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## First-line tuberculosis therapy and drug-resistant *Mycobacterium tuberculosis* in prisons

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### Summary

**Background** We assessed a programme of tuberculosis control in a prison setting in Baku, Azerbaijan. The programme used first-line therapy and DOTS (directly observed treatment, short course).

**Methods** 467 patients had sputum-positive tuberculosis. Their treatment regimens followed WHO guidelines, and they had regular clinical examinations and dietary supplements. Isolates were tested by standard methods for resistance to isoniazid, rifampicin, ethambutol, and streptomycin in three laboratories. Treatment success was defined as three consecutive negative sputum smears at end of treatment. Factors independently associated with treatment failure were estimated by logistic regression.

**Findings** Drug-resistance data on admission were available for 131 patients. 55% of patients had strains of *Mycobacterium tuberculosis* resistant to two or more antibiotics. Mortality during treatment was 11%, and 13% of patients defaulted. Overall, treatment was successful in 54% of patients, and in 71% of those completing treatment. 104 patients completed a full treatment regimen and remained sputum-positive. Resistance to two or more antibiotics, a positive sputum result at the end of initial treatment, cavitory disease, and poor compliance were independently associated with treatment failure.

**Interpretation** The effectiveness of a DOTS programme with first-line therapy fell short of the 85% target set by WHO. First-line therapy may not be sufficient in settings with a high degree of resistance to antibiotics.

*Lancet* 1999; **353**: 969–73

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### Introduction

Tuberculosis is more common within prison populations than in the general population, because of overcrowding, insufficient ventilation, poor hygiene, and generally low socioeconomic status, poor nutrition, and poor general health of inmates.<sup>1,2</sup> Late diagnosis and inappropriate case management may compound the problem. Despite these concerns, tuberculosis in prisons has been labelled as a “forgotten plague”.<sup>3</sup> Since 1991, there has been an increase in notification of tuberculosis cases and an increase in mortality rates from tuberculosis in the republics of the former Soviet Union.<sup>4</sup> In Azerbaijan, data from prisons are not included in Ministry of Health statistics: 1429 tuberculosis cases were reported to WHO in 1995 (18.8 per 100 000),<sup>5</sup> but an estimated 700 tuberculosis patients were held in Azerbaijani prisons at that time.<sup>6</sup>

The International Committee of the Red Cross (ICRC) visits prisoners in countries that are or have been in situations of armed conflict. Medical personnel of the ICRC work to ensure that conditions of detention, including health care, are adequate. In Azerbaijan, the ICRC found that tuberculosis was the most common cause of death among prisoners.<sup>6</sup> Accordingly, a pilot tuberculosis-treatment programme was started there in June, 1995, with the collaboration of the prison authorities and the Ministry of Justice.

The pilot programme used the direct observation of treatment, short course strategy (DOTS),<sup>7,8</sup> and was designed to convince prison authorities that such a programme would merit widespread application within the prison system. We report here the main outcomes of the programme, which was restricted to first-line therapy in a setting with high resistance to antibiotics.

### Patients and methods

#### Patients

The pilot programme took place in the Central Penitentiary Hospital in Baku, Azerbaijan. This hospital is the referral hospital for the Azerbaijan prison system, and has 450 beds for

| Resistance                              | Case classification |                   |                           |               |
|---|---------------------|-------------------|---------------------------|---------------|
|   | True-new (n=7)      | Pseudo-new (n=51) | Relapse or failure (n=73) | Total (n=131) |
| <b>None</b>                             | 4 (3%)              | 14 (11%)          | 10 (8%)                   | 28 (21%)      |
| <b>1 antibiotic</b>                     |                     |                   |                           |               |
| Isoniazid                               | 0                   | 1                 | 2                         | 3             |
| Rifampicin                              | 0                   | 1                 | 0                         | 1             |
| Streptomycin                            | 1                   | 11                | 16                        | 28            |
| Total                                   | 1 (1%)              | 13 (10%)          | 18 (14%)                  | 32 (24%)      |
| <b>2 antibiotics</b>                    |                     |                   |                           |               |
| Isoniazid, streptomycin*                | 1                   | 13                | 14                        | 28            |
| Rifampicin, streptomycin*               | 0                   | 0                 | 2                         | 2             |
| Isoniazid, ethambutol*                  | 0                   | 1                 | 0                         | 1             |
| Total                                   | 1 (1%)              | 14 (11%)          | 16 (12%)                  | 31 (24%)      |
| <b>3 antibiotics</b>                    |                     |                   |                           |               |
| Isoniazid, ethambutol, streptomycin*    | 0                   | 3 (2%)            | 7 (5%)                    | 10 (8%)       |
| Isoniazid, rifampicin, streptomycin†    | 0                   | 1 (1%)            | 6 (5%)                    | 7 (5%)        |
| <b>4 antibiotics†</b>                   | 1 (1%)              | 6 (5%)            | 16 (12%)                  | 23 (18%)      |
| <b>Overall resistance by antibiotic</b> |                     |                   |                           |               |
| Isoniazid                               | 2                   | 25                | 45                        | 72 (55%)      |
| Rifampicin                              | 1                   | 8                 | 24                        | 33 (25%)      |
| Ethambutol                              | 1                   | 10                | 23                        | 34 (26%)      |
| Streptomycin                            | 3                   | 34                | 61                        | 98 (75%)      |

