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Factors associated with sputum culture conversion in multidrug-resistant pulmonary tuberculosis

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SUMMARY

INTRODUCTION: Sputum culture conversion in pulmonary multidrug-resistant tuberculosis (MDR-TB) is important to make treatment-related decisions and prevent transmission of disease.

OBJECTIVE: To identify factors associated with sputum culture conversion, and to determine time to culture conversion and the impact of culture conversion on successful treatment outcomes in MDR-/rifampicin (RMP) resistant TB.

METHOD: Retrospective analysis of data from treatment cards and registers of MDR-/RMP-resistant patients initiated on treatment under India's Revised National TB Control Programme in Delhi, West Bengal and Kerala from January 2009 to December 2011. Proportions were calculated and logistic regression analysis was performed.

RESULTS: Of 836 patients, 787 were analysed, 651 (83%) of whom experienced culture conversion: respectively 57%, 73% and 79% culture converted by month 3, 4 and 6 of treatment. The median time to culture conversion was 91.3 days. Patients with body mass index (BMI) <16 kg/m^2 (OR 0.403, $P=0.001$) and 16–18 kg/m^2 (OR 0.519, $P=0.039$) were less likely to have culture conversion. High rates of culture conversion were observed in patients with successful treatment outcomes compared to those without treatment success (462/469, 99% vs. 183/311, 59%; $P < 0.0001$).

CONCLUSION: Low BMI is associated with poor sputum culture conversion in MDR-/RMP-resistant TB patients. Lack of culture conversion can impact successful treatment outcomes.

KEY WORDS: predictors; treatment outcomes; drug resistance; BMI

THERE WERE AN ESTIMATED 480 000 new cases of multidrug-resistant tuberculosis (MDR-TB, defined as TB resistant to at least both isoniazid [INH] and rifampicin [RMP]), and approximately 190 000 deaths from MDR-TB worldwide in 2014.[1] In the same year, in India, there were an estimated 71 000 MDR-TB cases among notified TB cases, with 2.2% in new and 15% in retreatment TB cases.[1] India's Revised National TB Control Programme (RNTCP) introduced the programmatic management of drug-resistant TB (PMDT) services in 2007 for the management of MDR-TB.[2] Under PMDT, MDR-/RMP-resistant TB patients are treated with a standardised treatment regimen for a duration of 24–27 months. Sputum culture conversion in MDR-/RMP-resistant TB assumes great importance in the PMDT context, as there are implications in terms of treatment-related decisions. The duration of treatment with the injectable agent, and the intensive phase of treatment, is determined by sputum culture conversion. According to PMDT guidelines, the latest available sputum culture conversion reports after the completion of 6 months of treatment determine the duration of the intensive phase of treatment.[2] The time to culture conversion determines the infectiousness of the patient and the potential to transmit the disease in the community.

Time to sputum culture conversion and conversion status can be considered as proxy markers of end-of-treatment outcomes in MDR-TB patients.[3] Data on factors likely to influence sputum culture conversion in MDR-TB patients are limited.[4–6] The objective of the present study was to identify factors associated with sputum culture conversion and to determine the time to sputum culture conversion in MDR-/RMP-resistant TB. The influence of sputum culture conversion on successful treatment outcomes (cure and treatment completed) was also determined.

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METHODOLOGY

This retrospective cohort study was conducted between January and September 2015. The states of West Bengal, Delhi and Kerala were randomly selected among states that had initiated PMDT treatment services before January 2011. Under PMDT, sputum samples obtained from patients with presumptive MDR-TB are examined at the state-level intermediate reference laboratory (IRL) using solid culture (Löwenstein-Jensen medium). Positive cultures are subjected to drug susceptibility testing (DST) against INH, RMP, ethambutol (EMB) and streptomycin (SM). Quality assurance is supervised at the IRL by the National Reference Laboratory, and is ensured by annual panel testing and certification.[2]

Patients diagnosed with MDR-/RMP-resistant TB, with or without additional resistance, are initiated on standardised treatment given in two phases: the intensive phase and the continuation phase. The total duration of treatment for the MDR-TB regimen is 24–27 months, depending on the duration of the intensive phase. Treatment consists of six drugs: kanamycin (KM), levofloxacin (LVX), ethionamide (ETH), pyrazinamide (PZA), EMB and cycloserine (CS) for the 6–9-month intensive phase, followed by four drugs, LVX, ETH, EMB and CS, during the 18-month continuation phase.[2] Based on culture positivity at months 4, 5 and 6, the intensive phase can be extended up to 9 months.

