Integration of HIV-testing in routine TB drug resistance surveillance in Kazakhstan and Kenya

Kazakhstan:
Aigul Tursynbaeva[1]
Svetlana Pak[2]
Susan van den Hof[3]

Kenya:
Hillary Kipruto[4]
Josephine Wahogo[5]
Amos Kutwa[6]
Eveline Klinkenberg[3]

Coordination:
Rene L'Herminez[3]

[1] National Center for Tuberculosis Problems, Ministry of Public Health Kazakhstan
[2] KNCV Tuberculosis Foundation, Almaty, Kazakhstan
[3] KNCV Tuberculosis Foundation, The Hague, The Netherlands
[4] Division of Leprosy, Tuberculosis, and Lung Disease, Ministry of Public Health and Sanitation, Kenya
[5] Central reference laboratory, Ministry of Public Health and Sanitation, Kenya
[6]KNCV Tuberculosis Foundation, Nairobi, Kenya

September 2010

Table of Content

Background overall project **5**
Integration of HIV testing in **9**
MDR surveillance in Kazakhstan **9**
Introduction Kazakhstan **10**
TB-HIV situation in the country 10
TB drug resistance situation in the country 11
Outline of organization of TB and HIV/AIDS services 11
TB and HIV screening policies 11
TB testing and diagnosis 11
HIV-testing and diagnosis 11
Definitions for TB/HIV in TB register and HIV/TB in HIV register 11
Policies for (preventive) therapy regarding TB/HIV 12
Eligibility criteria for isoniazid preventive therapy 12
Eligibility criteria for cotrimoxazol preventive therapy 12
Eligibility criteria for antiretroviral treatment 12
Process outline Kazakhstan **12**
TB and HIV surveillance systems in place at the start of the project 12
Overview of methodology used 13
Improvement of data completeness 13
Monitoring visits 13
Improvements in co-operation between the national TB and AIDS centers 14
Challenges during project implementation 14
Results data analysis Kazakhstan **14**
Patient characteristics 14
Completeness of HIV-testing results and DST results 15
Completeness of HIV-testing results 15
Completeness of smear and culture results for diagnosis of TB 20
Completeness of DST results at the time of the TB diagnosis 20
HIV-testing results and DST results 20
HIV-testing results 20
DST results 25
Association between HIV-status and drug resistance 25
Treatment outcomes related to HIV and drug resistance 25
Provision of antiretroviral treatment and co-trimoxazole preventive treatment 26
Key findings and recommendations Kazakhstan **35**
Key findings 35
Recommendations 36
Integrating HIV testing into routine drug resistance surveillance methods in Kenya **37**
Introduction Kenya **38**
Kenya 38
TB-HIV situation in the country 39
TB drug resistance situation in the country 40
Outline of organization of TB and HIV/AIDS services 40
National TB programme 40
National HIV programme 41
TB/HIV 41
TB and HIV screening policies 41
Policies for (preventive therapy) regarding TB/HIV 42
Process outline Kenya **42**
TB and HIV surveillance system in place at start of the project 42
Overview of methodology used 42
Additional data-collection 43
Monitoring Visits 43
Integration process 43
Challenges during project implementation 44

Results data analysis Kenya **45**
General overview data 45
Data completeness 45
General 45
HIV status 45
Smear, culture & DST results 46
Patients characteristics 49
Sex & age 49
Patient type 50
Geographic distribution 50
Drug resistance & MDR-TB results 51
HIV status results 54
HIV-MDR data 56
Key findings and recommendations Kenya **60**
Discussion of results and final recommendations for the integration of HIV screening in TB drug resistance surveillance 59
The association HIV infection and DR TB 61
Uptake of HIV screening data in routine MDR surveillance systems 62

Tables Kazakhstan

Table 1. Characteristics of notified TB cases in Kazakhstan in 2007-2009. 15
Table 2. HIV-testing by oblast in 2007-2009 17
Table 3. HIV by patient category in 2007-2009 18
Table 4. HIV by age group, sex and other patient characteristics in 2007-2009
Table 5. Culture coverage for all patients with a positive smear, stratified by oblast in 2007-2009 21
Table 6. Culture and DST coverage, stratified by smear and HIV status, 2007-2009 22
Table 7. DST coverage and results for those with a positive culture, stratified by oblast, in 2007-2009 23
Table 8. DST results by patient category, nationally, 2007-2009, for those with a positive culture 24
Table 9. Drug resistance by age group, sex and other patient characteristics in 2007-2009 27
Table 10. Drug resistance by smear and HIV status, in 2007-2009 29
Table 11. Drug resistance by treatment history, gender and HIV status, in 2007-2009 30
Table 12. Treatment outcome in 2007-2009Q2 cohort by smear status at diagnosis and DR 31
Table 13. Treatment outcome in 2007-2009Q2 cohort by smear status at diagnosis and HIV-Status 32
Table 14. Treatment outcome by HIV-status and drug resistance, stratified by previous treatment history and smear status at diagnosis (2007-2009Q2 patient cohort) 33

Figures Kazakhstan

Figure 1 Map of Kazakhstan 10
Figure 2. Age distribution by sex, for TB cases notified in Kazakhstan in 2007-2009 16
Figure 3. Percentage of cases with missing HIV-test results versus percentage of culture-positive TB cases with missing DST results, per oblast 26
Figure 4. Percentage of TB cases with MDR among those with known DST results versus the percentage of HIV-positive cases among those with a known HIV-test result, per oblast 26

Tables Kenya

Table 1: Basic Country Indicators-2009 estimates 39

Table 2 Coverage of HIV status reporting in the CRL database at different points in time during the project 44
Table 3 Overview of missing data among the general parameters 45
Table 4 HIV status reporting of retreatment cases 46
Table 5 HIV status reporting by gender 46
Table 6 Results of culture growth as reported of retreatment cases 46
Table 7 Results of direct smear of retreatment cases submitted to CRL 47
Table 8 Culture growth by smear result of retreatment cases submitted to CRL 47
Table 9 Negative smear results, culture growth and contamination by province 47
Table 10 Overview of time laps parameters (difference between date collected and date delivery at CRL) 48
Table 11a Culture growth results by time laps between date collection and date delivery for smear negative and positive direct smears 48
Table 12 Time laps between date collection and date delivery by province 49
Table 13 Gender and age of retreatment cases submitted to CRL 49
Table 14 Age groups, overall and by gender, of retreatment cases submitted to CRL 50
Table 15 Patient type (overall and by gender) of retreatment cases who sputum was submitted to CRL in 2009 50
Table 16 Geographic origin of retreatment cases whose sputum was submitted to CRL in 2009 and geographic origin of all retreatment cases reported 51
Table 17 Drug susceptibility status of samples submitted in 2009 to CRL 51
Table 18 Drug susceptibility to the four main TB drugs of samples submitted to CRL 51
Table 19 Resistance to four first line drug by gender 52
Table 20 Resistance to four first line drug by age group 52
Table 21 MDR-TB status stratified by gender 52
Table 22 MDR-TB status stratified by age-group 53
Table 23 MDR-TB status stratified by age-group and gender 53
Table 24 MDR-TB status stratified by patient type 53
Table 25 MDR-TB status stratified by province 54
Table 26 HIV status stratified by gender 54
Table 27 HIV status stratified by age group 54
Table 28 HIV status stratified by age group and gender 55
Table 29 HIV status stratified by patient type 55
Table 30 HIV status stratified by province 56
Table 31 Result of direct smear by HIV status 56
Table 32 Result of culture growth by HIV status 56
Table 33 HIV status stratified by MDR status 57
Table 34 HIV status stratified by MDR status and gender 57
Table 35 MDR-TB stratified by HIV status and age-group 57
Table 36 MDR-TB stratified by age-group and HIV status 58
Table 37 HIV status stratified by Isoniazid resistance status 58
Table 38 HIV status stratified by Ryfampicin resistance status 58
Table 39 HIV status stratified by Streptomycin resistance status 58
Table 40 HIV status stratified by Ethambutol resistance status 59
Table 41 MDR-TB stratified by HIV status and patient type 59

Figures Kenya

Figure 2 Map of Kenya 38
Figure 3 Trend of HIV Testing TB Patients in Kenya, 2005 To 2009 40
Figure 4 Sputum submission to CRL by province 2009 45
Figure 5 Age distribution in female (F) and male (M) retreatment cases submitted to CRL 49

Executive summary

For tuberculosis (TB), routine surveillance of both drug resistance against anti-TB drugs and HIV status among TB patients will enable programs to monitor whether drug resistance is more prevalent among HIV+ patients, or TB patients with drug resistant TB are more likely to be HIV+ than negative. It will allow programs to monitor trends of HIV-associated drug resistance TB, as a proxy of successful TB-IC. Except for a few countries, HIV status is not included routinely in TB drug resistance surveys or surveillance systems because of various reasons (logistics, fear of stigma, ethical issues around anonymous-unlinked testing of HIV in surveillance, which test to use). As routine HIV testing is scaling up rapidly in many areas, HIV information is becoming readily available and therefore opportunities to incorporate HIV testing into routine TB drug resistance surveillance systems are present. How effective this can be done best under different epidemiological and programmatic conditions needs to be explored. Through this project, we aimed to contribute to the development of two demonstration sites, one in Kenya and one in Kazakhstan, where the ongoing processes of developing routine programmatic TB drug resistance surveillance systems and routine HIV screening of TB patients offered an excellent opportunity to integrate these systems. Kenya as a country with high HIV prevalence and relative low multi-drug resistance (MDR) TB problem and Kazakhstan with a high MDR TB prevalence and a lesser but growing HIV problem provide different systems for screening, addressing the specific requirements in their settings.

In both countries, the project was carried out in close collaboration between the national TB programs, national TB reference laboratories, the MDR Treatment programs and other relevant partners. An initial review of existing status of surveillance and ongoing developments provided a set of recommendations and actions to address identified shortcomings in the routine surveillance systems. Over a period of one year the project provided technical guidance to the development of a programmatic screening system of HIV within the existing MDR surveillance. Regular checks of data and data analysis led to targeted interventions with relation to strengthening the screening systems and benefit the patients. Both country projects certainly contributed to further strengthen the ongoing development of routine programmatic MDR surveillance systems and routine HIV screening. In Kazakhstan drug resistance and HIV testing was already being been done routinely for all TB cases (new and retreatment) therefore it was much easier to integrate HIV surveillance into routine drug resistance surveillance for both patient groups. Still the project helped to improve both data completeness and data quality. A new electronic surveillance system with data included from 2007 onwards allowed for analysis of reliable data. In Kenya HIV testing is routinely done for all TB cases while drug resistance testing is only routinely done for retreatment cases. HIV testing is reported through the routine recording and reporting system of the national TB Program. TB drug resistance test results however come from a separate laboratory recording system and HIV status was not included herein. In Kenya, HIV status was integrated into drug resistance surveillance by adding HIV status to the laboratory form. This was implemented nationally starting January 1st, 2009. It was an effort to operationalize the integration of data collection on HIV in the routine MDR surveillance system as treatment providers initially did not see the importance of transferring the HIV-test results to a higher level. Similarly in Kazakhstan, before this project national HIV surveillance results were not fed back to the regional/local level. Therefore staff at the lower levels did not see the need for completing all information in the electronic register. Useful feedback after provision of data by the lower levels is an important motivation for completing data and therefore crucial activity in the procedure.

The main findings based on analysis of the data from both Kazakhstan (2007-2009) and Kenya (2009) collected in this project were:
As expected, HIV prevalence is much higher among retreatment cases in Kenya than in Kazakhstan, 50% versus 1%. Vice versa, MDR prevalence is much higher in Kazakhstan then in Kenya, 43% versus 7%. The HIV prevalence among TB patients in Kazakhstan is still low but rising, from 0.6% in 2007 to 1.2% in 2009. The HIV prevalence among TB patients in Kenya is declining, from 57% in 2005 to 44% in 2009. In both countries extensive analysis of the data obtained through the programmatic surveillance is possible, as presented in the country reports.
In Kazakhstan, we observed no relationship between DR-TB notification and HIV status. In Kenya we actually observed an inverse relation whereby MDR-TB was significantly more prevalent in HIV negative than in HIV positive cases, also when controlled for age and sex. Among retreatment cases, Rifampicin resistance was more prevalent in HIV-negative than HIV-positive cases, also when controlled for age and sex.
In Kazakhstan, analysis revealed interesting findings on the overlap of specific risk factors for MDR-TB and HIV, such as history of imprisonment, drug use and homelessness. In both new and retreatment patients, none HIV-infected and MDR-TB have the highest treatment success rates, while patients with both HIV-infection and MDR-TB have the lowest successful treatment outcome rates. HIV-positive TB patients without MDR had better treatment success rates with the standard first-line drug regimen than HIV-negative patients with MDR.
In Kenya, the majority of retreatment cases is pan-sensitive (75%), 14.4% mono-resistant, 3.5% poly-resistant and 6.8% MDR-TB. A disturbing finding is the relative high drug resistance for Rifampicin, Ethambutol and Streptomycin among females in the younger age group (< 25 years).
An additional finding was that in both countries, about thirty percent of cultures of smear-positive smears rendered negative, which percentage is considered too high. This needs to be investigated and actions should be taken to increase the yield of culture (and thus DST). Potential reasons are delay in transportation, dilemmas with decontamination or any other conditions in the laboratories. A stronger role for the SNLR could help to address these issues.
In summary the projects in Kenya and Kazakhstan have shown that integration of HIV into routine MDR surveillance is feasible and useful and should be continued in both countries. The integration led to overall improvement of the surveillance data and contributed to improved capacity of staff in data validation and also improved the overall data quality. Analysis of integrated HIV/MDR-TB surveillance data is a useful addition to the routine cohort and treatment outcome data. Besides the importance for the individual patient care, it provides trends of the MDR/HIV relation in routine program setting. It provides a useful epidemiologic basis for more specific studies on for example nosocomial outbreaks. If the system itself is sensitive enough to monitor possible outbreaks needs be further investigated.

Background overall project

Several studies [1] have clearly documented the association between drug resistant TB and HIV. Although outbreaks of Drug Resistant (DR) TB among HIV patients have been widely reported in nosocomial and other congregate settings, little is known about the association of DR TB and HIV in the population. The primary reason for lack of information is that HIV and drug susceptibility testing (DST) have not been combined in surveys or under routine program conditions. Despite the expansion of HIV testing and treatment in the World, only 7 countries were able to report DR notification data disaggregated by HIV status according to the 4th WHO/IUATLD report on the Global DR situation in the World. Data from Ukraine and Latvia showed significant association between HIV and MDR-TB. There are two main reasons why DR -TB may be associated with HIV: malabsorption of drugs in TB patients leading to suboptimal plasma concentrations, and nosocomial transmission of DR-TB to PLHIV. It is also possible, although no conclusive data have shown this, that HIV infected patients may be more susceptible to infection with a DR strain of M.TB once exposed.

The epidemiological impact of HIV on the epidemic of DR TB is not well known, and may depend on several factors. HIV infected TB cases are more likely to be smear negative resulting in a non-diagnosis or delayed diagnosis of DR, leading to high death rates in people living with HIV.
Both of these factors may suggest a lower rate of transmission. However, HIV infected patients progress rapidly to disease after infection, and in settings where MDR-TB is prevalent, either in the general population, or in the local population such as a hospital or other congregate setting, this may lead to rapid development of a cluster of DR TB patients with the realistic possibly of developing into an outbreak.

Early death in HIV-infected MDR-TB patients in both outbreaks and treatment cohorts has been widely documented. Anti-retroviral treatment for HIV does appear to benefit co-infected MDR-TB patients. Co-management of treatment for both diseases is very complicated. Currently, most TB control programs in high burden countries do not have the diagnostic infrastructure to either detect an outbreak nor the programmatic capacity to manage an outbreak. Given the impact on mortality, outbreaks should be avoided at all cost. This requires the development of infection control measures in congregate settings as well as diagnostic screening tools to rapidly identify DR TB are a priority, for all countries, but particularly for those with high prevalence of HIV or MDR-TB. From a global perspective, routine diagnosis of both HIV and DR TB should therefore be scaled up for patient benefit.

Routine surveillance of linked HIV status and DR data will enable programs to monitor whether DR is more prevalent among HIV+ patients, or MDR-TB patients are more likely to be HIV+ than negative. If this is the case then it points to nosocomial transmission of MDR-TB, and thus inadequate TB-IC measures. Since provider initiated testing in all TB patients is now considered the gold standard of patient care in countries with a significant TB/HIV dual epidemic, HIV status will be known for almost all patients undergoing C/DS.

Conducting linked and routine HIV/DR surveillance will thus allow a program to monitor trends of HIV-associated DR TB, as a proxy of successful TB-IC. Inversely the presence of a strong association between HIV and MDR TB relation will be an indicator of poor infection control practice in health care and congregate settings.

Except for a few countries, HIV status is not included routinely in MDR-TB surveys or routine surveillance systems because of various reasons (logistics, fear of stigma, ethical issues around anonymous-unlinked testing of HIV in surveillance, which test to use).
As routine HIV testing is scaling up rapidly in many areas, HIV information is becoming readily available and therefore opportunities to incorporate HIV testing into routine MDR

[1] The WHO/IUATLD global project on anti-TB drug resistance surveillance, Report number 4, WHO, Geneva 2008

TB surveillance systems are present. How effective this can be done best under different epidemiological and programmatic conditions needs to be explored.

The project has contributed to the development of two demonstration sites, one in Kenya and one in Kazakhstan, where the ongoing processes of developing routine programmatic MDR surveillance systems and routine HIV screening of TB patients offered an excellent opportunity to integrate these systems. Kenya as a country with high HIV prevalence and relative low MDR TB problem and Kazakhstan with a high MDR TB prevalence and a lesser but growing HIV problem provide different systems for screening, addressing the specific requirements in their settings. They are both excellent representative settings where MDR TB and HIV are main problems.

The projects in both countries closely collaborated with the national TB programs, national TB reference laboratories, the MDR Treatment programs and other relevant partners in the development of a routine programmatic system of HIV screening of all MDR TB patients. An initial review of existing status of surveillance and ongoing developments provided a set of recommendations and actions to assist the National Programs and laboratories to address identified shortcomings. Over a period of one year the project provided technical guiding to the development of a programmatic screening system of the existing MDR surveillance. Regular checks of data and data analysis lead to targeted interventions with relation to strengthening the screening systems and benefit the patients. Both Kenya and Kazakhstan KNCV office staff closely monitored the projects.

This final report provides a description of the set-up and development of the two country specific projects. It provides the local recommendations that were given during the year to strengthen the national systems and enhance data capture and quality of data. The report also provides extensive analysis and results of the collected data and the conclusions and final recommendations to the National TB Programs for each of the projects.
The final chapter of the report provides a summary of the main findings coming out of both projects, lessons learned and a summary of the overall conclusion on the usefulness of integrating HIV testing in routine MDR surveillance systems and a set of recommendations on how to do this best.

Integration of HIV testing in

MDR surveillance in Kazakhstan

Introduction Kazakhstan

Kazakhstan is a former Soviet Union country, situated in Central Asia. The neighboring countries are Russia, China, Kyrgyzstan, Uzbekistan and Turkmenistan. Kazakhstan covers an area over 2.7 million square kilometers and the population size is approximately 16 million. About 54% of the population lives in urban settings, and thus the rural areas are very sparsely populated. The country is divided into 16 districts: 14 provinces and the cities of Almaty and Astana. The districts are divided into 240 rayons. The GDP per capita in 2009 was 7.000 USD (CIA world factbook). Twenty-four percent of the population is under 15 years of age.

