Multidrug-resistant tuberculosis in Finland: treatment outcome and the role of whole-genome sequencing

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Shareable abstract (@ERSpublications)
In Finland, the success rate of individualised MDR-TB treatment is 74%, despite numerous adverse effects. Whole-genome sequencing could aid in the selection of optimal treatment regimen in the future. https://bit.ly/3fnMYfY

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Abstract

Treatment of multidrug-resistant tuberculosis (MDR-TB) is a global challenge requiring long treatment with costly drugs. We assessed treatment combinations, outcome and the utility of whole-genome sequencing (WGS) in MDR-TB cases.

Clinical, demographic and microbiological data were obtained of all patients with MDR-TB who started treatment in Finland in 2007–2016. Definitions of MDR, pre-extensively drug-resistant (pre-XDR) and XDR tuberculosis were those applicable at the study period. Treatment outcome was defined according to World Health Organization (WHO) guidelines. *Mycobacterium tuberculosis* isolates were analysed by WGS in addition to routinely performed phenotypic drug susceptibility testing and genotyping.

Among the 47 cases, 35 (74%) had a successful treatment outcome. Risk factors for non-successful outcome were Finnish origin and XDR. Almost 90% of our cases had an adverse event for at least one drug. Phenotypic and WGS drug resistance results were fully concordant for isoniazid, fluoroquinolones and amikacin, and >90% concordant for rifampicin, pyrazinamide, kanamycin and capreomycin. >60% of phenotypically ethambutol-susceptible isolates were genotypically resistant. The results of the rifampicin and isoniazid nucleic acid amplification tests (NAATs) performed for the isolates were identical to the WGS results except for three isolates having uncommon resistance mutations not included in the NAATs. WGS did not reveal unexpected clustering.

More training is needed for physicians treating MDR-TB, and especially XDR-TB, to improve treatment outcome. Phenotypic drug susceptibility testing was shown to be unreliable for ethambutol. WGS could aid in the selection of optimal treatment regimen in the future.

Introduction

Multidrug-resistant tuberculosis (MDR-TB) has been defined as strains resistant to the two most effective first-line drugs, rifampicin and isoniazid. Extensively drug-resistant (XDR) strains have additional resistance to at least one fluoroquinolone and one injectable agent, whereas pre-XDR strains have additional resistance to any fluoroquinolone or injectable drug, according to the definition used during our study period. The World Health Organization (WHO) has recently redefined pre-XDR as MDR-TB or rifampicin-resistant tuberculosis (TB) with additional resistance to any fluoroquinolone and has revised the definition of XDR as pre-XDR with additional resistance to bedaquiline and/or linezolid [1].

MDR- and XDR-TB are major challenges that threaten global progress in ending TB epidemics [2]. Currently, the global proportion of rifampicin-resistant TB, mostly MDR-TB, is estimated by WHO as 3% among new TB cases and 18% among previously treated cases, resulting in almost half a million cases

annually [3]. Three countries with the largest share of MDR-TB are India, China and the Russian Federation. The highest proportions of MDR-TB among TB cases are in countries of the former Soviet Union [3]. Despite the situation in our neighbouring countries, TB incidence is low (<5 per 100 000) in Finland, and only a few MDR cases have been reported annually [4, 5].

Successful treatment of MDR-TB necessitates a long treatment period with several second-line drugs, which are less effective, more expensive and cause more adverse events than the first-line drugs. Costs of MDR-TB treatment are much higher than of drug-susceptible TB, about EUR 150 000 *versus* EUR 26 000 per patient in Finland [6]. Treatment success rate for MDR/rifampicin-resistant TB is globally lower than for drug-susceptible TB. In the WHO European region, successful treatment outcome was achieved only in 59% of cases that started with a MDR treatment regimen in 2017 [3]. However, substantially higher treatment success rates, up to 72–86%, have been published from single centres or countries with high resources and individualised treatment regimens [7, 8].

Selecting an effective treatment regimen requires reliable drug susceptibility testing (DST) results. Culture-based phenotypic DST (pDST) takes several weeks and may underestimate the true rate of resistance for certain key drugs [9, 10]. To establish an effective treatment regimen, timely, fast and accurate drug susceptibility data are needed. Whole-genome sequencing (WGS) has been shown to have the best performance for DST among genotypic DST (gDST) methods and can be simultaneously used for characterisation of strains and transmission chains [9, 11].

