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Treatment outcomes of multidrug-resistant tuberculosis in Switzerland

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Summary

OBJECTIVE: To assess outcomes 24 months after treatment start for multidrug-resistant tuberculosis (MDR-TB).
METHODS: Cohort study of all culture-positive MDR-TB cases notified in Switzerland from 01/2003 to 07/2010.
RESULTS: Fifty-one cases were observed, with a median age of 26 years (range 2–56). Twenty-seven were male, five of Swiss origin, 46 of foreign origin (Asia 18, Africa 13, former Soviet Union 8), including 21 asylum seekers and refugees. Twelve had received a previous treatment for TB and 24 had not (15 unknown). Forty-four cases were pulmonary of which 25 were known to be sputum smear positive. All but two strains showed additional resistances: 29 to ethambutol, 27 to pyrazinamide, 6 to a fluoroquinolone, 5 to amikacin. None was resistant to both of the latter two classes. Molecular analyses showed three pairs of identical strains.
Fluoroquinolones were used in 48 patients and second-line injectable drugs in 37. The median duration of MDR treatment was 18 months (range 1–26).
The outcome after 24 months was successful in 39 (76%) and unsatisfactory in 12 (24%) patients: two deaths from TB; two treatments terminated owing to side effects of drugs and one owing to pregnancy; four defaults from treatment at months 0, 4, 8, and 21; two transfers abroad with unknown outcome; one outcome unknown. There was no significant association of unfavourable outcomes with age, sex, origin, previous treatment, treatment delay, resistance pattern, and classes of drugs used.
CONCLUSIONS: MDR-TB in Switzerland occurs mostly in persons of foreign origin. Results of decentralised treatments were satisfactory.

Key words: *tuberculosis; multidrug resistance; MDR; antituberculosis drug resistance; treatment outcomes; treatment results; epidemiology; Switzerland*

List of abbreviations

IBM	international business machines
IS6110 RFLP	restriction fragment length polymorphism analysis with insertion sequence 6110
MDR	multidrug resistance
MDR-TB	multidrug-resistant tuberculosis
mg/l	milligrams per litre
MIRU-VNTR	mycobacterial variable-number tandem repeats of mycobacterial interspersed repetitive units
SPSS	statistical package for the social sciences
TB	tuberculosis
WHO	World Health Organization
XDR-TB	extensively drug-resistant tuberculosis

Introduction

Multidrug-resistant (MDR) strains of the *Mycobacterium tuberculosis* complex are defined as resistant to both isoniazid and rifampicin. High MDR proportions and high numbers of MDR exist in the countries of the former Soviet Union and in China. South Asia and Southern Africa have lower proportions of MDR but high numbers of MDR cases due to a high overall tuberculosis (TB) incidence [1–4]. In many settings, prevalence of MDR has increased over the last years, while it has decreased in some countries with well-run treatment programmes [2]. Extensively drug-resistant TB (XDR-TB), by definition MDR strains additionally resistant to both fluoroquinolones and an injectable second-line drug such as amikacin, kanamycin or capreomycin, pose additional challenges for treatment.
In Switzerland, approximately 540 cases of TB are annually notified to the surveillance system with an incidence of seven cases per 100,000 population [5]. As in other countries of Western Europe, the incidence rate in the native population has been decreasing over many decades. Approximately 70% of cases are persons of foreign origin. Among immigrant populations, the occurrence of TB and the proportion of resistant strains are higher than in the native population [5, 6]. In Switzerland, reporting of results of first-line TB drug susceptibility testing by laboratories to the surveillance system became mandatory in 1996. Since then, a constant proportion of 1% to 2% of strains with MDR has been observed [5].
The drug combinations used and the duration of treatment are subject to debate. MDR treatment regimens may vary according to the setting, with availability of resources being key in many countries. Compared with standard first-line TB drugs, most second-line drugs are more costly, less effective, and more toxic [7].

Most TB patients in Switzerland start treatment in a public hospital and continue with ambulatory care in an outpatient department or in private practice with guidance from pulmonologists or infectious disease specialists. There is no standardised regimen but the choice of drugs for MDR basically follows recommendations of the World Health Organization (WHO) and is further individualised according to the drug susceptibility pattern.

