d | Highly successful treatment outcome of multidrug-resistant tuberculosis in the Netherlands, 2000-2009

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Summary

SETTING: Simultaneous resistance to the two key anti-TB drugs isoniazid (INH) and rifampin (RMP) characterizes multidrug-resistant tuberculosis (MDR-TB). MDR-TB is a scourge requiring toxic, prolonged treatment and is associated with poor outcome. The Netherlands is a country with a long-standing intertwined well-resourced TB service where all patients have a culture-confirmed diagnosis in a central reference laboratory.
OBJECTIVES: To assess treatment outcomes of MDR-TB patients over a period of ten years in The Netherlands.
DESIGN: Demographic, clinical and microbiological features of all patients with MDR-TB that started treatment in 2000-2009 in the Netherlands were analyzed, using national registry and patient records.
RESULTS: Characteristics of the 113 patients with MDR-TB were: M/F ratio 1.57; 96% foreign born; median age 29 yrs; 96 (85%) pulmonary TB, 56 (50%) smear-positive sputum; 14 (12%) HIV co-infected. Of the 104 (92%) that started MDR-TB treatment, 86% had a successful outcome using a median of 6 active drugs; 8 had pulmonary surgery. HIV negative status was associated with successful outcome (adjusted OR 2.1; 1.1-3.8).
CONCLUSION: High success rates in MDR-TB were achieved with close collaboration of all

stakeholders, reaching targets set for drug-susceptible TB. HIV remained an independent risk factor for unsuccessful treatment outcome.

KEY WORDS: Tuberculosis, Multidrug-Resistant, HIV, public health, microbial sensitivity test, therapeutic drug monitoring, outcome

INTRODUCTION

Multi-Drug Resistant Tuberculosis (MDR-TB) is an emerging epidemic, with 480,000 incident cases estimated annually, most from Eastern Europe, China and India [1-2]. The magnitude of the problem may be much larger, because in many highly TB-burdened areas, drug susceptibility testing is unavailable. The WHO European Region (WER), that includes former Soviet Union states, has the highest MDR-TB burden. Outcome of MDR-TB is generally poor; only 34% of the 2010 MDR-TB cohort in WER completed treatment; and only 48% of MDR-TB cases who started treatment globally in 2010 had a favourable outcome [3]. Studies reporting treatment success of 60-70% [4] therefore do not reflect service conditions [5].

Reports on maximally achievable favourable outcome from affluent countries are scant [6-9]. Follow-up of patients is limited in some studies [8], and selective reporting may result from failing registration systems.

In the Netherlands, with 17 million inhabitants, all TB cases are notified to Municipal Health Authorities with their Public Health TB teams (MHTB) that treat uncomplicated cases, and initiate contact investigation and screening activities. A national Tuberculosis Register (NTR) was maintained by KNCV; in 2012, the National Institute for Public Health and the Environment (RIVM) took over. Two dedicated TB centres provide care for patients with co-morbid and complicated TB, and all patients with MDR-TB are admitted to these units in accordance with the national TB guideline. We report treatment outcomes of MDR-TB in the Netherlands in 2000-2009.

METHODS

Data collection

Retrospective data were collected of all patients diagnosed with MDR-TB between January 2000 and December 2009. Patients diagnosed before, but starting therapy during the study period, were also included; patients diagnosed in 2009, but starting therapy in 2010, were excluded. MHTB physicians and pulmonologists were approached to follow-up MDR-TB patients and ascertain that they were either well, without symptoms suggesting absence of relapse; or had relapsed, had defaulted or deceased; and if so, from TB or any other cause. Data on all TB patients with *Mycobacterium tuberculosis* complex

culture confirmation were obtained from the NTR. Follow-up after treatment completion was either by the TB centres, the attending physician or the municipal health authorities.

