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Low rates of recurrence after successful treatment of multidrug-resistant tuberculosis in Tomsk, Russia

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SUMMARY

SETTING: Tomsk, Russia, where multidrug-resistant tuberculosis (MDR-TB) is prevalent.

OBJECTIVES: To report rates of recurrence following successful treatment of MDR-TB in a program providing individualized treatment regimens designed according to the current global standard of care.

DESIGN: A retrospective cohort study of 408 adults successfully treated for pulmonary MDR-TB from 10 September 2000 to 1 November 2004, and followed for up to 6 years post-treatment. We used Poisson regression with generalized estimating equations to assess whether recurrence rates changed significantly with time.

RESULTS: We analyzed 399 (97.5%) patients with at least one follow-up visit (15 850 person-months of observation [PMO]). Baseline resistance to second-line drugs was common (65.2%); 398 patients (99.7%) were human immunodeficiency virus (HIV) negative. In the first year of post-treatment follow-up, there were six episodes of recurrence (1.4/1000 PMO, 95%CI 0.5–3.0). After the first post-treatment year, there were 21 episodes of recurrence (1.8/1000 PMO, 95%CI 1.1–2.8). The rate did not change significantly with time.

CONCLUSION: Individualized regimens designed according to the current global standard of care achieved low rates of MDR-TB recurrence among non-HIV-infected persons treated in a programmatic setting.

KEY WORDS: anti-tuberculosis medications; cohort study; programmatic setting; drug-resistant tuberculosis

WITH THE RECENT APPROVAL of new drugs for the treatment of multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least isoniazid [INH] and rifampin [RMP]), and efforts underway to develop shorter, less toxic treatment regimens,[1,2] there is a need to delineate the baseline with which new treatments should be compared. While several studies have reported risk of failure and death in patients treated for MDR-TB, far fewer have reported rates of disease relapse, another important measure of treatment efficacy.[3] Relapse rates achieved in programmatic settings utilizing existing treatment approaches can be used as a benchmark when evaluating newer regimens for MDR-TB. However, disease following successful treatment—i.e., recurrence—may be due to either relapse or re-infection, and the genotypic analyses needed to differentiate between the two are rarely performed in programmatic settings. One pragmatic solution is to use the rate of recurrence during the first year of post-treatment follow-up as a proxy for the rate of relapse, as relapse has been demonstrated to account for the majority of recurrent disease during this period.[4,5] Using this approach, the recurrence rate is interpreted as an upper bound estimate of the relapse rate.

Approximately 4% of patients treated for fully drug-susceptible TB with an empiric first-line regimen experience recurrence of disease.[6] While recurrence might be expected to occur more frequently among MDR-TB patients, rates as low as those seen in drug-susceptible disease have also been reported.[7–9] In one study from Lima, Peru, low rates

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were achieved despite 69% of the cohort having isolates resistant to at least five anti-tuberculosis drugs.[7,10] If reproduced in other settings, these findings should set the benchmark for MDR-TB treatment, to be met or even exceeded by newer regimens.

We recently reported on treatment failure and death in a cohort of 614 patients treated for MDR-TB in Tomsk, Russia, among whom broad-spectrum resistance and extensively drug-resistant TB (XDR-TB, defined as MDR-TB plus resistance to fluoroquinolones and second-line injectables) were not infrequent.[11,12] In this cohort, 406 (66.1%) patients were successfully treated (cured or treatment completed), 54 (8.8%) failed, 30 (4.9%) died and 123 (20.0%) defaulted.[12] Here, we report rates of recurrence among successfully treated patients. During the period that this cohort was followed, both TB incidence and prevalence were declining in Tomsk (Appendix Figure).* Between 2002 and 2010, incidence fell from 114.0 to 80.2 per 100 000 population, and prevalence from 241.1 to 116.5/100 000.[13,14]

STUDY POPULATION AND METHODS

The Tomsk cohort comprised adult patients with culture-confirmed pulmonary MDR-TB enrolled on individualized treatment regimens between 10 September 2000 and 1 November 2004. The regimens were designed using an algorithm described by Mukherjee et al.[15] Enrollment, inclusion criteria, laboratory methods for culture and drug susceptibility testing (DST), laboratory quality control, and treatment regimens for this cohort have been reported previously.[11,12] To the original cohort, we added four patients (3 cured, 1 failed) whose sputum samples grew MDR-TB while on MDR-TB treatment, but whose pre-treatment sputum had been culture-negative. As this analysis focused on recurrence after MDR-TB treatment success, we included only study subjects with cure or treatment completion outcomes defined using standard criteria.[16]