Figure 6 Map of Kazakhstan

After the breakdown of the Soviet Union, tuberculosis (TB) reemerged in Kazakhstan and other eastern European and central Asian countries, due to strongly reduced funding for health care together with a deterioration of the economic situation of the inhabitants.

In response to the increasing incidence, DOTS was introduced in Kazakhstan in 1998 to reduce TB morbidity and mortality. TB control is organized vertically, under coordination of the National Center for Tuberculosis Problems (NCTP), through 138 specialized TB institutions at the national, oblast and rayon level. Primary health care (PHC) services have increasingly been involved in TB control activities since the early 2000s. The majority of pulmonary TB patients are hospitalized during the first months (intensive phase) of treatment. Treatment during the continuation phase is coordinated by the PHC facilities. The introduction of DOTS included the introduction of a national standardized surveillance sytem for TB. Since 2000, all oblasts electronically collect patient-based data on new and relapse TB cases. Since 2003, information on all TB cases is collected.

TB-HIV situation in the country

Kazakhstan is a country with a relatively low HIV and TB prevalence but with within TB drug resistance is a problem. Kazakhstan notifies about 30,000 TB patients yearly for a rate of about 200 per 100,000.
Although Kazakhstan is a country with low prevalence of HIV and TB-HIV, the number of notified TB cases registered as HIV-positive is increasing while the TB incidence is decreasing. In 2009 there were 249 HIV-positive TB cases notified in comparison with 187 in 2004.

TB drug resistance situation in the country

MDR-TB was present in about 1 in 6 new TB cases and over half of re-treatment cases (2002 drug resistance survey), and the proportion of re-treatment cases is increasing (31% in 2006). In prisons, TB prevalence is much higher than in the total population, and MDR-TB and HIV probably also has a higher prevalence. WHO estimates the yearly new number of MDR-TB cases in Kazakhstan to be 6,600. Since 2000 the country provides SLD treatment that was available only for a limited number of cases (about 25% of MDR-TB laboratory confirmed cases) throughout the country till 2009. Since 2009 the coverage of SLD treatment was increased. In 2008 GLC approved one pilot site for programmatic management of MDR-TB. Since 2009 GLC-approved PMDT is rolled out over the country including prison system.

Outline of organization of TB and HIV/AIDS services

TB service in Kazakhstan is represented by the National TB Center at the national level and 21 oblast and regional TB dispensaries at the oblast and regional levels. In every oblast, one laboratory performs smear microscopy, culture and DST for civil TB patients.
In addition there are 7 specialized TB prison colonies for isolation and treatment of TB patients in the country. There is only one bacteriological laboratory in prison system of Karaganda oblast that performs culture and DST for prisons located in the oblast.

HIV service is represented by the Republican HIV/AIDS center and 14 oblasts' and 2 cities' HIV/AIDS Centers. Republican HIV/AIDS center doesn't provide treatment but plays coordination, methodical and monitoring role in the country. HIV/AIDS Oblasts' centers provide services to prison system.

TB and HIV screening policies

TB testing and diagnosis

According to the prikaz no. 150 PLWHA should be regularly checked for TB. Screening should be provided at PHC institutions. For diagnostics of tuberculosis all TB suspects are referred to TB dispensaries.
All TB cases are screened for DR except prison system where access to culture and DST is limited. DST for prison system is conducted only in Karaganda oblast (because they have own bacteriological laboratory) and few oblasts where collaboration between prison system and TB service is good.

HIV-testing and diagnosis

Since 2002 according to the national order on TB/HIV (prikaz no. 150) all TB patients should be tested for HIV maintained by voluntary counseling. Common practice was that HIV testing was conducted without consent. Testing is performed at the City AIDS centres. TB specialists from 6 oblast TB dispensaries (Karaganda, South KZ, Almaty, Almatinsky, Pavlodar, East KZ) have been trained on providing voluntary counseling and testing for HIV in 2008.

Definitions for TB/HIV in TB register and HIV/TB in HIV register

Only PLWHA with active TB were registered in TB database. After successful completion of treatment they are not reported as TB-HIV cases. In HIV register all PLWHA who ever had TB are registered as TB-HIV cases and stay in the database forever because according to the national protocol PLWHA with active TB should be transferred to the stage 3 or 4 and cannot be transferred back or excluded from those stages even if they successfully finished TB treatment. Therefore, there were differences in the TB-HIV data reported by TB and HIV services.

Policies for (preventive) therapy regarding TB/HIV

Eligibility criteria for isoniazid preventive therapy

1. All HIV positive patients including those who had TB in the past independently from the result of skin test.
2. HIV positive patients who has contact with PTB or EPTB patient (independently from the result of smear microscopy) IPT or RPT is conducted once when contact is identified. If HIV positive patient is still in contact with infectious TB patient during the years, only Central doctors commission can make decision on repeated IPT.

IPT should be prescribed for 6 months.

Eligibility criteria for cotrimoxazol preventive therapy

All HIV positive patients diagnosed with TB should get CPT during the whole course of TB treatment.

Eligibility criteria for antiretroviral treatment

The main criteria to start ART are clinical stage of HIV infection (3 or 4) and number of CD4 cells.

Recommendations to start ART in HIV positives are:

Clinical stage (WHO)	*Number of CD4*	*Recommendations*
1	<200	Start ART
	200 - 350	Consider starting ART
2	<200	Start ART
	200 - 350	Consider starting ART
3	<200	Start ART
	200 -350	Start ART
4	Independently from number of CD4	Start treatment

In case if it is not possible to count CD4, decision on starting ART can be made based on the clinical symptoms (3 or 4).
According to informal information obtained from the Republican AIDS center, most of HIV positive TB patients receive ART after they complete TB treatment.

Process outline Kazakhstan

TB and HIV surveillance systems in place at the start of the project

At the start of the project (fall 2008), there is both a TB notification system as well as a national HIV/AIDS register, but staff from both programs cannot access or link each others registers. Data collection on HIV-test results is implemented already in the TB patient reporting system. No results on TB within HIV+ patients were available at the start of this project.
Also, there is no close collaboration between TB and HIV/AIDS programs in Kazakhstan. Despite a joint coordinating body on TB-HIV established in Feb 2006, there is no national plan for TB/HIV collaborative activities. According to the national order on TB/HIV (prikaz no. 150, first issued in Feb 2004) isoniazid preventive therapy (IPT) and co-trimoxazole preventive therapy (CPT) should be implemented in the country. The national AIDS center was involved in drafting the prikaz but unfortunately the TB centers had not been involved and also were not notified of the existence and contents of the prikaz. It is therefore not to be expected that the prikaz has been implemented fully in TB centers.
There are no standardized recording and reporting (R&R) forms on TB/HIV. M&E of TB-HIV collaborative activities were just started up in 2008 within the GFR6 project. The indicators

are being developed for Almaty city now, and should be finalized and nationally implemented in the coming years.

Overview of methodology used

The project was implemented in close collaboration with the national TB center. The national TB-HIV coordinator at the national TB center was involved in project implementation since she is responsible for coordination of TB and HIV collaborative activities and cooperation with the republican AIDS center but also for the national surveillance system of the NTP. In the beginning of project an action plan was developed together with the TB-HIV coordinator. Based on the action plan the following activities were conducted during the project:

1. Analysis of TB national database. (April – July 2009)
2. Development of form for evaluation of completeness of database and the list of TB patients missing results of examinations and tests per oblasts. (April – May 2009)
3. Improvement of completeness of database by oblasts. (July - March 2010)
4. Monitoring visits to the most problematic oblasts to improve completeness of database. (June – July 2009)
5. Assessment of reasons for missing data. (July – September 2009)
6. Analysis on prevalence of MDRTB and HIV for the period 2007 – 2008. (September - December 2009)
7. Development of report and recommendations (January – June 2010).

Supervision was provided by KNCV Senior epidemiologist and KNCV Representative Office in Central Asia.

Improvement of data completeness

As a first step, we assessed completeness of TB notification data from 2007-2008 with a focus on HIV-testing and DST results. During project implementation the national TB-HIV coordinator worked with the oblasts on improvement of database completeness. Software has been built which gives an overview of mistakes and missings in the database. Monthly, an overview of mistakes and missings are sent to the oblast TB dispensaries with the request to adjust and/or complete the data. After on the job training and a workshop for specialists responsible for data entry at the oblasts' level the completeness of data was improved in all oblasts. The table below shows the improvement in data completeness for HIV-testing and DST results. In conclusion, data completeness has increased since March 2009 as a result of active follow-up of missing data by the national TB center.

	March 2009	*March 2010*
Total number of TB cases	62,677	92,091
Number of TB cases without results of HIV test	7,256 (11.5%)	3,344 (3.6%)
Number of culture-positive TB cases*	1,1013 (17.6%)	3,0212 (32.8%)
Number of culture-positive TB cases without DST results*	3,554 (32.27%)	2,199 (7.2%)

* for recently notified cases, culture and DST results are not available yet and/or not registered yet. Therefore, the proportion of cases, who eventually will have culture and DST results will be higher.

Monitoring visits

Two monitoring visits were conducted in July 2009 by the specialist of organizational and methodical department of the National TB Center, and national TB/HIV coordinator. Karaganda and East Kazakhstan were visited because of the relatively high percentage of missing HIV and DST data in their data as of February 2009.
General data entry issues (double records, late entry of data, missing data, etc.) were discussed with the staff. Findings observed relevant for this project are:

1. Doctors did not order follow up laboratory examinations (smear microscopy, culture, DST) for all patients during treatment
2. Treatment was unduly prolonged for some patients. This also led to missing treatment outcomes.
3. About half of the missing data on DST results could be explained by the tests not having been performed, the other half because of not registering the existing results. In both oblasts, it was recommended that laboratory results should be sent to the registration department, and not only to the treating physicians.
4. In principle, HIV tests were performed in all patients (unless they refused), so missing data were all due to a failure to enter them in the database.

Improvements in co-operation between the national TB and AIDS centers

Since the start of the project, co-ordinators have been appointed at both national centers for co-operation between them. An updated prikaz is being developed which proposes appointment of coordinators at the oblast level who confer regularly on new co-infected cases and make sure they will be known/treated at both centers.
The national AIDS center at the moment has an electronic database which contains limited information only, which includes HIV laboratory test results, demographic information and information on risk factors like drug use. The center is preparing a new registration form with accompanying database which will include more detailed information, like on TB and HIV treatment.
The limited data that was received from the AIDS center is that in 2008, 7835 prevalent HIV cases were registered in the AIDS register. All of them had an X-ray to check for TB in 2008, 407 (5%) were registered to have received TB treatment of which 103 (25%) received ARV treatment. IPT was provided to 656 (8%) of HIV patients in 2008. (written information obtained from the AIDS center).

Challenges during project implementation

During the project implementation the following challenges were faced:
1. Lack of collaboration between TB and HIV services. Therefore, it took time to make relevant arrangements to implement the project.
2. Lack of electronic surveillance system at the AIDS program and very limited data.
3. Lack of access to HIV/AIDS database because of confidentiality.
4. Since 2007 NTP started revision of TB forms and adjustment of electronic surveillance system. All data from old database were transferred to the adjusted one. Therefore, time was needed to complete the database.
5. Improvement of completeness of database took more time because it required on-the-job training. Because of remoteness of some oblasts we had to work with them by phone. Since a lot of improvements had to be done, proper supervision was needed. For this purpose quarterly analysis of completeness of data base was conducted.

Results data analysis Kazakhstan

Patient characteristics

In 2007-2009, a total of 91,756 TB patients were notified and started treatment (data accessed 8 July 2010).
The distribution of notified cases by gender, age, region, TB localization, and patient category is shown in Table 1. The age distribution by sex is shown in Figure 1. In all age groups 20-74 years, more male cases were notified than female cases.
Also, results at diagnosis from HIV testing, sputum smear examination, culture, and DST for all patients combined are shown in Table 1. Of all new cases notified, 68% is sputum smear negative. In total, 43% of patients have a positive smear at diagnosis, and 36% a

positive culture. DST results are available for 39% of all patients. HIV-test results are available for 97% of TB patients.

Completeness of HIV-testing results and DST results

As a first step, completeness of HIV-testing and DST results were assessed.

Completeness of HIV-testing results

In 2007-2009, HIV-testing results were missing in the database for 3.3% of all 91,756 notified TB patients (Table 1). Nationally, this percentage decreased from 5.8% in 2007 to 2.0% in 2008 and 2.1% in 2009 (data not shown). There were large differences in the percentage of missing HIV-test results across oblasts, the overall percentage of cases with missing HIV test results in the different oblasts in 2007-2009 ranged between 0.2% and 13.7% (Table 2). Those oblasts with the highest missing proportions in 2007, most strongly improved from 2008 onwards (data not shown). For example, Astana city had 38% missing values in 2007 and 0.1% in 2009. Missing values for HIV-testing results ranged from 2.2% in new smear-positive patients to 5.2% in smear-negative failure patients (Table 3). Completeness of HIV-test results by age, gender and risk factors for TB was also within this range (Table 4).

Table 1. Characteristics of notified TB cases in Kazakhstan in 2007-2009

Characteristic		*Frequency*	*Percent*
gender	male	55432	60.4
	female	36324	39.6
age (years)	0-4	755	.8
	5-9	897	1.0
	10-14	1548	1.7
	15-19	8666	9.4
	20-24	14403	15.7
	25-29	12213	13.3
	30-34	11273	12.3
	35-39	9229	10.1
	40-44	8197	8.9
	45-49	8027	8.7
	50-54	5862	6.4
	55-59	4281	4.7
	60-64	2046	2.2
	65-69	2102	2.3
	70-74	1381	1.5
	75+	868	.9
	Missing	8	.0
localization	pulmon	83176	90.6
	extrapulm	8578	9.3
	missing	2	.0

patient category	new SS+	17485	19.1
	new SS-	37995	41.4
	Relapse SS+	10276	11.2
	Failure SS+	2723	3.0
	Default SS+	3521	3.8
	transfer in	9149	10.0
	relapse SS-	9056	9.9
	default SS-	1108	1.2
	failure SS-	443	.5
Region	Akmolinsk oblast	5697	6.2
	Aktyubinsk oblast	5022	5.5
	Almaty oblast	6602	7.2
	Atyrau oblast	3897	4.2
	West Kazakhstan oblast	4162	4.5
	Zhambyl oblast	4884	5.3
	Karaganda oblast	7743	8.4
	Kostanay oblast	6304	6.9
	Kyzylorda oblast	5095	5.6
	Mangistau oblast	3465	3.8
	South Kazakhstan oblast	9433	10.3
	Pavlodar oblast	5679	6.2
	North Kazakhstan oblast	4805	5.2
	East Kazakhstan oblast	8776	9.6
	Astana city	5417	5.9
	Almaty city	4775	5.2
HIV	positive	784	.9
	negative	87936	95.8
	missing	3036	3.3
smear	negative	51402	56.0
	positive	38219	41.7
	scanty	437	.5
	missing	1698	1.9
culture	negative	48516	52.9
	positive	32904	35.9
	contaminated	1516	1.7
	missing	8820	9.6
drug resistance	pansensitive	16057	17.5
	monoresistant	2913	3.2
	polyresistant	5490	6.0
	MDR	11444	12.5
	missing	55852	60.9

Table 2. HIV-testing by oblast in 2007-2009

Oblast		*positive*	*negative*	*missing*	*Total*	*% pos for those with test result*
Akmolinsk oblast	Count	35	5636	26	5697	
	%	.6%	98.9%	.5%	100.0%	0.6%
Aktyubinsk oblast	Count	7	4947	68	5022	
	%	.1%	98.5%	1.4%	100.0%	0.1%
Almaty oblast	Count	32	6527	43	6602	
	%	.5%	98.9%	.7%	100.0%	0.5%
Atyrau oblast	Count	1	3866	30	3897	
	%	.0%	99.2%	.8%	100.0%	0.0%
West Kazakhstan oblast	Count	16	4129	17	4162	
	%	.4%	99.2%	.4%	100.0%	0.4%
Zhambyl oblast	Count	23	4838	23	4884	
	%	.5%	99.1%	.5%	100.0%	0.5%
Karaganda oblast	Count	221	7403	119	7743	
	%	2.9%	95.6%	1.5%	100.0%	2.9%
Kostanay oblast	Count	77	6206	21	6304	
	%	1.2%	98.4%	.3%	100.0%	1.2%
Kyzylorda oblast	Count	3	5073	19	5095	
	%	.1%	99.6%	.4%	100.0%	0.1%
Mangistau oblast	Count	2	3450	13	3465	
	%	.1%	99.6%	.4%	100.0%	0.1%
South Kazakhstan oblast	Count	62	8632	739	9433	
	%	.7%	91.5%	7.8%	100.0%	0.7%
Pavlodar oblast	Count	116	5553	10	5679	
	%	2.0%	97.8%	.2%	100.0%	2.0%
North Kazakhstan oblast	Count	22	4701	82	4805	
	%	.5%	97.8%	1.7%	100.0%	0.5%
East Kazakhstan oblast	Count	31	7840	905	8776	
	%	.4%	89.3%	10.3%	100.0%	0.4%
Astana city	Count	16	4659	742	5417	
	%	.3%	86.0%	13.7%	100.0%	0.3%
Almaty city	Count	120	4476	179	4775	
	%	2.5%	93.7%	3.7%	100.0%	2.6%
Total	Count	784	87936	3036	91756	
	%	.9%	95.8%	3.3%	100.0%	0.9%

Table 3. HIV by patient category in 2007-2009

Patient category		*HIV-positive*	*HIV-negative*	*missing*	*Total*	*% pos for those with test result*
new SS+	Count	180	16925	380	17485	
	%	1.0%	96.8%	2.2%	100.0%	1.1%
new SS-	Count	215	36430	1350	37995	
	%	.6%	95.9%	3.6%	100.0%	0.6%
relapse	Count	93	9894	289	10276	
	%	.9%	96.3%	2.8%	100.0%	0.9%
failure	Count	23	2594	106	2723	
	%	.8%	95.3%	3.9%	100.0%	0.9%
default	Count	84	3347	90	3521	
	%	2.4%	95.1%	2.6%	100.0%	2.4%
transfer in	Count	67	8623	459	9149	
	%	.7%	94.3%	5.0%	100.0%	0.8%
relapse SS-	Count	86	8669	301	9056	
	%	.9%	95.7%	3.3%	100.0%	1.0%
default SS-	Count	29	1041	38	1108	
	%	2.6%	94.0%	3.4%	100.0%	2.7%
failure SS-	Count	7	413	23	443	
	%	1.6%	93.2%	5.2%	100.0%	1.7%
Total	Count	784	87936	3036	91756	
	%	.9%	95.8%	3.3%	100.0%	0.9%

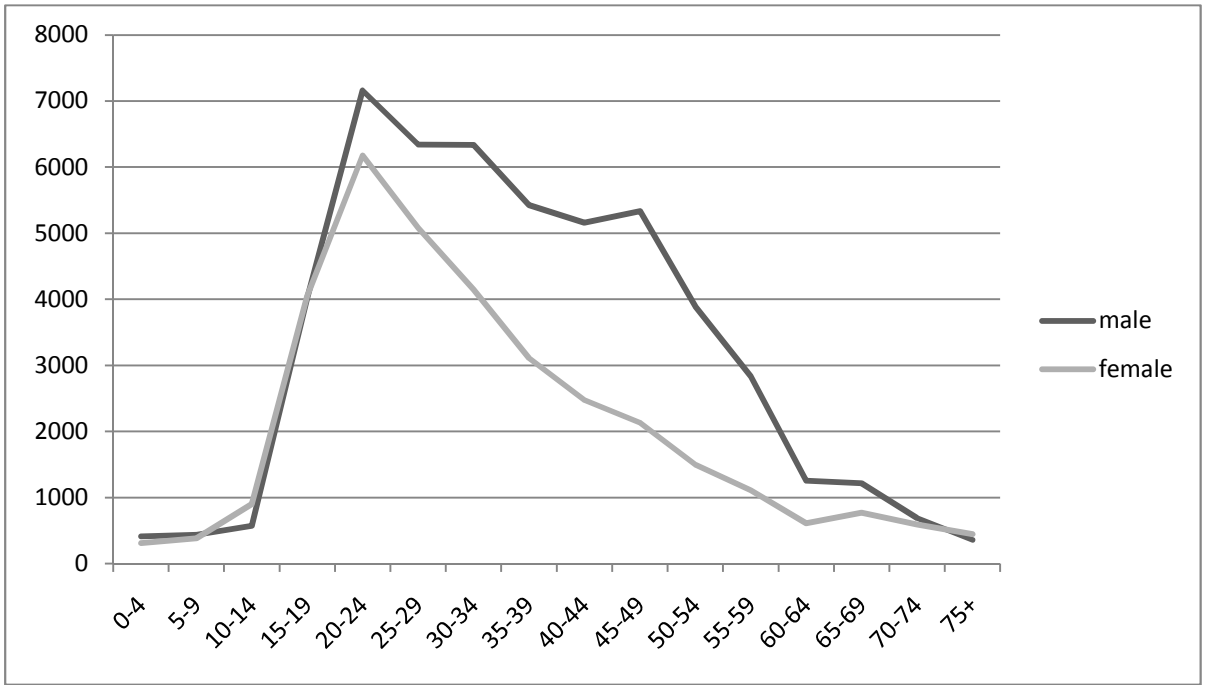

Figure 1. Age distribution by sex, for TB cases notified in Kazakhstan in 2007-2009.