Bacteriology including drug susceptibility testing (DST)

Demographic and clinical data on previous TB treatment, microbiology, hospitalization, drugs used, and outcome were retrieved from the two TB centres and the MHTB.
All *M. tuberculosis* isolates were submitted to the RIVM for identification and DST; the absolute concentration method was used for most second-line TB drugs; for moxifloxacin and linezolid three different concentrations were tested to assess the minimal inhibitory concentration (MIC).

MDR-TB treatment and monitoring of adverse effects (AE)

TB drug combinations were individually tailored. Treatment history, age, co-morbidities and co-infections (hepatitis B and C, HIV) were recorded. DST results and previous TB treatment were considered in designing treatment regimens. As a rule, treatment was continued for 18 months – and at least 12 months after (sputum) culture converted. Sputum conversion was defined as > 2 consecutive negative cultures performed at least 4 weeks apart. In the framework of ongoing studies, several patients had pharmacokinetic (PK) measurements and dosages were adjusted according to PK and MIC results [10-11].

Nursing staff of the two TB centres directly supervised treatment; specialised nurses from the MHTB continued Directly Observed Therapy (DOT) after discharge if necessary, or less stringent forms of adherence support if feasible. To monitor AE, regular laboratory tests for renal and liver injury, and monthly audiometry and ophthalmological assessments were made. AE were scored if medication was interrupted, stopped or the dosing adjusted.

The time to sputum conversion during MDR-TB treatment was defined as the time from the start of MDR-TB treatment to the time of collection of the first in a series of two or more consecutive negative culture results, at least 4 weeks apart.

Definitions

MDR-TB was defined as TB caused by *M. tuberculosis* complex isolates that are resistant to at least INH and RMP [1, 12, 13]. XDR-TB is defined by *M. tuberculosis* isolates resistant to INH, RMP, and to any of the tested fluoroquinolones (ciprofloxacin, ofloxacin, levofloxacin or moxifloxacin) and to at least one of three injectable second-line drugs (amikacin, capreomycin or kanamycin). INH, RMP, ethambutol, pyrazinamide and streptomycin were considered 1st line drugs.

The WHO standard definitions were also used to define treatment outcome: completion, cure, death during treatment, failure, default and transferred out [12-15].

Patients were categorized as either previously treated or treatment-naïve. Previous treatment was defined as a history of TB treatment for > 4 weeks. Delay was defined as the number of days between the start of 1st line TB treatment assuming drug-susceptible TB and start of MDR-TB treatment, an indirect measure for a cumulative delay caused by the time to *M. tuberculosis* culture positivity, for the time to report DST results, and for health care providers to start appropriate therapy.

Ethics

As this study was a chart review, no ethical approval was needed under Dutch law (WMO).

Statistical Analysis

For comparison of categorical variables, we used X^2 test with continuity correction or 2-sided Fisher exact test as appropriate. For comparison of the mean diagnostic delays, we used the Mann-Whitney U test. Bivariate logistic regression was performed to assess characteristics associated with MDR-TB among all culture-confirmed TB patients. Variables with a p-value <0.25 were considered for inclusion in multivariable modelling. By backward elimination, the most parsimonious model was selected through -2 log likelihood testing. A P value < 0.05 was considered statistically significant. For all statistical analysis we used SPSS version 20 (SPSS Inc., Chicago, Ill, USA).

RESULTS

Demographic and clinical characteristics

Of the 113 MDR-TB patients diagnosed during the study period, 5 (4.4%) patients were Dutch, 12 (10.6%) came from other European countries, 49 (43.4%) from Africa, 42 (37.2%) from Asia and five patients (4.4%) from elsewhere (Table 1); 66 (58.4%) of the patients had immigrated to the Netherlands < two years before diagnosis. Median age at diagnosis was 29 (IQR: 24-37) years; 37 (32.7%) were detected by active case finding (contact investigation or screening). Pulmonary TB was detected in 96 (85.0%) of the patients, 56 (58.9%) were sputum smear microscopy positive and another two tested positive in broncho-alveolar lavage (BAL) microscopy; 17 patients (15.0%) had extra-pulmonary TB only; 35 (31%) had previous TB treatment; 14 (12.4%) patients were co-infected with HIV.