The aim of the present study was to assess the treatment combinations used and the treatment outcome in MDR-TB cases, and factors potentially associated with non-successful treatment outcome. We also evaluated the role of WGS of MDR strains in DST and cluster analysis.

Methods

Study population and data collection

Our cohort study was based on TB cases registered during 2007–2016 in the National Infectious Diseases Register (NIDR), maintained at the Finnish Institute for Health and Welfare (THL). Physicians, clinical microbiology laboratories and Mycobacterial Reference Laboratory at THL, where DST for all *Mycobacterium tuberculosis* complex isolates is performed, mandatorily notify new *M. tuberculosis* cases to NIDR. Additionally, the national TB guidelines recommend contacting the national advisory group of TB treatment each time a new case with MDR-TB is diagnosed [12]. The advisory group meets every 4 months, and the individualised regimen for the next 4 months is planned for each patient.

This study included all notified MDR-TB cases, except cases that were initially diagnosed outside Finland and did not receive MDR-TB treatment in Finland, or cases diagnosed at autopsy. The register of the advisory group was reviewed to look for additional culture-negative MDR-TB cases not notified to NIDR (figure 1).

Patient records of the study cases were reviewed for epidemiological, clinical, laboratory, treatment and follow-up data. Treatment outcome for all the cases was defined by the study group according to WHO guidelines as cured, treatment completed, treatment failed, died, lost to follow-up (interrupted) or not evaluated (transferred) [13]. Treatment success is the sum of cases with outcomes cured and treatment completed, and other outcomes are classified as non-successful. In addition, treatment outcomes for pulmonary cases were defined according to simplified definitions set by the Tuberculosis Network European Trials group (TBNET) as cured, treatment failed, died, lost to follow-up and undeclared [14]. These criteria include 1 year of follow-up after treatment, and outcome cured is defined as a negative culture status at 6 months after treatment initiation, no positive culture thereafter and no relapses within 1 year after treatment completion (relapse-free cure).

Statistical methods

Analysis of the clinical data was performed using IBM SPSS statistics 25.0 (SPSS Inc., Rochester, MN, USA). Risk factors for non-successful outcome were modelled with R-program (R Core Team version 3.6.2.; R Foundation, Vienna, Austria). p-values <0.05 were considered statistically significant.

Laboratory methods

Culture-positive *M. tuberculosis* complex isolates isolated in Finland were routinely sent to the Finnish Institute for Health and Welfare (THL) for pDST mainly using the MGIT system (Becton, Dickinson and Company, Franklin Lakes, NJ, USA) and genotyping using spoligotyping and MIRU-VNTR (mycobacterial interspersed repetitive unit variable number of tandem repeats) [15–17]. One isolate from

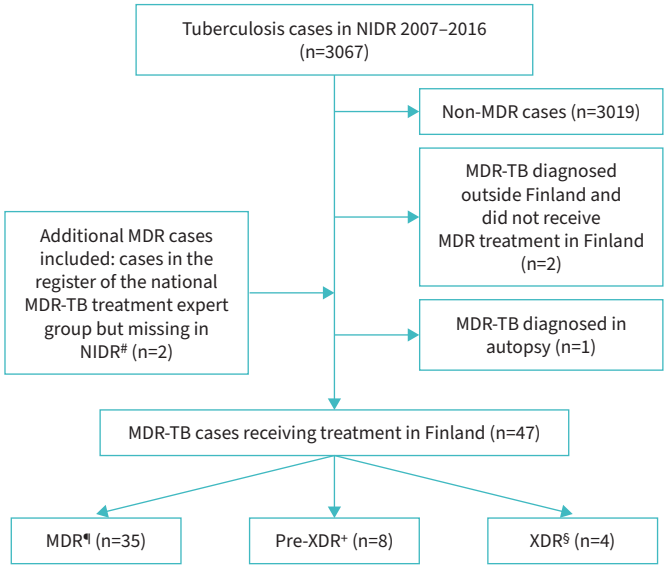

FIGURE 1 Steps in identifying multidrug-resistant tuberculosis (MDR-TB) cases with treatment started in Finland in 2007–2016. NIDR: National Infectious Diseases Register; XDR: extensively drug-resistant. #: culture-negative cases with diagnoses based on radiology as well as 1) a positive nucleic acid amplification test result with rifampicin resistance and 2) a Finnish-born child with interferon-γ release assay (IGRA) positivity and a known exposure to MDR-TB; ¶: strains resistant to rifampicin and isoniazid; +: MDR-TB with additional resistance to any fluoroquinolone or injectable drug; §: MDR-TB with additional resistance to at least one fluoroquinolone and one injectable agent.