Table 4. HIV by age group, sex and other patient characteristics in 2007-2009

Age (years)		*positive*	*negative*	*missing*	*Total*	*% pos for those with test result*
0-4	Count	3	712	40	755	
	%	.4%	94.3%	5.3%	100.0%	0.4%
5-14	Count	3	845	49	897	
	%	.3%	94.2%	5.5%	100.0%	0.4%
15-17	Count	1	1499	48	1548	
	%	.1%	96.8%	3.1%	100.0%	0.1%
18-24	Count	11	8408	247	8666	
	%	.1%	97.0%	2.9%	100.0%	0.1%
25-34	Count	55	13885	463	14403	
	%	.4%	96.4%	3.2%	100.0%	0.4%
35-44	Count	146	11693	374	12213	
	%	1.2%	95.7%	3.1%	100.0%	1.2%
45-54	Count	201	10702	370	11273	
	%	1.8%	94.9%	3.3%	100.0%	1.8%
55-64	Count	161	8738	330	9229	
	%	1.7%	94.7%	3.6%	100.0%	1.8%
65+	Count	93	7840	264	8197	
	%	1.1%	95.6%	3.2%	100.0%	1.2%
18-24	Count	62	7719	246	8027	
	%	.8%	96.2%	3.1%	100.0%	0.8%
25-34	Count	25	5622	215	5862	
	%	.4%	95.9%	3.7%	100.0%	0.4%
35-44	Count	12	4121	148	4281	
	%	.3%	96.3%	3.5%	100.0%	0.3%
45-54	Count	6	1973	67	2046	
	%	.3%	96.4%	3.3%	100.0%	0.3%
55-64	Count	4	2024	74	2102	
	%	.2%	96.3%	3.5%	100.0%	0.2%
65+	Count	1	1326	54	1381	
		.1%	96.0%	3.9%	100.0%	0.1%
Gender						
male	Count	570	52966	1896	55432	
	%	1.0%	95.6%	3.4%	100.0%	1.1%
female	Count	214	34970	1140	36324	
	%	.6%	96.3%	3.1%	100.0%	0.6%
Homeless						
yes	Count	54	2409	100	2563	
	%	2.1%	94.0%	3.9%	100.0%	2.2%
no	Count	730	85527	2936	89193	
	%	.8%	95.9%	3.3%	100.0%	0.8%
Drug use						
yes	Count	131	343	23	497	
	%	26.4%	69.0%	4.6%	100.0%	27.6%
no	Count	653	87593	3013	91259	
	%	.7%	96.0%	3.3%	100.0%	0.7%
Alcoholism						
yes	Count	132	5409	151	5692	
	%	2.3%	95.0%	2.7%	100.0%	2.4%
no	Count	652	82527	2885	86064	
	%	.8%	95.9%	3.4%	100.0%	0.8%
Prison history						
yes	Count	57	1279	46	1382	
	%	4.1%	92.5%	3.3%	100.0%	4.3%
no	Count	727	86657	2990	90374	
	%	.8%	95.9%	3.3%	100.0%	0.8%
Total	Count	784	87936	3036	91756	784
	%	.9%	95.8%	3.3%	100.0%	.9%

Completeness of smear and culture results for diagnosis of TB

Data on smear results are almost complete (98.1%) in the database, and similar for those with and without HIV. Of all smear-positive patients, 5.0% have missing information on culture results. This proportion varies from 0.0% to 15.7% across oblasts (Table 5). Contamination rates were 2.3% overall, and ranged between 0.1% and 9.7% per oblast. Contamination rates were highest in Almaty city, what may be due to the liquid culture system used here. There is no clear association between the proportion of contaminated cultures and the proportion of positive culture results between oblasts (data not shown).

Only 67.3% of all smear-positive TB patients had a positive culture result (or 71.7% of those with negative or positive culture results, see Table 5). Only 14.5% of all smear-negative TB patients had a positive culture result (16.1% of those with negative or positive culture result).

Completeness of DST results at the time of the TB diagnosis

At registration all patients should be tested for DST (until half 2007 at least sputum smear positive (SS+) patients should be tested), while during treatment only those with positive smears are cultured for DST.

In 2007-2009, DST results at diagnosis were missing in the database for 60.9% of all 91,756 notified TB patients (Table 1), and for 10.1% of the 32,904 TB patients with a positive culture (Table 7). Nationally, this latter percentage decreased from 14.0% in 2007 to 8.1% in 2008 (data not shown).

There were large differences in the percentage of missing DST results for patients with positive cultures across oblasts, the overall percentage of cases with missing DST results ranged between 3.7% and 24.8% (Table 7). Practically all oblasts improved the proportion of cases with missing DST results although data for 2009 may not be complete yet (data not shown). For those with a positive culture result, there were no relevant differences in completeness of DST results between patient categories (Table 8).

HIV-testing results and DST results

As a second step, HIV-testing and DST results were assessed.

HIV-testing results

Out of those with a known test result 0.9% had a positive test result for HIV (Table 2). This percentage increased from 0.6% in 2007 to 0.9% in 2008 and to 1.2% in 2009. Across oblasts, the percentage of TB patients with positive HIV test results ranged between 0.03% and 2.9%, and was highest in Karaganda (2.9%), Almaty city (2.6%), and Pavlodar (2.0%). There was no clear correlation within oblasts between the proportion of missing HIV test results and HIV-positivity among those with a known result (which would indicate that there may be selective testing of risk groups).

HIV was more prevalent among patients returning after default (2.6% for SS+ and 3.6% for SS-) (Table 3). HIV prevalence was 0.7% among new patients and 1.2% among retreatment patients.

Male TB patients more often were HIV-positive than females (1.1% versus 0.6%). HIV prevalence was highest among TB patients aged 25-44 years (1.5%) (Table 4). In univariate analysis, other risk factors for HIV among TB patients were drug use (odds ratio (OR) = 51.2, 94% CI 41.3-63.6), imprisonment history (OR=5.3, 95% CI 4.0-7.0), alcoholism (OR=3.1, 95% CI 2.6-3.7) and homelessness (OR=2.6, 95% CI 2.0-3.5).

Table 5. Culture coverage for all patients with a positive smear, stratified by oblast, in 2007-2009

	Oblast	*culture result*					*culture result for those without missing culture result*		
		negative	*positive*	*contaminated*	*missing*	*Total*	*negative*	*positive*	*contaminated*
Akmolinsk oblast	Count	684	1363	38	6	2091			
	%	32.7%	65.2%	1.8%	.3%	100.0%	32.8%	65.4%	1.8%
Aktyubinsk oblast	Count	376	1371	2	23	1772			
	%	21.2%	77.4%	.1%	1.3%	100.0%	21.5%	78.4%	0.1%
Almaty oblast	Count	711	2359	68	52	3190			
	%	22.3%	73.9%	2.1%	1.6%	100.0%	22.7%	75.2%	2.2%
Atyrau oblast	Count	476	1506	25	48	2055			
	%	23.2%	73.3%	1.2%	2.3%	100.0%	23.7%	75.0%	1.2%
West Kazakhstan oblast	Count	340	1057	50	23	1470			
	%	23.1%	71.9%	3.4%	1.6%	100.0%	23.5%	73.0%	3.5%
Zhambyl oblast	Count	627	1382	5	9	2023			
	%	31.0%	68.3%	.2%	.4%	100.0%	31.1%	68.6%	0.2%
Karaganda oblast	Count	782	2063	159	84	3088			
	%	25.3%	66.8%	5.1%	2.7%	100.0%	26.0%	68.7%	5.3%
Kostanay oblast	Count	774	2558	43	14	3389			
	%	22.8%	75.5%	1.3%	.4%	100.0%	22.9%	75.8%	1.3%
Kyzylorda oblast	Count	426	1742	6	47	2221			
	%	19.2%	78.4%	.3%	2.1%	100.0%	19.6%	80.1%	0.3%
Mangistau oblast	Count	340	993	3	0	1336			
	%	25.4%	74.3%	.2%	.0%	100.0%	25.4%	74.3%	0.2%
South Kazakhstan oblast	Count	2121	1167	106	202	3596			
	%	59.0%	32.5%	2.9%	5.6%	100.0%	62.5%	34.4%	3.1%
Pavlodar oblast	Count	430	1537	61	106	2134			
	%	20.1%	72.0%	2.9%	5.0%	100.0%	21.2%	75.8%	3.0%
North Kazakhstan oblast	Count	462	1806	39	279	2586			
	%	17.9%	69.8%	1.5%	10.8%	100.0%	20.0%	78.3%	1.7%
East Kazakhstan oblast	Count	630	2199	77	541	3447			
	%	18.3%	63.8%	2.2%	15.7%	100.0%	21.7%	75.7%	2.6%
Astana city	Count	420	1132	1	252	1805			
	%	23.3%	62.7%	.1%	14.0%	100.0%	27.0%	72.9%	0.1%
Almaty city	Count	520	1092	195	209	2016			
	%	25.8%	54.2%	9.7%	10.4%	100.0%	28.8%	60.4%	10.8%
Total	Count	10119	25327	878	1895	38219			
	%	26.5%	66.3%	2.3%	5.0%	100.0%	27.9%	69.7%	2.4%

Table 6. Culture and DST coverage, stratified by smear and HIV status, 2007-2009

Smear status (SS)	*HIV-status*	*Culture result*					*If pos or neg culture, % with pos culture result*	*If pos culture, % with DST*	*Of all, % with DST*
		negative	*positive*	*contaminated*	*missing*	*Total*			
SS+	HIV-positive	90	275	20	24	409			
	%	22.0%	67.2%	4.9%	5.9%	100.0%	75.3%	95.6%	64.3%
	HIV-negative	9779	24757	849	1423	36808			
	%	26.6%	67.3%	2.3%	3.9%	100.0%	71.7%	90.4%	60.8%
	Total	9869	25032	869	1447	37217			
	%	26.5%	67.3%	2.3%	3.9%	100.0%	71.7%	90.4%	60.8%
SS-	HIV-positive	209	77	23	41	350			
	%	59.7%	22.0%	6.6%	11.7%	100.0%	26.9%	93.5%	20.6%
	HIV-negative	37176	7123	576	4384	49259			
	%	75.5%	14.5%	1.2%	8.9%	100.0%	16.1%	89.2%	12.9%
	Total	37385	7200	599	4425	49609			
	%	75.4%	14.5%	1.2%	8.9%	100.0%	16.1%	89.2%	13.0%

Table 7. DST coverage and results for those with a positive culture, stratified by oblast, in 2007-2009

Oblast	*resistance*						*resistance distribution for those with non-missing test result*			
	pansensitive	*monoresistant*	*polyresistant*	*MDR*	*missing*	*Total*	*pansensitive*	*monoresistant*	*polyresistant*	*MDR*
Akmolinsk oblast	554	143	397	450	152	1696				
	32.7%	8.4%	23.4%	26.5%	9.0%	100.0%	35.9%	9.3%	25.7%	29.1%
Aktyubinsk oblast	639	152	223	576	490	2080				
	30.7%	7.3%	10.7%	27.7%	23.6%	100.0%	40.2%	9.6%	14.0%	36.2%
Almaty oblast	1346	245	348	834	122	2895				
	46.5%	8.5%	12.0%	28.8%	4.2%	100.0%	48.5%	8.8%	12.5%	30.1%
Atyrau oblast	448	166	207	811	173	1805				
	24.8%	9.2%	11.5%	44.9%	9.6%	100.0%	27.5%	10.2%	12.7%	49.7%
West Kazakhstan oblast	749	70	248	512	73	1652				
	45.3%	4.2%	15.0%	31.0%	4.4%	100.0%	47.4%	4.4%	15.7%	32.4%
Zhambyl oblast	755	45	144	824	88	1856				
	40.7%	2.4%	7.8%	44.4%	4.7%	100.0%	42.7%	2.5%	8.1%	46.6%
Karaganda oblast	1043	135	234	706	219	2337				
	44.6%	5.8%	10.0%	30.2%	9.4%	100.0%	49.2%	6.4%	11.0%	33.3%
Kostanay oblast	1488	173	532	565	105	2863				
	52.0%	6.0%	18.6%	19.7%	3.7%	100.0%	54.0%	6.3%	19.3%	20.5%
Kyzylorda oblast	496	346	675	673	88	2278				
	21.8%	15.2%	29.6%	29.5%	3.9%	100.0%	22.6%	15.8%	30.8%	30.7%
Mangistau oblast	276	226	200	625	110	1437				
	19.2%	15.7%	13.9%	43.5%	7.7%	100.0%	20.8%	17.0%	15.1%	47.1%
South Kazakhstan oblast	692	134	140	398	450	1814				
	38.1%	7.4%	7.7%	21.9%	24.8%	100.0%	50.7%	9.8%	10.3%	29.2%
Pavlodar oblast	837	136	393	703	94	2163				
	38.7%	6.3%	18.2%	32.5%	4.3%	100.0%	40.5%	6.6%	19.0%	34.0%
North Kazakhstan oblast	817	144	209	486	416	2072				
	39.4%	6.9%	10.1%	23.5%	20.1%	100.0%	49.3%	8.7%	12.6%	29.3%
East Kazakhstan oblast	871	247	440	1103	379	3040				
	28.7%	8.1%	14.5%	36.3%	12.5%	100.0%	32.7%	9.3%	16.5%	41.5%
Astana city	556	84	296	362	214	1512				
	36.8%	5.6%	19.6%	23.9%	14.2%	100.0%	42.8%	6.5%	22.8%	27.9%
Almaty city	505	114	235	404	146	1404				
	36.0%	8.1%	16.7%	28.8%	10.4%	100.0%	40.1%	9.1%	18.7%	32.1%
Total	12072	2560	4921	10032	3319	32904				
	36.7%	7.8%	15.0%	30.5%	10.1%	100.0%	40.8%	8.7%	16.6%	33.9%

Table 8. DST results by patient category, nationally, 2007-2009, for those with a positive culture

	resistance						*resistance for those with known DST result*			
	pansensitive	*monoresistant*	*polyresistant*	*MDR*	*missing*	*Total*	*pansensitive*	*monoresistant*	*polyresistant*	*MDR*
new SS+	5219	1024	1771	2488	1082	11584				
	45.1%	8.8%	15.3%	21.5%	9.3%	100.0%	49.7%	9.8%	16.9%	23.7%
new SS-	2064	399	672	1065	530	4730				
	43.6%	8.4%	14.2%	22.5%	11.2%	100.0%	49.1%	9.5%	16.0%	25.4%
relapse	1854	493	1049	2822	666	6884				
	26.9%	7.2%	15.2%	41.0%	9.7%	100.0%	29.8%	7.9%	16.9%	45.4%
failure	334	85	208	802	210	1639				
	20.4%	5.2%	12.7%	48.9%	12.8%	100.0%	23.4%	5.9%	14.6%	56.1%
default	785	181	422	821	207	2416				
	32.5%	7.5%	17.5%	34.0%	8.6%	100.0%	35.5%	8.2%	19.1%	37.2%
transfer in	1221	243	503	1165	409	3541				
	34.5%	6.9%	14.2%	32.9%	11.6%	100.0%	39.0%	7.8%	16.1%	37.2%
relapse SS-	502	120	252	747	166	1787				
	28.1%	6.7%	14.1%	41.8%	9.3%	100.0%	31.0%	7.4%	15.5%	46.1%
default SS-	77	11	28	79	31	226				
	34.1%	4.9%	12.4%	35.0%	13.7%	100.0%	39.5%	5.6%	14.4%	40.5%
failure SS-	16	4	16	43	18	97				
	16.5%	4.1%	16.5%	44.3%	18.6%	100.0%	20.3%	5.1%	20.3%	54.4%
Total	12072	2560	4921	10032	3319	32904				
	36.7%	7.8%	15.0%	30.5%	10.1%	100.0%	40.8%	8.7%	16.6%	33.9%

DST results

Out of all notified TB patients with a known test result, 39% had pansensitive TB and 33% had MDR-TB. These percentages varied strongly across oblasts in the range of 21%-54% for pansensitivity and 20%-50% for MDR-TB (Table 7).
For patients with known DST results, MDR-TB is least prevalent among new patients (24%) and most prevalent among failure patients (56%) (Table 8).
Drug resistance patterns by age, sex and patient characteristics previously found to be associated with drug resistance are shown in Table 9. MDR-TB rates are lower in those over 45 years of age, and no difference is observed between male and female patients, also not by age (data not shown).
In univariate analysis, statistically significant risk factors for MDR-TB were imprisonment history (OR=2.2, 95% CI 1.9-2.6), and homelessness (OR=1.2, 95% CI 1.1-1.4). Drug use (OR=1.3, 95% CI 1.0-1.7) was borderline statistically significantly associated with a higher MDR-TB prevalence while alcoholism was not associated with MDR-TB prevalence (OR=1.0, 95% CI 0.9-1.1).
Taking into account treatment history and smear status or gender, there were no relevant differences in the proportion of MDR-TB among those with and without HIV infection (Tables 10 and 11).