Treatment initiation and follow-up case management are performed at the drug-resistant TB (DR-TB) centre, a tertiary care government hospital. Treatment is decentralised and all drugs are given as a single daily dosage under directly observed treatment (DOT) by a DOT provider. All patients receive drugs under DOT on 6 days of the week. On Sunday, the oral drugs are administered unsupervised and the KM injection is not given. Patients are reviewed at the DR-TB centre at monthly intervals during the intensive phase, and at 3-monthly intervals during the continuation phase until the end of treatment. Sputum specimens are collected and examined by smear and culture at least 30 days apart from months 3 to 7 of treatment (i.e., at the end of months 3, 4, 5, 6 and 7), and at 3-monthly intervals from month 9 onwards until the completion of treatment (i.e., at the end of months 9, 12, 15, 18, 21 and 24).

Patients initiated on treatment from January 2009 to December 2011 in the DR-TB centres of West Bengal, Delhi and Kerala comprised the study population. The following details were collected from treatment cards and registers using a structured data collection format: age, sex, height, weight, human immunodeficiency virus (HIV) status, associated illnesses, reasons for suspecting MDR-TB, date of DST results, date of start of treatment, pre-treatment sputum culture grading; DST profile of INH, RMP, EMB and SM; previous treatment details, culture results after treatment and treatment outcomes.

Sputum culture-positive patients with DST showing resistance to INH+RMP (i.e., MDR-TB) and RMP resistance with or without additional resistance were considered for analysis. The following outcome definitions were used in the study: 1) culture conversion: two consecutive negative cultures, taken at least 1 month apart;[2] 2) time to sputum culture conversion: interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive cultures;[2] 3) cured: completed treatment and consistently culture-negative (with at least five consecutive negative results in the last 12–15 months) or one positive follow-up culture in the last 9 months, followed by at least three consecutive negative cultures taken at least 30 days apart, provided that there is clinical evidence of improvement;[2] 4) treatment completed: patient who has completed treatment according to guidelines but who does not meet the definition for cure or treatment failure due to lack of bacteriological results;[2] 5) failure: two or more of the five cultures recorded in the final 12–15 months are positive, or any of the final three cultures are positive;[2] death: death due to any reason during the course of treatment;[2] default (lost to follow-up [LTFU]): treatment interrupted for $\geqslant$2 consecutive months for any reason;[2] 6) treatment stopped: due to adverse drug reactions or other reasons;[2] and 7) switched to XDR-TB (defined as MDR-TB plus resistant any of the fluoroquinolones and at least one of the three injectables) regimen: MDR-TB patient diagnosed with XDR-TB and initiated on XDR-TB treatment.[2]

Data analysis

Data were double-verified, entered in EpiData (EpiData Association, Odense, Denmark) and analysed using Statistical Package for the Social Sciences, version 20.0 (IBM Corp, Armonk, NY, USA). Proportions were computed for categorical variables. Values are expressed as percentages, means, medians and interquartile ranges (IQRs). Simple and multiple logistic regression analysis was performed to identify the factors associated with culture conversion. Odds ratios (ORs) were calculated and adjusted ORs (aORs) with 95% confidence intervals (CIs) were estimated using a stepwise selection model after testing at each step for variables at a significance level of $P < 0.20$. Receiver operating characteristics (ROC) curve was used to evaluate the month of culture conversion at which the chance of successful treatment was high. $P < 0.05$ was considered statistically significant.