Russian protocol requires successfully treated patients to be followed for 1–3 years post-treatment by the regional TB dispensary, and an additional 3 years by primary care facilities.[17] TB dispensary follow-up includes clinical, chest X-ray (CXR), and microbiologic (smear/culture) examinations every 3–6 months. Follow-up at primary care facilities includes clinical examination and CXR every 6 months, and, if recurrence is suspected, microbiologic evaluation and referral to a TB specialist. Incarcerated patients undergo clinical examination and CXR at least every 6 months, sputum smear examination for all those with cough, and sputum culture when disease recurrence is suspected.

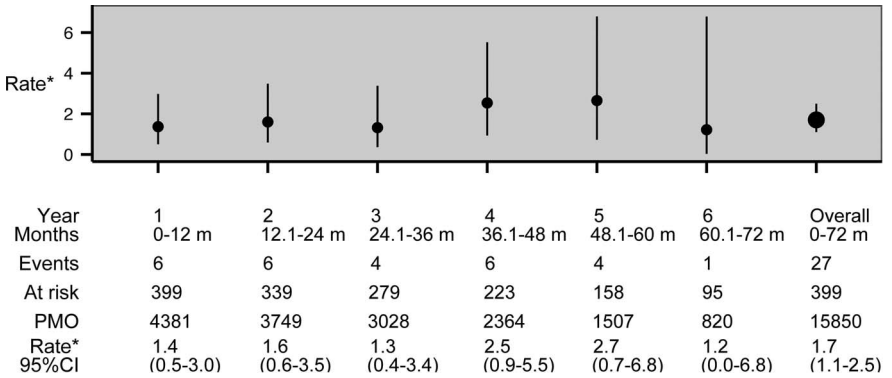
In Russia, initiation of anti-tuberculosis treatment outside the TB system is illegal, and all positive cultures and TB-related deaths are reported to the regional TB dispensary. The TB dispensary routinely checks government registries of vital statistics to identify TB deaths, and records any non-TB causes of death among patients under post-treatment follow-up (Russian civil registration coverage of cause of death has exceeded 99% since 1999).[14,18] The penitentiary sector maintains its own separate recording system for TB events. We therefore used both regional TB dispensary and penitentiary records to collect data on recurrence, follow-up, and death events. Data were not collected from primary care facilities; however, once patients were transferred to complete their post-treatment surveillance at these facilities, the dates and results of subsequent culture, DST, and referrals to TB specialists were recorded in their TB dispensary file.

TB providers performed data collection prospectively on standardized forms. The study team retrospectively verified this data and completed missing results of post-treatment investigations. The collected data included dates of the last medical assessment; dates and results of smears, cultures, and DST; information on TB regimens initiated during the follow-up period; and dates and causes of death.

We classified patients as having recurrent MDR-TB if during the follow-up period a sputum culture growing TB was followed by another positive culture or death, or regardless of culture results if MDR-TB treatment was initiated. Patients with recurrent MDR-TB contributed person-time until the date of the first event used to identify recurrence. Patients who did not experience recurrence contributed follow-up time until the date of their last medical evaluation (smear/culture result, or assessment by medical personnel at the TB dispensary or prison). As we did not collect data at primary care facilities, non-incarcerated patients stopped contributing person-time in our study once they were transferred from TB dispensaries to complete post-treatment surveillance at primary care facilities, unless they were subsequently incarcerated or experienced one of the following: sputum TB culture, referral to TB specialists, or diagnosis of recurrent MDR-TB.

For the first year following successful treatment, we determined both the incidence rate of recurrence and the proportion of patients experiencing recurrence. We chose a conservative approach to calculate the latter—the denominator only included patients who had either experienced recurrence or who remained in follow-up by the end of the first post-treatment year. All patients contributed person-time when calculating rates. For the second to the sixth year of follow-up, we estimated the annual and overall rates of recurrence.