\*Not multidrug-resistant. †Multidrug-resistant.

Table 1: Antibiotic resistance patterns by case classification at admission

tuberculosis patients. The ICRC programme was limited to two wards with 160 beds in total. Patients with suspected tuberculosis in prisons throughout the Azerbaijan prison system are sent to the Central Penitentiary Hospital, and may then be referred to the ICRC programme if a bed is available. Admission criteria include confirmation of the diagnosis by two of three consecutive positive sputum smears, written consent, and a prison sentence that exceeds the expected duration of treatment. This study reports on all patients admitted for treatment between June 8, 1995, and Oct 10, 1997. Follow-up continued until July 9, 1998.

### Treatment regimens

Our treatment regimens followed WHO guidelines for DOTS programmes, and therefore depended on the patient's history of tuberculosis treatment.<sup>8,9</sup> The WHO guidelines define new cases as patients who have never been treated or who have had treatment for less than 1 month. These patients should undergo an initial phase of treatment with four drugs (rifampicin, isoniazid, pyrazinamide, streptomycin) once daily for 2 months, then a continuation phase with two drugs (rifampicin, isoniazid) for 4 months. After a high degree of drug resistance was found, streptomycin was replaced by ethambutol.

Patients who interrupt a treatment course after at least 1 month and who still have a smear positive for tuberculosis are defined as failure cases by WHO. Relapse cases are patients who complete a full treatment course and are classed as cured, but who subsequently develop sputum-positive tuberculosis. Failure and relapse cases undergo an initial phase of treatment with five drugs for 3 months (rifampicin, isoniazid, pyrazinamide, streptomycin, ethambutol; streptomycin for 2 months only) then a continuation phase with three drugs for the next 5 months (rifampicin, isoniazid, ethambutol).

In accordance with WHO recommendations,<sup>10</sup> patients in our study who were new cases and whose smears remained positive at the end of the initial phase of treatment were reclassified as failure cases. Patients who were failure or relapse cases and whose smears were positive at the end of the initial phase of treatment had that phase extended for 1 month. We assessed outcomes separately for those patients who reported no previous history of tuberculosis treatment (who we classed as "true-new" cases) and those who had had treatment for less than 1 month (who we classed as "pseudo-new" cases). Patients' reports of previous treatment for tuberculosis were validated by use of prison registries for those who had been treated in prison. We were unable to validate reports of treatment or self-medication outside prison. Cure was defined

as three consecutive negative sputum smears at the end of the treatment period.

### Methods

Clinical examinations were completed on admission, every 2 weeks in the initial phase of treatment, and monthly during the continuation phase of treatment. On admission, patients received treatment for scabies, and a daily food supplement that consisted of a high-energy milk drink, 150 g lentils, and two eggs. Patients with a low body-mass index also received a high-energy biscuit supplement.

Supervised collection of sputum samples was done in the early morning on 3 consecutive days before entry to the study. This procedure was repeated at the end of the first treatment phase, at the middle of the continuation phase of treatment, and at the end of treatment. Smears were stained by the Ziehl-Neelsen method and read for 300 fields at  $\times 1000$ . Routine crosschecks of smear results were done at a reference laboratory in Antwerp, Belgium.

