstitutet, SMI) on external quality control. The Central Bacteriological Laboratory is the only laboratory performing DST in Latvia.

Drug resistance surveillance was established in 1997 and reports are published yearly. The laboratory reports all DST results weekly to the TB registry. The third WHO/IUTLD drug resistance surveillance data shows improvement in drug resistance trends in Latvia [7].

The rapid diagnostic method BACTEC-MGIT is used for patients suspected to have MDR-TB. Early diagnosis and treatment initiation with proper isolation of MDR-TB patients facilitates infection control within healthcare facilities and decreases transmission. New rapid diagnostic methods are studied in Latvia for implementation in the future for routine use [8].

Treatment

The treatment of TB was changed to short course chemotherapy according to the WHO guidelines in 1995. Patients routinely receive treatment in hospitals, for a minimum of two weeks, until smear conversion to negative. After smear conversion, patients are discharged for ambulatory treatment using daily DOT. To help patients complete treatment and to improve treatment adherence, patients receive social aid provided by districts social departments of Ministry of Welfare during the ambulatory phase. Treatment outcomes have improved from a 59.6% treatment success rate in 1996 to 77.5% in 2003. MDR-TB treatment is centralised. As soon as MDR-TB is confirmed, the patient is directed to the expert group of physicians to confirm diagnosis and to design treatment regimen with second line drugs and follow-up treatment effectiveness. Individually tailored treatment regimens are used based on the results of in vitro susceptibility tests of *M. tuberculosis* obtained from patients before the initiation of treatment. Treatment of MDR-TB usually starts with an empiric regimen of 5 to 7 drugs. It takes approximately 3 - 8 weeks to adjust the treatment regimen according to DST results. Injectable drugs are used daily until culture conversion, and then continued 5 times per week for an additional 2 to 3 months, and 3 times per week depending on the clinical status of the each patient.

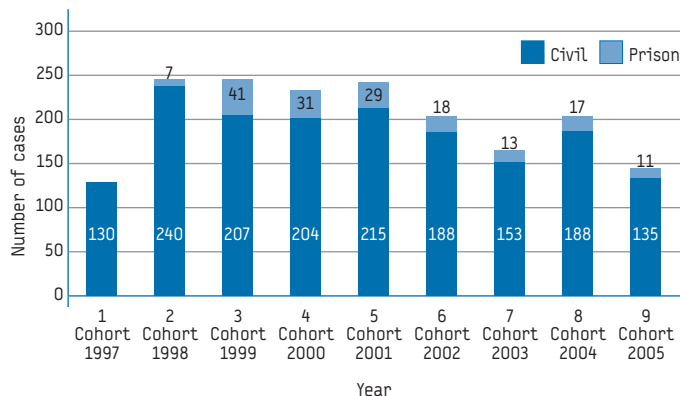
MDR-TB patients receive treatment at four specialised treatment centres that rely on inpatient care, followed by outpatient DOT when possible. Duration of hospital admission depends on sputum culture conversion to negative. During ambulatory phase treatment for all TB patients is provided in one case management system.

Every year from year 1998 to 2004 in addition to newly detected cases of TB and re-treatment cases, more than 200 patients from both civilian and penal sectors have begun treatment under the DOTS-plus programme in Latvia, decreasing to 146 in 2005 reflecting the trend of newly diagnosed MDR-TB patients [FIGURE 1].

Latvia applied to the WHO Green Light Committee (GLC) and got approval to treat 350 MDR-TB patients with inexpensive second-line anti-TB drugs which ensured treatment for all diagnosed MDR-TB patients.

FIGURE 1

Annual number of MDR-TB patients, Latvia, 1997 to 2005



All registered MDR-TB patients who start treatment during the year are included in cohort analysis. For patients who began MDR-TB treatment in the years 2000 and 2002, treatment outcomes show treatment success from 66% to 73%.

Under DOTS plus conditions, treatment efficacy (treatment outcome excluding default) has improved over time. Positive outcome (treatment completed and patient cured) increased from 70% in 2000 to 83% in 2002, and negative outcome (treatment failure and patient death) decreased from 30% to 17% [9]. For treatment outcome analysis, internationally accepted outcome definitions are used [10].

The WHO goal to cure 85% of patients under DOTS programme conditions in settings with high levels of MDR-TB is difficult to achieve without treatment for MDR-TB. To estimate the impact of MDR-TB on treatment outcome we use the additional outcome: MDR-TB patients who continued treatment. Cohort analysis of the DOTS programme in Latvia shows that the cure rate for new bacteriological confirmed patients during the 1998–2002 period increased from 74% (747/1010) in 1998 to 78% in 2002 (729/934). In addition, between 8% MDR-TB cases were counted as still under treatment in the treatment outcome in 2002. After completing MDR-TB treatment for these patients the overall cure rate increased from 76% to 82% in 2002 [11] [TABLE 2].

Surveillance of TB in Latvia

The national tuberculosis registry was established in 1996 when the old registration system was replaced by new international standards. Standardised forms and registries recommended for effective TB control are used at district and national level. TB notification is mandatory for both physicians and laboratory on district and national levels.

