What is the best culture conversion prognostic marker for patients treated for multidrug-resistant tuberculosis?

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What is the best culture conversion prognostic marker for patients treated for multidrug-resistant tuberculosis?

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SUMMARY

INTRODUCTION: Identification of good prognostic marker for tuberculosis (TB) treatment response is a necessary step on the path towards a surrogate marker to reduce TB trial duration.

METHODS: We performed a retrospective analysis on routinely collected data in 6 drug-resistant TB (DRTB) programs. Culture conversion, defined as two consecutive negative cultures, was assessed, and performance of culture conversion at Month 2 and Month 6 to predict treatment success were explored. To explore factors associated with positive predicted value (PPV) and the specificity of culture conversion, a multinomial logistic regression was fitted.

RESULTS: This study included 634 patients: 68.5% were males; the median age was 35 years, 75.2% were previously treated for TB, 59.4% were resistant only to isoniazid and rifampicin and 18.1% resistant to fluoroquinolones. Culture conversion at Month 2 and 6 showed similar PPV while specificity was much higher for culture conversion at Month 2: 91.3% (95%CI 86.1–95.1). PPV of culture conversion at Month 2 did not vary strongly according to patients' characteristics, while specificity was slightly higher among patients with fluoroquinolone-resistant strains.

CONCLUSION: Culture conversion at Month 2 is an acceptable prognostic marker for MDR-TB treatment. Considering the advantage of using an earlier marker, further evaluation as a surrogate marker is warranted to shorten TB trials.

KEY WORDS: MDR-TB; culture conversion; treatment outcomes; performance; prognostic marker

DESPITE THE REGISTRATION of two new drugs for multidrug-resistant tuberculosis (MDR-TB) by the US Food Drug Administration (FDA) or the European Medical Agency (EMA), the development of new anti-tuberculosis drugs remains restricted due to limited funding.[1] Nevertheless, TB represents a major public health concern with an estimated 10.4 million incident cases in 2016 and 600 000 MDR or rifampicin-monoresistant cases worldwide.[2] In addition, the absence of a good surrogate marker for TB treatment response is leading to the long duration and high cost of therapeutic TB trials. Indeed, surrogate biomarkers can accelerate drug development by serving as a surrogate for clinical or definitive endpoint (free relapse cure in the context of TB trials).[3] Despite its imperfect ability to predict relapse in individual patients, the 2 months sputum culture conversion remains the most classically used surrogate marker in Phase II therapeutic trials for drug-susceptible TB.[4–6] In the context of drug development for life-threatening illnesses, there is the possibility of accelerated approval by the US FDA based on a surrogate endpoint that is 'reasonably likely to predict clinical benefit' and this was the case for the use of the Month 2 culture conversion in MDR-TB.[7,8] The latest new registered drugs (bedaquiline and delamanid) were accorded conditional regulatory approval after Phase II trial, and were thereafter endorsed by the WHO for the treatment of MDR-TB in specific conditions.[9–11] Adaptive trial design has been proposed to accelerate drug development in TB, including MDR-TB. In these designs, early microbiological endpoints (so called intermediate endpoints) play a critical role in the decision to drop or continue an arm, as in the case of seamless or multistage multi-arm (MAMS) designs or to adjust the probability of treatment allocation such as the adaptive randomisation design.[12,13]

Prognostic marker identification is a necessary step on the path toward identification of a good surrogate

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marker. Recent data from two MDR-TB cohort studies have suggested that a Month 6 culture conversion could be a more accurate prognostic biomarker than Month 2 culture conversion when compared to end of treatment outcomes.[14,15] Given the urgency of drug development for MDR-TB, and knowing that meta-analysis of culture conversion as surrogate biomarker will only be possible when phase 3 trials of new MDR-TB regimens are completed, we wanted to assess the accuracy of Month 2 and Month 6 culture conversion as prognostic biomarker in a large international MDR-TB cohort. The aim was to have more information on the potential use of early sputum culture conversion results as proxy for treatment outcome. Considering that some groups are evaluating different treatment regimens for MDR-TB according to the resistance to fluoroquinolones (FQs), the analysis was stratified by FQ resistance before starting treatment.[12,16,17]

METHODS

Study setting

Data from six countries where Médecins Sans Frontières (MSF) conducted drug resistant TB (DRTB) programmes were collected and were analysed in this study: Armenia (period 2005–2013), Georgia (2001–2013), Colombia (2009–2013), Kenya (2008–2013), Kyrgyzstan (2012–2013) and Swaziland (2007–2013), with an updated dataset from a previous publication on MDR-TB treatment outcomes.[18]