Before facilities for testing of antibiotic susceptibility became available in Baku, Azerbaijan, a series of sputum isolates were tested in reference laboratories in Antwerp, Belgium, and Zurich, Switzerland.<sup>8</sup> From October, 1996, isolates obtained from all patients on admission were cultured in Baku, and positive cultures were tested for antibiotic susceptibility. After this time, a sample of all isolates was sent to Antwerp or Zurich for routine crosschecks. Tests of antibiotic susceptibility used the proportion method<sup>11</sup> in Baku and Antwerp, and the Bactec 460 method<sup>12</sup> in Zurich.

|                            | Number of patients (n=467) | Mean (SD) treatment duration (days) |
|----------------------------|----------------------------|-------------------------------------|
| <b>Treatment completed</b> | 357 (76%)                  | 253 (38)                            |
| <b>Death</b>               |                            |                                     |
| First 2 weeks              | 24 (5%)                    | 6 (4)                               |
| Phase I                    | 18 (4%)                    | 62 (39)                             |
| Phase II                   | 9 (2%)                     | 202 (44)                            |
| <b>All deaths</b>          | 51 (11%)                   | 60 (77)                             |
| <b>Judicial defaults</b>   |                            |                                     |
| Transfer                   | 12 (3%)                    | 87 (64)                             |
| Retrial                    | 5 (1%)                     | 110 (46)                            |
| Release                    | 32 (7%)                    | 153 (75)                            |
| <b>Medical defaults</b>    |                            |                                     |
| Voluntary                  | 5 (1%)                     | 147 (65)                            |
| Medical indication         | 5 (1%)                     | 76 (77)                             |
| <b>All defaults</b>        | 59 (13%)                   | 130 (74)                            |

Table 2: Course and duration of treatment

|                            | All patients               |                       | Excluding death in first 2 weeks |                       | Excluding death in first 2 weeks and judicial default |                       | Excluding death and all defaults (completed treatment) |                       |
|----------------------------|----------------------------|-----------------------|----------------------------------|-----------------------|---|-----------------------|--|-----------------------|
|                            | Phase I sputum conversion* | Treatment success (%) | Phase I sputum conversion        | Treatment success (%) | Phase I sputum conversion                             | Treatment success (%) | Phase I sputum conversion                              | Treatment success (%) |
| <b>All patients</b>        | 467 (42%)                  | 54                    | 443 (44%)                        | 57                    | 394 (48%)   | 64                    | 357 (52%)  | 71                    |
| <b>Case classification</b> |                            |                       |                                  |                       |   |                       |  |                       |
| True-new                   | 64 (36%)                   | 64                    | 58 (40%)                         | 71                    | 49 (45%)  | 84                    | 45 (49%)   | 91                    |
| Pseudo-new                 | 171 (41%)                  | 58                    | 164 (43%)                        | 61                    | 147 (44%)   | 68                    | 137 (47%)  | 73                    |
| Relapse                    | 30 (57%)                   | 50                    | 28 (61%)                         | 54                    | 26 (65%)  | 58                    | 20 (70%)   | 75                    |
| Failure                    | 202 (43%)                  | 48                    | 193 (45%)                        | 50                    | 172 (49%)   | 56                    | 155 (54%)  | 63                    |
| <b>Drug resistance</b>     |                            |                       |                                  |                       |   |                       |  |                       |
| None                       | 28 (61%)                   | 79                    | 28 (61%)                         | 79                    | 25 (64%)  | 88                    | 25 (64%)   | 88                    |
| 1                          | 32 (56%)                   | 56                    | 31 (58%)                         | 58                    | 26 (62%)  | 69                    | 25 (64%)   | 72                    |
| 2                          | 31 (35%)                   | 42                    | 28 (39%)                         | 46                    | 27 (37%)  | 48                    | 23 (43%)   | 57                    |
| 3†                         | 10 (10%)                   | 30                    | 9 (11%)                          | 33                    | 7 (14%)   | 43                    | 7 (14%)  | 43                    |
| 3‡                         | 7 (29%)                    | 29                    | 7 (29%)                          | 29                    | 5 (40%)   | 40                    | 5 (40%)  | 40                    |
| 4‡                         | 23 (22%)                   | 26                    | 21 (24%)                         | 29                    | 19 (26%)  | 32                    | 16 (31%)   | 38                    |

\*3 consecutive negative sputums at end of initial treatment phase. †Not multidrug-resistant. ‡Multidrug-resistant.

Table 3: Treatment success by patient group and loss to follow-up

Susceptibility to pyrazinamide was done in only one laboratory, and therefore our data give resistance results for isoniazid, rifampicin, streptomycin, and ethambutol. Data on antibiotic resistance was used only if tests showed whether or not a given isolate was resistant to all four drugs. If one laboratory showed that an isolate was resistant to an antibiotic, but another laboratory did not, then that isolate was classed as resistant to the antibiotic.