* The appendix is available in the online version of this article, at http://www.ingentaconnect.com/content/iuatld/ijtld/2015/00000019/00000004/art00008



Year	1	2	3	4	5	6	Overall
Months	0-12 m	12.1-24 m	24.1-36 m	36.1-48 m	48.1-60 m	60.1-72 m	0-72 m
Events	6	6	4	6	4	1	27
At risk	399	339	279	223	158	95	399
PMO	4381	3749	3028	2364	1507	820	15850
Rate*	1.4	1.6	1.3	2.5	2.7	1.2	1.7
95%CI	(0.5-3.0)	(0.6-3.5)	(0.4-3.4)	(0.9-5.5)	(0.7-6.8)	(0.0-6.8)	(1.1-2.5)

Figure Rates of recurrence following successful treatment of MDR-TB in Tomsk, Russia. Recurrence rates did not change significantly over the follow-up period ($P > 0.05$ from Poisson regression with generalized estimating equations).* Rate per 1000 PMO. Year = year of post-treatment follow-up; months = months of post-treatment follow-up; events = number of patients experiencing recurrence of MDR-TB during the period; at risk = number of patients contributing follow-up time during the period. MDR-TB = multidrug-resistant tuberculosis; PMO = person-months of observation.

To assess whether recurrence rates changed with time, we used Poisson regression with generalized estimating equations and robust standard errors to calculate the rate ratio (RR) per 1 year increase in time since treatment completion. We also compared the rate in the first year of post-treatment follow-up with the rate over the subsequent years. The threshold for statistical significance was $P < 0.05$.

Analyses were performed using Access (Microsoft, Redmond, WA, USA, 2008), Excel (Microsoft, 2011) and SAS software, version 9.3 (Statistical Analysis System Institute, Cary, NC, USA). The Figure was generated using the package *ggplot2* in *R* (R Core Team, R Foundation for Statistical Computing, Vienna, Austria, 2013).[19]

Ethics approval was obtained from the Institutional Review Boards of the Harvard School of Public Health (Boston, MA, USA) and the Siberian State Medical University (Tomsk, Russian Federation).

RESULTS

Treatment success was achieved in 409/618 (66.2%) episodes of MDR-TB, among 408 patients (one patient contributed person-time for two episodes, each ending in cure). Data from 399 (97.5%) individuals with at least one post-treatment follow-up visit were used for reporting recurrence rates. Outcome at the end of treatment was 'cured' in 376 (94.2%) and 'treatment completed' in 23 (5.8%). Resistance to at least five anti-tuberculosis drugs (including INH and RMP) was documented in 209 (52.4%) patients, and resistance to at least one second-line anti-tuberculosis medication in 260 (65.2%). The median duration of treatment was 18.6 months (interquartile range [IQR] 18.0–21.2). One patient had human immunodeficiency virus (HIV) infection. All patients were treated with regimens that included second-line drugs, fluoroquinolones and parenteral agents. Forty-one (10.3%) patients underwent a thoracic surgical procedure during treatment. One hundred and thirty-eight (34.6%) patients were incarcerated at some point during the follow-up period. The median duration of post-treatment follow-up was 42.4 months (IQR 20.5–59.5).

For each post-treatment year, Table 1 enumerates patients who contributed person-time during the year (column 2), followed by those who did not complete the full year of follow-up (columns 3 to 8), and whether this was due to non-TB death, leaving the Tomsk region, defaulting from follow-up at the TB dispensary, being transferred to primary care facilities, or diagnosis of recurrent MDR-TB. For the first post-treatment year, recurrence status was known for 364/399 (91.2%): 6 experienced recurrence, 339 survived without recurrence, and 19 died without recurrence. The most common reason for incomplete follow-up in the first post-treatment year was transfer out of Tomsk; in all other years, it was transfer to primary care facilities with no subsequent incarceration, TB investigations or referrals to TB specialists.

There were 27 episodes of recurrence, six of which occurred in the first year of post-treatment follow-up. Table 2 lists the criteria for classifying recurrence when each occurred, and DST results. Two patients were classified as recurrent disease despite being culture-negative because they initiated MDR-TB treatment during follow-up. The remaining 25 had positive cultures at the time of recurrence; of these, isolates were confirmed as MDR-TB in 5/5 (100%) episodes diagnosed in the first post-treatment year, and 16/20 (80%) in subsequent years. No recurrence isolates were XDR-TB.