All MDR-TB patients received an individualised treatment regimen based on drug susceptibility testing (DST) results, including an injectable drug during the intensive phase (kanamycin [KM] or capreomycin [CPM]), a FQ throughout, and other WHO Group 4 second-line drugs (para-aminosalicylic acid, ethionamide or prothionamide, cycloserine) or Group 5 drugs (clofazimine, amoxicillin-clavulanate acid and/or clarithromycin).[19]

Study population

Databases were censored in July 2015. Patients were eligible for the study if they had a positive baseline culture and a DST confirming MDR-TB, at least one culture follow-up during treatment course and if they started on MDR-TB treatment at least 24 months before the closure date of the database to have a treatment outcome assessed. Patients who were lost to follow-up (LTFU) during MDR-TB treatment were excluded from the study.

Definitions

Resistance profile at treatment initiation were defined as follows: MDR with DST to second-line drugs not known; pre-extensively drug-resistant TB (XDR-TB) one injectable (resistance to either KM or CPM and ofloxacin [OFX] susceptible); pre-XDR two injectables (resistance to KM and CPM and OFX-susceptible); pre-XDR OFX (resistance to OFX and susceptibility to both KM and CPM); and XDR (resistance to OFX and resistance to either KM or CPM).

Culture conversion at a given month (from 2 to 12) was defined as two consecutive negative cultures before or at this given month from samples collected at least 30 days apart. Time to initial sputum culture conversion was then defined as the time in months from the start date of MDR-TB treatment to the date of specimen collection for the first of these two consecutive negative cultures.

Treatment outcomes were defined based on the 2008 WHO definition—a treatment outcome was defined as successful if the patient was cured or had completed treatment, and unsuccessful if patient died or failed treatment.[20]

Statistical analysis

Patient characteristics at treatment initiation were summarised using frequencies and percentages for categorical variables, and median and interquartile range (IQR) for continuous variables.

Kaplan-Meier estimates and log-rank test were used to assess culture conversion and to assess for differences in time to culture conversion between subgroups. Performance of culture conversion at Month 2, 3, 4, 5, 6, 9 and 12 after treatment start were first explored. Sensitivity, specificity, positive and negative predicted values and area under the curve (AUC) were calculated along with their 95% confidence intervals and were presented worldwide and stratified by FQ resistance profile. A multinomial logistic regression was fitted to explore the effect of baseline confounders on the positive predictive value and specificity of culture conversion including sex, age, body mass index (BMI), HIV, history of treatment, presence of cavities, resistance to FQ, project location and year of treatment start.[21] Finally, the association between culture conversion at Month 2 (and Month 6) and treatment success was assessed using multivariate logistic regression. Missing values were imputed through multiple sequential imputation using chained equations by creating 50 imputations using all variables including the outcome variable. Covariates of clinical interest and that are known to be associated with treatment outcomes and those associated with a $P < 0.4$ in univariate analysis were included in initial multivariate model; a manual backward stepwise approach was used to obtain the final multivariate model. Statistical significance ($P < 0.05$) was assessed with likelihood ratio test. Analyses were performed using Stata v15.0 software and the MI procedure (Stata Corporation, College Station, TX, USA).