Table 1 provides details of culture-confirmed MDR and non-MDR-TB cases. MDR-TB cases were typically in age group 15-29 years, foreign-born, and < 2 years resident in the Netherlands. MDR-TB cases were more often identified by active case finding than non-MDR-TB cases. MDR-TB cases had more often pulmonary disease, a history of TB treatment and were more often HIV co-infected. In multivariate analysis, MDR-TB cases were less often > 45 years, more often were born in other European countries, Asia or Africa, had a

duration of stay in the Netherlands < 2 years, had pulmonary disease, a history of previous TB treatment, and HIV co-infected.

Of the 113 patients (M:F: 69 : 44), 104 were treated for MDR-TB - nine patients never started MDR-TB treatment: two were asylum seekers who had to leave the country before Immigration Authorities were notified about their disease status. One asylum seeker could not be traced, two immigrant MDR-TB cases had already returned to their home country when DST results became available. In a 9-year old child with TB lymphadenitis clinicians decided not to start MDR-TB treatment, because the lymph node almost completely regressed after three months standard TB treatment by the time DST results became available; the child was closely monitored thereafter. Three patients were only diagnosed with MDR-TB post-mortem.

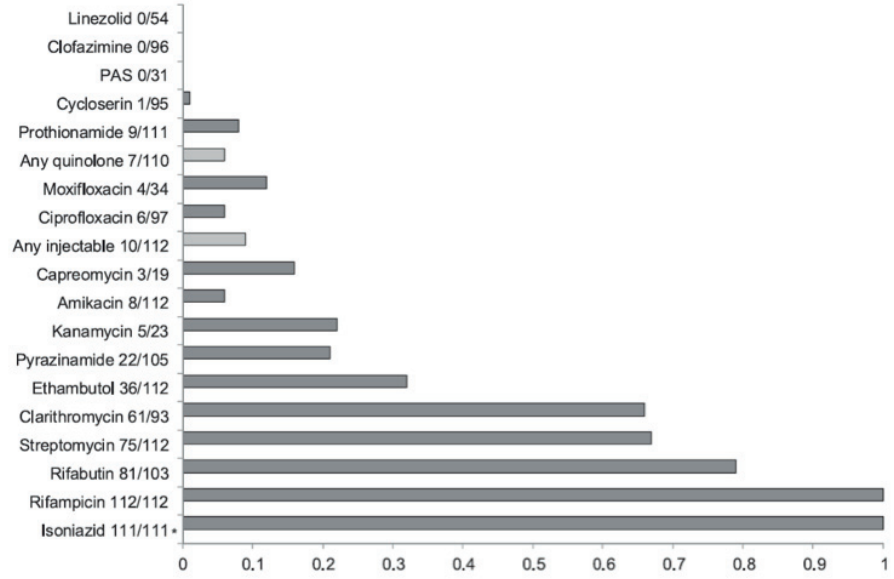

FIGURE 1 In vitro drug resistance of *M. tuberculosis* isolates of patients with MDR-TB in the Netherlands, 2000–2009.* One isolate of a rifampicin-resistant case had an inhA mutation; however, drug susceptibility against isoniazid could not be determined and the case was considered as MDR-TB. PAS¼para-aminosalicylic acid; MDR-TB¼multidrug-resistant tuberculosis.

Drug resistance patterns

Figure A shows the drug susceptibility test results for 112 of the 113 MDR-TB patients. The remaining case was clinically and epidemiologically diagnosed with MDR-TB based on documented exposure to a relative with MDR-TB, but without culture confirmation. *M. tuberculosis* isolates were resistant to median 5 drugs (IQR: 4-5, maximum 10); see Figure 1.