Treatment results (outcomes) of pulmonary cases overall, resistant or not, had shown a treatment success of 79% in a nationwide Swiss study in 1996 [8]. The WHO target is 85%. Routine collection of treatment results has since been suggested to the cantonal health authorities but, as it is not mandatory, results were lacking in 26% of cases in 2010 [5].

Due to the long duration and complexity of treatment, treatment results for MDR-TB are usually inferior to those of drug-susceptible TB [9–11]. The present study assesses the epidemiology of MDR-TB in Switzerland, the treatment outcomes of MDR cases, factors potentially associated with favourable or unfavourable outcomes and some aspects of patient management. In terms of public health policy, the overall results should serve as an orientation for the health authorities as to whether there is a need for changes in the, quite decentralised, setting for treatment of MDR-TB.

Methods

All culture-positive MDR cases notified to the national surveillance system between January 2003 and July 2010 were included. Baseline epidemiological data and initial drug susceptibility test data were available from the mandatory notifications of physicians and laboratories.

From mid-2008 onward, a questionnaire was sent to each clinician in charge of an MDR case notified since 2003 for a retrospective case assessment two years after diagnosis. Questions related to the dates of start and end of MDR treatment and to the outcome at 24 months (or any definitive outcome before). The standard outcome categories used after 2005 were chosen [12]. Cases that never started treatment for MDR were included in the analysis, in line with more recent recommendations [13]. All drugs used during treatment, apart from isoniazid and rifampicin, were ascertained. Follow-up data beyond 24 months were not routinely assessed, but the surveillance data were last checked in February 2014 for recurrence of cases at a later point in time.

All culturing laboratories are asked routinely to send rifampicin-resistant strains to the National Reference Laboratory for Mycobacteria at the University of Zurich for evaluation by molecular fingerprinting (analysis of the restriction fragment-length polymorphism with insertion sequence 6110 [RFLP], spacer oligotyping, and analysis of mycobacterial interspersed repetitive units [MIRU] at 24 loci, the latter being a *Mycobacterium tuberculosis*-specific analysis of variable number of tandem repeats [VNTR]). In the years up to 2005, not all strains were re-tested for drug susceptibilities at the National Reference Laboratory so that the diagnosis had to rely on other tertiary laboratories. All drug susceptibilities refer to initial isolates, i.e. strains collected before the start of the present treatment episode. Levels of resistance for a strain to be defined as resistant are given in table 2.

The data were analysed using IBM Statistical Package for the Social Sciences (SPSS) Version 21 and Stata SE 12.0 for Windows.

Approval by an ethics committee was not sought for this retrospective study as the Federal Office of Public Health is legally entitled to collect additional epidemiological data on statutorily reported cases.

Results

Epidemiological baseline data

Fifty-one individuals with MDR-TB were reported to the national surveillance system in the study period, representing 2% of all culture-confirmed TB cases with phenotypic susceptibility test results for isoniazid and rifampicin in the respective period (n = 3,404). Clinicians of three of these patients did not participate in the study, but partial information became available through public health departments for two of these cases.

The 51 cases average to seven cases per year with a range of 4 to 10 per year. Twenty-seven of them were male and 24 were female. The median age was 26 years (range 2–56).

Five were of Swiss origin, of whom two (7 and 30 years old) had been living in Asia; one patient's strain was identical to the one isolated from his father in 1986; and no details are known as to the exposure of the other two cases of Swiss origin.

Forty-six were of varied foreign origin, with sizable groups of Tibetans from China, Africans from the Horn of Africa, and persons from countries of the former Soviet Union (table 1).

The length of stay in Switzerland before the start of a TB treatment was known for 35 of 45 persons born abroad. The median time was 47 weeks with a range from less than one week to 33 years. A two-year-old child of asylum seekers had been born in Switzerland.

Among the 20 adult patients notified as belonging to the pre-defined category of asylum seekers and refugees, the median time from claiming asylum to the start of TB treatment was six months (range 0 days to 14 years). Six of them started treatment within nine days of claiming asylum; four started within six and eleven weeks; and the remaining ten patients between 10 months and 14 years afterwards.

Information on prior TB treatment was lacking in 29% of cases. One third of the cases with available information had received a previous TB treatment (table 1).