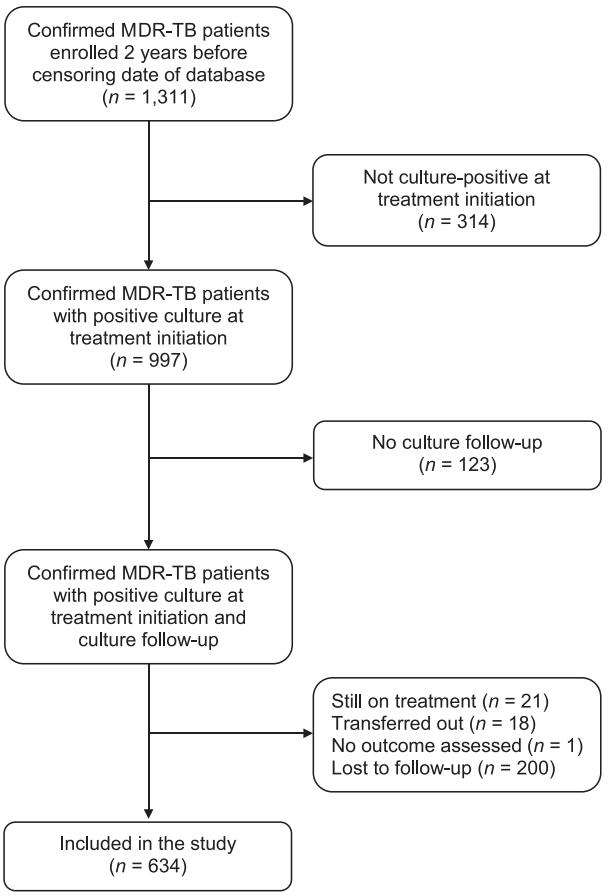

Figure 1 Flow chart of the study. MDR-TB = multidrug-resistant tuberculosis.

Ethical approval

The study was approved by all the relevant health ministries. This research fulfilled the exemption criteria set by the MSF Ethics Review Board (MSF ERB) for a posteriori analyses of routinely collected clinical data and thus did not require MSF ERB review.

RESULTS

A total of 634 patients were eligible and included in this study (Figure 1). The majority came from Armenia (48.1%) and were males (68.5%), with a median age of 35 years [IQR 27–47]. About three quarters were previously treated patients, while 64.0% had cavities. TB strains DST profiles at treatment initiation were distributed as follow: 59.4% were resistant only to isoniazid and rifampicin, 10.2% were pre-XDR with resistance to one injectable only, 12.2% were pre-XDR with resistance to the two injectables only, 8.9% were pre-XDR with resistance to FQs only and 9.2% were XDR (Table 1).

Culture conversion was achieved in 504 (79.5%) of the patients in a median time of 2.9 months [IQR 1.9–4.6]. Kaplan-Meier estimates of culture conversion were shown in Figure 2A. Patients harbouring an FQ-resistant strain at treatment initiation were less likely to convert compare to those with strains susceptible to FQs (Figure 2B, log-rank test: $P = 0.006$).

Successful treatment was achieved by 461 patients (72.7%): 331 (52.2%) cured, 130 (20.5%) completed treatment. Among those with an unsuccessful treatment outcome, 79 (12.5%) died and 94 (14.8%) failed treatment. Success rate was significantly lower among patients with FQ-resistant strains (34.5% vs.

Table 1 Characteristics of MDR-TB patients at treatment start ($n = 634$)

Characteristics	*n* (%)
Project location	
Abkhazia	96 (15.1)
Armenia	305 (48.1)
Colombia	14 (2.2)
Kenya	60 (9.5)
Kyrgyzstan	23 (3.6)
Swaziland	136 (21.4)
Sex	
Male	434 (68.5)
Female	200 (31.5)
Age, years	
Median [IQR]	35 [27–47]
<35	308 (49.0)
≥35	321 (51.0)
Missing, *n*	5
Ex-prisoner	
No	503 (79.3)
Yes	131 (20.7)
Contact of a MDR-TB case	
No	571 (90.1)
Yes	63 (9.9)
HIV	
Negative	236 (63.6)
Positive	135 (36.4)
Missing, *n*	263
History of previous anti-TB treatment	
New case	139 (22.3)
Previously treated with FLD	334 (53.7)
Previously treated with SLD	134 (21.5)
Transferred in	15 (2.4)
Missing, *n*	12
BMI, kg/m^2	
<18.5	190 (35.9)
≥18.5	340 (64.1)
Missing, *n*	104
Cavities on CXR	
No	228 (36.0)
Yes	406 (64.0)
Smear result	
Negative	108 (18.8)
1+	129 (22.5)
2+	108 (18.8)
3+	229 (39.9)
Missing, *n*	60
DST profile	
H and R resistant only	180 (59.4)
Pre-XDR-TB (1 injectable)	31 (10.2)
Pre-XDR-TB (2 injectables)	37 (12.2)
Pre-XDR-TB fluoroquinolones	27 (8.9)
XDR-TB	28 (9.2)
SLD line resistance missing, *n*	331

MDR-TB = multidrug-resistant TB; IQR = interquartile range; HIV = human immunodeficiency virus; TB = tuberculosis; FLD = first-line drug; SLD = second-line drug; BMI = body mass index; CXR = chest X-ray; DST = drug susceptibility testing; H = isoniazid; R = rifampicin; XDR-TB = extensively drug-resistant TB.