Table 1 Outcome of follow-up by post-treatment year among successfully treated patients*

Year of post-treatment follow-up	Patients contributing person-time in this post-treatment year *n* (%)	Non-TB death† *n* (%)	Incarcerated transfers‡ *n* (%)	Migration out of Tomsk region§ *n* (%)	Default from TB dispensary¶ *n* (%)	Transfer from TB dispensary to primary care facility# *n* (%)	Recurrent MDR-TB** *n* (%)	Follow-up limited by the end of study date†† *n* (%)
1	399	19 (4.8)	24 (6.0)	6 (1.5)	5 (1.3)‡‡	0	6 (1.5)	0
2	339	6 (1.8)	11(3.2)	6 (1.8)	10 (2.9)§§	21 (6.2)¶¶	6 (1.8)	0
3	279	3 (1.1)	3 (1.1)	3 (1.1)	0	43 (15.4)##	4 (1.4)	0
4	223	2 (0.9)	0	2 (0.9)	0	55 (24.7)***	6 (2.7)	0
5	158	0	3 (1.9)	3 (1.9)	0	47 (29.7)†††	4 (2.5)	6 (3.8)
6	95	0	0	0	0	28 (29.2)	1 (1.0)	17 (17.7)

* 10 patients did not have any follow-up visits and are not included in the above table (see Results); among these, the vital statistics registry documented 5 deaths from causes other than TB (2 trauma, 2 poisoning, 1 stroke), of which 2 occurred on the day after completion of treatment. Of the remaining 5, it is known that 2 transferred out of the Tomsk region.

† Refers to death from a cause other than TB. In cases of non-TB death, the last medical assessment (smear, culture, CXR) before death was used as the last date of follow-up. Cause-of-death coverage in Russia was >99% during our study period.[18] The reliability of data for non-TB causes of death in our cohort is very high: autopsy is commonly performed in all suspicious cases; in our unpublished data, the rates of autopsy of those who died while on anti-tuberculosis treatment for suspected non-TB death were >70%. No patients with autopsy-confirmed non-TB death in this column had had positive cultures while under post-treatment surveillance.

‡ Incarcerated patients transferred to prisons outside of Tomsk region, or prisoners released to other regions (prisons outside the Tomsk region referred cases of MDR-TB to Tomsk's prisons for treatment, after which they were transferred back).

§ Non-incarcerated patients who moved to a different region.

¶ Patients who did not return for follow-up visits while under post-treatment surveillance at the TB dispensary. Non-incarcerated patients are followed for 1–3 years at the TB dispensary (1.5–2 years is the most common duration; the length depends on severity of lung damage on CXR and some clinical characteristics) before being transferred to primary care facilities for 3 additional years of surveillance for recurrent disease.

Patients who completed their TB dispensary follow-up and were transferred to primary care facilities to continue their post-treatment surveillance. These patients completed their TB dispensary follow-up, and were transferred to primary care facilities to continue their TB surveillance (by clinical examination and biannual CXR, sputum smear if coughing). After they were transferred, they did not contribute person-time to our study because they remained non-incarcerated, were not referred to a TB specialist and were not diagnosed with recurrent TB.

** Among patients diagnosed with recurrent MDR-TB, 9 died: in 6 of these the cause of death was TB, and all died within 1 year of recurrence; in the remaining 3 the cause of death was non-TB-related (2 of these patients died more than 1 year after diagnosis of recurrence).

†† Patients who were censored because they were still in follow-up when data collection ended for our study.

‡‡ Two of these patients died from non-TB causes in subsequent years (their second and third post-treatment years) (information obtained from vital statistics registries).

§§ Two of these patients died from non-TB causes in subsequent years (their third and fourth post-treatment years) (information obtained from vital statistics registries).

¶¶ One of these patient died from a non-TB cause during his sixth post-treatment year (information obtained from vital statistics registries).

Three of these patients died from a non-TB cause in subsequent years (their fourth and fifth post-treatment years) (information obtained from vital statistics registries).

*** Two of these patients died from a non-TB cause in subsequent years (their fifth and sixth post-treatment years) (information obtained from vital statistics registries).