each of the 45 culture-positive cases was included in this study. Nucleic acid amplification tests (NAATs) were performed for the primary samples of 25 (53%) cases in the clinical laboratory and for the bacterial isolate of 37 (79%) cases at THL if requested by the treating clinician. For this study, WGS was performed retrospectively for the 45 isolates using the technology of Illumina (San Diego, CA, USA). WGS-based relatedness analysis was performed with the allele-based cgMLST (core genome multi-locus sequence typing) and single-nucleotide polymorphism (SNP) methods on the 2891 loci included in the cgMLST scheme using the Ridom SeqSphere+ software (Ridom GmbH, Münster, Germany). Detailed methods are described in the supplementary material.

Ethics

This was a retrospective cohort study without contact with patients. Therefore, approval by ethics committee and informed consent to participate were not required. Permission for collecting data from national registers and medical records was given by the Finnish Institute for Health and Welfare.

Results

Among the 47 cases, median age was 34 years (interquartile range (IQR) 21–52), and 29 (61.7%) cases were male (table 1). 45 (95.7%) cases were culture-positive. The site of disease was pulmonary in 38 (80.9%) and origin was foreign-born in 33 (70.2%) cases. Two (4.3%) cases were co-infected with HIV, and five (10.6%) cases were immunocompromised for other reasons. Altogether, 14 (29.8%) cases had at least one comorbidity. Eight (17.0%) cases had a previous history of TB.

Laboratory results

NAAT for *M. tuberculosis* complex from the primary sample was positive for 19 (40.4%), negative for six (12.8%) and not performed for 22 (46.8%) cases. The median interval between the first TB sample given and pDST available for the first line, and all tested drugs for each case were 48 (IQR 34–62) and 55 (IQR 46–67) days, respectively. Additional drug resistance was not observed to develop during treatment.

All the isolates included in this study were MDR isolates and thus resistant to rifampicin and isoniazid by pDST. Using WGS, all the sequenced isolates had isoniazid resistance mutations, whereas a rifampicin resistance mutation was not found in one isolate. The results of the rifampicin and isoniazid NAATs

TABLE 1 Risk factors for non-successful outcome among multidrug-resistant (MDR) tuberculosis cases diagnosed and treatment started in Finland in 2007–2016

Variable	All	Successful	Non-successful	Univariate OR (95% CI)	Univariate p-value	Multivariate OR (95% CI)	Multivariate p-value
Subjects	47	35	12				
Age years, median	34	30	38.5				
Age/1 year				1.0 (0.99–1.05)	0.25	1.0 (0.96–1.05)	0.85
Sex							
Male	29	22 (75.9)	7 (24.1)	Ref		Ref	
Female	18	13 (72.2)	5 (27.8)	1.2 (0.3–4.4)	0.76	4.6 (0.79–48.8)	0.09
Origin							
Foreign	33	29 (87.9)	4 (12.1)	Ref		Ref	
Finnish	14	6 (42.9)	8 (57.1)	8.6 (2.2–39.0)	0.002	12.8 (2.0–142.9)	0.006
Site of disease							
Extrapulmonary	9	8 (88.9)	1 (11.1)	Ref		Ref	
Pulmonary	38[#]	27 (71.1)	11 (28.9)	2.4 (0.4–24.1)	0.33	1.5 (0.2–22.1)	0.71
Resistance							
MDR	43	35 (81.4)	8 (18.6)	Ref		Ref	
XDR	4	0 (0)	4 (100)	37.6 (3.5–5167.1)	0.001	62.3 (2.8–12 291.9)	0.006
Immunocompromised[¶]							
No	40	30 (75.0)	10 (25.0)	Ref		Ref	
Yes	7	5 (71.4)	2 (28.6)	1.3 (0.2–6.3)	0.77	3.1 (0.38–27.0)	0.28

Data are presented as n or n (%), unless otherwise stated. Ref: reference; XDR: extensively drug-resistant. [#]: concomitant extrapulmonary tuberculosis n=8 out of 38 (21.1%); [¶]: HIV (n=2), immunosuppressive medication (n=4), uncontrolled diabetes mellitus type 1 (n=1).

performed for the isolates were identical to the WGS results except for three isolates having uncommon resistance mutations that were not included in the NAATs.