The study was approved by the Institutional Ethics Committee of the National Institute for Research in TB, Chennai, India.

Table 1 Baseline characteristics of MDR-/RMP-resistant pulmonary TB patients

Characteristics	*n* (%)
Sex (*n* = 787)	
Male	534 (68)
Female	253 (32)
Age, years (*n* = 787)	
⩽14	13 (2)
15–30	369 (47)
31–45	222 (28)
46–60	153 (19)
>60	30 (4)
Body mass index, kg/m^2 (*n* = 693)	
<16	262 (38)
16–18	168 (24)
>18	263 (38)
HIV status (*n* = 391)	
Reactive	15 (4)
Non-reactive	376 (96)
Associated illnesses (*n* = 359)	
Yes	108 (30)
No	251 (70)
Type of associated illnesses (*n* = 108)	
Diabetes	85 (79)
Psychiatric illness	3 (3)
Renal disease	1 (1)
Others	19 (18)
Pre-treatment sputum smear grading (*n* = 787)	
Negative	199 (25)
Scanty	88 (11)
1+	205 (26)
2+	146 (19)
3+	149 (19)
Pre-treatment sputum culture grading (*n* = 787)	
Scanty	98 (12)
1+	204 (26)
2+	208 (26)
3+	277 (35)
Drug resistance profile (*n* = 787)	
RMP monoresistance	16 (2)
RMP+SM	12 (2)
RMP+SM+EMB	6 (1)
MDR-TB (resistance to INH+RMP)	165 (21)
MDR-TB+SM	216 (27)
MDR-TB+EMB	39 (5)
MDR-TB+SM+EMB	333 (42)
Last received treatment before MDR-TB diagnosis (*n* = 756)	
Category I	125 (17)
Category II	619 (82)
Others	12 (2)
Patient type at Category II initiation (*n* = 606)	
Failure	355 (59)
Relapse	183 (30)
Default	68 (11)
Previous treatment with second-line drugs (*n* = 654)	
Yes	28 (4)
No	626 (96)

MDR- = multidrug-resistant; RMP = rifampicin; TB = tuberculosis; HIV = human immunodeficiency virus; SM = streptomycin; EMB = ethambutol; INH = isoniazid.

RESULTS

From January 2009 to December 2011, a total of 836 patients were initiated on treatment under PMDT at the study sites. After exclusion of 49 patients (due to non-availability of records, *n* = 11; negative pre-treatment sputum culture, *n* = 2; lack of information on pre-treatment sputum cultures, *n* = 28; DST profile not available, *n* = 7; and culture resistant only to SM and EMB, *n* = 1), 787 patients with a minimum of two consecutive sputum specimens available in the intensive phase remained for analysis. Of the 787 patients, respectively 309 (39%), 297 (38%) and 181 (23%) were from Delhi, West Bengal and Kerala.

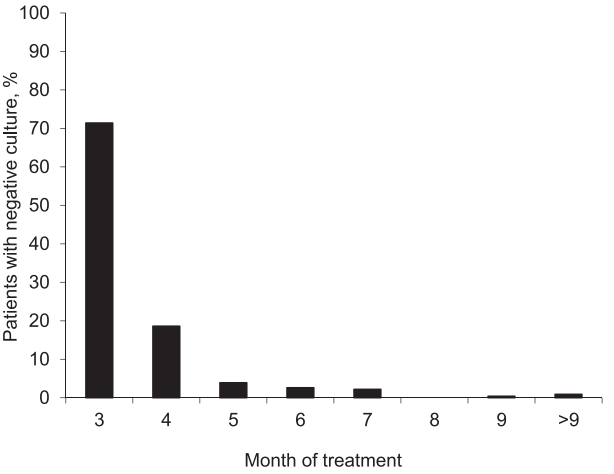

Figure Sputum culture conversion by month of treatment in multidrug-resistant/rifampicin-resistant pulmonary tuberculosis (*n* = 651).