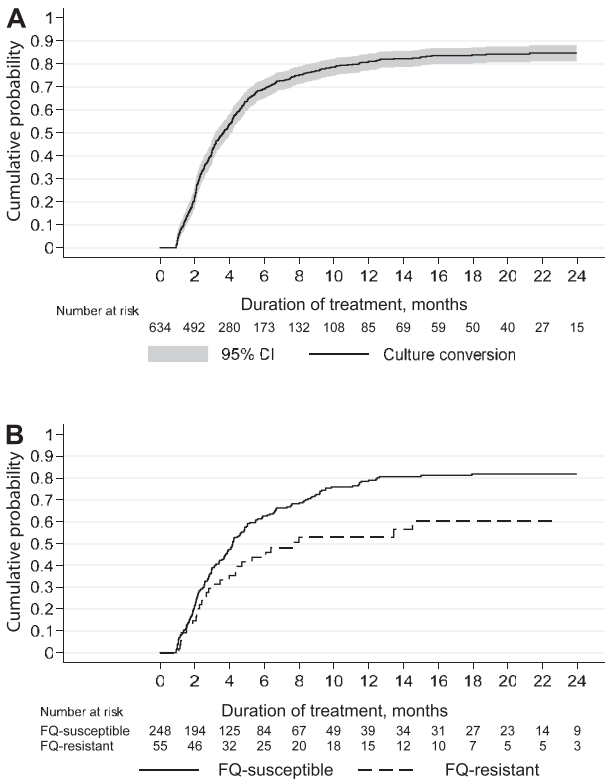

Figure 2 Kaplan-Meier estimates of culture conversion **A)** overall; **B)** by FQ resistance at treatment start. CI = confidence interval; FQ = fluoroquinolone.

65.5%, $P < 0.001$). Performance of culture conversion at different time points to predict treatment success are given in Table 2.

The probability of success among those who converted (positive predictive value, PPV) was constantly high showing that >80% of MDR-TB patients who converted had a successful treatment outcome, independently of the time to culture conversion. The specificity of Month 2 culture conversion (probability of not converting at Month 2 among those with unsuccessful outcome) was 91.3% (95%CI 86.1–95.1) and then decreased to 67.6% (95%CI 60.1–74.5) for conversion at Month 6. Performance differed according to the resistance profile: PPV was much lower among FQ-resistant patients at baseline whatever the time to culture conversion, except at Month 2. However, no difference in specificity was observed according to FQ resistance.

Multiple-imputation estimates of the multinomial logistic regression to jointly model PPV and specificity of culture conversion at month 2 and 6 were presented in Table 3. The PPV of culture conversion at Month 2 did not vary strongly according to baseline patients' clinical and demographic characteristics. Specificity was slightly higher among patients with FQ-resistant strains, although not statistically significant (adjusted relative risk ratio

Table 2 Performance of monthly culture conversion to predict treatment success ($n = 634$)*