††† One patient died from a non-TB cause during their sixth post-treatment year (information obtained from vital statistics registries).

TB = tuberculosis; MDR-TB = multidrug-resistant TB; CXR = chest X-ray.

Table 2 Year of post-treatment follow-up in which recurrence occurred, criteria for diagnosis of recurrence, and DST results of *Mycobacterium tuberculosis* isolates in 27 patients with recurrent MDR-TB*

Patient	Year of post-treatment follow-up when recurrence occurred	Recurrence criteria	Results of last DST before the end of treatment	Results of DST at the time of recurrence or later
1	1	2 positive cultures†	Resistance: HRSE Susceptibility: KmCsCpmOfxPAS	Resistance: HRSE Susceptibility: Km
2	1	2 positive cultures†	Resistance: HRS	Resistance: HRSKm Susceptibility: EEthCsCpmOfxPAS
3	1	2 positive cultures†	Resistance: HRSEKmEthCpm Susceptibility: CsOfx	Resistance: HRKmEthPAS Susceptibility: SECsCpmOfx
4	1	2 positive cultures†	Resistance: HRSZEth Susceptibility: EKmCsCpmOfxPASAmkCip	Resistance: HRS Susceptibility: EKm
5	1	New MDR-TB treatment‡	Resistance: HRSKm Susceptibility: EEthCsCpmOfxPAS	No positive culture and DST
6	1	2 positive cultures†	Resistance: HRS Susceptibility: EKmEthCsCpmOfxPAS	Resistance: HRSE Susceptibility: KmCsCpmOfxPAS
7	2	2 positive cultures†	Resistance: HRS Susceptibility: Km	Resistance: HRSEKm Susceptibility: EthCsCpmOfxPAS
8	2	New MDR-TB treatment‡	Resistance: HRSEEthOfx Susceptibility: KmCsCpm	No positive culture and DST
9	2	2 positive cultures†	Resistance: HRS Susceptibility: EKmEthCsCpmOfx	Resistance: HRS Susceptibility: EKmEthCsCpmOfxPAS
10	2	2 positive cultures†	Resistance: HREEth Susceptibility:	Resistance: HRSKm Susceptibility: EEthCsCpmOfxPAS
11	2	2 positive cultures†	Resistance: HRS Susceptibility: EKm	Resistance: RS Susceptibility: HEKmEthCsCpmOfxPAS
12	2	2 positive cultures†	Resistance: HRSE Susceptibility: KmEthCsCpmOfx	Resistance: HRSE Susceptibility: KmEthCsCpmOfxPAS
13	3	2 positive cultures†	Resistance: HRSEKm Susceptibility: EthCsCpmOfxPAS	Resistance: HRSEKm Susceptibility: EthCsCpmOfxPAS
14	3	2 positive cultures†	Resistance: HRSE Susceptibility: Km	Resistance: None Susceptibility: HRSEKmCsCpmOfxPAS
15	3	2 positive cultures†	Resistance: HRSEKmEth Susceptibility: CsCpmOfx	Resistance: HRSKmCpm Susceptibility: ECsOfxPAS
16	3	2 positive cultures†	Resistance: HRSEKm Susceptibility: EthCsCpmOfx	Resistance: HRSEKm
17	4	2 positive cultures†	Resistance: HRSKmPAS Susceptibility: EEthCsCpmOfx	Resistance: HRSEKmPAS Susceptibility: EthCsCpmOfx
18	4	2 positive cultures†	Resistance: HRS Susceptibility: EKmCsCpmOfxPAS	Resistance: HRS Susceptibility: EKm
19	4	New MDR-TB treatment‡	Resistance: HRSEPAS Susceptibility: KmCsCpmOfx	Resistance: HRSOfx Susceptibility: EKmEthCsCpmPAS
20	4	2 positive cultures†	Resistance: HRSKm Susceptibility: E	Resistance: None Susceptibility: HRSEKmEthCsCpmOfxPAS
21	4	2 positive cultures†	Resistance: HRSE Susceptibility: Km	Resistance: HRSE Susceptibility: Km
22	4	2 positive cultures†	Resistance: HRSEEth Susceptibility: KmCsCpmOfx	Resistance: HRS Susceptibility: EKmEthCsCpmOfxPAS
23	5	2 positive cultures†	Resistance: HRSEKmZEth Susceptibility: CsCpmOfxPAS	Resistance: HRSKm Susceptibility: EEthCsCpmOfxPAS
24	5	2 positive cultures†	Resistance: HRSKmCpm Susceptibility: ECsOfxPAS	Resistance: HRSKCpm Susceptibility: EEthCsOfxPAS
25	5	2 positive cultures†	Resistance: HRSEKm	Resistance: HRSEKm Susceptibility: EthCsCpmOfxPAS
26	5	2 positive cultures§	Resistance: HRSE Susceptibility: Km	Resistance: None Susceptibility: HRSEKm
27	6	2 positive cultures†	Resistance: HRS	Resistance: HRSOfx Susceptibility: EKmEthCsCpmPAS