Association between HIV-status and drug resistance

At oblast level, there is no clear correlation between completeness of HIV and culture/DST results (Table 2 vs. Table 5 and 4, Figure 3), suggesting that there may be different reasons for incompleteness of HIV and culture/DST results.
Overall, for patients with DST and HIV test results, 64.4% are HIV-negative and do not have MDR-TB, 1.2% are HIV-positive, 34% have MDR –TB and 0.4% have both HIV-infection and MDR-TB. At oblast level, there is no clear correlation between HIV prevalence and MDR-TB prevalence (Table 3 vs. Table 8, Figure 2).
There were no statistically significant differences between HIV-positive and HIV-negative TB patients in any resistance to isoniazid, any resistance to rifampin and in resistance to both (MDR-TB) (Table 12).
Patients with drug use and prison history are (univariately) associated with an increased risk of having both HIV and MDR-TB (Tables 4 and 9). Among drug using TB patients 9.2% has both HIV and MDR-TB versus 0.4% among non-drug using TB patients. Among TB patients with a prison history 2.3% has both HIV and MDR-TB versus 0.4 of those without a prison history (data not shown).

Treatment outcomes related to HIV and drug resistance

Treatment outcomes were more often incomplete for those patients diagnosed in the second half of 2009 so we excluded those from the analysis on outcome. Before 2009, an insufficient amount of second-line drugs were available to treat all MDR-TB patients with second-line drug treatment. Therefore, the proportion of MDR-TB patients transferred to category IV is incomplete in this database on the years 2007-2009. The proportion of patients transferred to category 4 has increased considerably in 2009 (data not shown). It seems reasonable to assume that the patients transferred to category IV were patients failing the standardized treatment with first-line drugs.
Treatment outcomes were less often successful with increasing drug resistance (Table 12). Overall, smear-negative patients had higher treatment success rates than smear-positive patients (Table 12). In patients diagnosed in the period 2007 Q1-2009 Q2, treatment outcomes for 343 HIV-positive SS+ and for 278 HIV-positive SS- TB patients were registered (Table 13). Overall, the proportion of patients with successful treatment outcome is lower in HIV-positive patients than in HIV-negative patients while the proportion of patients with outcome death, failure and default is higher.
After stratifying both for HIV and MDR-TB status (Table 14), patients with both HIV and multidrug resistance have the lowest successful treatment outcome rates, both in new and retreatment patients. Treatment outcomes are better in the group being HIV-positive

without having MDR-TB, than being HIV-negative but having MDR-TB. As to be expected, treatment outcomes are best in those without neither, HIV and MDR-TB.

Provision of antiretroviral treatment and co-trimoxazole preventive treatment

Of all HIV-positive TB patients, 9.8% are registered to be on ARV treatment and 13.0% on CPT. The number of patients on ARV's is too small to assess the effect on treatment outcome in this database. Unlike in previous versions of the database, no patients were on ARV or CPT while being registered as HIV-negative.

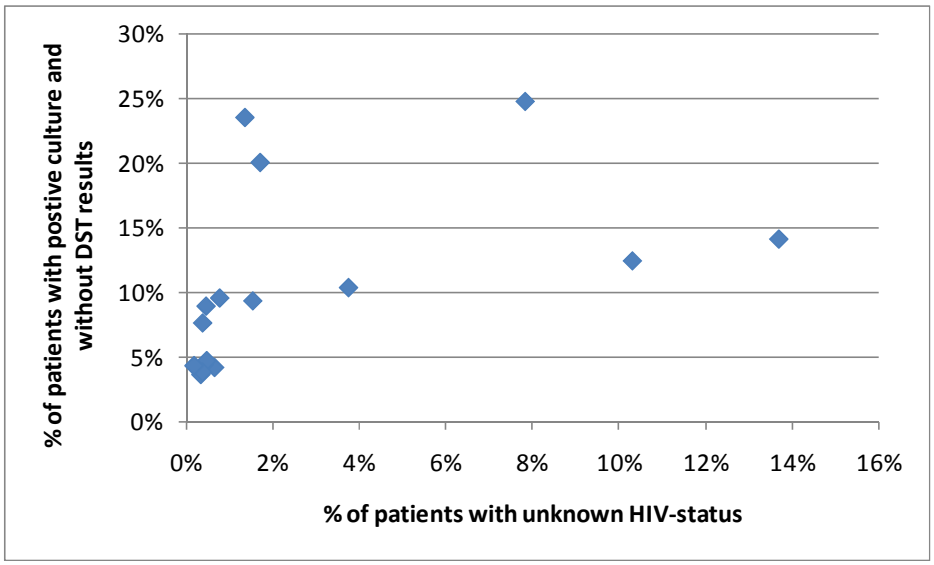

Figure 2. Percentage of cases with missing HIV-test results versus percentage of culture-positive TB cases with missing DST results, per oblast

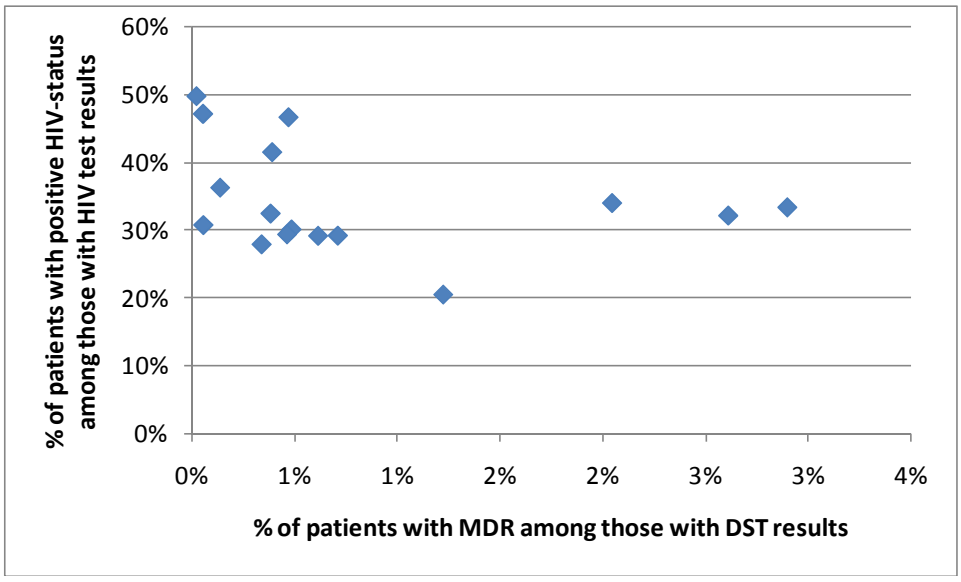

Figure 3. Percentage of TB cases with MDR among those with known DST results versus the percentage of HIV-positive cases among those with a known HIV-test result, per oblast

Table 9. Drug resistance by age group, sex and other patient characteristics in 2007-2009

	resistance						*resistance for those with known DST result*			
	pansensitive	*monoresistant*	*polyresistant*	*MDR*	*missing*	*Total*	*pansensitive*	*monoresistant*	*polyresistant*	*MDR*
Age (years)										
0-4	9	1	2	10	7	29				
	31.0%	3.4%	6.9%	34.5%	24.1%	100.0%	40.9%	4.5%	9.1%	45.5%
5-9	16	2	3	6	6	33				
	48.5%	6.1%	9.1%	18.2%	18.2%	100.0%	59.3%	7.4%	11.1%	22.2%
10-14	98	23	41	85	21	268				
	36.6%	8.6%	15.3%	31.7%	7.8%	100.0%	39.7%	9.3%	16.6%	34.4%
15-19	952	183	353	729	271	2488				
	38.3%	7.4%	14.2%	29.3%	10.9%	100.0%	42.9%	8.3%	15.9%	32.9%
20-24	1613	336	653	1574	469	4645				
	34.7%	7.2%	14.1%	33.9%	10.1%	100.0%	38.6%	8.0%	15.6%	37.7%
25-29	1567	277	594	1457	401	4296				
	36.5%	6.4%	13.8%	33.9%	9.3%	100.0%	40.2%	7.1%	15.3%	37.4%
30-34	1519	317	630	1365	402	4233				
	35.9%	7.5%	14.9%	32.2%	9.5%	100.0%	39.7%	8.3%	16.4%	35.6%
35-39	1233	274	543	1227	392	3669				
	33.6%	7.5%	14.8%	33.4%	10.7%	100.0%	37.6%	8.4%	16.6%	37.4%
40-44	1251	273	482	1001	348	3355				
	37.3%	8.1%	14.4%	29.8%	10.4%	100.0%	41.6%	9.1%	16.0%	33.3%
45-49	1247	286	551	920	352	3356				
	37.2%	8.5%	16.4%	27.4%	10.5%	100.0%	41.5%	9.5%	18.3%	30.6%
50-54	894	199	389	681	251	2414				
	37.0%	8.2%	16.1%	28.2%	10.4%	100.0%	41.3%	9.2%	18.0%	31.5%
55-59	643	157	280	446	165	1691				
	38.0%	9.3%	16.6%	26.4%	9.8%	100.0%	42.1%	10.3%	18.3%	29.2%
60-64	299	59	127	190	74	749				
	39.9%	7.9%	17.0%	25.4%	9.9%	100.0%	44.3%	8.7%	18.8%	28.1%
65-69	312	74	140	191	80	797				
	39.1%	9.3%	17.6%	24.0%	10.0%	100.0%	43.5%	10.3%	19.5%	26.6%
70-74	240	57	87	104	48	536				
	44.8%	10.6%	16.2%	19.4%	9.0%	100.0%	49.2%	11.7%	17.8%	21.3%
75+	179	42	46	45	32	344				
	52.0%	12.2%	13.4%	13.1%	9.3%	100.0%	57.4%	13.5%	14.7%	14.4%
Gender										
male	7753	1693	3256	6576	2245	21523				
	36.0%	7.9%	15.1%	30.6%	10.4%	100.0%	40.2%	8.8%	16.9%	34.1%
female	4319	867	1665	3456	1074	11381				
	37.9%	7.6%	14.6%	30.4%	9.4%	100.0%	41.9%	8.4%	16.2%	33.5%
Homeless										

yes	447	83	203	451	159	1343				
	33.3%	6.2%	15.1%	33.6%	11.8%	100.0%	37.8%	7.0%	17.1%	38.1%
no	11625	2477	4718	9581	3160	31561				
	36.8%	7.8%	14.9%	30.4%	10.0%	100.0%	40.9%	8.7%	16.6%	33.7%
Drug use										
yes	71	23	41	90	22	247				
	28.7%	9.3%	16.6%	36.4%	8.9%	100.0%	31.6%	10.2%	18.2%	40.0%
no	12001	2537	4880	9942	3297	32657				
	36.7%	7.8%	14.9%	30.4%	10.1%	100.0%	40.9%	8.6%	16.6%	33.9%
Alcoholism										
Yes	1103	237	471	904	385	3100				
	35.6%	7.6%	15.2%	29.2%	12.4%	100.0%	40.6%	8.7%	17.3%	33.3%
No	10969	2323	4450	9128	2934	29804				
	36.8%	7.8%	14.9%	30.6%	9.8%	100.0%	40.8%	8.6%	16.6%	34.0%
Prison history										
Yes	163	33	75	303	85	659				
	24.7%	5.0%	11.4%	46.0%	12.9%	100.0%	28.4%	5.7%	13.1%	52.8%
No	11909	2527	4846	9729	3234	32245				
	36.9%	7.8%	15.0%	30.2%	10.0%	100.0%	41.0%	8.7%	16.7%	33.5%
Total	12072	2560	4921	10032	3319	32904				
	36.7%	7.8%	15.0%	30.5%	10.1%	100.0%	40.8%	8.7%	16.6%	33.9%

Table 10. Drug resistance by smear and HIV status, in 2007-2009

		resistance						*resistance for those with known DST result*			
		pansensitive	*monoresistant*	*polyresistant*	*MDR*	*missing*	*Total*	*pansensitive*	*monoresistant*	*polyresistant*	*MDR*
Smear positive											
New	HIV-positive	56	7	22	26	5	116				
	%	48.3%	6.0%	19.0%	22.4%	4.3%	100.0%	50.5%	6.3%	19.8%	23.4%
	HIV-negative	5129	1002	1728	2441	1044	11344				
	%	45.2%	8.8%	15.2%	21.5%	9.2%	100.0%	49.8%	9.7%	16.8%	23.7%
	Total	5185	1009	1750	2467	1049	11460				
	%	45.2%	8.8%	15.3%	21.5%	9.2%	100.0%	49.8%	9.7%	16.8%	23.7%
Retreatment	HIV-positive	40	4	23	60	6	133				
	%	30.1%	3.0%	17.3%	45.1%	4.5%	100.0%	31.5%	3.1%	18.1%	47.2%
	HIV-negative	2874	742	1625	4274	1030	10545				
	%	27.3%	7.0%	15.4%	40.5%	9.8%	100.0%	30.2%	7.8%	17.1%	44.9%
	Total	2914	746	1648	4334	1036	10678				
	%	27.3%	7.0%	15.4%	40.6%	9.7%	100.0%	30.2%	7.7%	17.1%	44.9%
Smear negative											
New	HIV-positive	19	2	9	9	2	41				
	%	46.3%	4.9%	22.0%	22.0%	4.9%	100.0%	48.7%	5.1%	23.1%	23.1%
	HIV-negative	1968	377	638	1023	495	4501				
	%	43.7%	8.4%	14.2%	22.7%	11.0%	100.0%	49.1%	9.4%	15.9%	25.5%
	Total	1987	379	647	1032	497	4542				
	%	43.7%	8.3%	14.2%	22.7%	10.9%	100.0%	49.1%	9.4%	16.0%	25.5%
Retreatment	HIV-positive	12	1	4	12	3	32				
	%	37.5%	3.1%	12.5%	37.5%	9.4%	100.0%	41.4%	3.4%	13.8%	41.4%
	HIV-negative	577	129	293	842	200	2041				
	%	28.3%	6.3%	14.4%	41.3%	9.8%	100.0%	31.3%	7.0%	15.9%	45.7%
	Total	589	130	297	854	203	2073				
	%	28.4%	6.3%	14.3%	41.2%	9.8%	100.0%	31.5%	7.0%	15.9%	45.7%

Note: the drug resistance profiles within groups with similar smear status and treatment history are not statistically significantly different for HIV-negative and HIV-positive patient groups.

Table 11. Drug resistance by treatment history, gender and HIV status, in 2007-2009

		resistance						*resistance for those with known DST result*			
		pansensitive	*monoresistant*	*polyresistant*	*MDR*	*missing*	*Total*	*pansensitive*	*monoresistant*	*polyresistant*	*MDR*
Male											
New	HIV-positive	58	7	25	25	7	122				
	%	47.5%	5.7%	20.5%	20.5%	5.7%	100.0%	50.4%	6.1%	21.7%	21.7%
	HIV-negative	4333	869	1446	2047	973	9668				
	%	44.8%	9.0%	15.0%	21.2%	10.1%	100.0%	49.8%	10.0%	16.6%	23.5%
	Total	4391	876	1471	2072	980	9790				
	%	44.9%	8.9%	15.0%	21.2%	10.0%	100.0%	49.8%	9.9%	16.7%	23.5%
		41	6	23	59	7	136				
Retreatment	HIV-positive	30.1%	4.4%	16.9%	43.4%	5.1%	100.0%	31.8%	4.7%	17.8%	45.7%
	%	2454	624	1368	3506	886	8838				
	HIV-negative	27.8%	7.1%	15.5%	39.7%	10.0%	100.0%	30.9%	7.8%	17.2%	44.1%
	%	2495	630	1391	3565	893	8974				
	Total	27.8%	7.0%	15.5%	39.7%	10.0%	100.0%	30.9%	7.8%	17.2%	44.1%
	%	58	7	25	25	7	122				
Female											
New	HIV-positive	17	3	8	12	0	40				
	%	42.5%	7.5%	20.0%	30.0%	.0%	100.0%	42.5%	7.5%	20.0%	30.0%
	HIV-negative	2802	522	932	1436	576	6268				
	%	44.7%	8.3%	14.9%	22.9%	9.2%	100.0%	49.2%	9.2%	16.4%	25.2%
	Total	2819	525	940	1448	576	6308				
	%	44.7%	8.3%	14.9%	23.0%	9.1%	100.0%	49.2%	9.2%	16.4%	25.3%
		11	0	4	16	2	33				
Retreatment	HIV-positive	33.3%	.0%	12.1%	48.5%	6.1%	100.0%	35.5%	0.0%	12.9%	51.6%
	%	1033	254	558	1658	356	3859				
	HIV-negative	26.8%	6.6%	14.5%	43.0%	9.2%	100.0%	29.5%	7.3%	15.9%	47.3%
	%	1044	254	562	1674	358	3892				
	Total	26.8%	6.5%	14.4%	43.0%	9.2%	100.0%	29.5%	7.2%	15.9%	47.4%
	%	17	3	8	12	0	40				

Note: the drug resistance profiles within groups with similar sex and treatment history are not statistically significantly different for HIV-negative and HIV-positive patient groups.