TABLE 2

Treatment outcomes of TB new cases in 2002 (n=934), Latvia

Treatment outcomes	After 12 months	After 24 months	After 24 months
	All cases	MDR-TB cases	All cases
Cured	709 (75.9%)	53 (70.7%)	762 (81.6%)
Completed	20 (2.1%)	2 (2.7%)	22 (2.4%)
Failure	10 (1.1%)	1 (1.3%)	11 (1.2%)
Default	51 (5.5%)	12 (16%)	63 (6.7%)
Transferred out	3 (0.3%)	-	3 (0.3%)
Died*	66 (7.1%)	4 (5.3%)	70 (7.5%)
Still on treatment (DOTS-Plus)	75 (8%)	3 (4%)	3 (0.3%)

*Includes 11 MDR-TB patients: 5 died before MDR-TB diagnosis, 4 died under DOTS-Plus treatment, 2 were not enrolled in DOTS-Plus treatment

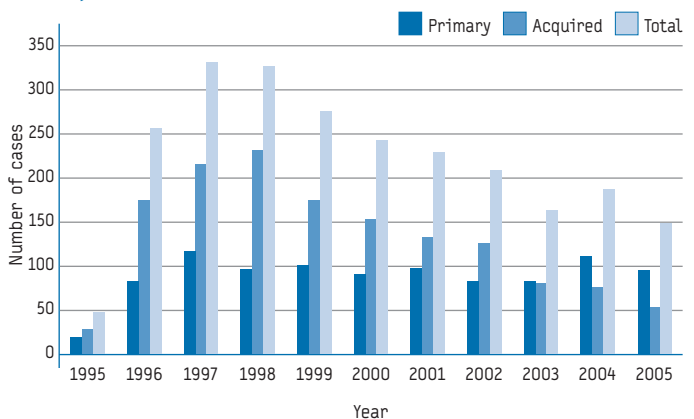
Cohort analysis of treatment outcomes was introduced in 1996, using international definitions. Database for MDR-TB registration and outcome analysis were developed in 1999 and implemented in 2002. Data of cohort 2000 have been entered and analysed [12].

All MDR-TB cases detected in laboratory are registered in the national tuberculosis registry. In 1997, 332 new MDR-TB cases were registered; data from previous years are incomplete and not comparable. After the peak of diagnosed MDR-TB cases in 1997, the number began to decline, with 163 cases diagnosed in 2003, followed by a slight increase in 2004 to 187 cases, and a decline thereafter to 148 diagnosed cases in 2005 [FIGURE 2].

The total number of annually registered MDR-TB cases has decreased by 51% since 1997.

FIGURE 2

Number of patients with primary and acquired MDR-TB in Latvia, 1994–2005



The annual report on TB and MDR-TB surveillance is prepared by TB registry staff. The report is presented at the meeting of the society of tuberculosis and lung physicians, and submitted to the responsible department at the Ministry of Health. NTAP TB registry participates in voluntary reporting of individual data to the EuroTB network [13].

The problem of TB/HIV coinfection

Since the first patient was registered with TB/HIV co-infection in 1994, the number of patients diagnosed with both infections continues to increase each year [TABLE 3].

Screening for HIV-1 was introduced in Latvia in 1989, and is voluntary in the general population, except for blood donors. TB infection is a one of the risk groups for HIV-1 screening. All TB

patients are counselled and offered tested for HIV; the coverage is about 90% of all TB patients. Data from testing is collected nationally by the National AIDS Prevention Programme. Information exchange is established between the TB and HIV programmes.

The NTAP of Latvia and HIV/AIDS Centres of Latvia have, under the umbrella of the Ministry of Health, established a coordination board to address emerging issues in TB/HIV since 2005. Links between the TB and HIV registries have been established, and intensified case finding in high risk groups of HIV, and consultation and screening on TB in harm reduction programmes have been implemented. The initial results of the intensified case finding are encouraging, with 5% TB case detection among those tested.

TABLE 3
HIV prevalence among TB patients, Latvia, 1998-2003

Year	Among TB patients		Among MDR-TB patients	
	Number tested TB	Number HIV positive (%)	Number tested MDR-TB	Number HIV positive (%)
1998	1945	1 (0.1)	327	0 (0)
1999	1758	9 (0.5)	276	1 (0.4)
2000	1893	14 (0.7)	243	2 (0.8)
2001	1882	27 (1.4)	234	13 (5.6)
2002	1840	25 (1.6)	209	3 (1.4)
2003	1755	40 (2.3)	163	7 (4.2)
Total	11 073	116	1452	22

Between 1994 and 2004, 158 cases of TB/HIV coinfection were notified. HIV seroprevalence increased from 0.1% of TB patients tested [14] in 1998 to 2.3% in 2003 [15]. Similar trends have been observed for MDR-TB patients. HIV seroprevalence in MDR-TB patients increased from 0.4% in 1999 to 5.6% in 2001. In 2001, an outbreak, 13 primary MDR-TB cases with HIV co-infection was registered. Only three cases were registered in 2002, and seven cases in 2003. The average number of cases registered since 2002 is seven, and 4% of our newly diagnosed MDR-TB cases are co-infected.