In addition to isoniazid, phenotypic and genotypic drug resistance results obtained by WGS were fully concordant for fluoroquinolones and amikacin. All the isolates (n=16) that were phenotypically resistant to ethambutol (EMB) were also found to have a resistance mutation in the *emb*B gene by WGS. However, 18 phenotypically EMB-sensitive isolates also had a resistance mutation in the *emb*B gene. The most common EMB resistance mutation among the isolates with discrepant results was *emb*B Met306Val (n=8, 44.4%), which was also the most common mutation (n=12, 87.5%) among the isolates that were resistant to EMB with both methods. Various pyrazinamide (PZA) resistance mutations in the *pnc*A gene were found by WGS in 92% of the isolates that showed PZA resistance in pDST (n=26), whereas all the isolates that were PZA susceptible by pDST also had the wild-type *pnc*A gene.

For kanamycin and capreomycin the agreement of phenotypic and genotypic DST was good (⩾94%). Five of the 45 isolates were resistant to streptomycin only by the phenotypic method whereas one phenotypically sensitive isolate had a putative resistance mutation in the *gid*B gene. The concordance of the phenotypic and genotypic DST results for all the drugs studied is shown in figure 2.

The most common spoligotype (n=23, 51.1%) was the Beijing genotype SIT1. By traditional genotyping methods (spoligotyping and MIRU-24), six clusters containing 22 isolates were found and the largest cluster, SIT1+ 100-32, contained 11 isolates. Based on the WGS clustering analysis, three isolate pairs could be suspected to be epidemiologically linked. Of these, one contained isolates from patients that had been infected before their arrival in Finland. In addition to a fairly obvious mother–daughter pair, two Finnish-born cases may be epidemiologically linked. The rest of the isolates had an allelic distance of more than five and cannot be assumed to be closely related by WGS (supplementary material).

MDR-TB treatment

Median duration of the first-line anti-TB medication before MDR-TB treatment was 6 days (IQR 0–31, mean 20). 43 (91.5%) cases received an MDR treatment regimen and stayed in Finland until the end of treatment (table 2). Median interval between the date of TB sample with an MDR isolate given and onset of effective MDR treatment was 36 days (IQR 12–49). Median duration of effective MDR treatment regimen was 23.8 months (IQR 17.8–25.8).