* Early in the programme, external quality control was performed by the Massachusetts State Laboratory Institute (MA, USA), a member of the supranational TB reference laboratory network. Later on, the external quality control continued at least twice each year by the Federal civilian and prison laboratories. Tomsk civilian and prison laboratories had high concordance of results with the supervising laboratory.
† Within 6 months of each other.
‡ Culture-negative at time of treatment initiation for recurrent MDR-TB.
§ Consecutive cultures taken more than 6 months apart, with no negative cultures in the interval.
DST = drug susceptibility testing; MDR-TB = multidrug-resistant tuberculosis; H = isoniazid; R = rifampicin; S = streptomycin; E = ethambutol; Km = kanamycin; Cs = cycloserine; Cpm = capreomycin; Ofx = ofloxacin; PAS = para-aminosalicylic acid; Eth = ethionamide; Z = pyrazinamide; Amk = amikacin; Cip = ciprofloxacin.

During the first post-treatment year, the rate of recurrence was 1.4/1000 PMO (95%CI 0.5–2.9); 1.7% (95%CI 0.6–3.8) of patients who were not lost to follow-up and did not die during this year ($n = 345$) experienced recurrence. Over the remainder of the follow-up period (post-treatment years 2 to 6), the rate was 1.8/1000 PMO (95%CI 1.1–2.8). The Figure shows the overall rate and the rate during each year of post-treatment follow-up.

The association between time and recurrence was not statistically significant when modeling year as a continuous variable (RR 1.1, 95%CI 0.9–1.4, $P = 0.36$, per 1-year increase in post-treatment follow-up), or as a binary variable comparing the last 5 years with the first year (RR 1.3, 95%CI 0.5–3.3, $P = 0.53$).

In a post-hoc analysis, we determined whether rates differed between the two categories of treatment success. One patient whose outcome was 'treatment completed' experienced recurrence. Rates were not significantly different between this group and the group of 'cured' patients (comparing rates in first post-treatment year: Wilcoxon $P = 0.38$, log-rank $P = 0.59$; comparing rates in subsequent period: Wilcoxon $P = 0.53$, log-rank $P = 0.78$).

DISCUSSION

These findings add to a growing body of evidence demonstrating that low rates of MDR-TB recurrence can be achieved in programmatic settings among HIV-negative patients using the current global standard of care, i.e., second-line regimens that include fluoroquinolones, parenteral antibiotics and additional second-line anti-tuberculosis medications used according to the algorithm described by Mukherjee et al., even when resistance to second-line medications is common.[7,10,15] While our study has several strengths, a number of important limitations should be taken into consideration when interpreting our observations.

First, because genotyping was not performed, we could not distinguish between relapse of the original disease and re-infection. To address this limitation, we assumed that the temporal dynamics of relapse and re-infection following successful MDR-TB treatment are similar to those described for non-MDR-TB,[4,5] such that the recurrence rate in the first year is a reasonable upper-bound estimate of the relapse rate. This is supported by our observation that all culture-positive recurrence isolates were confirmed to be MDR-TB in the first post-treatment year. Given the prevalence of MDR-TB in Tomsk's prisons and the frequency of incarceration in our sample population (34.6%), it is likely that some recurrence episodes with culture-confirmed MDR-TB were caused by re-infection rather than relapse, particularly after the first year of follow-up. Future studies on MDR-TB recurrence should incorporate genotypic analyses to advance our understanding of the associations between relapse, re-infection and time since treatment completion.