	Sensitivity % (95% CI)	Specificity % (95% CI)	PPV % (95% CI)	NPV % (95% CI)	AUC (95% CI)
Culture conversion at Month 2					
Overall	26.9 (22.9–31.2)	91.3 (86.1–95.1)	89.2 (82.8–93.8)	31.9 (27.8–36.2)	0.59 (0.56–0.62)
FQ-susceptible	24.7 (18.6–31.7)	87.1 (77.0–93.9)	83.0 (70.2–91.9)	31.3 (24.8–38.3)	0.56 (0.51–0.61)
FQ-resistant	36.8 (16.3–61.6)	97.2 (85.5–99.9)	87.5 (47.3–99.7)	74.5 (59.7–86.1)	0.67 (0.56–0.79)
Culture conversion at Month 3					
Overall	51.2 (46.5–55.8)	81.5 (74.9–87.0)	88.1 (83.6–91.7)	38.5 (33.5–43.7)	0.66 (0.63–0.70)
FQ-susceptible	46.6 (39.1–54.2)	81.4 (70.3–89.7)	86.5 (78.0–92.6)	37.5 (29.8–45.7)	0.64 (0.58–0.70)
FQ-resistant	47.4 (24.4–71.1)	80.6 (64.0–91.8)	56.3 (29.9–80.2)	74.4 (57.9–87.0)	0.64 (0.51–0.77)
Culture conversion at Month 4					
Overall	64.0 (59.4–68.4)	75.7 (68.6–81.9)	87.5 (83.5–90.9)	44.1 (38.4–50.0)	0.70 (0.66–0.74)
FQ-susceptible	56.7 (49.1–64.1)	78.6 (67.1–87.5)	87.1 (79.6–92.6)	41.7 (33.2–50.6)	0.68 (0.62–0.74)
FQ-resistant	52.6 (28.9–75.6)	75.0 (57.8–87.9)	52.6 (28.9–75.6)	75.0 (57.8–87.9)	0.64 (0.50–0.77)
Culture conversion at Month 5					
Overall	75.1 (70.8–78.9)	70.5 (63.1–77.2)	87.2 (83.5–90.3)	51.5 (44.9–58.0)	0.73 (0.69–0.77)
FQ-susceptible	68.5 (61.2–75.3)	72.9 (60.9–82.8)	86.5 (79.8–91.7)	47.7 (37.9–57.5)	0.71 (0.64–0.77)
FQ-resistant	63.2 (38.4–83.7)	72.2 (54.8–85.8)	54.5 (32.2–75.6)	78.8 (61.1–91.0)	0.68 (0.54–0.81)
Culture conversion at Month 6					
Overall	80.7 (76.8–84.2)	67.6 (60.1–74.5)	86.9 (83.3–90.0)	56.8 (49.7–63.7)	0.74 (0.70–0.78)
FQ-susceptible	73.0 (65.9–79.4)	68.6 (56.4–79.1)	85.5 (78.9–90.7)	50.0 (39.6–60.4)	0.71 (0.64–0.77)
FQ-resistant	63.2 (38.4–83.7)	69.4 (51.9–83.7)	52.2 (30.6–73.2)	78.1 (60.0–90.7)	0.66 (0.53–0.80)
Culture conversion at Month 9					
Overall	88.9 (85.7–91.7)	64.7 (57.1–71.8)	87.0 (83.7–89.9)	68.7 (61.0–75.7)	0.77 (0.73–0.81)
FQ-susceptible	84.3 (78.1–89.3)	67.1 (54.9–77.9)	86.7 (80.7–91.4)	62.7 (50.7–73.6)	0.76 (0.70–0.82)
FQ-resistant	73.7 (48.8–90.9)	63.9 (46.2–79.2)	51.9 (31.9–71.3)	82.1 (63.1–93.9)	0.69 (0.56–0.82)
Culture conversion at Month 12					
Overall	93.1 (90.3–95.2)	64.2 (56.5–71.3)	87.4 (84.1–90.2)	77.6 (69.9–84.2)	0.79 (0.75–0.82)
FQ-susceptible	91.0 (85.8–94.8)	65.7 (53.4–76.7)	87.1 (81.4–91.6)	74.2 (62.5–84.5)	0.78 (0.72–0.84)
FQ-resistant	73.7 (48.8–90.9)	63.9 (46.2–79.2)	51.9 (31.9–71.3)	82.1 (63.1–93.9)	0.69 (0.56–0.82)

* Sensitivity = probability (converted/success); specificity = probability (not converted/failure); PPV = probability (success/converted); NPV = probability (failure/not converted).
CI = confidence interval; PPV = positive predictive value; NPV = negative predictive value; AUC = area under the curve; FQ = fluoroquinolone.

Table 3 Results of the multinomial logistic regression to jointly model the PPV and the specificity of culture conversion at Month 2 and Month 6 ($n = 634$)*

	Month 2				Month 6			
	PPV		Specificity		PPV		Specificity	
Characteristics	aRRR	95% CI	aRRR	95% CI	aRRR	95% CI	aRRR	95% CI
Sex								
Female	1		1		1		1	
Male	0.80	0.20–3.18	2.67	0.64–11.15	0.40†	0.17–0.94	1.03	0.39–2.71
Age, years								
<35	1		1		1		1	
≥35	0.85	0.24–2.93	1.21	0.35–4.21	0.66	0.33–1.30	1.07	0.51–2.23
BMI, kg/m^2								
<18.5	1		1		1		1	
≥18.5	3.14	0.80–3.71	1.78	0.45–7.08	1.28	0.60–2.71	0.87	0.39–1.94
HIV								
Negative	1		1		1		1	
Positive	0.32	0.04–2.35	0.66	0.09–4.88	0.50	0.16–1.53	1.10	0.31–3.87
History of previous anti-TB treatment								
New case	1		1		1		1	
Previously treated	0.48	0.11–2.11	0.92	0.20–4.15	0.29†	0.11–0.75	0.47	0.17–1.34
Cavities on CXR								
No	1		1		1		1	
Yes	0.87	0.20–3.71	1.88	0.43–8.14	1.03	0.46–2.35	1.82	0.73–4.51
DST profile								
FQ-susceptible	1		1		1		1	
FQ-resistant	1.23	0.12–12.84	8.62	0.89–83.35	0.19†	0.06–0.56	1.85	0.66–5.17