In the first four years of the study period, isoniazid was prescribed in 15 patients because of a positive in vitro catalase reaction, suggesting that some of the organisms were still isoniazid-susceptible; later this practice was abandoned; no high-dose isoniazid was prescribed. Fifteen (14.3%) of 105 isolates tested for all first-line agents - from the total pool of 112 MDR-TB cases - were resistant to all first-line TB drugs. Of 103 MDR isolates, 22 (21.4%) tested susceptible to rifabutin; the rifabutin-susceptible strains were predominantly identified in the first few years of the study period. Ten of 112 MDR isolates (8.9%) were resistant to at least one of the aminoglycosides and 7 of 110 (6.4%) isolates for at least one of the fluoroquinolones. Four (3.6%) fulfilled the criteria for XDR-TB.

TABLE 1 Demographic and disease-related factors of MDR-TB and culture-confirmed non-MDR-TB cases in the Netherlands, 2000–2009

	MDR-TB (n = 113)* n (%)	Culture-confirmed non-MDR-TB (n = 8915) n (%)	OR (95%CI)	aOR (95%CI)†
Demographic factors				
Sex				
Female	44 (38.9)	3605 (40.4)	1	
Male	69 (61.1)	5310 (59.6)	1.1 (0.73–1.6)	
Age, years				
0–14	2 (1.8)	233 (2.6)	0.39 (0.10–1.6)	0.99 (0.24–4.2)
15–29	64 (56.6)	2937 (32.9)	1	1
30–44	36 (31.9)	2639 (29.6)	0.63 (0.42–0.95)	0.71 (0.46–1.1)
45–59	8 (7.1)	1393 (15.6)	0.26 (0.13–0.55)	0.41 (0.19–0.89)
≥ 60	3 (2.7)	1713 (19.2)	0.08 (0.03–0.26)	0.19 (0.06–0.64)
Country or region of birth				
The Netherlands	5 (4.4)	2588 (29.0)	1	1
Rest of Europe	12 (10.6)	468 (5.2)	13.7 (4.6–37.8)	4.1 (1.3–12.2)
Asia	42 (37.2)	1967 (22.1)	11.1 (4.4–28.0)	4.8 (1.8–13.0)

	MDR-TB (n = 113)* n (%)	Culture-confirmed non-MDR-TB (n = 8915) n (%)	OR (95%CI)	aOR (95%CI)†
Africa	49 (43.4)	3165 (35.5)	8.0 (3.2–20.1)	3.0 (1.1–7.9)
Americas and Oceania	5 (4.4)	727 (8.2)	3.6 (1.0–12.3)	1.2 (0.28–5.2)
Arrived in the Netherlands <2 years				
No	44 (38.9)	7114 (79.8)	1	1
Yes	66 (58.4)	1718 (19.3)	6.2 (4.3–9.1)	2.9 (1.9–4.5)
Unknown	3 (2.7)	83 (0.9)	5.8 (1.8–19.2)	14.6 (2.9–72.6)
Disease-related factors				
Active case finding				
Yes (contact investigation/ screening)	37 (32.7)	1471 (16.5)	2.5 (1.7–3.7)	
No	76 (67.3)	7444 (83.5)	1	
Site of tuberculosis				
Extra-pulmonary TB	17 (15.0)	2875 (32.2)	1	1
PTB	96 (85.0)	6040 (67.8)	2.7 (1.6–4.5)	2.4 (1.4–4.1)
PTB sputum smear-positive	56 (58.9)	3465 (48.6)		
PTB BAL microscopy-positive	2 (2.1)	530 (10.8)		
PTB sputum/BAL microscopy-negative	38 (40.0)	2575 (42.6)		
Previous history of anti-tuberculosis treatment				
Yes	35 (31.0)	361 (4.0)	10.6 (7.0–16.1)	9.5 (6.1–14.9)
No or unknown	78 (69.0)	8554 (96.0)	1	1
HIV co-infection				
Yes	14 (12.4)	451 (5.1)	2.7 (1.5–4.7)	2.1 (1.1–3.8)
No or unknown‡	99 (87.6)	8464 (94.9)	1	1

* Including one MDR-TB case without culture-confirmation (see text). All MDR-TB isolates were *Mycobacterium tuberculosis*, except for one isolate identified as *M. bovis*.
† Including adjustment for year of diagnosis (not shown).
‡ 9 MDR-TB and 7646 non-MDR-TB cases had unknown HIV status.
MDR-TB = multidrug-resistant TB; OR = odds ratio; CI = confidence interval; aOR = adjusted OR; TB = tuberculosis; PTB = pulmonary TB; BAL = bronchoalveolar lavage; HIV = human immunodeficiency virus.