A second important limitation is attrition during the follow-up period, particularly after the first post-treatment year. Attrition would bias our estimates if it was associated with the risk of recurrence. For example, if participants with unknown outcomes were more likely to have experienced recurrence than those who remained in follow-up, we would have underestimated the true rate of recurrence. However, it is unlikely that we missed cases of recurrence because Russia's centralized TB system requires all TB diagnoses, and TB-related deaths, to be reported to the dispensaries, which were the source of our follow-up data. Conversely, it is possible that we overestimated the true rate. This is because once patients were transferred to primary care facilities, those in whom the risk of recurrence was lower, i.e., those who were not subsequently incarcerated and whom clinicians judged as not requiring TB investigations, stopped contributing person-time on the date of their last visit to the TB dispensary despite remaining under observation for some additional time at their primary care facility. This premature censoring of the lower risk group would result in overestimation of recurrence rates. Overall, underestimation due to unidentified cases of recurrence may be exceeded or balanced by overestimation due to earlier censoring of low-risk patients, thereby minimizing the effect of attrition bias.

Despite these limitations, our results have important implications. First, rates observed during the first year of follow-up in this programmatic setting provide information that can be used to evaluate the benefit of new regimens. Because some patients may have experienced re-infection even in the first post-treatment year, our observed rate can be regarded as an upper bound estimate of the true relapse rate that new regimens should meet or exceed in non-HIV-infected populations.

Our findings also have implications for the surveillance of patients following successful treatment of MDR-TB. Rates of recurrence did not decline significantly over the follow-up period. This implies that successfully treated patients remain at risk of MDR-TB for a prolonged period of time, and should be followed beyond the first post-treatment year. Genotypic analyses to differentiate between relapse and re-infection would help to further interpret these findings and assess their generalizability. For example, if genotypic analyses demonstrate that relapse remains an important cause of recurrent MDR-TB after the first post-treatment year, then lowering recurrence risk will require a more effective treatment regimen. Conversely, if re-infection is predominant, prevention of recurrence will necessitate reducing transmission (e.g., through improved case detection,

infection control, and time to initiation of the correct treatment). Furthermore, if recurrence is primarily due to re-infection, our recommendation for prolonged follow-up may not be applicable to areas where MDR-TB is less prevalent.

CONCLUSION

Recurrence of disease during the first year of follow-up after successful treatment of MDR-TB is a proxy indicator of true relapse, which is an important measure of the effectiveness of a treatment strategy. Data from Tomsk and other settings[7] suggest that low rates of recurrence can be achieved using individualized regimens designed according to the current global standard of care.[15] Additional analyses of observational data to identify patient and treatment characteristics that predict recurrence will facilitate the efficient design and planning of trials evaluating new regimens. Future studies of MDR-TB recurrence should include genotyping to clarify associations between relapse, re-infection, and time since completion of treatment.