Table 12. Treatment outcome in 2007-2009Q2 cohort by smear status at diagnosis and DR

		Treatment outcome								
		cure	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*total*	*Treatment success*
Smear-positive	pansensitive	6392	99	633	642	605	253	433	9057	
	%	70.6%	1.1%	7.0%	7.1%	6.7%	2.8%	4.8%	100.0%	71.7%
	monoresistant	1261	26	113	175	125	38	117	1855	
	%	68.0%	1.4%	6.1%	9.4%	6.7%	2.0%	6.3%	100.0%	69.4%
	polyresistant	1868	31	242	290	279	87	670	3467	
	%	53.9%	.9%	7.0%	8.4%	8.0%	2.5%	19.3%	100.0%	54.8%
	MDR	624	25	472	510	234	110	5312	7287	
	%	8.6%	.3%	6.5%	7.0%	3.2%	1.5%	72.9%	100.0%	8.9%
	Total	6114	194	1297	740	874	541	1099	10859	
	%	56.3%	1.8%	11.9%	6.8%	8.0%	5.0%	10.1%	100.0%	58.1%
Smear-negative	pansensitive	0	4014	82	153	169	83	105	4606	
	%	.0%	87.1%	1.8%	3.3%	3.7%	1.8%	2.3%	100.0%	87.1%
	monoresistant	0	482	12	23	31	5	23	576	
	%	.0%	83.7%	2.1%	4.0%	5.4%	.9%	4.0%	100.0%	83.7%
	polyresistant	0	799	24	40	44	20	111	1038	
	%	.0%	77.0%	2.3%	3.9%	4.2%	1.9%	10.7%	100.0%	77.0%
	MDR	0	430	47	161	53	22	1468	2181	
	%	.0%	19.7%	2.2%	7.4%	2.4%	1.0%	67.3%	100.0%	19.7%
	Total	10	30953	836	676	1198	1284	474	35431	
	%	.0%	87.4%	2.4%	1.9%	3.4%	3.6%	1.3%	100.0%	87.4%

Table 13. Treatment outcome in 2007-2009Q2 cohort by smear status at diagnosis and HIV-status

		cure	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*Total*	*Treatment success*
Smear-positive	HIV-positive	98	3	100	29	38	8	67	343	
	%	28.6%	.9%	29.2%	8.5%	11.1%	2.3%	19.5%	100.0%	29.4%
	HIV-negative	15840	368	2490	2241	2004	924	7416	31283	
	%	50.6%	1.2%	8.0%	7.2%	6.4%	3.0%	23.7%	100.0%	51.8%
	Total	15938	371	2590	2270	2042	932	7483	31626	
	%	50.4%	1.2%	8.2%	7.2%	6.5%	2.9%	23.7%	100.0%	51.6%
Smear-negative	HIV-positive	1	157	44	16	30	9	21	278	
	%	.4%	56.5%	15.8%	5.8%	10.8%	3.2%	7.6%	100.0%	56.8%
	HIV-negative	8	35381	881	1007	1400	1153	2123	41953	
	%	.0%	84.3%	2.1%	2.4%	3.3%	2.7%	5.1%	100.0%	84.4%
	Total	9	35538	925	1023	1430	1162	2144	42231	
	%	.0%	84.2%	2.2%	2.4%	3.4%	2.8%	5.1%	100.0%	84.2%

Table 14. Treatment outcome by HIV-status and drug resistance, stratified by previous treatment history and smear status at diagnosis (2007-2009Q2 patient cohort)

		Treatment outcome								
new SS+		*cure*	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*Total*	*Treatment success*
no hiv-no mdr	Count	5722	50	230	722	342	126	327	7519	
	%	76.1%	.7%	3.1%	9.6%	4.5%	1.7%	4.3%	100.0%	77%
hiv-no mdr	Count	46	1	16	11	6	3	0	83	
	%	55.4%	1.2%	19.3%	13.3%	7.2%	3.6%	.0%	100.0%	57%
no hiv-mdr	Count	267	5	81	218	46	18	1612	2247	
	%	11.9%	.2%	3.6%	9.7%	2.0%	.8%	71.7%	100.0%	12%
hiv and mdr	Count	1	1	7	4	3	0	13	29	
	%	3.4%	3.4%	24.1%	13.8%	10.3%	.0%	44.8%	100.0%	7%
Total	Count	6036	57	334	955	397	147	1952	9878	
	%	61.1%	.6%	3.4%	9.7%	4.0%	1.5%	19.8%	100.0%	62%

new SS-		*cure*	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*Total*	*Treatment success*
no hiv-no mdr	Count	44	3866	48	135	109	45	88	4335	
	%	1.0%	89.2%	1.1%	3.1%	2.5%	1.0%	2.0%	100.0%	90%
hiv-no mdr	Count	2	29	7	3	4	0	0	45	
	%	4.4%	64.4%	15.6%	6.7%	8.9%	.0%	.0%	100.0%	69%
no hiv-mdr	Count	0	258	11	102	9	7	700	1087	
	%	.0%	23.7%	1.0%	9.4%	.8%	.6%	64.4%	100.0%	24%
hiv and mdr	Count	0	0	2	2	0	0	9	13	
	%	.0%	.0%	15.4%	15.4%	.0%	.0%	69.2%	100.0%	0%
Total	Count	46	4153	68	242	122	52	797	5480	
	%	.8%	75.8%	1.2%	4.4%	2.2%	.9%	14.5%	100.0%	77%

Retreatment SS+		*cure*	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*Total*	*Treatment success*
no hiv-no mdr	Count	2840	74	586	275	511	113	717	5116	
	%	55.5%	1.4%	11.5%	5.4%	10.0%	2.2%	14.0%	100.0%	57%
hiv-no mdr	Count	22	0	18	4	15	1	9	69	
	%	31.9%	.0%	26.1%	5.8%	21.7%	1.4%	13.0%	100.0%	32%
no hiv-mdr	Count	289	9	294	199	132	61	2975	3959	
	%	7.3%	.2%	7.4%	5.0%	3.3%	1.5%	75.1%	100.0%	8%
hiv and mdr	Count	2	0	11	1	3	0	35	52	
	%	3.8%	.0%	21.2%	1.9%	5.8%	.0%	67.3%	100.0%	4%
Total	Count	3153	83	909	479	661	175	3736	9196	
	%	34.3%	.9%	9.9%	5.2%	7.2%	1.9%	40.6%	100.0%	35%

Retreatment SS-		*cure*	*completed*	*died*	*failure*	*default*	*transfer out*	*transfer to cat IV*	*Total*	*Treatment success*
no hiv-no mdr	Count	0	1014	52	57	94	40	128	1385	
	%	0%	73.2%	3.8%	4.1%	6.8%	2.9%	9.2%	100.0%	8%
hiv-no mdr	Count	0	10	4	1	2	0	1	18	
	%	0%	55.6%	22.2%	5.6%	11.1%	.0%	5.6%	100.0%	28%
no hiv-mdr	Count	0	136	30	44	33	8	646	897	
	%	0%	15.2%	3.3%	4.9%	3.7%	.9%	72.0%	100.0%	8%
hiv and mdr	Count	0	1	1	1	0	0	8	11	
	%	0%	9.1%	9.1%	9.1%	.0%	.0%	72.7%	100.0%	18%
Total	Count	0	1161	87	103	129	48	783	2311	
	%	0%	50.2%	3.8%	4.5%	5.6%	2.1%	33.9%	100.0%	8%

Key findings and recommendations Kazakhstan

Key findings

1. Completeness of data has improved clearly since March 2009, also retrospectively, as a result of active follow-up of missing and potentially flawed data by the national TB center. The data validation program that is run monthly was extended with additional checks based on inconsistensies found during preliminary analyses of the data for this project. As a consequence, reliability of the surveillance data is expected to have improved considerably. Still, there are large differences in data completeness between oblasts for both HIV and DST.
2. At oblast level, there is no clear correlation between completeness of HIV and DST results, suggesting that there may be different reasons for incompleteness of HIV and DST results.
3. The fact that new SS- patients have a lower yield of culture than retreatment patients with negative smears probably can be explained by over-diagnosis of TB in this group. A considerable part of the adult population in Kazakhstan (including students, men at military service, women after giving birth, hair dressers, factory staff, health care staff, kitchen staff, kindergarten and school staff) is targeted for obligatory yearly TST and X-rays for active detection of TB. In case of a positive TST or suspicion of active TB, X-rays are performed. In 2008, 9.0510 million TSTs were performed (in children and adults), and 7.0845 million X-rays were made for active detection of TB. X-rays can be made for all >12 years, so about 74% of the population > 12 years has had an X-ray in 2008 for TB detection.
4. Thirty percent of cultures of positive smears renders negative, which is too high. One reason for this may be too rigorous decontamination, but this should be investigated further.
5. At oblast level, there is no clear correlation between % of missing HIV test results and HIV-positivity among those with a known result (which would indicate that there may be selective testing of risk groups).
6. The HIV prevalence among TB patients in Kazakhstan is still low but rising, from 0.6% in 2007 to 1.2% in 2009.
7. The estimated HIV prevalence among the general population is 48.1 per 100.000 so about 0.5%. HIV prevalence is approximately 2 times increased among TB patients compared to the general population. The overall percent of patients with MDR-TB is 34%, which is, as expected, higher in retreatment patients than new patients. Overall, for patients with known DST and HIV test results, 0.4% of TB patients have both MDR-TB and HIV.
8. There are differences in HIV prevalence among TB patients within the country (highest in Eastern KZ except in East-KZ oblast). The proportion of all cases with drug resistance varied greatly across oblasts. This is being analyzed in more detail already, and results will be reported separately.
9. At oblast level, there is no clear correlation between HIV prevalence and MDR-TB prevalence. Also, within patient groups stratified by treatment history and smear status or gender, there is no association with HIV prevalence.
10. HIV prevalence is highest in patients returning after default. This can be explained by the fact that a higher prevalence of HIV was observed in patients with characteristics that are also risk factors for being a patient that has defaulted previous TB treatment (drug use, prison history, alcohol abuse, homelessness).
11. Some of these risk factors for HIV and default are known risk factors for MDR-TB. In our data, prison history, drug use and homelessness, but not alcoholism, were associated with having MDR-TB in univariate analysis. So the risk factors for MDR-TB and HIV are largely overlapping.

12. In both new and retreatment patients, patients without HIV and MDR-TB have the highest treatment success rates, while patients with both HIV and multidrug resistance have the lowest successful treatment outcome rates. Only being HIV-positive gives better treatment success rates than only having MDR-TB.
13. IPT (or RPT) is recommended for all HIV-positive individuals, but may not clear the infection in 50% (40%) of HIV-infected individuals because of resistance (assuming that resistance in HIV-patients with TB disease is similar as in those with TB infection).
14. According to the database, 10% of HIV-positive TB patients are on ARV treatment. According to the database, 12% of HIV-positive patients are on CPT, while this should be 100% according to the prikaz.
15. There are discrepancies between the number of co-infected TB/HIV patients in the HIV/AIDS and TB register. Reasons for this are being assessed currently in two regions in Kazakhstan, as well as the proportion of TB/HIV patients on CPT, and ART.

Recommendations

1. Supervision visits to oblasts with the highest proportion of incomplete and flawed data should be include the data validation reports to learn reasons for the reduced reliability of the data, and to give recommendations for further improvement of the quality of the data.
2. The reasons for the discrepancy between the number of co-infected TB/HIV patients in the HIV/AIDS and TB register could be investigated by comparing definitions for TB/HIV and HIV/TB, by doing a capture-recapture analysis of both registration systems and subsequently finding out reasons for HIV-positive patients with active TB/being registered in only one register. This is currently undertaken in two regions of Kazakhstan.
3. The low proportion of HIV-positive TB patients on CPT and ART according to the database should be validated, and reasons for this low proportion should be investigated as these are not according to the prikaz. This analysis also is part of the project in two regions of Kazakhstan, and should lead to practical recommendations on how to improve care to co-infected patients.
4. The fact that new sputum smear negative patients have a lower yield of culture than retreatment patients with negative smears probably can be explained by overdiagnosis of TB in this group. Reasons for overdiagnosis and diagnostic algorithms to reduce overdiagnosis of TB in Kazakhstan should be considered within the NCTP.
5. Thirty percent of cultures of smear-positive smears renders negative, which percentage is too high. The reason for this high percentage should be investigated and actions taken to increase the yield of culture (and thus DST). Potential reasons are the long transportation time due to the vastness of the country, or too rigorous decontamination or other conditions in the laboratories. Another potential reason is that no culture is done, and the result actually should be missing.

Integrating HIV testing into routine drug resistance surveillance methods in Kenya

Introduction Kenya

Kenya

Kenya an eastern Africa country with 582,650 km^2 area, shares borders with Uganda to the west, Tanzania to the south, Sudan and Ethiopia to the North, Somalia and Indian Ocean to the East.

Kenya has eight (8) administrative provinces namely Nairobi, Western, Rift Valley, Coast, Central, Eastern, Nyanza and North eastern province. These are further divided into 254 districts.

The projected population for 2009 is 39 million people[2].The population is young with forty two percent (42.3%) of the population being under 14 years. Population growth rate is estimated at 2.7 per annum. Infant mortality rate is 55 deaths per 1,000 live births and life expectancy at birth has improved to 58 years. Approximately 66% of the population still lives in rural areas[3] though in recent past there has been a significant migration to urban areas which has led to a proliferation of slums in peri-urban areas.

Figure 7 Map of Kenya

The estimated Gross Domestic Product GDP per capita for Kenya is $ 650 USD, the real GDP growth rate in 2008 was 2.2%[1]. Agriculture accounts for 70% of employment. The HDI for Kenya is 0.521, ranking her 148th out of 177 countries with data[4] on Human Development Index. In 2007, Kenya experienced post election violence leading formation of a Government of National Unity (GNU) in 2008 after the international pressure prevailed on the incumbent president to share power with the opposition. GNU split the health sector into two ministries, namely; Ministry of Medical services and Ministry of Public Health and Sanitation. The Division of TB, Leprosy and Lung Diseases (DLTLD) is in the Ministry of Public Health and Sanitation. Table 1 below gives a summary of basic country indicators[2].

[2] Kenya People 2009
http://www.theodora.com/wfbcurrent/kenya/kenya_people.html
SOURCE: 2009 CIA WORLD FACTBOOK
[3] Annual report, HMIS 2007
[4] Human Development index 2007/2008: http://hdrstats.undp.org/en/countries/country_fact_sheets/cty_fs_KEN.html

Table 1: Basic Country Indicators-2009 estimates

Estimated 2009 Population	39,002, 772
Annual population growth rate	2.7%
Total fertility rate	4.56 children born/woman
Infant mortality rate	54.7 deaths/1,000 live births
Under five mortality rate	105 per 100,000 children
Maternal mortality ratio	560 per 100000 live births (UNICEF-2007)
GDP Per capita	650 US dollars(CBS 2008)
Human Development Index	0.521
Adult literacy rate	85.1%
HIV/AIDS adult prevalence	7.4%(KAIS 2007)
PLWHIV	1.2 million
Percent of central government expenditure (1997–2006*) allocated to: health (UNICEF)	7%

TB-HIV situation in the country

The Kenya government has committed itself to the realization of the Millennium Development Goal (MDG) of halving and reversing the prevalence and mortality of TB by 2015. Despite successfully implementing the DOTS strategy for TB control, prevalence remains high. Kenya is ranked 13th among the 22 highest TB burden countries worldwide. Both burden and rates of TB have dramatically increased over the years, tenfold from 10,000 in 1987 to 96,000 in 2003 and then to 110,065 in 2009. The rise in TB cases in Kenya is attributable to a combination of factors including HIV infection, poverty, over-crowding and malnutrition. In 2007, the HIV prevalence in the general population between 15-64 years stood at 7.4% (KAIS 2007). The increasing numbers of new TB cases are linked with HIV infection, with a reported prevalence among the co-infected population of 44% in 2009. Many of these cases present as sputum smear negative. In 2009, 33% of all cases were new smear positive, while 32% were smear negative. Among smear negative 52% was HIV positive while this was 31% among smear positive cases.

The Division of Leprosy, Tuberculosis and Lung Disease (DLTLD) achieved the WHO international target of 70% case detection rate and 85% treatment success rate in the year 2006. In 2009 a case notification rate of 326 cases per 100,000 population (all forms of TB) was reported. Current TB data indicates that more males than females are notified (ratio males to females of 1.6:1). Most patients notified are in the age group 15 to 44 years, the age group with highest HIV prevalence rates.
In 2009, for the second year in a row Kenya reported a decline in the number of notified TB cases which could be due to stagnation and beginning of the decline in the number of TB cases notified due to concerted efforts in TB control.

TB diagnostic centers in Kenya offer HIV testing and counseling to all patients, seeking treatment for TB. In 2009, 88% of TB patients were tested for HIV and 44% (42,294/96,676) of the tested TB cases were HIV positive. The trend of HIV Testing and Counseling for TB patients increased steadily from 20% in 2004 to 88% in 2009[5], just below the 90% target the country set (see figure 1). Of those co-infected patients, 14,250 (34%) of are on ART while 38,989 (92%) of the TB/HIV patients are receiving Co-trimoxazole preventive therapy. Twenty percent of People Living with HIV were screened for TB in 2009. PLHIV diagnosed with TB are provided with TB treatment and linked to the HIV comprehensive care centres (CCC's) for HIV care.

[5] Annual Report 2009,DLTLD

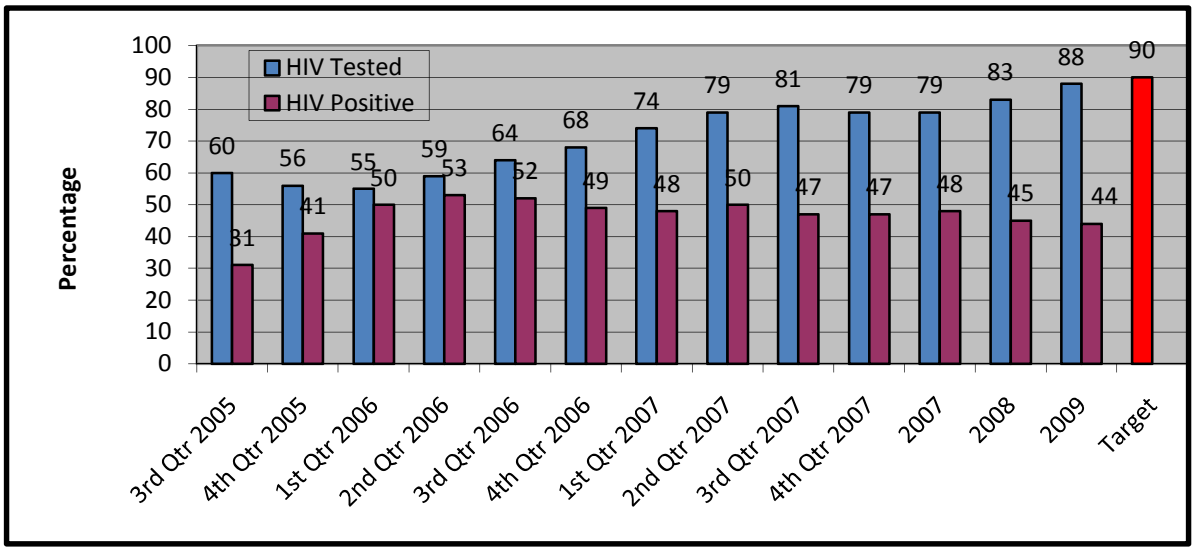

Figure 8 Trend of HIV Testing TB Patients in Kenya, 2005 To 2009

TB drug resistance situation in the country

The last official national Drug Resistance Surveys done in 1994 reported no MDR-TB. 6.3% of patients has a strains resistant to either (Isoniazid 5.3%) or both Isoniazid and streptomycin (1%); no resistance to either Rimfampicine or Ethambutol was reported[6]. Other studies indicated that drug resistance was significantly higher in patients from the refugee population[7] (18.3%) compared to patients from the non-refugee population (5.7%); 2.9% cases among the refugee population were MDR-TB while the non-refugee population had no MDR-TB. Kenya plans to carry out a national Drug resistance survey in the year 2010/2011 and it is anticipated that the results from the survey will inform the program of the current status of drug resistance in the country.

Routine surveillance for drug resistance and drug susceptibility testing (DST) among re-treatment cases of TB was introduced in 2002. By 2009, the Central Reference Laboratory (CRL) was receiving only 62% of the expected specimens despite an elaborate specimen transport system. Out of 18,887 specimens received by CRL since 2006, a cumulative 414 MDR TB cases were reported.

Outline of organization of TB and HIV/AIDS services

National TB programme

The National TB, Leprosy program was established in 1980 and adopted the DOTS strategy in 1993. A HIV survey conducted among TB patients in 1994 established that 40% of the TB cases were co-infected with HIV8. Workshops to forge closer working relationship between TB and HIV program were held in 1996 and 2001. This culminated in bringing the two programs under the division of AIDS/STI, TB and Leprosy within the department of preventive and promotive health services. In 2007, NLTP was upgraded to the Division of Leprosy, Tuberculosis and Lung Diseases (DLTLD).