Of the 44 pulmonary cases, 25 were known to be sputum smear positive (table 1). Fifteen patients had extrapulmonary involvement, seven of whom exclusively so (table 1).

Drug susceptibility test results

All 51 strains were of the species *Mycobacterium tuberculosis*. The type and number of drugs tested per strain differed over time as not all strains were tested for all drugs at the National Reference Laboratory in the early years. Drug susceptibility testing results available from other

laboratories were therefore also included when results from the National Reference Laboratory were missing. All strains were resistant to isoniazid at a concentration above 0.1 milligrams per litre (mg/l), except for one in which resistance at 0.1 mg/l was reported (1.0 mg/l unknown). The level of 0.1 mg/l is the level of resistance that is still (easily) overcome by isoniazid at regular dosage [14].

Results of susceptibility testing of an average number of nine drugs per strain were known (median 10 drugs, range 4–13), not including isoniazid and rifampicin (and usually cross-resistance to rifabutin), counting the class of usually cross-resistant fluoroquinolones as one drug, and including more rarely tested drugs (thioacetazone, clarithromycin, and clofazimine). There were, on average, resistances to 3.6 drugs (median 4, range 0–8).

Two strains were resistant to isoniazid and rifampicin only (out of 6 and 11 drugs tested, respectively). Resistance to ethambutol and pyrazinamide was common (table 2), and 19 strains of 50 tested showed resistance to all four first line drugs isoniazid, rifampicin, pyrazinamide, and ethambutol (one test result for pyrazinamide lacking). Resistance was also frequent to streptomycin, ethionamide, cycloserine, and para-aminosalicylic acid (table 2). Two strains were only susceptible to second-line injectables (of 9 and 10 drugs tested, respectively). One strain was susceptible to second-line injectables and pyrazinamide only (of 10 drugs tested).

Six out of 51 strains had any resistance to a fluoroquinolone and 5/50 had any resistance to a second-line injectable drug (5/50 to amikacin, and 1/34 additionally to capreomycin). All strains resistant to fluoroquinolones were susceptible to injectable drugs and all strains resistant to amikacin were susceptible to fluoroquinolones. There was, therefore, no case meeting the definition of XDR-TB (extensive drug resistance) with resistance to fluoroquinolones and at least one second-line injectable drug. The patients with strains resistant either to second-line injectables or to fluoroquinolones originated from the former Soviet Union (4), India (2), Tibet (2), Central or Western Africa (2), and Switzerland (1).

Molecular fingerprints were available for 50 of the 51 strains. Molecular analysis showed three pairs of identical strains within this cohort, all in asylum seekers or refugees, while 44 strains were unique. One transmission event was from an adult friend of the family repeatedly visiting the home of a two-year-old Tibetan child who subsequently died from TB meningitis while on first-line treatment with culture results pending. One transmission event is likely to have occurred between distant relatives of Tibetan origin who had lived together for several weeks in Switzerland. The third cluster consisted of two Ethiopians, a spinal TB case diagnosed one year before a pulmonary case, but without further contact information so that the transmission event remained unclear.

Case management

Treatment with second-line drugs for MDR-TB was initiated in 48 of the 51 patients; two had died and one had disappeared before the start of MDR treatment. The median time lapse between initiation of any TB treatment and initiation of an MDR treatment was 5.5 weeks (range 0–26) with 10 patients starting on second-line drugs from the beginning of their TB treatment episode.

Treatment regimens over the course of treatment could not be assessed in detail, but "ever use" of any drug (except isoniazid and rifampicin) at any time during MDR treatment was assessed:

Ethambutol was used in 35 and pyrazinamide in 30 patients. Most commonly prescribed second-line drugs were fluoroquinolones (48 patients), mostly moxifloxacin (39 patients). There was a trend over time to favour moxifloxacin over other fluoroquinolones. Injectable drugs given were amikacin (35 patients) and/or capreomycin (3) and streptomycin (7). Eight of 48 patients did not receive any injectable drug. Among the 40/48 who did receive an injectable drug, three received streptomycin only and no injectable second-line drug.

Linezolid was used in 18 patients, ethionamide/prothionamide in 25 and cycloserine in 11. Less frequently used drugs were para-aminosalicylic acid, rifabutin, clofazimine, clarithromycin and thioacetazone.