Discussion

The DOTS strategy, endorsed by WHO, is the world's most effective tool to combat TB. The DOTS-Plus programme is developed by WHO and partners to manage MDR-TB using second-line antiTB drugs.

MDR-TB requires longer duration of treatment (up to 2 years) to achieve cure, in comparison with 6 months treatment for drug susceptible TB. MDR-TB has much higher level of mortality than drug susceptible TB, lower cure rates and even higher default rates. Infection control of MDR-TB are more difficult to implement in hospitals due long time until DST results available, and start adequate treatment as well worse response to treatment with second line antiTB drugs. The cost of drugs to treat a MDR-TB case can be up to 100 times more than the cost of treating a drug susceptible TB case.

If drug sensitive TB is not treated properly develops drug resistance to I line antiTB drugs and I line drugs will no longer be effective. The first measure of TB program is to stop create new MDR-TB cases.

The establishment of sound TB control strategies in Latvia has led to a 65% reduction in acquired MDR-TB cases over 10 years. However, primary MDR-TB rates remained stable during this period. Unless it was possible to reduce MDR-TB with good DOTS programme only, our data demonstrates that reduction of MDR-TB was not achieved in settings with high levels of drug resistance. If

MDR-TB patients are untreated, or treated with first line drugs, they continue to spread deadly disease, and become increasingly resistant to drugs. Therefore, the DOTS-Plus programme to treat and cure the existing reservoir of MDR-TB should be built on a well functioning DOTS programme to stop the development of drug resistance and interrupt the chain of transmission.

DOTS and MDR-TB treatment and case management in Latvia have been implemented as integral parts of NTAP. All five components with MDR-TB related elements were included: MDR-TB case detection strategy; individualised treatment regimens using second line drugs; individualised approach to case management; recording and reporting and treatment outcome analysis; drug supply and distribution without interruptions in treatment for patients.

By addressing drug sensitive and drug resistant TB, the Latvian National TB programme achieved a decrease of TB incidence by 21%, an improvement of cure rates for all bacteriologically confirmed TB cases, reaching the WHO target for 85% cure. Most important is that development of drug resistance was prevented through proper treatment and management of newly diagnosed TB cases (improving cure rates, decreasing number of re-treatment cases, decreasing default rate). As a result, the number of patients with acquired MDR-TB decreased by 65%. Every year, two thirds of patients who began treatment for MDR-TB were cured.

In cooperation with CDC, the Nordic countries within the No-TB Baltic project, and University of Arkansas of Medical Sciences (UAMS), the Centre of Excellence for MDR-TB treatment and management and self sustained International Training Centre in Latvia (TPSVA/SIZN) were established. They use state-of-the-art equipment, world-class diagnostic and treatment methods, and operational research. In 2004, ITC has been recognised as a WHO Collaborating Centre for Research and Training in Management of MDR-TB. ITC and National TB programme receives full government support. Over the past five years, the demand for training has increased dramatically. Training programmes are based on evidence gained through scientific and operational research, as well as field experience in DOTS and DOTS-Plus implementation, and aim to develop the competences and skills of trainees.

Prioritising TB control activities, coordinating at local, national and international level, following international recommendations for TB and MDR-TB treatment and management have all improved TB programme effectiveness in controlling the TB and MDR-TB epidemic.

Some remaining areas of concern for MDR-TB management in Latvia include treatment interruptions and the country's growing HIV epidemic.

Treatment interruptions and default are closely linked with the development of extensive drug resistance (resistance to 8 or more antiTB drugs) which in most cases becomes incurable. Although patients receive therapy under direct observation, on average 5% of new patients and 13% of MDR-TB patients have defaulted each year. Individual case management approach and patient trace back are used to promote patients' adherence. To improve patients' adherence to the regimen during ambulatory treatment, the NTAP, with the support of district social service departments and the Ministry of Welfare, provides daily food coupons and transport reimbursement for people who attend medical facilities for directly observed treatment. Improving treatment adherence, especially among those previously treated, should improve overall treatment success.

Strengthening case management of new case, rapid MDR-TB diagnosis, contact investigation and genotyping to detect chain of transmission are the next steps to improve MDR-TB control in Latvia.

An emerging HIV epidemic also threatens recent progress in TB control. Although the number of cases with TB/HIV or MDR-TB/HIV coinfections is low, they require prompt interventions to reduce HIV-related TB morbidity and mortality.

Conclusion

These results demonstrate that a MDR-TB treatment and management using the individualised treatment approach can be effectively provided within the overall TB programme on a national scale, and can successfully treat a large number of MDR-TB patients.

Rapid diagnostic methods combined with early intensified case finding, isolation and infection control measures could decrease transmission of TB and MDR-TB in hospitals and in the community.

It is highly important that MDR-TB management follows WHO recommendations in order to stop creating drug resistance to first and to second line drugs.

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