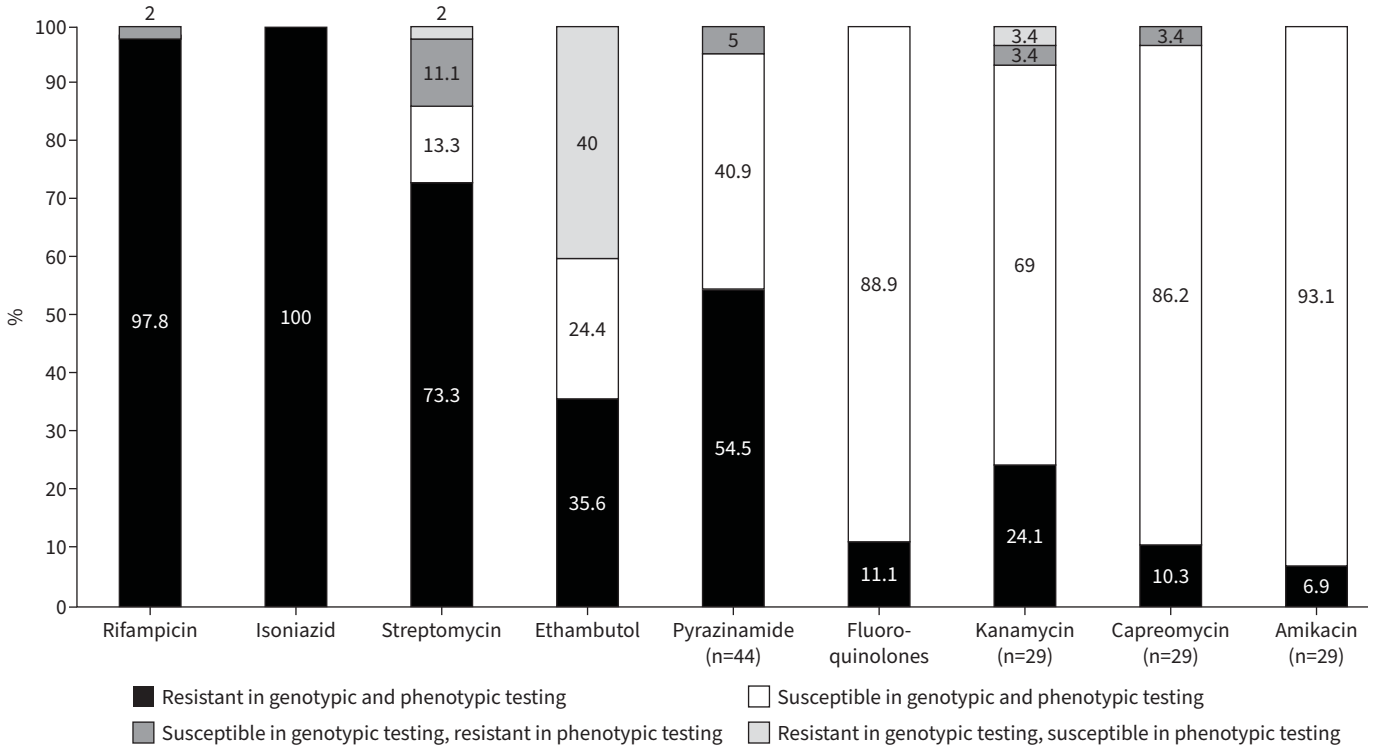

FIGURE 2 Concordance of the phenotypic and genotypic (whole-genome sequencing) drug susceptibility testing results of the sequenced isolates (n=45).

Adverse events were most common with linezolid treatment (68.4%). Median duration for linezolid was 9.6 months. Of the 38 linezolid users, 63.2% stopped linezolid treatment because of adverse events. Linezolid was paused at least once among 28.9% of the users. Only five cases received bedaquiline, and no adverse events were noticed. Four patients with pulmonary MDR-TB underwent surgery during treatment. Three cases died during MDR treatment after at least 1.5 years of treatment.

TABLE 2 Multidrug-resistant tuberculosis (MDR-TB) treatment data for the 43 cases diagnosed and treated in Finland, 2007–2016[#]

	Cases, n (%)	Duration, median (IQR)	Adverse events, n (%)	Drugs, median (IQR)
Injectable drug[¶]	39 (90.7)	6.2 (5.2–7.4) months	22 (56.4)	
Linezolid	38 (88.4)	9.6 (5.6–14.8) months	26 (68.4)	
Fluoroquinolone[+]	40 (93.0)	23.3 (15.8–24.8) months	10 (25.0)	
Clofazimine	23 (53.5)	12.3 (5.6–21.1) months	2 (8.7)	
Bedaquiline[§]	5 (11.6)	5.9 (4.5–15.6) months	0 (0)	
Duration of effective MDR-TB treatment		23.8 (17.8–25.8) months		
Adverse event for any drug			38 (88.4)	
Number of drugs in intensive phase				6 (5–6)
Number of drugs in continuation phase				4 (4–5)
Duration of hospitalisation		50 (38–108) days		
Cases with all MDR-TB medicines paused	14 (32.6)			
Duration of pauses for cases with pauses in medication		9.0 (5.5–14.0) days		
DOT used	42 (97.7)			

IQR: interquartile range; DOT: directly observed treatment. [#]: cases that received only standard tuberculosis treatment with first-line drugs (n=1) or left Finland during MDR-TB treatment (n=3) were excluded; [¶]: amikacin (n=37), streptomycin (n=2), non-recipient of an injectable drug due to drug resistance (n=3) and due to young age (n=1); [+]: non-recipient of fluoroquinolone due to drug resistance (n=3); [§]: extensively drug-resistant (n=3), pre-extensively drug-resistant (n=1), MDR (n=1).