The median duration of MDR treatment was 18 months (mean 16, range 1–26, n = 48).

Treatment outcomes

The main objective of the study was to determine the treatment outcome at 24 months or any earlier definite outcome (table 3).

Cure with at least five negative cultures in the last 12 months of treatment was reached in two cases. Treatment completion with one to four negative cultures was reached in 27 cases. Treatment completed, defined as ending treatment after the duration intended by the treating physician, was reached in ten cases, after a median duration of 18 months (range of 4–19 months). These two categories of "favourable" outcomes together made up 39 cases (76.4%).

There were two deaths, one due to disseminated TB in 2004 and one due to TB meningitis in 2007. Each occurred after four weeks of antituberculosis treatment not covering MDR while drug susceptibility results were still pending.

There were no bacteriological treatment failures. Treatment of two cases was terminated early, at 12 months, owing to adverse drug effects. In one patient with TB of cervical lymph nodes, treatment for MDR was interrupted after one month owing to a pregnancy.

Four patients were classified as treatment defaulters: one never started treatment, and the others stopped on their own after 4, 8, and 21 months of MDR treatment.

Two patients were to continue treatment abroad after two and four months, but no information on their outcome became available. For another patient, no information was available, as the treating physician did not participate in the study.

The 39 (76.5%) patients with a favourable outcome (often categorised as "treatment success"), defined as the sum of "cured" patients and patients with "treatment completed", were compared with the 12 (23.5%) other outcomes (unfavourable and potentially unfavourable) by means of a logistic regression model. None of the factors age, sex, origin, previous TB treatment, time lapse to initiation of MDR treatment, resistance pattern, and classes of second-line drugs used was identified as being predictive for an un-

favourable outcome. Outcomes tended to be more favourable in patients diagnosed from 2008 onward (15/16 vs 24/35 before 2008).

The median duration of favourable ("successful") MDR treatments was 18 months (mean 17.5, range 4–26, n = 39). Six successfully treated patients had an MDR treatment of 12 months or less. The patient with only four months of MDR treatment had initially received three months of first line treatment. The median duration of favourable ("successful") MDR treatments with at least one negative culture in the last 12 months was also 18 months (mean 18.1, range 7–26, n = 29).

Beyond the follow-up time of two years, late recurrent disease was reported to the surveillance system six years later in the patient who had stopped treatment after one month due to a pregnancy. This second treatment episode was not included in the study. It remained the only recurrent case (last data check in February 2014).

Discussion

Main findings

In this cohort of all MDR-TB cases reported in Switzerland over 7.5 years, favourable outcomes were seen in three out of four patients. Two deaths occurred before the start of MDR treatment. Default from treatment was rare and there were no treatment failures with positive cultures at the end of treatment.

Median treatment duration was 18 months, which is shorter than the duration currently recommended by WHO. Some patients received only a few months (e.g. four, seven or nine) of MDR treatment before the treating physicians de-

Table 2: Susceptibility test results at diagnosis (n = 51).

	Number of strains tested	Number of resistant strains	Concentrations defining resistance (mg/l)*
First-line antituberculosis drugs			
Isoniazid	51	51	>0.1
Rifampicin	51	51	1.0
Ethambutol	51	29	5
Pyrazinamide	50	27	100
Streptomycin	51	42	1
Second-line antituberculosis drugs			
Second-line injectable (any)	50	5	
Amikacin	50	5	1
Kanamycin	0	0	n.a.
Capreomycin	34	1	5
Fluoroquinolone (any)	51	6	
Moxifloxacin	28	6	0.5
Ofloxacin	46	6	2
Levofloxacin	4	0	1
Ethionamide	49	28	1.25 mg/l (2.5 mg/l from November 2007 onward, for 20 cases tested)
Cycloserine	36	18	50
Linezolid	37	7	0.4
Para-Aminosalicylic Acid	37	19	4
Rifabutin	31	29	0.1

* For 7 strains, test concentrations for second-line drugs were not known. For one strain, the isoniazid test concentration was only known at 0.1 mg/l.

Table 3: Treatment outcomes at 24 months after start of MDR treatment (or any definite endpoint reached before).