### Statistical analysis

We used logistic regression to construct a model of variables to predict treatment failure for those who did not die in the first 2 weeks of treatment, and who did not default because of transfer, release, or retreat. The full model included all variables that were predictors of treatment failure in univariate analyses. Variables that did not reach a significance of 0.20, according to the Wald test, were dropped sequentially.

Since our model included data on resistance profiles, the estimation sample size was reduced from 365 to 104. We report here two models, one that included resistance-profile data as a potential explanatory variable, and one that did not. Goodness of fit was assessed with the Hosmer-Lemeshow  $\chi^2$  statistic. Comparison of the results of antibiotic susceptibility tests and sputum tests between raters at Baku and the reference laboratories used the  $\kappa$  statistic. All statistical analyses used the STATA software package (StataCorp, College Station, TX, USA, version 5.0).

### Results

467 men (mean age 29.7 years [SD 8.3]) presented with poor nutritional status and advanced pulmonary disease. Mean body-mass index was 18.0 (SD 2.2), and 38% of the patients had cavitory disease. By use of the WHO classification,<sup>9</sup> 235 (50.3%) patients were classified as new cases, 30 (6.4%) as relapse cases, and 202 (43.3%) as failure cases. Of the new cases, 64 men reported no previous treatment for tuberculosis. We analysed results separately for 64 true-new cases, and 171 pseudo-new cases.

The drug-resistance patterns of the 131 patients for whom complete results of the antibiotic tests were available (table 1) show that there were proportionally more relapse and failure cases in the subset of patients who had antibiotic tests than in the study population as a whole. 36 of the 131 results came from either the Antwerp or Zurich reference laboratory, and 95 results were from Baku. Of the 95 results from Baku, 58 isolates also had complete results from the Zurich or Antwerp laboratory. There were 27 discordant susceptibility results among the 244 results from Baku and at least one of the other laboratories. There was

substantial agreement between raters at the Baku laboratory and the two reference laboratories ( $\kappa=0.77$ ). 21% of patients had strains of *Mycobacterium tuberculosis* sensitive to all antibiotics, and 23% of individuals had multidrug-resistant strains (resistant to both rifampicin and isoniazid). Overall, resistance to the various antibiotics was very high (75% resistant to streptomycin, 55% isoniazid, 26% ethambutol, 25% rifampicin). Monoresistance to ethambutol did not occur. The resistance profile of pseudo-new cases was much closer to the resistance profile of relapse cases or failure cases than to that of true-new cases.

76% of patients completed treatment, 11% died, and 13% did not complete treatment (table 2). Almost half of all deaths occurred during the first 2 weeks, and over 80% of deaths occurred during the initial treatment phase. Movement of prisoners within the prison system accounted for 83% of failure to complete treatment.

Treatment was successful for 54% of the study population (table 3)—71% of those who completed treatment. Success rates ranged from 26% for those resistant to all four antibiotics (with no exclusions made for incomplete treatment) to 91% for true-new cases who completed treatment. Overall, the sputum-conversion rate was 42%, and this proportion varied roughly threefold between those with a non-resistant strain of *M tuberculosis* and those with a strain resistant to three or four antibiotics. There was substantial agreement about sputum positivity between raters at the Baku laboratory and the Antwerp reference laboratory ( $\kappa=0.79$ ).

|   | Odds ratio (95% CI) |
|---|---------------------|
| <b>Model excluding resistance-profile data (n=365)</b>                      |                     |
| Sputum positive at end of initial treatment phase                           | 6.9 (4.0–12.0)      |
| Pseudo-new cases  | 3.9 (1.2–12.1)      |
| Failure or relapse cases  | 7.2 (2.3–22.2)      |
| Compliance <98.8%   | 3.9 (2.0–7.7)       |
| Cavitory chest disease on admission   | 2.2 (1.3–3.7)       |
| <b>Model including resistance profile data (n=104)</b>                      |                     |
| Resistance to 2 or 3 antibiotics*   | 14.6 (1.4–152.6)    |
| Resistance to 3 or 4 antibiotics†   | 63.2 (5.6–710.2)    |
| Cavitory chest disease on admission   | 26.6 (2.5–277.8)    |
| Oedema on admission   | 9.1 (1.3–64.7)      |
| Compliance <98.8%   | 8.7 (1.3–58.9)      |
| Sputum positive at end of initial treatment phase                           | 7.1 (1.9–25.8)      |
| Body-mass index <16 on admission  | 5.7 (1.3–24.5)      |
| Cavitory disease and infection with strain resistant to 3 or 4 antibiotics† | 0.01 (0.0005–0.3)   |

\*Not multidrug-resistant. †Multidrug-resistant.