Treatment

MDR-TB patients received on average 44 days (median 35 days) standard TB treatment prior to MDR treatment; in the period 2000-2004 the median delay in initiating MDR-TB treatment was 45 days (IQR: 28-79), in the period 2005-2009, the delay was reduced to 26 days (IQR: 13-50; P<0.01; data not shown).

Most (95) patients started in-patient MDR-TB treatment in one of the TB centres, according to protocol. Patients were hospitalized for a median of 92 (IQR: 61-154; maximum 512) days.

MDR-TB patients were treated with median six active drugs (IQR: 5-6; range: 3-10), and the regimen almost invariably included an aminoglycoside, initially given daily, but if discharged with this drug, to be continued typically 5d/wk; based on PK and MIC, we typically prescribed 7.5 mg/kg of kanamycin or amikacin bodyweight daily for 6 months) and a fluoroquinolone – usually, moxifloxacin 400mg (Table 2). If susceptible, ethambutol and pyrazinamide were added. Second-line drugs often prescribed were prothionamide/ethionamide, clofazimine 100mg 5-7 d/wk, typically started after cessation of injectables; and linezolid (from 2003 onward; typically 300 mg bid or less as assessed by PK/PD). Prothionamide was the drug most often discontinued due to side effects. Of the 104 patients that started MDR treatment, 43 experienced adverse effects (Table 2).

Eight patients had thoracic surgery (lobectomy or pneumonectomy); three patients underwent pneumonectomy because of persistently positive sputum smears with culture conversion soon after surgery. One patient needed pleuro-pneumonectomy of a destroyed lung. Two other patients with aspergillomas had a lobectomy after therapy completion; the two others had limited procedures.

Sputum smear microscopy and culture conversion

Sputum smear and cultures were performed weekly during admission. Figure 2A shows time to smear and Figure 2B time to culture conversion; 24 of 55 sputum smear-positive MDR-TB cases (one sputum smear-positive patient died before MDR-TB treatment) had already negative smears at initiation of MDR-TB treatment. In the other 31 cases sputum smear conversion occurred after median 49 days (IQR 25-131 days). Four still had positive smears after 180 days, and converted after 208, 273, 307 and 426 days. Forty-five of 89 culture-positive pulmonary MDR-TB cases had one or more sputum samples culture-positive during treatment, with culture conversion after median 46 (IQR 20-76) days; one patient only converted 280 days after start of treatment.

TABLE 2 Anti-tuberculosis drug treatment and discontinuation of drugs due to side effects for 104 multidrug-resistant cases treated in the Netherlands, 2000–2009