Outcome	**Definition [12]**	**n (%)**	**Notes**
Cure	≥5 negative cultures in last 12 months of treatment	2 (3.9%)	
Treatment completed after the intended duration	1–4 negative cultures in last 12 months of treatment No documentation of negative culture	27 (52.9%) 10 (19.6%)	End of treatment decided by the treating physician was taken as a proxy for intended duration.
Death	Due to any reason during treatment	2 (3.9%)	Both deaths were due to TB and occurred before start of MDR treatment*.
Failure	More than 1 culture of the final 5 positive or any of the final three cultures positive. Treatment stopped due to adverse events	0 (0%) 3 (5.8%)	2 stops due to adverse drug effects, 1 due to pregnancy
Default from treatment (lost to follow-up)	Interruption of treatment for >2 months	4 (7.8%)	1 patient defaulted before the start of TB treatment*
Transfer out	Transfer abroad and no information available on outcome	2 (3.9%)	
No result known	–	1 (1.9%)	Non-participation of treating physician
Total		**51 (100%)**	

* MDR cases who died or were lost to follow-up before start of MDR treatment remained in the cohort for analysis (contrary to [12] and [15], but in line with [13])

clared them successfully treated. All patients received a fluoroquinolone, but only three out of four received a second-line injectable drug. Linezolid was used in more than one-third of patients.

Most of the MDR cases were foreign born, diagnosed after a median stay of one year in Switzerland, and many of them were asylum seekers or refugees. Geographical origins varied, but the Horn of Africa, the countries of the former Soviet Union and Tibet made up one half of the cases. Only two cases can reliably be attributed to transmission in Switzerland.

Resistance to other first-line (pyrazinamide and/or ethambutol) and to second-line antituberculosis drugs was frequent, with approximately one of five strains either resistant to fluoroquinolones or to injectable drugs. However, no strain was resistant to both of the latter classes, so that none fulfilled the definition of extensively drug-resistant TB (XDR-TB).

Table 1: Epidemiological baseline data of all 51 MDR-TB cases notified between 01-2003 and 07-2010.

	n = 51
Origin	
Switzerland	5
Asia	18
China (Tibet)	8
Thailand	3
India	2
Mongolia	2
Viet Nam	1
Philippines	1
South Korea	1
Africa	13
Somalia	4
Ethiopia	3
Eritrea	1
Sudan	1
Angola	1
DR Congo	1
Cameroon	1
Ivory Coast	1
Former Soviet Union	8
Russia	3
Ukraine	1
Georgia	2
Azerbaijan	1
Armenia	1
South-eastern Europe	4
Romania	1
Serbia	1
Kosovo	1
Turkey	1
Latin America	3
Brazil	1
Dominican Republic	1
Ecuador	1
Sex	
Male	27
Female	26
Previous history of TB treatment	
Yes	12
No	24
Unknown	15
Localisation of disease	
Pulmonary	44
Sputum smear positive	25
Sputum smear negative	7
Sputum smear unknown	12
Concomitant extrapulmonary localisations:	8
Disseminated	2
Abdominal	2
Pleural	3
Intrathoracic lymphatic	1
Extrapulmonary only	7
Meningeal	1
Spinal	1
Other osteoarticular	1
Pleural	1
Extrathoracic lymphatic	3

Previous work

Treatment results for MDR-TB in Switzerland have been published for a series of 20 cases of one clinic in the period 1986 to 2001 [16]. In that series, 18 cases were of foreign origin, six of Tibetan ethnicity. A retrospective assessment from the text, using the same outcome criteria as in the present study, shows successful outcomes in 14 of 20 cases. In countries of the European Union with more than 50 cases of MDR in 2009, the proportion of successful outcomes varied between 16% of 624 cases in Romania and 75% of 60 cases in the United Kingdom [17]. In a meta-analysis of studies worldwide, treatment success was higher (69%) when treatment was longer than 18 months and administered under direct observation throughout the entire treatment period compared to shorter treatments and/or without directly observed treatment (58%) [10]. Another worldwide meta-analysis reported a pooled success in 62% [11]. Treatment success was 70% in Latvia in 2004 [18]. In a region of Bangladesh, a highly noted observational study designed to minimise failure and default under routine conditions reached relapse-free cure in 89% with a nine-month regimen among more than 200 patients [19].