* The dependent variable in this model is a variable which is the grouping of the two variables treatment outcomes (success/failure) and culture conversion (yes/no) leading to four categories: 1 = treatment outcome failure and no culture conversion; 2 = treatment outcome success and no culture conversion; 3 = treatment outcome failure and culture conversion; 4 = treatment outcome success and culture conversion; estimates of the effects of covariates on PPV: estimates of the submodel category 4 outcome with category 3 outcome as base outcome; estimates of the effects of covariates on specificity: estimates of the submodel category 1 outcome with category 3 outcome as base outcome.

† $P < 0.05$; adjusted for year of treatment start and project location.

PPV = positive predictive value; aRRR = adjusted relative risk ratio; CI = confidence interval; BMI = body mass index; HIV = human immunodeficiency virus; TB = tuberculosis; CXR = chest X-ray; DST = drug susceptibility testing; FQ = fluoroquinolone.

[aRRR] 8.62, 95%CI 0.89–83.35) and did not differ according to other patients' characteristics. At Month 6, the PPV for culture conversion was significantly lower among males (aRRR 0.40, 95%CI 0.17–0.94), previously treated patients (aRRR 0.29, 95%CI 0.11–0.75) and among those with FQ-resistant strains at baseline (aRRR 0.19, 95%CI 0.06–0.56). However, the specificity did not vary significantly according to baseline characteristics. Furthermore, HIV status did not impact on performance of culture conversion to predict treatment success.

When adjusting for age, sex, BMI, HIV, history of previous treatment, presence of cavities, DST profiles at treatment initiation, project location and year of treatment start, culture conversion at Month 2 and at Month 6 remained a strong independent predictor of treatment success (Table 4).

DISCUSSION

Few studies have evaluated the accuracy of sputum culture conversion in predicting treatment outcomes in MDR-TB. Our results are consistent with results from the three main cohort studies: one in Latvia ($n = 167$), one multicentre in Estonia, Latvia, Peru, Philippines, Russia, South Korea, South Africa, Thailand and Taiwan ($n = 1712$) and one in China ($n = 139$).[14,15,22] Month 2 sputum culture conversion was 22.0% in our study compared to 38.8%, 29.1% and 28.0% in the three published cohorts and Month 6 culture conversion was 69.1% compared to 67.7%, 80.7% and 71.9%. Success rate (after excluding LTFU) was 72.7% in our cohort compared to 77.7%, 65.8% and 60.4% in the three respective cohorts. Of note, extensively drug-resistant patients were excluded from the large multicentre cohort.[15]

Compared to other studies, after adjustment only Month 2 culture conversion was associated with treatment success in our study, whereas it was independently associated only in HIV-negative patients in the published multicentre cohort.[15] Sensitivity and specificity of Month 2 (26.9% and 91.3%) and Month 6 (80.7% and 67.6%) culture conversion were very close to what has been reported at Month 2 and 6 in the multicentre cohort (Month 2, 27.3% and 89.8%; Month 6, 91.8% and 65.4%) and Chinese (Month 2, 33.3% and 80.0%; Month 6, 90.5% and 56.4%) cohorts, respectively.[14,15]

In a context of 73% treatment success on average after exclusion of patients who are LTFU, both the Month 2 (PPV 89.2%) and Month 6 (PPV 86.9%) culture conversion predicts very well treatment success. However, there is a much higher number of patients with negative culture among those with a

Table 4 Results of the logistic regression to assess the effect of culture conversion on treatment success ($n = 634$)