The DLTLD has three tiers, namely the central unit, the province and district. The Central unit is charged with stewardship of DLTLD, resource mobilization, setting policy and

[6]Antituberculosis drug resistance surveillance in Kenya, 1995. Githui WA, Juma ES, van Gorkom J, Kibuga D, Odhiambo J, Drobniewski F. Int J Tuberc Lung Dis. 1998 Jun;2(6):499-505.

[7] Githui WA, Hawken MP, Juma ES, Godfrey-Faussett P, Swai OB, Kibuga DK et al. Surveillance of drug-resistant tuberculosis and molecular evaluation of transmission of resistant strains in refugee and non-refugee populations in North-Eastern Kenya. Int J Tuberc Lung Dis 2000 October;4(10):947-55

[8]HIV Sera prevalence among TB patients by Van Gorkom J et al 1995

developing guidelines. Provinces are represented as thirteen TB control zones, each under a Provincial TB and Leprosy Coordinator (PTLC). Each zone is made up of a number of districts. TB, leprosy and TB/HIV control and surveillance activities in each district are coordinated by a district TB/Leprosy coordinator. Diagnosis and treatment is mainly done by general health care workers in the health facilities all over the country. 2280 (40%) out of 5589 public and private health facilities in the country currently implement TB program control activities. Smear microscopy and examination for TB is available in 930 out of 959[9] laboratories countrywide.

National HIV programme

The first case of HIV was reported in Kenya in 1984. HIV cases increased exponentially amidst denial by the government of the day. The Ministry of Health responded by forming a committee, which developed the 1st strategic plans culminating in formation of the National AIDS/STI control program (NASCOP) in 1987. NASCOP has program officers at the provinces and districts.

In 1999, Kenya formed a National AIDS Control Council through legal notice 170, under the state agencies act. The process involved presenting a session paper no.4 of 1997 to parliament for discussion. Kenya declared HIV/AIDS a national disaster in 1999 and developed a multi-sectoral strategy, with AIDS control units in all ministries. National Aids Control Council (NACC) is mandated to develop policy framework on HIV/AIDS in Kenya and mobilize resources required to control AIDS. The work of NACC is reflected at the provinces through Provincial Aids Control Council (PACC), which ensures the mainstreaming of HIV/AIDS control in all relevant Aids Control Units (ACUs) in the province.

HIV is controlled through a number of broad structures. At the top most is National Aids Council, which works through Aids coordinating units in a number of ministries. The ACU for Ministry for Health is NASCOP. NASCOP currently has two directors and program officers in charge of 8 programs. Prevention programs include VCT, Blood safety; Provider initiated testing and counseling (PITC) and male circumcision among others. The other programs are Prevention of Mother to Child Transmission (PMTCT), Treatment care support, ART program, TB/HIV collaboration, STI and M&E. NASCOP has Aids coordinators at the provinces and districts who coordinate program activities.

Management of HIV/AIDs is done in comprehensive care centers in hospitals where all services from various programs in HIV/AIDS care are availed. In most instances, the CCC has a clinician who takes lead. The clinician is assisted by nurses and other health care workers with specific skills in the program they work in, be it counseling or nutrition etc.

TB/HIV

In 2002, the Director of Medical Services established TB/HIV technical working group whose main agenda was to facilitate collaboration between TB and HIV programs. The TB/HIV working group is still in existence today and membership is drawn from the NASCOP, DLTLD, WHO, CDC and partners with vested interests in both TB and HIV control. The achievements of the TB/HIV technical working group and DLTLD at large include HIV Testing and counseling in all TB diagnostic centers. In 2008, 83% of reported TB cases were tested for HIV as a gateway to HIV care services.

TB and HIV screening policies

The DLTD, with guidance of the TB/HIV technical working group, developed guidelines for diagnostic testing and counseling in 2006. This was followed up with training TB care providers on HIV counseling and testing. All TB patients are therefore offered testing for HIV and counseled accordingly, with an option to opt out. HIV positive PTB patients access co-trimoxazole therapy and referred for ARVs to the HIV/AIDS clinics

Likewise, the HIV program developed guidelines for HIV testing and counseling in Kenya. It encompasses all forms of counseling and testing, be it clients or provider initiated, in

[9] Annual report 2009, DLTLD

or without health care setting. This has encouraged health care workers to initiate HIV testing and counseling to all patients seeking care in health facilities in Kenya. HIV positive patients' access care through the Comprehensive Care Centres (CCCs) which includes ARVs for TB/HIV dually infected patients referred from TB clinics and screening for TB on a monthly basis.

Policies for (preventive therapy) regarding TB/HIV

Kenya adapted the WHO TB/HIV collaborative framework in the TB/HIV guidelines of 2006 whose main objectives are;

- To establish mechanisms for collaboration between TB and HIV programs
- To decrease the burden of tuberculosis amongst PLWHA
- To decrease the burden of HIV amongst TB patients

In order to achieve these objectives, the guidelines are implemented through twelve point activities as shown below;

- Set up a coordinating body for TB/HIV activities at all levels: Nationally, Province and Districts
- Conduct surveillance of HIV prevalence amongst TB patients
- Carry out joint TB/HIV planning
- Conduct monitoring and evaluation
- Establish intensified TB case finding
- Introduction of IPT in settings where this is feasible like in research, prisons etc
- Ensure infection control in health care and congregate settings
- Provide HIV testing and counseling (DTC)
- Introduce HIV prevention methods
- Introduce co-trimoxazole preventive therapy (CPT)
- Ensure HIV/AIDS care and support

Process outline Kenya

TB and HIV surveillance system in place at start of the project

Since introduction of the Diagnostic HIV Testing and Counseling guidelines in 2004 TB patients in Kenya are routinely offered HIV testing with an option to opt out. The majority of TB patients are tested for HIV. Information on HIV screening is available in the revised monitoring and evaluation tools (Patient record card, TB facility and district registers). The routine surveillance for Drug resistance in the country is only done for retreatment cases and contacts of MDR TB. Thus all sputum samples from patients started on re-treatment regimen (cat II), are collected at facility level and send to the Central Reference Laboratory (CRL) for Culture/ Drug Susceptibility Testing (C/DST). However, HIV status has not been included routinely in MDR-TB surveys or routine surveillance systems despite the availability of the information in records during the initial treatment.

Overview of methodology used

This study was conducted by the staff of DLTLD, including the CRL with involvement of KNCV regional office and headquarters. TB patients on retreatment for tuberculosis disease for whom sputum is submitted to CRL for culture and drug susceptibility testing were the main target. New TB cases were excluded from the study since it was not policy then to carry out surveillance for drug resistance amongst new cases. The main activities involved meetings with the program officers in CRL and DLTLD, developing a study implementation plan, which was then funded through TBCAP. Officers working at CRL travelled to all provinces to introduce the study giving clearly the objectives of the study and elaborating the procedures which will be involved in the implementation, in addition the staff followed up patient information on requests which were not filled adequately in districts including health facilities.

Additional data-collection

The existing data collection tool (culture request form) initially did not include the HIV indicators, hence there was need to revise the request forms to incorporate the HIV indicators. These forms were printed and distributed to all the regions for onward transmission to the health facilities. After a pilot at the end of 2008 the new form was introduced country wide from 1st January 2009 onwards.
The pretested laboratory request form was used to collect data from the TB treatment register, the treatment cards of study subjects. Information provided included age, gender, history of previous TB treatment, HIV testing and status, and CD4 count where available. MDRTB Patients for whom HIV testing information was not available or tested negative were followed up. The principal investigator handled and coded the data during the collection, Epi info version 3.5. Statistical software was used for data entry and analysis. Cleaning of data and validation was done prior to analysis. Each request form had a unique identifier. The prevalence of HIV was calculated for various categories of drug resistant and the drug susceptible groups. Prevalence ratio was used as a measure of association. Chi square test was used to test statistical significance.

Monitoring Visits

After the sensitization of health care workers on the use of the new culture request form they were asked to use the new tools when they submit the samples to the central reference laboratory. Quarterly monitoring were conducted by the staff at the central to ensure that the data collection tools being used were the revised forms.

One of the key experience during the monitoring visits was that health care workers had not initially been taken through the changes in the data capture tool which was an omission even though the PTLC's were sensitized the information seemed not to have cascaded to the DTLC's and eventually to the health care workers for the implementation of the changes in the sputum and culture request form. Since most of the samples are sent to the CRL from the district level there was always a disconnect between the flow of information from the district level to the facility level and this was corrected and the DTLC and DMLT were asked to counter check the completeness of the records before being sent to the CRL. Those which had missing information were followed and those which had no information relating to the facility details in and in particular the district of origin were very limiting as we could not locate the initial facility but this was addressed by first asking the DTLC's and DMLT's to counter check before the samples were sent to the CRL we have already addressed the issues.

Integration process

HIV status was integrated in the culture request form starting from 1st January 2009. At different times during the year the proportion of records with HIV status reported was determined. Coverage of HIV status clearly improved during the project and reached 55% with routine inclusion of HIV status (Table 2). For data analysis purpose a final request to update records with missing HIV status was made to all PTLCs which resulted in coverage of HIV status of 74% in the final database.

Table 2 Coverage of HIV status reporting in the CRL database at different points in time during the project

Date	*Period*	*Total number cases submitted*	*%HIV reported*
March 2009	Till 18 March 2009	1188	33%
April 2009	Till 27 April 2009	1894	35%
January 2010	Till august 2009		57%
May 2010	Whole year 2009	6568	55%
July 2010	Whole year 2009	6554	74%

Reasons for missing data

- Health care workers not very keen to update the data since they could not understand the information was critical at all levels since they thought once they have all the information in the registers when they receive the results from the CRL they just update their records. This impression was corrected by sensitizing the health care workers on the importance of this information at all levels especially for decision making regarding policy issues.
- For HIV testing some health care workers felt this was sensitive information to be put in the culture request form hence their reluctance to fill in the details, they were assured though that the information so collected was being treated confidentially just like any other patient information
- Another challenge with HIV testing was that at the time of specimen submission the patient may not have consented to be tested for HIV
- Some of the health facilities were still using the old request forms since the information about the revision had not reached them and in some instances they could not understand why use the new forms when there still had forms in their facilities hence the need for DLTLD to develop a recall procedure for the obsolete forms

Challenges during project implementation

One of the major challenge faced during the project implementation as mentioned above was the fact that sensitization of all the health care workers was not done hence the flow of information was not well articulated. Most of the samples are sent from either the TB clinic or the Hospital laboratory and unfortunately not everybody was informed or knew how to fill the form initially and additional sensitization of the DMLTS, some nurses at the TB clinics and facility. Also, the modification of the original form also meant slight modification of the electronic data capture tool which took some time to be implemented.

Results data analysis Kenya

General overview data

The final database contains data for the full year 2009: 1st January up to 31st December 2009 and consisted of 6567 records. Eleven records were omitted as they were records from follow up cultures of MDR patients, two records were omitted that were from 2 patients from Sudan and two records were omitted as they were samples from extra pulmonary patients and where no sputum samples. As they were just two it was decided to omit them, also no DST results were available for these two samples. The final database consisted of 6552 records, all from retreatment cases whose sputum was submitted to CRL. Coverage of retreatment cases by CRL was reported to be about 65% in 2009, an improvement compared to 2008. The figure below gives the estimated coverage of retreatment cases by province (figure adapted from DLTLD annual report 2009). Coverage of HIV- and HIV+ retreatment cases was similar at 46 and 42% respectively. Two provinces, Nairobi North and Central submitted more samples then reported, this should be further investigated.

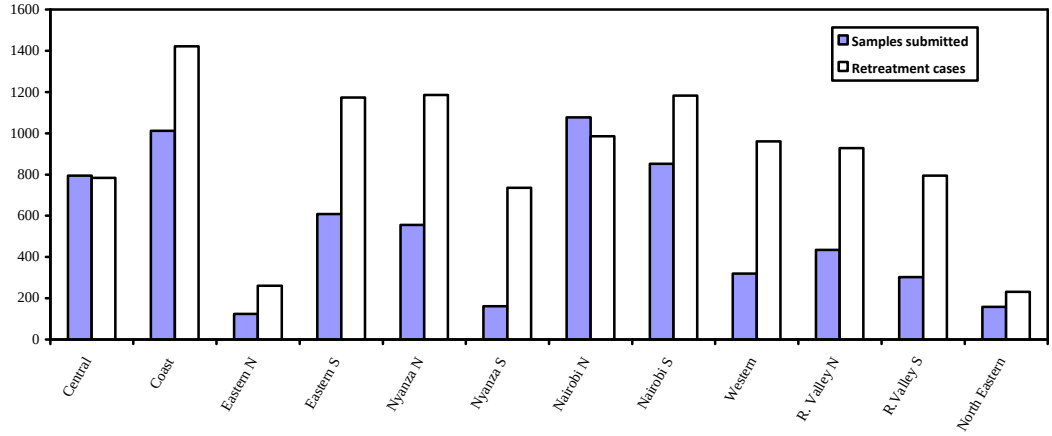

Figure 9 Sputum submission to CRL by province 2009 (figure from DLTLD annual report)

Data completeness

General

All parameters had some records with missing data. Table 3 gives an overview of missing data among the general parameters. Percentage of missing data varied from 0% for gender to nearly 80% for district.

Table 3 Overview of missing data among the general parameters

	age	***sex***	***patient type***	***facility name***	***province***	***district***	***data collection***	***data received***
n missing	332	0	896	138	113	5116	327	105
% missing	5.1%	0.0%	13.7%	2.1%	1.7%	78.1%	5%	1.6%

HIV status

HIV status was introduced countrywide into the culture request form from 1st January 2009 onwards. It was however not always reported upon by the different facilities however reporting improved during the year from a low 33% in the first quarter of 2009

(see 2.1. above), to 74% in the final database (Table 4). Proportion not done or declined was similar between male and female patients (Table 5). This is lower than the overall percentage of retreatment cases being tested countrywide. The annual program data indicate that 91% of retreatment cases are tested for HIV of which 52% tested positive (DLTLD annual data 2009).

Table 4 HIV status reporting of retreatment cases

HIV status	*frequency*	*percentage*
HIV Negative	2153	32.9%
HIV Positive	2143	32.7%
Declined	4	0.1%
Not Done	553	8.4%
Not indicated	1699	25.9%
total	6552	100.0%

Table 5 HIV status reporting by gender

Sex	*Unknown*	*Declined*	*Not Done*	*Test Result*
Female	24.2%	0.0%	8.3%	67.5%
Male	26.9%	0.1%	8.5%	64.5%

Smear, culture & DST results

A total of 6552 samples were submitted for culture which were all culture. For 4196 samples (64%) culture growth was 0 (Table 6). 2.6% of cultures was contaminated. Before being cultured a smear is made, for the direct smear 4163 samples (63.5% of all samples) had a negative smear result (Table 7). Smear result and culture growth were partly linked as the negative and scanty smear the largest proportion with no culture growth and the +++ smear the highest proportion with >100 colonies (Table 8). Samples with no culture growth and negative smear results varied over the provinces. No culture growth ranged from 53 to 79% and negative smear result from 52 to 78%, both where highest in North Eastern (Table 9). For all cultures with growth DST results were available.

Table 6 Results of culture growth as reported of retreatment cases

result of culture growth	*frequency*	*percentage*
0 (no growth)	4196	64.0%
1 to 19 col	4	0.1%
20 to 100 col	993	15.2%
>100 col	1189	18.1%
Contaminated	170	2.6%
total	6552	100.0%

Time between date sample collected and date delivered at CRL was on average nearly 8 days with a maximum of 282 days (table 10). The correct use of this parameter needs to be verified. Seventy-five percent of samples reached the CRL within 9 days. Although a substantial amount of samples took longer than the advised 5 days to reach CRL this

seemed not have had a significant results on culture growth or smear result (Table 11a&b). As culture growth was affected by direct smear result, time laps was investigated taking both into account. For those with a negative direct smear there seemed little effect except for contamination rate that increased slightly with increased time laps. For those with a positive direct smear percentage of those with no growth increased when time laps increased to over 9 days. Comparing the time laps of the different provinces indicated that several provinces take substantially longer than others (Table 13).

Table 7 Results of direct smear of retreatment cases submitted to CRL

smear result	***count***	***frequency***
0 (negative)	4163	63.5%
scanty	564	8.6%
+	692	10.6%
++	493	7.5%
+++	634	9.7%
no result	6	0.1%
overall	*6552*	*100.0%*

Table 8 Culture growth by smear result of retreatment cases submitted to CRL

	smear result					
culture growth	negative	scanty	+	++	+++	no result
no growth (0)	87.4%	53.2%	20.1%	11.8%	8.7%	83.3%
1 to 19 col	0.0%	0.2%	0.3%	0.0%	0.0%	0.0%
20 to 100 col	8.3%	32.3%	34.4%	26.4%	15.5%	16.7%
>100 col	1.6%	12.1%	42.3%	60.4%	73.2%	0.0%
Contaminated	2.7%	2.3%	2.9%	1.4%	2.7%	0.0%

Table 9 Negative smear results, culture growth and contamination by province

Province	***smear result negative***	***no culture growth***	***culture contaminated***
Central	61.0%	61.4%	1.1%
Coast	58.4%	57.0%	5.4%
Eastern North	59.3%	56.9%	4.9%
Eastern South	58.2%	57.2%	3.9%
Nairobi North	70.1%	68.1%	1.4%
Nairobi South	68.6%	72.5%	1.4%
North Eastern	77.5%	79.3%	2.4%
Nyanza N	68.8%	72.3%	1.8%
Nyanza S	67.3%	67.3%	3.1%
Rift valley N	59.9%	62.0%	2.3%
Rift valley S	55.0%	53.2%	3.9%
Western	62.1%	63.9%	0.6%
not reported	52.2%	61.1%	4.4%

Table 10 Overview of time laps parameters (difference between date collected and date delivery at CRL)

Time laps date received and date collected	
average (SD)	7.7 days (12.6)
25% (quartile)	2 days
50% (median)	4 days
75% (quartile)	9 days
Max nr days	282 days

Table 11a Culture growth results by time laps between date collection and date delivery for smear negative and positive direct smears

	< 5 days	***5-9 days***	***>9 days***
No growth	63.1%	64.1%	65.0%
1 to 19 col	0.1%	0.0%	0.0%
20 to 100 col	15.1%	15.1%	15.8%
>100 col	19.9%	18.0%	14.8%
CONTAMINATED	1.8%	2.8%	4.4%

Table 11b Smear results by time laps between date collection and date delivery

	< 5 days	***5-9 days***	***>9 days***
0 (negative)	62.7%	64.0%	63.6%
scanty	8.7%	8.4%	9.0%
+	10.8%	10.9%	9.9%
++	7.7%	6.9%	8.6%
+++	10.0%	9.7%	8.8%
no smear result	0.1%	0.1%	0.0%

Table 12 Culture growth for different time between date collection and date delivery by smear status

smear status	***culture growth***	*< 5 days*	*5-9 days*	*>9 days*
negative	no growth (0)	1937 (88.0%)	671 (87.6%)	740 (85.9%)
	positive growth	227 (10.3%)	71 (9.3%)	78 (9.1%)
	contaminated	38 (1.7%)	24 (3.1%)	43 (5.0%)
positive	no growth (0)	278 (21.3%)	95 (22.1%)	139 (28.3%)
	positive growth	1003 (76.7%)	324 (75.5%)	336 (68.3%)
	contaminated	26 (2.0%)	10 (2.3%)	17 (3.5%)

Table 12 Time laps between date collection and date delivery by province

Province	*average*	*SD**	*< 5 days*	*5-9 days*	*>9 days*
Central	5.7	7.7	65.5%	19.7%	14.7%
Coast	10.8	17.4	46.8%	18.7%	34.5%
Eastern North	5.9	8.3	69.2%	15.4%	15.4%
Eastern South	6.1	12.6	68.6%	18.6%	12.9%
Nairobi North	7.4	11.4	56.9%	23.1%	20.0%
Nairobi South	7.6	8.7	47.9%	25.4%	26.8%
North Eastern	6.5	10.9	68.9%	19.5%	11.6%
Nyanza N	6.1	8.3	65.0%	17.7%	17.3%
Nyanza S	5.8	8.0	64.7%	19.0%	16.3%
Rift valley N	11.3	17.3	39.0%	20.8%	40.2%
Rift valley S	7.3	17.1	71.8%	12.6%	15.6%
Western	7.5	11.8	64.6%	14.5%	20.9%
not reported	5.9	11.6	76.8%	8.1%	15.2%

SD=standard deviation

Patients characteristics

Sex & age

The majority of patients (65%) were male (Table 14). Age of patients ranged from 2 to 95 years old with an average age of 36.3 years (SD[10] 12.5 years). Age distribution in male and female patients was similar (Table 14; Figure 10). For data analysis three age groups were defined, <25 years old, 25-45 years old and >45 years old. The majority of patients was 25-45 years old; this was similar in male and female patients (Table 15).