Table 4: Variables independently associated with treatment failure by multivariate logistic regression

The first logistic-regression model (table 4), which did not include resistance-pattern data as a potential confounder, showed that a positive sputum result at the end of the initial treatment phase, cavitory disease on admission, and a compliance rate of less than 98.8% were all independently associated with treatment failure. Compliance of 98.8% was derived from the distribution of this variable in the treatment setting: 75% of our study population had rates of compliance above 98.8%. Failure or relapse cases and pseudo-new cases were also independently associated with treatment failure. The Hosmer-Lemeshow goodness-of-fit test gave a  $\chi^2$  of 4.53 ( $p=0.72$ ). First-order interaction terms between cavitory disease and case classification were assessed, but none reached  $p=0.20$  according to the Wald test, and therefore none was retained by the model.

In the second logistic-regression model, which included resistance profile data, infection with a strain of *M tuberculosis* that was either multidrug resistant, or not multidrug resistant but resistant to either two or three antibiotics, was strongly associated with treatment failure. Other factors independently associated with treatment failure included admission with cavitory disease, oedema, or a body-mass index of less than 16. In addition, a positive sputum result at the end of the initial treatment phase and poor compliance were also associated with treatment failure. The Hosmer-Lemeshow goodness-of-fit test gave a  $\chi^2$  of 1.72 ( $p=0.98$ ). First-order interaction terms between cavitory disease, case classification, and resistance profile were assessed. An interaction term between cavitory disease and infection with a multidrug-resistant strain was significant ( $p=0.01$ ) and was retained in the model. Since both main terms are also present in the model, the effect of cavitory disease and infection with a multi-drug resistant strain is less than multiplicative.

## Discussion

In a population with a high degree of resistance to antibiotics, a DOTS programme with first-line therapy resulted in an overall cure of 54%, despite excellent compliance. This figure falls short of the programme objective of 85% recommended by WHO for national tuberculosis programmes.<sup>9</sup> This result should help to open the debate on the most appropriate response or responses to the limited effectiveness of first-line therapy in such settings.

There were several limitations of our study. Our study population was referred to our programme, and thus there were some selection factors beyond our control. This may have led to a disproportionate representation of patients with highly resistant strains of *M tuberculosis*, which lowers the degree to which our findings can be generalised, and which biases our results towards more modest rates of treatment success. However, this bias does not change the fact that our cure rates were generally low, and that the degree of drug-resistance that we observed, while admittedly high, is likely to occur in other settings where tuberculosis control programmes are undertaken. 22 of our 73 failure or relapse cases had multidrug-resistant strains of *M tuberculosis*: a prevalence of 30% in our setting. A global surveillance effort has shown that the prevalence of acquired multidrug-resistance among patients who present to tuberculosis-control programmes is 22.2% in Argentina, 27.3% in Russia, 27.5% in the Republic of Korea, and 54.4% in Latvia.<sup>13</sup>

We are unable to comment on the possible effect of HIV-1 infection on our data, since testing was not done. Rates of HIV-1 infection are low in Azerbaijan<sup>14</sup> and we have no evidence that HIV-1 infection plays an important part in tuberculosis control. Low rates of treatment success might be explained by substandard medications, but the medications used for the programme were obtained from a source in Amsterdam cited by WHO,<sup>15</sup> and we have no reason to believe that the medications were in any way substandard.

There were some operational constraints inherent in implementing a tuberculosis programme in a prison. Great effort was needed to convince staff of the usefulness of direct observation of medicines being swallowed. Despite discussions with authorities, 44 patients who met our admission criteria were prematurely released or transferred from prison. Although these patients were given additional information on the importance of completing their treatment, the lack of good treatment programmes elsewhere in Azerbaijan precluded their appropriate treatment after release. Late identification of tuberculosis cases meant that a relatively large number of patients was admitted with advanced disease and died within the first 2 weeks of therapy. Late identification means that interruption of the transmission cycle within prisons may be difficult, and implies that intermittent or prolonged trials of inappropriate drug regimens are more likely to occur.