	Model including Month 2 culture conversion		Model including Month 6 culture conversion	
Characteristics	aOR	95% CI	aOR	95% CI
Culture conversion at Month 2			—	—
No	1			
Yes	3.35*	1.77–6.36		
Culture conversion at Month 6				
No			1	
Yes	—	—	7.13*	4.48–11.37
Sex				
Female	1		1	
Male	0.40*	0.22–0.72	0.37*	0.20–0.68
Age, years				
<35	1		1	
≥35	0.68	0.43–1.07	0.70	0.43–1.14
BMI, kg/m^2				
<18.5	1		1	
≥18.5	1.36	0.81–2.29	1.31	0.76–2.24
HIV				
Negative	1		1	
Positive	0.59	0.25–1.38	0.62	0.24–1.58
History of previous anti-TB treatment				
New case	1		1	
Previously treated	0.50*	0.28–0.90	0.48*	0.25–0.91
Cavities on CXR				
No	1		1	
Yes	0.85	0.46–1.57	0.92	0.48–1.75
DST profile				
FQ-susceptible	1		1	
FQ-resistant	0.20*	0.10–0.40	0.23*	0.11–0.49

* $P < 0.05$ adjusted for year of treatment start and project location.
aOR = adjusted odds ratio; CI = confidence interval; BMI = body mass index; HIV = human immunodeficiency virus; TB = tuberculosis; CXR = chest X-ray; DST = drug susceptibility testing; FQ = fluoroquinolone.

final unsuccessful treatment outcome at Month 6 (32.4%) compared to Month 2 (8.7%). Therefore, using the month 6 culture conversion as a prognostic biomarker would tend to overestimate the effect of the treatment. On the other hand, the probability of culture conversion among patients with treatment success (sensitivity) is very low at Month 2 and increase up above 80% at Month 6, meaning that at Month 2 there is a significant number of patients who are still culture-positive and will succeed the treatment. Therefore, using the Month 2 culture conversion as a prognostic biomarker would tend to underestimate the treatment effect.

At Month 2, results remain the same in subgroups of patients with FQ-susceptible and resistant MDR-TB. However, at Month 6, there is a major decline of the PPV in among patients with FQ-resistant TB. This could be explained by a higher proportion of positive culture reversion in this group of patients.

In the case of the adaptive RCT design aiming to identify one of two treatment regimens among several that could be evaluated in late stage clinical trial based on early microbiological response, we require intermediate endpoints with relatively high negative predictive value. This allows a treatment or regimen that has very low effect on the early endpoint to be dropped in the knowledge that it is predicting well the effect on the definitive endpoint.[23] The Month 6 culture conversion has a higher negative predictive value (NPV) (56.8%) than the Month 2 culture conversion (31.9%). However, among patients with FQ-resistant TB, the Month 2 culture conversion has a relatively high NPV (74.5%) and might be a good intermediate endpoint for such a population.

Our study has several limitations: 1) we used programmatic data, which explains the missing observations. For example, 123 patients did not have follow-up culture results recorded, the two main reasons being death ($n = 33$) and LTFU ($n = 54$). For the same reason, there was no post-treatment follow-up and culture conversion endpoint could not be correlated with the relapse-free success, which is the standard efficacy endpoint used in phase III TB trials. Therefore, end of treatment success might overestimate true success, which could result in an overestimation of specificity of the culture conversion endpoint; 2) the exclusion of 200 patients who were LTFU could introduce a bias in the estimates used. However, treatment interruption can have many reasons that may or may not relate to the treatment effect, and it is difficult to assess the overall bias on the estimates. Patient characteristics at treatment

start did not differ between those LTFU (and excluded) and those included in the study (data not shown), which may attenuate the bias in the estimates. We decided to exclude these patients to be able to assess culture conversion as a prognostic marker of the treatment response. 3) MDR-TB treatment was based on WHO-recommended, individualised treatment regimen, with treatment adapted based on drug-resistant change, or poor tolerability. It is therefore possible that the treatment success of patients who did not convert culture was partially due to the treatment change and not only due to the poor accuracy of the culture conversion as a prognostic biomarker. This could have resulted in an overestimation of the specificity of the culture conversion endpoint. All programmes followed the MSF guidelines for MDR-TB management based on the WHO recommendations, which limits the potential variability across programmes regarding treatment change.[19,24] 4) Finally, the results of this analysis apply only to the use of the lengthy individual MDR-TB treatment regimen and cannot be generalised to the standardised 9 month regimen, recently endorsed by the WHO for the treatment of FQ-susceptible patients.