Table 13 Gender and age of retreatment cases submitted to CRL

Gender	*Frequency (%)*	*Average age (SD)*
Female	2291 (35.0%)	34.2 (12.3)
Male	4261 (65.0%)	37.3 (12.5)
Overall	6552 (100.0%)	36.3 (12.5)

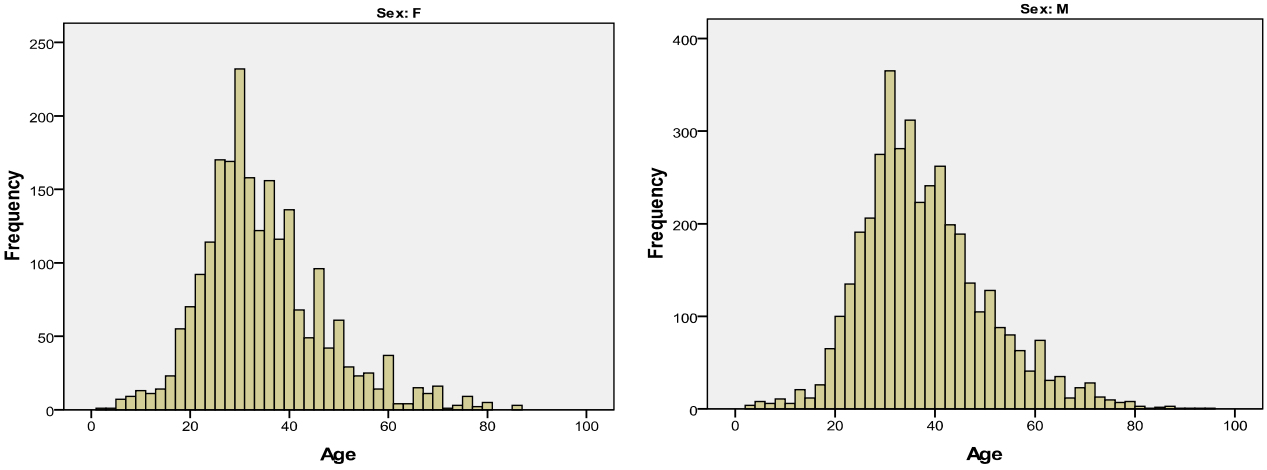

Figure 10 Age distribution in female (F) and male (M) retreatment cases submitted to CRL

[10] SD= Standard Deviation

Table 14 Age groups, overall and by gender, of retreatment cases submitted to CRL

	Overall		*Male*		*Female*	
Age group	***frequency***	***percentage***	***frequency***	***percentage***	***frequency***	***percentage***
<25 yrs	885	13.5%	475	11.1%	410	17.9%
25-45 yrs	4094	62.5%	2662	62.5%	1431	62.4%
>45 yrs	1242	19.0%	895	21.0%	347	15.1%
age not reported	331	5.1%	229	5.4%	103	4.5%
total	6552	100.0%	4261	100.0%	2291	100.0%

Patient type

All cases that were included in the database are retreatment cases for which sputum is submitted for culture to CRL. The majority of patients are relapse patients (Table 16), in males there were significantly more positive relapse then negative relapse then in female patients (p=0.008).

Table 15 Patient type (overall and by gender) of retreatment cases who sputum was submitted to CRL in 2009

	overall		***male***		***female***	
Patient type	*count*	*frequency*	*count*	*frequency*	*count*	*frequency*
FLT	488	7.4%	308	7.2%	180	7.9%
FRT	217	3.3%	148	3.5%	69	3.0%
NR	1930	29.5%	1138	26.7%	792	34.6%
PR	2095	32.0%	1434	33.7%	661	28.9%
RAD	928	14.2%	687	16.1%	241	10.5%
missing	894	13.6%	546	12.8%	348	15.2%
overall	6552	100.0%	4261	100.0%	2291	100.0%

FLT: Failure to first line treatment; FRT=failure to retreatment; NR=negative relapse; PR=positive relapse; RAD=return after default

Geographic distribution

Percentage of samples submitted to CRL varied from as low as 22.0% to over 100.0%. Nairobi North and Central provinces submitted samples for all retreatment cases to CRL and even more than reported annually (Table 16). Overall 61% of retreatment cases were submitted to CRL.

Table 16 Geographic origin of retreatment cases whose sputum was submitted to CRL in 2009 and geographic origin of all retreatment cases reported nationally in 2009

	CRL database		***national data (2009)***		***percentage***
	# retreatment cases		**# retreatment cases**		**submitted**
Province	*frequency*	*percentage*	*frequency*	*percentage*	
Central	801	12.2%	783	7.3%	102.4%*
Coast	1011	15.4%	1422	13.3%	71.1%
Eastern North	123	1.9%	260	2.4%	47.3%
Eastern South	608	9.3%	1174	11.0%	51.8%
Nairobi North	1072	16.4%	985	9.2%	108.9%*
Nairobi South	850	13.0%	1182	11.1%	71.9%
North Eastern	169	2.6%	231	2.2%	73.2%
Nyanza N	552	8.4%	1185	11.1%	46.6%
Nyanza S	162	2.5%	735	6.9%	22.0%
Rift valley N	439	6.7%	928	8.7%	47.3%
Rift valley S	333	5.1%	829	7.8%	40.2%
Western	319	4.9%	961	9.0%	33.2%
not reported	113	1.7%		0.0%	
overall	6552	100.0%	10675	100.0%	61.4%

*this seems a discrepancy between annual figures and CRL submitted data

Drug resistance & MDR-TB results

DST results were available for all samples with culture growth, a total of 2186 samples. Of those with DST results available 75.3% was pan-sensitive, 14.4% mono-resistant, 3.5% poly-resistant and 6.8% MDR-TB (Table 17). Of those with DST results available 18.7% was resistant to Isoniazid, 8.6% to Rifampicin, 8.6% to Ethambutol and 8.1% to Streptomycin (Table 19). For Rifampicin, Ethambutol and Streptomycin resistance was significantly higher in female then in males (Table 20). Looking at resistance in the different age groups indicated a significantly higher prevalence in the younger age group for all four drugs.

Table 17 Drug susceptibility status of samples submitted in 2009 to CRL

DR status	***frequency***	***percentage***
pan-sensitive	1646	75.3%
mono-resistant	315	14.4%
poly-resistant	77	3.5%
MDR-TB	148	6.8%
total	2186	100.0%

Table 18 Drug susceptibility to the four main TB drugs of samples submitted to CRL

	Isoniazid		***Rifampicin***		***Ethambutol***		***Streptomycin***	
	frequency	*percentage*	*frequency*	*percentage*	*frequency*	*percentage*	*frequency*	*percentage*
Resistant	408	18.7%	187	8.6%	187	8.6%	177	8.1%
Sensitive	1778	81.3%	1999	91.4%	1999	91.4%	2009	91.9%
total	2186	100.0%	2186	100.0%	2186	100.0%	2186	100.0%

Table 19 Resistance to four first line drug by gender

first line drug	*Sex*	*resistant*	*susceptible*	*%resistant*	*p-value*
Isoniazid	Female	122	496	19.7%	p=0.41
	Male	286	1282	18.2%	
Rifampicin	Female	65	553	10.5%	p=0.039
	Male	122	1446	7.8%	
Ethambutol	Female	66	552	10.7%	p=0.025
	Male	121	1447	7.7%	
Streptomycin	Female	70	548	11.3%	p=0.005
	Male	107	1461	6.8%	

Table 20 Resistance to four first line drug by age group

first line drug	*Age group*	*resistant*	*susceptible*	*%resistant*
Isoniazid	<25 yrs	74	247	23.1%
	25-45 yrs	254	1181	17.7%
	>45 yrs	59	253	18.9%
	age not reported	21	97	17.8%
Rifampicin	<25 yrs	43	278	13.4%
	25-45 yrs	113	1322	7.9%
	>45 yrs	18	294	5.8%
	age not reported	13	105	11.0%
Ethambutol	<25 yrs	30	291	9.3%
	25-45 yrs	113	1322	7.9%
	>45 yrs	27	285	8.7%
	age not reported	17	101	14.4%
Streptomycin	<25 yrs	34	287	10.6%
	25-45 yrs	109	1326	7.6%
	>45 yrs	18	294	5.8%
	age not reported	16	102	13.6%

Among women more MDR-TB was reported than among men although not statistically significant (p=0.55; Table 21). MDR-TB was significantly more prevalent in the age group below 25 years (p=0.009; Table 22). Stratifying MDR-TB by age group and gender indicated a slightly higher prevalence among female than male in all age groups although not significant in any age group (Table 23).

Table 21 MDR-TB status stratified by gender

gender	*MDR-TB*	*no MDR-TB*	*%MDR-TB*
female	52	566	8.4%
male	96	1472	6.1%
overall	148	2038	6.8%

Table 22 MDR-TB status stratified by age-group

age-group	***MDR-TB***	***no MDR-TB***	***%MDR-TB***
<25 yrs	32	289	10.0%
25-45 yrs	90	1299	6.5%
>45 yrs	14	298	4.5%
age not reported	*12*	*152*	*7.3%*
overall	*148*	*2038*	*6.8%*

Table 23 MDR-TB status stratified by age-group and gender

Age group	*gender*	*MDR-TB*	*no MDR-TB*	*%MDR-TB*	*p-value*
<25 yrs	Female	15	122	10.9%	NS
	Male	17	167	9.2%	
25-45 yrs	Female	29	366	7.3%	NS
	Male	61	979	5.9%	
>45 yrs	Female	5	51	8.9%	NS
	Male	9	247	3.5%	
age not reported	Female	3	27	10.0%	NS
	Male	9	79	10.2%	

NS= not significant

Stratifying MDR-TB status by patient type indicates that more MDR-TB patients can be found among retreatment cases that failed first line or retreatment (Table 24). The lowest percentages are observed among cases that returned after default and negative relapse cases.

Table 24 MDR-TB status stratified by patient type

Patient type	*MDR-TB*	*no MDR-TB*	*%MDR-TB*
FLT	28	72	28.0%
FRT	19	33	36.5%
NR	8	218	3.5%
PR	63	1118	5.3%
RAD	11	403	2.7%
not indicated	19	194	8.9%
overall	148	2038	6.5%

FLT: Failure to first line treatment; FRT=failure to retreatment;
NR=negative relapse; PR=positive relapse; RAD=return after default

Assessing the geographical distribution of MDR-TB (Table 26) indicates among retreatment cases, more MDR-TB seems to be found in North Eastern, Nyanza North and South, Eastern South and Coast, which had higher than percentage than the overall percentage of 6.5%. Due to lower case number for some provinces like North Eastern results need to be interpreted with caution.

Table 25 MDR-TB status stratified by province

Province	*MDR-TB*	*no MDR-TB*	*%MDR-TB*
Central	11	289	3.7%
Coast	29	351	7.6%
Eastern North	2	45	4.3%
Eastern South	17	219	7.2%
Nairobi North	21	306	6.4%
Nairobi South	13	209	5.9%
North Eastern	8	23	25.8%
Nyanza N	17	126	11.9%
Nyanza S	4	44	8.3%
Rift valley N	8	149	5.1%
Rift valley S	9	134	6.3%
Western	5	108	4.4%
not reported	4	35	10.3%
overall	148	2038	6.8%

HIV status results

Overall 49.9% of retreatment cases submitted to CRL tested positive. This is similar to the national figure for 2009 of 52%. Of the women a higher percentage is HIV% than of the men (61.2 vs. 43.6% respectively, p<0.0001). Overall among retreatment cases there are less women than men (35.0 vs. 65.0% respectively; Table 14). HIV status by age group (Table 26) indicates that highest HIV prevalence is among the 25-45 year old retreatment cases and is significantly higher (p<0.001) than in the age group < 25 years and > 45 years. HIV prevalence was also significantly higher in the > 45 years compared to the < 25 years old (p=0.014) Looking at gender difference within the age groups (Table 28) indicates that in all three age-groups significantly more females are HIV positive.

Table 26 HIV status stratified by gender

	HIV+	*HIV-*	**HIV status unknown¶**	*%HIV+ by Gender**
Female	945	601	*745*	61.1%
Male	1198	1552	*1511*	43.6%
overall	*2143*	*2153*	*2256*	*49.9%*

¶cases declined and not done where grouped with cases for whom status was not known; *percentage among those with HIV test results reported

Table 27 HIV status stratified by age group

Age group	*HIV+*	*HIV-*	**HIV status unknown¶**	*%HIV+**
<25 yrs	216	367	302	37.0%
25-45 yrs	1479	1232	1382	54.6%
>45 yrs	356	460	426	43.6%
age not reported	92	94	146	49.5%
total	2143	2153	2256	49.9%

¶cases declined and not done where grouped with cases for whom status was not known; *percentage among those with HIV test results reported

Table 28 HIV status stratified by age group and gender

Age group	*Gender*	*HIV+*	*HIV-*	*HIV status unknown¶*	*%HIV+**	*p-value*
<25 yrs	**Female**	138	137	135	50.2%	P<0.0001
	Male	78	230	167	25.3%	
25-45 yrs	**Female**	655	318	458	67.3%	P<0.0001
	Male	824	914	924	47.4%	
>45 yrs	**Female**	119	121	107	49.6%	p=0.026
	Male	237	339	319	41.1%	
age not reported	**Female**	33	25	45	56.9%	NS
	Male	59	69	101	46.1%	
overall	***overall***	*2143*	*2153*	*2256*	49.9%	

¶cases declined and not done where grouped with cases for whom status was not known; *percentage among those with HIV test results reported; NS not significant

HIV status stratified by patient type (Table 30) indicates that there are small differences between patient types but all have a similar range of HIV prevalence. HIV prevalence was significantly higher in negative relapse patients as compared to positive relapse patients (53.7 vs 45.5 % p=0.02). Other differences were not significant.

Table 29 HIV status stratified by patient type

Patient type	*HIV+*	*HIV-*	*HIV status unknown¶*	*% HIV+**
FLT	161	178	149	47.5%
FRT	70	70	77	50.0%
NR	716	589	625	54.9%
PR	632	757	706	45.5%
RAD	299	313	316	48.9%
not recorded	265	246	383	51.9%
overall	2143	2153	2256	49.9%

¶cases declined and not done where grouped with cases for whom status was not known; *percentage among those with HIV test results reported; FLT: Failure to first line treatment; FRT=failure to retreatment; NR=negative relapse; PR=positive relapse; RAD=return after default; EP=extra pulmonary TB

HIV status stratified by province (Table 30) shows similar variation as found in co-infection rates reported in the national data by province although differences could be observed. Highest HIV prevalence rates among retreatment cases submitted to CRL are reported in Nairobi South and Nyanza province. Lowest rates were observed in North Eastern Province. North Eastern province also has lowest rate reported in national data reported in 2009. Retreatment cases submitted to CRL from Central, Nairobi North and Western province had lower HIV prevalence rate as would be expected based on national data for retreatment cases for 2009. Rift Valley North on the other hand had much higher HIV prevalence among cases submitted to CRL then expected based on the national data for 2009. These differences need to be looked at more closely. HIV positive cases has slightly higher percentage of negative smear results and negative culture growth (Table 31; Table 32)

Table 30 HIV status stratified by province

Province	*HIV+*	*HIV-*	*HIV status unknown¶*	*HIV+**	*HIV+% among retreatment cases national data 2009*
Central	186	403	212	31.6%	44%
Coast	337	423	251	44.3%	45%
Eastern North	15	32	76	31.9%	25%
Eastern South	175	256	177	40.6%	44%
Nairobi North	299	303	470	49.8%	61%
Nairobi South	258	148	444	63.5%	61%
North Eastern	19	125	25	13.2%	9%
Nyanza N	367	129	56	74.0%	78%
Nyanza S	80	67	15	54.4%	61%
Rift valley N	273	77	89	78.0%	47%
Rift valley S	62	63	208	49.6%	53%
Western	52	95	172	35.4%	49%
not reported	20	32	61	38.5%	-
total	2143	2153	2256	49.9%	

¶cases declined and not done where grouped with cases for whom status was not known; *percentage among those with HIV test results reported

Table 31 Result of direct smear by HIV status

	Result direct smear						
HIV status	**0**	**scanty**	**+**	**++**	**+++**	**no result**	
NEGATIVE	59.0%	8.5%	11.4%	8.9%	12.1%	0.1%	p<0.0001
POSITIVE	67.8%	8.4%	9.7%	6.2%	7.7%	0.1%	
unknown	63.8%	8.9%	10.6%	7.4%	9.2%	0.0%	

Table 32 Result of culture growth by HIV status

	Result culture growth					
HIV status	**0**	**1 to 19 col**	**20 to 100 col**	**>100 col**	**CONTAMINATED**	
NEGATIVE	60.3%	0.1%	15.4%	21.6%	2.6%	p<0.0001
POSITIVE	67.8%	0.0%	14.9%	14.7%	2.6%	
unknown	64.0%	0.0%	15.2%	18.1%	2.6%	

HIV-MDR data

One of the objectives of this project was to asses if there is a relation between HIV status and drug resistance (MDR-TB) when linking these data in surveillance. The data for retreatment cases submitted to CRL in 2009 show a significant higher prevalence of MDR-TB among HIV negative as compared to HIV positive cases (8.3 vs 4.7% respectively, p=0.008). In both male and female this difference between HIV status and MDR-TB was visible (Table 34) although only among male the difference was significant. MDR-TB was more prevalent in the younger age groups (see 0), which was visible in both HIV positive as well as HIV negative cases (Table 36) although not significant. In the age groups under 45 years, MDR-TB was more prevalent in the HIV-negative persons. This was a significant difference in the 25-45 year age group (Table 36). As there seems interaction between HIV and MDR by age group and sex multivariate analysis (logistic regression) was done. There was a significant effect of HIV on MDR, when adjusted for

age group and sex, HIV negative retreatment patients were 1.6 times (95%CI 1.02-2.06), p=0.043) more likely to have MDR-TB. The effect of age (p=0.054) and gender (p=0.93) were not significant in multivariate analysis. Assessing HIV status by resistance to the four main TB drugs (Isoniazid, Rifampycin, Streptomycin and Ethambutol) indicated that Rifampycin resistant was significantly more prevalent under HIV negative cases compared to HIV positive cases (Table 38), also when controlled for age and sex (OR=1.69, 95%CI 1.13-2.53, p=0.009). For the other main drugs difference were not significant, also not when controlling for age and sex (Table 37; Table 40). When looking at HIV and MDR by patient type small differences are observed (Table 41) although none are significant.