A combination of drugs aims at curing the patient and preventing further amplification of drug resistance. In Switzerland, no standardised regimen for MDR has been recommended. As some drugs have to be individually procured from abroad, the choice of the treatment regimen may be influenced by logistical reasons. Treatment regimens basically complied with WHO recommendations, individually adapted according to drug susceptibility results. In published studies, the use of injectable drugs, later-generation fluoroquinolones (levofloxacin, gatifloxacin, or moxifloxacin) and prothionamide/ethionamide is associated with favourable outcomes [9]. The Bangladesh study compared six different standardised regimens in consecutive cohorts of patients. A minimum of nine months of treatment were finally advocated, with gatifloxacin, clofazimine, ethambutol and pyrazinamide throughout the treatment period, supplemented by prothionamide, kanamycin and high-dose isoniazid during the initial phase of a minimum of four months [19]. The Union (International Union against Tuberculosis and Lung Disease) currently proposes this regimen in its guidelines [13]. In WHO recommendations, high-dose isoniazid and clofazimine rank low, but cycloserine is included in standard treatments [20]. There are published observations on the effectiveness of linezolid but the drug is associated with a high risk of adverse effects [21, 22]. MDR treatments in Switzerland have included fluoroquinolones as recommended in current guidelines, but second-line injectable drugs have not been used consistently.

The long duration of treatment for MDR-TB primarily aims at preventing relapses after the end of treatment. The optimal duration has never been established in clinical trials, contrary to drug-susceptible TB [23, 24]. WHO has been recommending a duration of at least 21 months since 1996, 24 months since 2008, and currently recommends at least 20 months, including eight months of an injectable second-line drug during the initial phase of treatment. The actual duration should depend on the time to smear and culture conversion [20]. The worldwide meta-analysis of individual data of 9,153 MDR patients favoured such a long duration [9]. Other guidelines propose shorter treatment durations [13]. The regimen of a minimum of nine months in Bangladesh preliminarily showed no relapses over two years of observation after treatment [19].

Methodological issues

There is no mandatory follow-up to establish the treatment outcomes of TB patients in Switzerland. Nevertheless, information on the main outcome became available for all but one patient. Contrary to other studies that consider only patients starting treatment for MDR, the full cohort of MDR patients was included in the outcome analysis. Three of 51 patients never started treatment and were classified as unsuccessful outcomes.

This retrospective part of the study, starting in 2009 to assess outcomes of cases diagnosed in 2003, could introduce some information bias compared to collecting data from providers of MDR treatment at exactly two years after diagnosis.

Cure for patients with MDR-TB was defined according to established standards at the time of the data collection [12]. As in many other settings, the number of negative cultures was lower than in the standard definition for cure [12]. In 2013, the WHO definitions had changed, and three negative cultures now define cure [15]. Usually, the proportion of patients with a successful outcome (defined as the number of patients with cure and treatment completion) lends itself for the comparison of studies. Even the duration of treatment in patients having completed treatment, however, leaves room for interpretation as the intended duration may be varied according to the clinical course. For instance, in our study, the shortest "completed treatment" was four months of MDR treatment for pulmonary and pleural TB after three months of first-line treatment. This may only technically constitute a favourable outcome due to the classification based on the judgment of the treating physician (despite too short a treatment by any standard) without the possibility of a longer follow up. Likewise, on the other hand, a patient spontaneously stopping treatment after 21 months qualifies as a "defaulter from treatment" although he is unlikely to relapse.

No patient failed bacteriologically. A single late recurrence six years after abandoning treatment after one month was recorded in the surveillance system up to February 2014. However, recurrent cases would have been missed if patients had moved abroad before relapsing. Nevertheless, it can be concluded that treated MDR patients do not continue to pose a public health problem. A study with a mean follow up of 5.7 years has found 0.75 relapses per 100 person-years of follow up after successful treatment [25].

None of the factors studied in a logistic regression model was significantly associated with unfavourable outcomes. This may be due to the small numbers in this study.

What does it mean for practice?