Anti-tuberculosis drugs used	Patients n	Treatment duration, days Mean (min–max)	Median [IQR]	Discontinuation n	Side effects
Isoniazid	15	400 (37–723)	378 [274–548]		
Rifampicin	0				
Ethambutol	68	405 (6–730)	456 [270–548]	2	Visual
Pyrazinamide	55	297 (6–730)	209 [62–546]	6	Gastro-intestinal, joint, liver
Rifabutin	14	394 (263–617)	364 [328–468]		
Amikacin	64	165 (6–549)	165 [89–193]	3	Hearing
Kanamycin	23	147 (47–394)	113 [92–197]	2	Hearing, renal
Capreomycin	3	394 (243–691)	249 [243–243]		
Any injectable	88*	172 (6–691)	160 [92–209]		
Ciprofloxacin	4	218 (56–550)	133 [56–465]	1	Gastro-intestinal
Levofloxacin	43	448 (6–730)	508 [365–549]	1	Gastro-intestinal
Moxifloxacin	57	400 (37–611)	442 [277–548]	2	Neurological, tendon
Any fluoroquinolone	101*	425 (6–730)	485 [364–549]		
Prothionamide	72	323 (6–638)	348 [146–528]	16	Gastro-intestinal, liver, psychiatric
Cycloserine	14	317 (7–598)	360 [129–417]	2	Psychiatric
PAS	3	354 (12–659)	12 [394–394]	1	Gastro-intestinal
Clofazimine	74	343 (7–706)	374 [91–547]	2	Itching, gastro-intestinal
Clarithromycin	8	398 (61–579)	491 [219–529]		
Linezolid	53	99 (12–706)	56 [26–91]	5	Renal dysfunction, hearing
Cotrimoxazole	4	341 (90–502)	386 [155–482]		
Thiacetazone	7	153 (7–357)	116 [8–314]		
Doxycyclin	2	27 (26–27)	27 [26–26]		

* Two patients switched between injectables, three patients switched between fluoroquinolones.
IQR = interquartile range; PAS = para-aminosalicylic acid.

TABLE 3 Treatment outcome of all MDR-TB cases diagnosed and of those who started drug treatment, The Netherlands, 2000–2009

	All MDR-TB cases (n = 113)* n (%)	Cases who started MDR-TB treatment in the Netherlands (n = 104) n (%)
Favourable outcome	89 (78.8)	89 (85.6)
Cured	47 (41.6)	47 (45.2)
Completed	42 (37.2)	42 (40.4)
Unfavourable outcome	24 (21.2)	15 (14.4)
Died	9 (8.0)*	6 (5.8)
Defaulted/stopped	8 (7.1)	8 (7.7)
Transferred out	1 (0.9)	1 (1.0)
Unknown or no treatment	6 (8.0)*	

* Nine MDR TB patients did not start MDR-TB treatment (see text).
MDR-TB = multidrug-resistant tuberculosis.

Treatment outcome

Of the 104 MDR-TB patients starting MDR-TB treatment, 85.6% had favourable outcome (Table 3); of the total of 113 patients diagnosed with MDR-TB, 78.8% had successful treatment outcome. Only 7 out of 14 (50%) HIV-infected MDR-TB patients completed treatment (5 died during treatment and 2 defaulted/stopped treatment; 91.1% of MDR-TB patients with negative or unknown HIV status completed treatment ($p < 0.01$).

The median duration of treatment was 445 days. For those completing treatment, treatment lasted median 18.2 months or 546 (IQR: 424-549; range 183-730) days.

Only 28 of 98 patients were consistently followed up for at least 24 months; 28 patients had zero follow-up days after treatment discontinuation or completion, mainly because they left the country. One patient died during the follow-up period. No relapses were observed.

After completion, one patient still had arthritis due to pyrazinamide, one other had visual impairment (ethambutol), and two had symptomatic bronchiectasis.

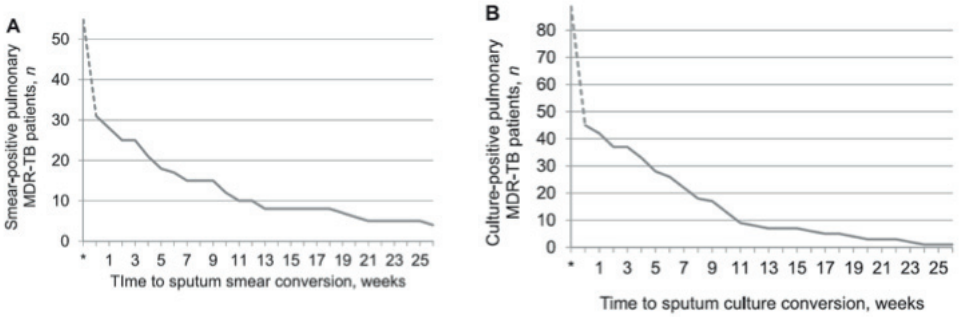

FIGURE 2 A) Time to smear microscopy conversion during MDR-TB treatment in the Netherlands, 2000–2009. The survival curve shows the time to smear conversion of 31 patients with a positive smear at the start of MDR-TB treatment. An additional 24 patients had one or more positive smears at the start of drug-susceptible anti-tuberculosis treatment, but negative smears at the start and throughout MDR-TB treatment (shown with dashed line).