TABLE 3 Treatment outcomes for multidrug-resistant tuberculosis cases in Finland by different definitions, 2007–2016

Outcome	Cases, n (%)
Treatment outcome (WHO/ECDC)[#]	
Cured	19 (40.4)
Treatment completed	16 (34.0)
Failed	0 (0)
Lost to follow-up	6 (12.8)
Died	3 (6.4)
Not evaluated	3 (6.4)
Treatment outcome for pulmonary cases (TBNET)[¶]	
Cured	20 (52.6)
Failed	1 (2.6)
Lost to follow-up	1 (2.6)
Died	3 (7.9)
Undeclared	13 (34.2)

WHO: World Health Organization; ECDC: European Centre for Disease Prevention and Control; TBNET: Tuberculosis Network European Trials group. [#]: outcome assessed for all multidrug-resistant cases (n=47); [¶]: outcome assessed for pulmonary multidrug-resistant cases only (n=38).

Treatment outcome and risk factors for non-successful treatment

As shown in table 3, 35 (74.4%) patients had a successful treatment outcome (cured or treatment completed), six (12.8%) were defined as lost to follow-up (interrupted) and three (6.4%) as not evaluated (transferred), three (6.4%) died and none failed according to the WHO outcome definitions. Five of the six cases with outcome lost to follow-up received MDR treatment for 7–16 months. Four of these showed no relapses during at least 2 years of follow-up after treatment cessation, and one case disappeared after 14 months of treatment. The sixth case was a child who responded well to standard TB treatment and was monitored for 3 years after treatment without a relapse. Among pulmonary cases, 27 (71.1%) patients had a successful treatment outcome. One case was suspected of having a recurrent MDR-TB episode during the study period, but the second TB episode was not microbiologically confirmed. Using simplified treatment outcome definitions set by TBNET for pulmonary cases, the proportion of 1-year relapse-free cure was 52.6% and of undeclared outcome 34.2%. In univariate and multivariate analyses, Finnish origin and having XDR-TB were associated with non-successful outcome defined with criteria set by the WHO (table 1).

Discussion

Regardless of the alarming MDR-TB situation in Finland's neighbourhood, the proportion of MDR-TB strains in Finland is still low, less than 2%. Treatment success rate was 74% in our national cohort study using individually tailored treatment regimens with directly observed treatment and treatment supervised by a national advisory group. We found that extensive drug resistance, meaning MDR with additional resistance to at least one fluoroquinolone and one injectable agent, and surprisingly also Finnish origin, predicted non-successful treatment outcome. Furthermore, our data show that MDR-TB is not transmitted inside Finland, reflecting cases being found and treatment started on time.

Phenotypic and genotypic drug resistance results were fully concordant for isoniazid, fluoroquinolones and amikacin. One isolate had contradictory results for rifampicin as a mutation was not found in the *rpo*B gene. On the other hand, more than half of phenotypically EMB-sensitive isolates were genotypically resistant. Most (90%) of the mutations found were high-confidence mutations at the positions 306, 406 or 497 of the *emb*B gene, and based on earlier studies, the isolates should be assumed EMB resistant [18, 19]. The critical concentration of 5 $mg \cdot L^{-1}$ for EMB may be too high and can mis-classify strains as susceptible [10]. One phenotypically streptomycin-sensitive isolate had a mutation in the *gid*B gene causing low-level resistance to streptomycin.

With current diagnostic tools, initial MDR treatment regimen is often based on NAAT results. However, NAAT from direct sample was requested by the treating clinician for only slightly more than half of the cases in our study, suggesting that MDR was not initially suspected by the physician. NAAT directly from sample has been recommended in Finnish guidelines for all TB suspects only since 2020 [12]. A need for

faster and reliable DST methods exists. In our study, an effective MDR treatment regimen was started almost a median of 2 weeks before pDST results were reported for first-line drugs. WGS was performed retrospectively for the study cohort. Our data show that using WGS as a primary DST method would accelerate diagnosis of MDR-TB.

~70% of our MDR cases are of foreign origin, and the different resistance mutation profiles in the otherwise similar isolates emphasise that the MDR cases detected in Finland are sporadic infections of MDR clusters very common elsewhere [20, 21]. Furthermore, most Finnish-born MDR cases had stayed for longer periods in countries with high MDR-TB incidences (data not shown), and active transmission of MDR-TB in Finland was not found. In this study, two Finnish-born patients could be suspected of being clustered, but the fairly long allelic distance (5) and different resistance mutations indicate that the patients most probably have not transmitted the isolate to each other but are likely to have been infected abroad.