Two groups of patients can be distinguished in this cohort: (1) those with immediate initiation of an appropriate treatment including second-line drugs based on clinical suspicion and/or molecular drug susceptibility test results, and (2) those with a delay of several weeks pending results of drug susceptibility testing based on liquid or solid cultures and who temporarily received inadequate antituberculosis treatment. Delay until the diagnosis of MDR-TB and initiation of appropriate treatment is a problem and may have contributed to two deaths. Delays in starting treatment for MDR can also potentially increase drug resistance [26, 27]. In our study, half of the strains tested were also resistant to pyrazinamide and 19 out of 50 were resistant to all four first-line drugs so that for weeks only one active drug or none at all was given in some patients. Phenotypic drug susceptibility testing takes several weeks to obtain a result, even if liquid culture systems are used. Genotypic testing for rifampicin resistance should be used whenever a patient originates from a region with a high prevalence of MDR or has a history of previous TB. While a prior TB treatment is a risk factor for MDR in a patient, half of MDR-TB cases worldwide now occur in patients without a history of prior TB treatment [28]. In the present study, the great majority had no such history and MDR was suspected because of origin or, more rarely, a history of contact with a case of MDR-TB.

Improvements seen over the course of the period may be due to experience gained by all actors involved in the healthcare system, as shown by the increasing use of injectable second-line drugs (data for this trend not shown) in line with the 2008 WHO guidelines and a higher proportion of successful outcomes. The Swiss Lung Association (www.tbinfo.ch) has improved access to second-line drugs through regular updates of the list of procurement channels. Transmission of MDR-TB was seemingly limited to close contacts in family and school settings. Transmission may be somewhat underestimated due to cross-border mobility of immigrants (cases with identical strains can arise abroad) and a short duration of observation by surveillance data.

Conclusion

Based on the results of this study, there is no urgent need to change the current management structure, e.g. by designating one or two clinics where MDR-TB is treated for all of Switzerland, despite the limited experience with MDR-TB in the country. A forum for discussion of individual cases among specialists presently exists under the guidance of the Swiss Lung Association. For the management of patient adherence, including referrals and transfers from one canton to another, public health authorities are to maintain a TB network across cantons.

Compared to many countries, the availability of resources, including most second-line drugs, a generally high standard of health care and a limited number of patients appear to fa-

cilitate satisfactory results in the absence of a special MDR treatment programme. The future availability of new drugs (bedaquiline and delamanid) may further improve treatment of MDR [29–31].

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References

1 World Health Organization. Global Tuberculosis Report 2013. WHO/HTM/TB/2013.11.

2 Zignol M, van Gemert W, Falzon D, Sismanidis C, Glaziou P, Floyd K, et al. Surveillance of anti-tuberculosis drug resistance in the world: an updated analysis, 2007–2010. Bull World Health Organ. 2012;90(2):111–119D.

3 Zhao Y, Xu S, Wang L, Chin DP, Wang S, Jiang G, et al. National survey of drug-resistant tuberculosis in China. N Engl J Med. 2012;366(23):2161–70.

4 Skrahina A, Hurevich H, Zalutskaya A, Sahalchyk E, Astrauko A, Hoffner S, et al. Multidrug-resistant tuberculosis in Belarus: the size of the problem and associated risk factors. Bull World Health Organ. 2013;91(1):36–45.

5 Office fédéral de la santé publique. La tuberculose en Suisse 2005–2011. Bulletin OFSP 2013;21:343–53.

6 Minion J, Gallant V, Wolfe J, Jamieson F, Long R. Multidrug and extensively drug-resistant tuberculosis in Canada 1997–2008: demographic and disease characteristics. PLoS One. 2013;8(1):e53466.

7 Caminero JA, Sotgiu G, Zumla A, Migliori GB. Best drug treatment for multidrug-resistant and extensively drug-resistant tuberculosis. Lancet Infect Dis. 2010;10(9):621–9.

8 Helbling P, Medinger C, Altpeter E, Raeber PA, Beeli D, Zellweger JP. Outcome of treatment of pulmonary tuberculosis in Switzerland in 1996. Swiss Med Wkly. 2002;132(35-36):517–22.

9 Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, et al. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLoS Med. 2012;9(8):e1001300.

10 Orenstein EW, Basu S, Shah NS, Andrews JR, Friedland GH, Moll AP, et al. Treatment outcomes among patients with multidrug-resistant tuberculosis: systematic review and meta-analysis. Lancet Infect Dis. 2009;9(3):153–61.