In our study, both the Month 2 and Month 6 culture conversion were independently associated with treatment success and both had high PPV. However, Month 2 culture conversion has a higher specificity than the Month 6 marker, limiting the risk of wrongly concluding of treatment efficacy in patients with culture conversion. Compared to the Month 6 culture conversion, the Month 2 conversion has also a higher PPV and specificity in the subpopulation of patients with FQ-resistant TB. Therefore, based on these findings and considering the advantage of using an earlier surrogate marker in terms of trial duration and cost, and the emerging research on short MDR-TB treatment regimens (9 to 6 months), Month 2 culture conversion is a preferable prognostic marker than Month 6. This deserves further evaluation as surrogate marker using trial data with post-treatment outcomes.[25]

Further assessment of other sputum culture intermediate markers that take into account the longitudinal microbiological response over time in MDR-TB patients[5,26] and more research on biomarkers other than sputum culture conversion, is also warranted.[3]

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RÉSUMÉ

CONTEXTE : L'identification d'un bon marqueur prognostique de la réponse au traitement de la tuberculose multirésistante (MDR-TB) est une étape nécessaire vers l'identification d'un marqueur substitut pour réduire la durée des essais cliniques.

MÉTHODE : Nous avons réalisé une étude rétrospective des données de six programmes MDR-TB. La conversion de culture, défini comme deux cultures négatives consécutives, a été estimée et les performances de la conversion de culture à 2 et 6 mois de traitement pour prédire le succès du traitement ont été calculées. Les facteurs associés à la valeur prédictive positive (PPV) et à la spécificité de la conversion de culture ont été explorés à l'aide d'un modèle logistique multinomiale.

RÉSULTATS : L'étude incluait 634 patients : 68,5% d'hommes, d'âges médian de 35 ans, 75,2% déjà traités pour une TB, 59,4% résistant seulement à l'isoniazide et la rifampicine et 18,1% résistants aux fluoroquinolones. Une PPV similaire a été trouvée pour la conversion de culture à 2 et 6 mois, alors que la spécificité était bien meilleure pour la conversion à 2 mois : 91,3% (IC 95% 86,1–95,1). La PPV de la conversion à 2 mois n'était pas influée par les caractéristiques du patient alors que la spécificité apparaissait légèrement meilleure chez les patients résistants aux fluoroquinolones.

CONCLUSION : La conversion à 2 mois est un marqueur prognostique acceptable pour le traitement de la MDR-TB. Etant donné l'avantage d'utiliser un marqueur précoce, l'évaluation de de marqueur comme marqueur de substitut pour raccourcir la durée des essais cliniques est nécessaire.

RESUMEN

MARCO DE REFERENCIA: Definir un buen marcador pronóstico de la respuesta al tratamiento antituberculoso es una etapa necesaria en la trayectoria de búsqueda de un marcador indirecto que permita acortar la duración de los ensayos clínicos de tuberculosis multiresistente (MDR-TB).

MÉTODOS: Se llevó a cabo un análisis retrospectivo a partir de los datos corrientes recogidos en seis programas de MDR-TB. Se analizó la conversión del cultivo, definida como dos cultivos consecutivos negativos y la eficacia de la conversión del cultivo a los 2 meses y 6 meses para predecir el éxito del tratamiento. Mediante un modelo de regresión logística polinómica ajustado se examinó el valor pronóstico de un resultado positivo del cultivo (PPV) y la especificidad de la conversión del cultivo.

RESULTADOS: Se incluyeron en el estudio 634 pacientes, el 68,5% de sexo masculino, la mediana de la edad fue 35 años, un 75,2% tenía antecedente de tratamiento antituberculoso, el 59,4% albergaba cepas resistentes solo a isoniazida y rifampicina y el 18,1% cepas resistentes a fluoroquinolonas. La conversión del cultivo a los 2 meses y 6 meses exhibió un PPV equivalente, pero la especificidad a los 2 meses de 91,3% fue mucho más alta (IC 95% 86,1–95,1). El PPV de la conversión del cultivo a los 2 meses no presentó una gran variación con respecto a las características de los pacientes, pero la especificidad fue un poco mayor en pacientes con cepas resistentes a fluoroquinolonas.

CONCLUSIÓN: La conversión del cultivo a los 2 meses es un marcador aceptable del pronóstico, en el tratamiento de la MDR-TB. Teniendo en cuenta la ventaja de adoptar un marcador más temprano, se justifican nuevas investigaciones que evalúen su utilización como marcador indirecto con el fin de acortar los ensayos clínicos de tratamiento de la TB.