Linezolid, a fluoroquinolone, and amikacin were each used for about 90% of our patients. Our results support earlier observations of a need for better tolerated treatment regimens [22]. With our treatment regimens, adverse events were extremely common; almost 90% of our cases had an adverse event for at least one drug. More than two-thirds of our patients receiving linezolid and more than half of our patients receiving amikacin had an adverse event for the drug, in contrast to an earlier meta-analysis showing that only 10% of patients using amikacin and 14% of patients using linezolid had an adverse event leading to permanent discontinuation of the drug [23]. Clofazimine caused adverse events very rarely, in line with results from earlier studies [7, 24]. As our study period ended a few years before WHO announced the new recommendations for bedaquiline-based treatment for all MDR patients [25], bedaquiline was used only for a minority of cases.

Our treatment success rate of almost 75% for MDR-TB cases is higher than in the WHO European region on average [3] and in line with a few studies from European low-incidence countries using individualised treatment [7, 8]. However, targeting even higher success rates is still warranted. We need to improve our treatment programme as for almost one-fifth of our cases MDR-TB treatment was interrupted or the patient transferred to another country during treatment resulting in high risk of treatment interruption. On the other hand, our treatment success rate of 71% among pulmonary MDR-TB cases is close to the rate published earlier for pulmonary non-MDR-TB cases in Finland [26]. Nevertheless, direct conclusions about MDR *versus* non-MDR cases cannot be made as demographics among these two cohorts differ substantially; MDR cases are much younger, have less comorbidities and are more often of foreign origin [26].

The rate of outcome cured using TBNET outcome definitions for pulmonary MDR-TB cases was not considerably higher compared to using WHO outcome definitions in our study, in contrast to earlier studies [27]. That is mainly caused by the high proportion of undeclared outcome due to deficiency of sputum samples at 6 months after treatment initiation and patients being transferred out during treatment or not showing up at post-treatment assessment. This calls for a special effort to collect sputum samples regularly during treatment, to improve the reliability of treatment outcome data. However, acquired drug resistance during MDR treatment and microbiologically confirmed relapses after treatment cessation were not found in our study. Earlier studies have shown that most relapses occur within 12 months of treatment completion [14, 28].

Our observation of extensive drug resistance as a clear predictor for non-successful outcome is in line with earlier studies [29, 30] even though some centres have published similar treatment success rates for patients with XDR- and MDR-TB [7]. Our finding is alarming, considering that most of our patients with XDR-TB were on bedaquiline-based regimens, and calls for a special effort on guiding treatment by the national advisory group each time XDR-TB is diagnosed. Surprisingly, Finnish origin was a risk factor for non-successful outcome mostly because treatments were interrupted, or patients died during treatment (data not shown). One explanation might be comorbidities, as 50% of cases with Finnish origin and only 21% of foreign-born cases had at least one comorbidity ($p=0.048$).

This study has several limitations. As this is a retrospective cohort study of 10 years, diagnostic methods and recommendations for treatment and treatment outcome evaluation have developed during the study period. We did not use the definition for (pre-)XDR recently announced by WHO [1]. The impact of different treatment regimens on treatment outcome could not be assessed as our cohort was small and especially the newer bedaquiline-based treatment regimen was infrequently used. Treatment success relied more often on patients completing treatment than on microbiologically confirmed cure, which is common also in other countries with a low incidence of TB [14]. Sampling of sputum becomes more difficult when a patient improves, and an intent to induce sputum samples, *e.g.* using nebulised hypertonic saline during

TB treatment, is not mentioned in our national TB guidelines. The laboratory methods, especially DST for EMB and PZA, are challenging [31]. In this study, the concordance of phenotypic and genotypic DST was poor especially for EMB, as more than half of phenotypically EMB-sensitive isolates were genotypically resistant. Hopefully more comprehensive resistance mutation catalogues and refined pDST methods will clarify the field in the future [32].

In conclusion, our national cohort study of 10 years shows treatment success in three-quarters of cases when treatment regimens are individualised, and treatment is supervised by an advisory group. The high number of adverse effects supports the need for more tolerable treatment regimens partly adopted in new guidelines as well as through follow-up of patients. Reliable and early DST is a key element in composing adequate drug regimens. WGS most probably will speed up the selection of an optimal treatment regimen in the future.

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