Table 33 HIV status stratified by MDR status

	MDR-TB	***no MDR***	***%MDR-TB***	***p-value***
HIV+	30	604	4.7%	p=0.008
HIV-	66	733	8.3%	
no HIV status reported	52	701	6.9%	
overall	*148*	*2038*	6.8%	

Table 34 HIV status stratified by MDR status and gender

Gender	***HIV status***	***MDR-TB***	***no MDR***	***%MDR-TB***	***p-value***
Female	Negative	14	160	8.0%	
	Positive	14	237	5.6%	p=0.31
	unknown	24	169	12.4%	
Male	Negative	52	573	8.3%	p=0.011
	Positive	16	367	4.2%	
	unknown	28	532	5.0%	
	overall	148	2038	6.8%	

Table 35 MDR-TB stratified by HIV status and age-group

HIV status	*Age group*	*MDR-TB*	*no MDR-TB*	*%MDR-TB*	*p-value*
HIV+	<25 yrs	5	55	8.3%	
	25-45 yrs	21	445	4.5%	P=0.34
	>45 yrs	4	73	5.2%	
	age not reported	0	31	0.0%	
HIV-	<25 yrs	17	137	11.0%	
	25-45 yrs	38	448	7.8%	
	>45 yrs	6	115	5.0%	p=0.20
	age not reported	5	33	13.2%	
unknown	<25 yrs	10	97	9.3%	
	25-45 yrs	31	452	6.4%	NS
	>45 yrs	4	110	3.5%	
	age not reported	7	42	14.3%	

Table 36 MDR-TB stratified by age-group and HIV status

Age group	*HIVTESTING*	*MDR-TB*	*no MDR-TB*	*%MDR-TB*	*p-value*
<25 yrs	POSITIVE	5	55	8.3%	p=0.38
	NEGATIVE	17	137	11.0%	
	unknown	10	97	9.3%	
25-45 yrs	POSITIVE	21	445	4.5%	p=0.023
	NEGATIVE	38	448	7.8%	
	unknown	31	452	6.4%	
>45 yrs	POSITIVE	4	73	5.2%	p=0.59
	NEGATIVE	6	115	5.0%	
	unknown	4	110	3.5%	
age not reported	POSITIVE	0	31	0.0%	p=0.045
	NEGATIVE	5	33	13.2%	
	unknown	7	42	14.3%	
overall		148	2038	6.8%	

Table 37 HIV status stratified by Isoniazid resistance status

	Isoniazid-R	***Isoniazid -S***	***% Resistant****	***p-value***
HIV+	103	531	16.2%	p=0.066
HIV-	160	639	20.0%	
no HIV status reported	145	608	19.3%	
overall	*408*	*1778*	18.7%	

Table 38 HIV status stratified by Ryfampicin resistance status

	Rifampycin-R	***Rifampycin -S***	***% Resistant****	***p-value***
HIV+	41	593	6.5%	p=0.011
HIV-	82	717	10.3%	
no HIV status reported	64	689	8.5%	
overall	187	1999	8.6%	

Table 39 HIV status stratified by Streptomycin resistance status

	Streptomycin-R	***Streptomycin -S***	***% Resistant****	***p-value***
HIV+	48	586	7.6%	p=0.631
HIV-	66	733	8.3%	
no HIV status reported	63	690	8.4%	
overall	177	2009	8.1%	

Table 40 HIV status stratified by Ethambutol resistance status

	Ethambutol-R	***Ethambutol -S***	***% Resistant****	***p-value***
HIV+	49	585	7.7%	p=0.777
HIV-	65	734	8.1%	
no HIV status reported	73	680	9.7%	
overall	187	1999	8.6%	

Table 41 MDR-TB stratified by HIV status and patient type

Patient type	*HIV status*	*MDR-TB*	*no MDR-TB*	*%MDR-TB*
FLT	NEGATIVE	18	30	37.5%
	POSITIVE	7	20	25.9%
	unknown	3	22	12.0%
FRT	NEGATIVE	9	14	39.1%
	POSITIVE	3	9	25.0%
	unknown	7	10	41.2%
NR	NEGATIVE	2	53	3.6%
	POSITIVE	2	89	2.2%
	unknown	4	76	5.0%
PR	NEGATIVE	27	419	6.1%
	POSITIVE	13	325	3.8%
	unknown	23	374	5.8%
RAD	NEGATIVE	5	154	3.1%
	POSITIVE	3	115	2.5%
	unknown	3	134	2.2%
not reported	NEGATIVE	5	63	7.4%
	POSITIVE	2	46	4.2%
	unknown	12	85	12.4%

Key findings and recommendations Kenya

Process

- HIV status information was linked to drug resistance in routine surveillance by adding HIV indicators to the existing culture request from.
- Sensitization of new forms at all levels is important to ensure the new form is appropriately used.

Limitations of the data

- Not all data are complete, data completeness varies by parameter. Also not all provinces submitted a similar proportion of their retreatment cases, varying from 20 to over 100%. The percentage of retreatment cases covered by CRL improved substantially over the last years with a low 13% coverage in 2004 to 61% coverage in 2009.
- 64% of cultures have no growth so the analysis is only done on samples that have growth.
- Issues are observed with recording of certain parameters, i.e. date received seems date sample is registered in lab book. Date sample collected might not be used appropriately as some samples take very long to reach CRL. The use of these parameters should be further investigated. The time laps between date received and date collected could be used as indicator for transport of sputum samples.
- The current available data indicate a higher MDR-TB prevalence than earlier reported by CRL due to the use of the wrong denominator. The denominator is the number of samples for whom DST results are available and not all cases who submitted sputum samples to CRL

Results observed

- The majority of retreatment cases was pan-sensitive (75%), 14.4% mono-resistant, 3.5% poly-resistant and 6.8% MDR-TB.
- Drug resistance for Rifampicin, Ethambutol and Streptomycin was significantly more prevalent in females and for all four first line drugs in the younger age group (< 25 years)
- MDR-TB seemed more prevalent in the females overall and in all age groups although differences were not significant
- MDR-TB was significantly more prevalent in the younger age group below 25 years of age.
- Most MDR-TB cases were found among cases that failed first line treatment or retreatment regimens.
- Significantly more women than men are HIV positive among retreatment cases; this is visible in all three age groups. National TB data also indicate higher TB-HIV co-infection rates among females than males
- HIV prevalence showed large variation over the regions as also observed in the National TB data.
- MDR-TB was significantly more prevalent in HIV negative than in HIV positive cases, also when controlled for age and sex.

Discussion of results and final recommendations for the integration of HIV screening in TB drug resistance surveillance

The association HIV infection and DR TB

Reports on the association of HIV infection and drug resistant TB have been contradictory. Although several studies[11] show a positive association between DR-TB and HIV during outbreaks in nosocomial and other congregate settings, other studies failed to prove that HIV infection favors the transmission of DR-TB. In the routine programmatic surveillance system that was developed in Kazakhstan, we observed no relationship between DR-TB notification and HIV status. In Kenya we actually observed an inverse relation whereby MDR-TB was significantly more prevalent in HIV negative than in HIV positive cases, also when controlled for age and sex. Among retreatment cases, Rifampicin resistance was more prevalent in HIV-negative than HIV-positive cases, also when controlled for age and sex.

Early mortality in HIV-infected MDR-TB patients could be one of the reasons for the higher prevalence of drug resistance among HIV-negative TB cases. Early diagnosis and access to anti-retroviral treatment should benefit co-infected MDR-TB patients by increasing survival in the initial stage. In Kenya however only 35% of all tested TB patients has access to anti-retroviral treatment in the first quarter after diagnosis. An unknown proportion of TB patients die within this first quarter. This inverse relationship should be further investigated.

Through this project, both in Kazakhstan and Kenya the existing programmatic routine MDR surveillance system and the uptake of programmatic routine HIV screening data were strengthened, what contributed to better quality of the national surveillance for both MDR and HIV. The results in both countries coming out of this project are in line with the published and non published results of earlier DR and HIV prevalence surveys of both countries. As expected, HIV prevalence is much higher among retreatment cases in Kenya than in Kazakhstan, 50% versus 1%. Vice versa, MDR prevalence is much higher in Kazakhstan then in Kenya, 43% versus 7%. The HIV prevalence among TB patients in Kazakhstan is still low but rising, from 0.6% in 2007 to 1.2% in 2009. The HIV prevalence among TB patients in Kenya is declining, from 57% in 2005 to 44% in 2009. In both countries extensive analysis of the data obtained through the programmatic surveillance is possible, as presented in the country reports.

In Kazakhstan, analysis revealed interesting findings on the overlap of specific risk factors for MDR-TB and HIV, such as history of imprisonment, drug use and homelessness. In both new and retreatment patients, none HIV-infected and MDR-TB have the highest treatment success rates, while patients with both HIV-infection and MDR-TB have the lowest successful treatment outcome rates. Being HIV-positive only gives better treatment success rates with the standard first-line drug regimen than only having MDR-TB.

IPT (or RPT) is recommended for all HIV-positive individuals, but may not clear the infection in 50% (40%) of HIV-infected individuals in Kazakhstan because of resistance,

[11] S Suchindran, E S Brouwer, A van Rie (2009) Is HIV Infection a Risk Factor for Multi-drug Resistant Tuberculosis? A systematic review. PloS One: 4,5, e5561.

assuming that resistance in HIV-infected with TB disease is similar as in those with only TB infection.

In Kenya, the majority of retreatment cases is pan-sensitive (75%), 14.4% mono-resistant, 3.5% poly-resistant and 6.8% MDR-TB. A disturbing finding is the relative high drug resistance for Rifampicin, Ethambutol and Streptomycin among females in the younger age group (< 25 years). MDR-TB seemed more prevalent in the females overall and in all age groups although differences were not statistically significant. MDR-TB however was significantly more prevalent in the age group below 25 years of age. There was no relationship with HIV-infection except that among retreatment cases significantly more women than men are HIV positive; this is visible in all three age groups. National TB data also indicate higher TB-HIV co-infection rates among female than male TB cases. Most MDR-TB cases were found among cases that failed first line treatment or retreatment regimens. HIV prevalence showed large variation over the regions which is also observed in the National TB data and previous HIV/TB surveys.

In both Kenya and Kazakhstan distribution of the different types of retreatment (failure, relapse, return after default and other) was similar. In both countries, relapse cases, smear negative and smear positive combined, make up about two thirds of the total number of retreatment cases.

Although the national program of Kenya is planning to implement a national DRS in 2010-2011 one should question if there is still need for this type of costly surveys in countries with routine surveillance data. In Kenya there is no information on MDR in new new cases as only retreatment cases are routinely analyzed and as the last published results from a national DRS are from 1994 this DRS is planned to obtain figures of drug resistance among new cases. The same can be said on the need for national HIV surveys in a county where >80% of the TB patients is screened, although the benefit here is that this will also include new TB cases. These types of surveys might remain valuable to examine specific research questions, risk groups etc. If routine surveillance is based on electronic data collection and reporting systems, more specific indicators can be added which will reduce the need for other surveys even further. These indicators can both relate to general M&E (i.e. data completeness for key parameters and laboratory performance indicators like percentage of samples with culture growth and contamination) or relate to specific determinants for drug resistance, some of which are already collected in Kazakhstan. In both countries, the project showed that routine surveillance of linked HIV status to DR TB data does enable programs to monitor whether DR-TB is more prevalent among HIV+ patients, or MDR-TB patients are more likely to be HIV+ than negative. Nevertheless, if this is also a good proxy of successful TB-Infection Control is doubtful and needs to be further investigated. The inverse relationship in Kenya for example should not conclude that infection control practices in health care and congregate settings are of good quality. More likely the opposite is true.

Uptake of HIV screening data in routine MDR surveillance systems

Kenya as a country with high HIV prevalence and relative low MDR TB problem and Kazakhstan with a high MDR TB prevalence and a lesser but growing HIV problem provide different systems for screening, addressing the specific requirements in their settings.

Both country projects certainly contributed to further strengthen the ongoing development of routine programmatic MDR surveillance systems and routine HIV

screening. In Kazakhstan DR and HIV testing are both done for all TB cases (new and retreatment) therefore it was much easier to integrate HIV surveillance into routine DR surveillance for both patient groups. Still the project helped to improve both data completeness and data quality. In Kenya HIV testing is routinely done for all TB cases while DR testing is only routinely done for all forms of retreatment. HIV testing is reported through the routine recording and reporting system of the national TB Program. DR test results however come from a separate laboratory recording system. It took an effort to operationalize the integration of data collection on HIV in the routine MDR surveillance system. Facilities as the treatment providers initially did not see the importance of transferring the HIV-test results to a higher level. Similarly in Kazakhstan, before this project national HIV surveillance results were not fed back to the regional/local level. Therefore staff at the lower levels did not see the need for completing all information in the electronic register. Useful feedback after provision of data by the lower levels is an important motivation for completing data and therefore crucial activity in the procedure. DR testing of retreatment cases in Kenya significantly improved over the last years from low 13% coverage in 2004 to 61% in 2009.

In Kazakhstan the routine case notification is done electronically and therefore full coverage was reached much easier. The percentage of missing data was considerable less in Kazakhstan. In Kenya notification is based on a paper based system and DR testing is requested using a specific laboratory request form.
Independent of the system used, clear instruction at the start, supervision, data quality checks and correction are crucial for a successful implementation.

In general both projects have contributed to a critical review of the processes of data collection and reporting for both MDR TB and HIV screening. This, on its own, has contributed to better quality of data. The paper based system in Kenya initially lacked (the newly introduced) HIV characteristics. Rigorous follow-up at the facility level improved the completion of the data. The electronic based recording and reporting system in Kazakhstan in general provided better quality data and it was easier to feedback missing values and mistakes to the lower level for rectification. Completeness and quality of data significantly improved further by introduction of data validation checks of which the results were fed back to the lower level on a monthly basis. So an important lesson learned in both countries is that good sensitization of the staff involved up to facility level, with a thorough follow up and supervision are crucial activities to make the introduction of these new processes successful.
In Kenya, data completeness varied by parameter. We know that approximately 85% of all retreatment TB patients are tested for HIV and receive an HIV result. Also not all provinces submitted the same proportion of their retreatment cases, which varied from 20 to over 100%. The current available data therefore indicate a higher national MDR-TB prevalence than previously reported by CRL due to the use of the wrong denominator. The denominator is the number of samples for whom DST results are available and not all cases who submitted sputum samples to CRL. The system in Kenya is currently able to culture all reported retreatment cases.

In Kazakhstan we found discrepancies between the number of co-infected TB/HIV patients in the HIV/AIDS and TB register. Reasons for this are currently being assessed in two regions in Kazakhstan, as well as the proportion of TB/HIV patients on CPT, and ART.

Both countries had a high percentage of cultures that did not grow, 66% among new patients and 45% among retreatment patients in Kazakhstan and 64% among retreatment patients in Kenya. In both countries this was related to smear result, resulting in 75% for smear negative and around 25% for smear positive cases being culture negative. One of the possible reasons could be a delay in the submission of sputum samples from the periphery. This was investigated in Kenya and could not be linked to none growth of cultures. (Almost) all samples with a positive growth were tested for drug-susceptibility.

	Kazakhstan		***Kenya***
general overview data	**new patients**	**retreatment patients**	**retreatment patients**
Period	**2007-2009**	**2007-2009**	**2009**
number new patients reported country wide	55,480		99,354
number retreatment patients reported country wide		27,127	10,675
notification rates (per 100,000), new patients	118		294
notification rates (per 100,000), retreatment patients		58	32
number of patients in database	55,480	27,127	6,552
coverage of patients reported country wide	100%	100%	61.4%
missing data for			
age	0.01%	0.01%	5.1%
sex	0.00%	0.00%	0.0%
patient type	0.00%	0.00%	13.7%
HIV status	3.1%	3.1%	34.4%
culture/DST results			
no culture growth - overall	65.8%	45.3%	64.0%
no culture growth - smear negative	84.7%	75.7%	87.4%
no culture growth - smear positive	29.0%	26.6%	23.2%
DST result (for those with culture growth)	90.1%	90.1%	100.0%
patient characteristics			
% Male sex	60.8%	69.9%	65.0%
Mean age (SD) in years	32.7 (14.9)	40.7 (14.5)	36.3 (12.5)
Patient type			
new patients, smear-positive	31.6%		
new patients, smear-negative	68.4%		
failure		11.8%	10.7%
negative relapse		33.4%	29.5%
positive relapse		37.8%	32.0%
default		16.9%	14.2%
missing	10% (transfer in)		13.6%
% HIV+ (of those tested)	0.7%	1.2%	49.9%
% pansensitive (of those with DST results)	53.9%	33.5%	75.3%
% mono resistant	8.9%	7.3%	14.4%
% polyresistant	14.8%	15.9%	3.5%
% MDR-TB	22.4%	43.4%	6.8%
% of HIV+ with MDR-TB	75.0%	54.8%	4.7%
% of HIV- with MDR-TB	77.7%	56.8%	8.3%
% of MDR-TB who are HIV+	1.1%	1.4%	31.3%
% of non-MDR-TB who are HIV+	1.2%	1.5%	45.2%

In Kazakhstan, new sputum smear negative patients had a lower yield of culture than retreatment patients with negative smears which may be explained by over diagnosis of TB in this group resulting from active case finding by fluorography. Diagnostic algorithms to reduce over diagnosis of TB in Kazakhstan should be considered within the NCTP.

In both countries, about thirty percent of cultures of smear-positive smears renders negative, which percentage is considered too high. This needs to be investigated and actions should be taken to increase the yield of culture (and thus DST). Potential reasons are delay in transportation, dilemmas with decontamination or any other conditions in the laboratories. A stronger role for the SNLR could help to address these issues.
In summary the projects in Kenya and Kazakhstan have shown that integration of HIV into routine MDR surveillance is feasible and useful and should be continued in both countries. The integration led to overall improvement of the surveillance data and contributed to improved capacity of staff in data validation and also improved the overall data quality. Analysis of integrated HIV/MDR-TB surveillance data is a useful addition to the routine cohort and treatment outcome data. Besides the importance for the individual patient care, it provides trends of the MDR/HIV relation in routine program setting. It provides a useful epidemiologic basis for more specific studies on for example nosocomial outbreaks. If the system itself is sensitive enough to monitor possible outbreaks needs be further investigated. Especially for Kenya the more complete 2010 data should be added to the current data set and analyzed to confirm findings and possible trends.