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APPENDIX

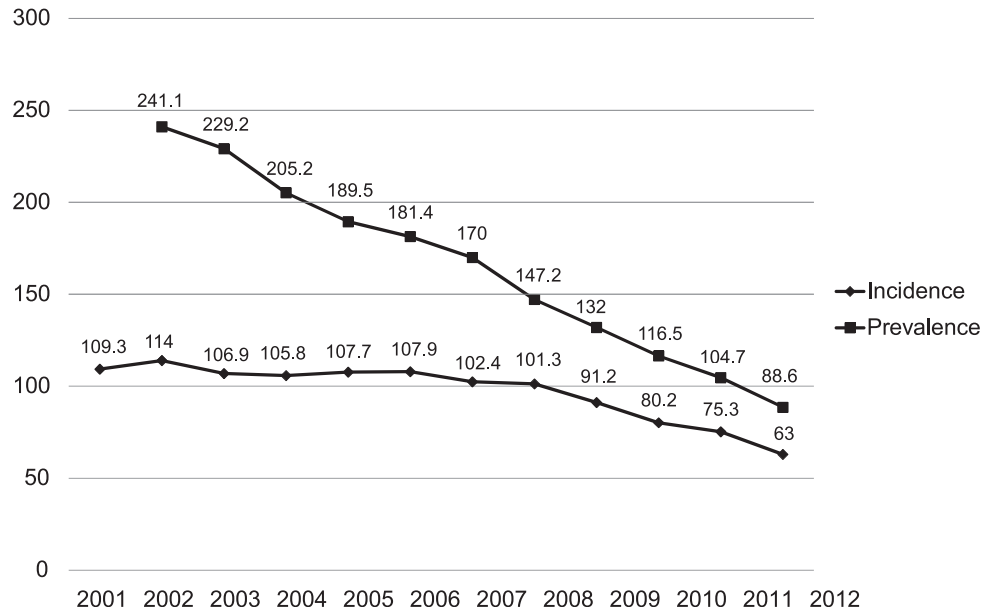

Figure A TB incidence and prevalence per 100 000 population in Tomsk region, 2001–2012. Adapted from references 1 and 2.

References

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RESUME

CONTEXTE : Tomsk, Russie, où la tuberculose multirésistante (TB-MDR) est prévalente.

OBJECTIF : Rapporter les taux de récurrence suivant un traitement réussi de TB-MDR dans un programme offrant des protocoles de traitement individualisés conçus selon les standards de soins actuels dans le monde.

SCHÉMA : Etude rétrospective de cohorte de 408 adultes traités avec succès pour une TB-MDR pulmonaire entre le 10 septembre 2000 et le 1e novembre 2004 et suivis jusqu'à 6 ans après leur traitement. Nous avons utilisé la régression de Poisson avec équation d'estimation généralisée pour évaluer si le taux de récurrence changeait significativement avec le temps.

RÉSULTATS : Nous avons analysé 399 (97,5%) patients ayant eu au moins une consultation de suivi (15 850 personnes-mois d'observation [PMO]). La résistance de départ aux médicaments de deuxième ligne était fréquente (65,2%) ; 398 patients (99,7%) étaient négatifs pour le virus de l'immunodéficience humaine (VIH). Pendant la première année suivant le traitement, il y a eu six épisodes de récurrence (1,4/1000 PMO, IC95% 0,5–3,0). Après la première année suivant le traitement, il y a eu 21 épisodes de récurrence (1,8/1000 PMO, IC95% 1,1–2,8). Le taux n'a pas changé significativement avec le temps.

CONCLUSION : Des protocoles individualisés de traitement élaborés en fonction des standards de soins mondiaux actuels ont abouti à un faible taux de rechute de TB-MDR chez des personnes non-infectées par le VIH dans le cadre d'un programme.

RESUMEN

MARCO DE REFERENCIA: Tomsk, en Rusia, donde es frecuente la tuberculosis multidrogorresistente (TB-MDR).

OBJETIVOS: Comunicar las tasas de recurrencia después de un tratamiento exitoso de la TB-MDR, en un programa que ofrece pautas de tratamiento individualizadas, definidas en conformidad con las normas mundiales vigentes de tratamiento.

METODO: Se llevó a cabo un estudio retrospectivo de cohortes de 408 pacientes que recibieron un tratamiento eficaz por TB-MDR del 10 de septiembre del 2000 al 1 de noviembre del 2004 y cumplieron con un seguimiento hasta de 6 años después de haber terminado el tratamiento. Se aplicó una regresión de Poisson con ecuaciones de estimación generalizadas a fin de verificar si las tasas de recurrencia se modificaban de manera significativa con el transcurso del tiempo.

RESULTADOS: Se analizaron 399 pacientes (97,5%) con registro de por lo menos una cita de seguimiento (15 850 meses-persona de observación [PMO]). La resistencia inicial a los medicamentos de segunda línea fue frecuente (65,2%) ; 398 pacientes (99,7%) fueron negativos frente al virus de la inmunodeficiencia humana (VIH). Durante el primer año de seguimiento después del tratamiento, se presentaron seis episodios de recurrencia (1,4/1000 PMO ; IC95% 0,5–3,0). Después del primer año de seguimiento, ocurrieron 21 episodios de recurrencia (1,8/1000 PMO ; IC95% 1,1–2,8). La tasa de recurrencia no se modificó de manera significativa con el trascurso del tiempo.

CONCLUSION: Las pautas terapéuticas individualizadas, formuladas en conformidad con las normas mundiales vigentes de atención, lograron bajas tasas de recurrencia de la TB-MDR en las personas sin infección por el VIH tratadas en un contexto programático.