FIGURE 2 B) Time to culture conversion during MDR-TB in the Netherlands, 2000–2009. The survival curve shows the time to culture conversion of 45 patients with culture-positive smear at the start of MDR-TB treatment. An additional 44 patients had 71 positive cultures at the start of drug-susceptible anti-tuberculosis treatment but negative cultures at the start and throughout MDR-TB treatment (shown with dashed line). * Before MDR-TB treatment. MDR-TB = multidrug-resistant tuberculosis.

DISCUSSION

Here, we show that MDR-TB can be cured in the vast majority of cases treated in The Netherlands. This high success rate is the compound result of many different factors. With our data we are unable to determine the relative contribution of each individual component: adequate drug combination; DST performed in a well-coordinated fashion in a central reference laboratory; drug treatment tailored to DST and PK; TB centres and MHTB workers that apply DOT; a well-coordinated TB program; and a well-resourced setting.

Using all of these components, we show that outcome in the 104 MDR-TB patients (including four patients with XDR-TB) were equal to targets set for drug-susceptible TB: 85.6 % of the patients that started treatment achieved a favourable outcome (i.e., cured or completed treatment). Outcome was similar in the two decades preceding the current study period [16]. A recently published meta-analysis provides evidence that drug susceptibility-targeted therapy provides added value for survival [17]. These results were achieved in patients with significant physical and psychiatric co-morbidities and language and cultural barriers, and with considerable input of human and financial resources.

Treatment duration is the major challenge for case holding. The updated 2011 WHO guidelines [1, 14] suggest extending the minimum duration of treatment by two more months, as improved treatment success has been associated with the longer treatment duration of MDR-TB 18. Intensive phase of treatment should therefore last at least 8 months, and total duration of treatment should be extended to 20 months. The duration may be adjusted for some patients based on their clinical and bacteriologic response. Studies from Bangladesh 19 and Niger 20 suggest that fluoroquinolone-based treatment of MDR-TB might be shortened under specific circumstances to 9-12 months, well below the target currently set for MDR-TB at 20 months [1, 15]. Although treatment was typically individually tailored and based on DST results for second line drugs, many patients received linezolid [10,21] which is now considered a powerful WHO group 5 drug; and clofazimine, which has been associated with improved outcome [22-23], possibly because of its activity against *M. tuberculosis* persisters [24-25]. The added value of rifabutin prescribed to a minority of our patients, and the regular dose-INH to those with strains showing catalase activity, remains questionable; we largely abandoned these in recent years without apparent loss of efficacy.

Our results contrast with most of reported series from well-resourced settings [6-9] and even more to reports reflecting service conditions [1, 5]. Collaboration of all stakeholders may be the key to this success. Public-private collaborations are important to improve TB outcome [1,15,18].

Current guidelines for MDR-TB treatment have low level of evidence, and controversies remain [18], e.g., on the number of anti-TB drugs required, duration of (parenteral) drug administration, standardized versus individualised regimens, and the role of surgery [26]. Indeed, MDR-TB management is predominantly based on observational studies and expert opinion [27]. Our results were obtained without adding any of the new drugs - bedaquiline [28, 29], delamanid [30], sutezolid [28, 31, 32] and pretomanid [28,33].

CONCLUSIONS

With close collaboration of all stakeholders, MDR-TB outcome equalled that of the target for drug-susceptible TB in The Netherlands. Absence of HIV co-infection favoured successful outcome.

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