11 Johnston JC, Shahidi NC, Sadatsafavi M, FitzGerald JM. Treatment outcomes of multidrug-resistant tuberculosis: a systematic review and meta-analysis. PLoS One. 2009;4(9):e6914.

12 Laserson KF, Thorpe LE, Leimane V, Weyer K, Mitnick CD, Riekstina V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005;9(6):640–5.

13 Caminero JA, ed. Guidelines for clinical and operational management of drug-resistant tuberculosis. Paris, France: International Union Against Tuberculosis and Lung Disease; 2013.

14 Bottger EC. The ins and outs of Mycobacterium tuberculosis drug susceptibility testing. Clin Microbiol Infect. 2011;17(8):1128–34.

15 World Health Organization. Definitions and reporting framework for tuberculosis – 2013 revision. WHO/HTM/TB/2013.2.

16 Gimmi R, Pfyffer GE, Brändli O. Tuberculose multirésistante – guérissable en Suisse. Forum Med Suisse. 2003;4:80–90.

17 European Centre for Disease Prevention and Control. Tuberculosis surveillance and monitoring in Europe 2013. European Centre for Disease Prevention and Control; Stockholm, 2013.

18 Leimane V, Dravniece G, Riekstina V, Sture I, Kammerer S, Chen MP, et al. Treatment outcome of multidrug/extensively drug-resistant tuberculosis in Latvia, 2000–2004. Eur Respir J. 2010;36(3):584–93.

19 Van Deun A, Maug AK, Salim MA, Das PK, Sarker MR, Daru P, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med. 2010;182(5):684–92.

20 World Health Organization. Guidelines for the programmatic management of drug-resistant tuberculosis – 2011 update. WHO/HTM/TB/2011.6.

21 Lee M, Lee J, Carroll MW, Choi H, Min S, Song T, et al. Linezolid for treatment of chronic extensively drug-resistant tuberculosis. N Engl J Med. 2012;367(16):1508–18.

22 Yew WW, Lange C, Leung CC. Treatment of tuberculosis: update 2010. Eur Respir J. 2011;37(2):441–62.

23 Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946-1986, with relevant subsequent publications. Int J Tuberc Lung Dis. 1999;3(10 Suppl 2):S231–S279.

24 Mitchison D, Davies G. The chemotherapy of tuberculosis: past, present and future. Int J Tuberc Lung Dis. 2012;16(6):724–32.

25 Leung EC, Yew WW, Leung CC, Leung WM, Tam CM. Shorter treatment duration for selected patients with multidrug-resistant tuberculosis. Eur Respir J. 2011;38(1):227–30.

26 Cox HS, Niemann S, Ismailov G, Doshetov D, Orozco JD, Blok L, et al. Risk of acquired drug resistance during short-course directly observed treatment of tuberculosis in an area with high levels of drug resistance. Clin Infect Dis. 2007;44(11):1421–7.

27 van der Werf MJ, Langendam MW, Huitric E, Manissero D. Multidrug resistance after inappropriate tuberculosis treatment: a meta-analysis. Eur Respir J. 2012;39(6):1511–9.

28 Royce S, Falzon D, Van WC, Dara M, Hyder K, Hopewell P, et al. Multidrug resistance in new tuberculosis patients: burden and implications. Int J Tuberc Lung Dis. 2013;17(4):511–3.

29 Gler MT, Skripconoka V, Sanchez-Garavito E, Xiao H, Cabrera-Rivero JL, Vargas-Vasquez DE, et al. Delamanid for multidrug-resistant pulmonary tuberculosis. N Engl J Med. 2012;366(23):2151–60.

30 Diacon AH, Donald PR, Pym A, Grobusch M, Patientia RF, Mahanyele R, et al. Randomized pilot trial of eight weeks of bedaquiline (TMC207) treatment for multidrug-resistant tuberculosis: long-term outcome, tolerability, and effect on emergence of drug resistance. Antimicrob Agents Chemother. 2012;56(6):3271–6.

31 Diacon AH, Dawson R, Hanekom M, Narunsky K, Venter A, Hittel N, et al. Early bactericidal activity of delamanid (OPC-67683) in smear-positive pulmonary tuberculosis patients. Int J Tuberc Lung Dis. 2011;15(7):949–54.