A positive sputum result at the end of the first treatment phase was strongly associated with treatment failure in both multivariate models. This midtreatment outcome suggests that a more comprehensive response is needed than is given by WHO,<sup>10</sup> which currently recommends re-registration of sputum-positive patients as failure cases if they are new cases, or the extension of the initial treatment phase for an additional month.

Our results also suggest that there is an inherent limitation in the WHO case-classification system. We made extensive efforts to ascertain previous history of tuberculosis treatment, and to verify this treatment in prison by use of registry data, but treatment outcomes for our pseudo-new cases were more like those for failure cases than those for true-new cases. Since resistance is unlikely to occur over the course of 1 month, this finding suggests that patients classified as pseudo-new cases may well have had more than 1 month of previous treatment. If our findings can be replicated elsewhere, particularly in settings with a high degree of drug resistance, the WHO new-case classification should be modified to include only those patients who report no previous treatment.

The main question raised by our results is whether a DOTS approach limited to first-line therapy is sufficient in settings such as ours. 104 patients completed a full treatment regimen under daily supervision, but these patients nevertheless remained sputum-positive (table 3). The mean compliance of these patients was 99.2% (data not shown). Isolation of these cases, as recommended by WHO,<sup>16</sup> creates great logistical and ethical difficulties for authorities, inmates, and staff. Full resistance-profile data were available for 37 of the 104 patients, and 27 of them had strains of *M tuberculosis* resistant to at least two antibiotics on admission. Three patients had fully drug-sensitive strains on admission: acquisition of resistant strains of *M tuberculosis* during treatment may explain

why these patients did not respond to treatment.<sup>17</sup> We have few data on patterns of resistance to antibiotics at the end of treatment for those who remain sputum-positive, because there was a relatively large number of sputum-negative cultures, and because collection of these data became standard practice in Baku only recently. We constructed two drug-resistance profiles for each of 13 patients who were not resistant to all four antibiotics on their first profile. Nine of the 13 patients had developed additional drug-resistances on their second profile, despite nearly perfect compliance with therapy. Some of these patients acquired up to three additional resistances, suggesting that exogenous reinfection may have occurred.

A tuberculosis-control programme that follows DOTS principles is feasible in prison, but serious organisational, logistical, and medical-policy difficulties must be overcome. Furthermore, strict adherence to WHO treatment guidelines may result in relatively modest rates of treatment success if the prevalence of drug resistance is high. There is a risk of transmission of tuberculosis from prisoners to the general population, since the prisoners are in contact with families, other inmates, and prison staff. 7% of our study population was released from prison during treatment, and a further 3% was transferred to other prison facilities: tuberculosis-control programmes in prisons should take these difficulties into account.

There are two elements to a DOTS programme: the directly observed ingestion of medications; and the selection of medicines to be ingested. A simplistic interpretation of the modest success of the DOTS methods and the choice of treatment is flawed, particularly since DOTS becomes increasingly important if second-line or third-line treatment regimens are used. Existing guidelines may need to be modified to take account of the prevalence of antibiotic resistance. The effect of a DOTS approach limited to first-line therapy in a setting such as ours may simply be the removal of drug-sensitive strains of *M tuberculosis*, to leave behind the more resistant strains. Thus, the short-term benefits of the modest treatment success that we observe may be outweighed by high treatment-failure rates in the long term.

#### Contributors

Rudi Coninx initiated and coordinated the project, and took part in data analysis. Christine Mathieu participated in project design and data

analysis, and was in charge of patient management and data collection. Martine Debacker did laboratory analysis and participated in data analysis. Fuad Mirzoev took part in management of patients, data collection and analysis, and managed the database. Ali Ismaelov participated in laboratory and data analysis. Rodolphe de Haller was involved in setting up the programme and in data analysis. David Meddings was involved in setting up the database and coordinated the data analysis. All investigators contributed to discussion and to writing of the paper.

#### Acknowledgments

We thank F Portaels of the Institute of Tropical Medicine, Department of Microbiology, Antwerp, Belgium, for assistance in setting up the laboratory in Baku, for comments and feedback, and for crosschecking of the smears, cultures, and sensitivity tests; G E Pfyffer, Department of Medical Microbiology, Swiss National Centre for Mycobacteria, University of Zurich, Switzerland, for help with crosschecks of culture and sensitivity results from the Baku laboratory, and for continued support of the laboratory programme; and J Crofton for comments and assistance with the tuberculosis programme.

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