Baseline characteristics of patients

Of the 787 patients, 534 (68%) were males, 369 (47%) were in the 15–30 years age group and 262/693 (38%) had a body mass index (BMI) of <16 kg/m^2 (Table 1); 376/391 (96%) were HIV-negative and 108/359 (30%) had associated illnesses, including diabetes mellitus (DM) (*n* = 85, 79%); 588 (75%) were pre-treatment sputum smear-positive and 485 (62%) had a pre-treatment sputum culture grade of 2+/3+. Resistance to SM and EMB in addition to MDR-TB was observed in 333/753 (44%) patients, while RMP resistance was detected in 34 (4%). Of the 606 patients who had received the Category II regimen, respectively 355 (59%) and 183 (30%) were classified as failure and relapse at initiation of Category II treatment. Of 654 patients for whom the information was available, 626 (96%) had received no previous second-line treatment (Table 1). Failure of previous treatment, relapse and default were the main reasons for investigating for MDR-TB in respectively 459 (58%), 195 (25%) and 76 (10%) of the 787 patients.

Sputum culture conversion

Of the 787 patients analysed, 651 (83%) had sputum culture conversion; respectively 451 (57%), 573 (73%) and 622 (79%) had culture converted by month 3, 4 and 6 of treatment. Of the 651 patients with sputum culture conversion, respectively 451 (69%) and 122 (19%) converted by month 3 and 4 of treatment (Figure). The median time to sputum culture conversion was 91.3 days (IQR 91.3–121.7).

Table 2 Factors associated with sputum culture conversion in MDR-/RMP-resistant pulmonary TB ($n = 580$)*

Characteristics	Total *n*	Sputum culture conversion: Yes ($n = 490$) *n* (%)	Sputum culture conversion: No ($n = 90$) *n* (%)	OR (95%CI)	*P* value
Sex					
Male	402	338 (69)	64 (71)	0.903 (0.551–1.481)	0.687
Female	178	152 (31)	26 (29)	Reference	
Median age, years					
>32	289	240 (49)	49 (54)	0.803 (0.512–1.261)	0.341
⩽32	291	250 (51)	41 (46)	Reference	
Body mass index, kg/m^{2†}					
<16	212	168 (34)	44 (49)	0.403 (0.230–0.705)	0.001
16–18	148	123 (25)	25 (28)	0.519 (0.279–0.967)	0.039
>18	220	199 (41)	21 (23)	Reference	
Sputum culture grade					
2+/3+	358	301 (61	57 (63)	0.922 (0.579–1.469)	0.733
Scanty/1+	222	189 (39)	33 (37)	Reference	
Sputum smear grade					
2+/3+	190	166 (34)	24 (28)	1.729 (0.975–3.068)	0.061
Scanty/1+	225	192 (39)	33 (37)	1.455(0.855–2.474)	0.167
Negative	165	132 (27)	33 (37)	Reference	
Median time between diagnosis and treatment start, days					
>68	295	243 (50)	52 (58)	0.719 (0.456–1.132)	0.154
⩽68	285	247 (50)	38 (42)	Reference	
Drug resistance					
MDR-TB+SM/EMB/SM+EMB	442	374 (76)	68 (76)	0.407 (0.095–1.753)	0.228
MDR-TB	109	89 (18)	20 (22)	0.330 (0.072–1.501)	0.151
RMP+SM/EMB/SM+EMB	29	27 (6)	2 (2)	Reference	
Previous treatment with second-line drugs					
Yes	14	10 (2)	4 (4)	0.448 (0.137–1.461)	0.183
No	566	480 (98)	86 (96)	Reference	
Missed doses in intensive phase					
Yes	131	105 (21)	26 (29)	0.671 (0.405–1.112)	0.121
No	449	385 (79)	64 (71)	Reference	

* Stepwise logistic regression was performed to calculate adjusted OR with variables that satisfied the criterion of $P < 0.20$ in the model.
† Values remained the same after adjusting for other predictor variables.
MDR- = multidrug-resistant; RMP = rifampicin; TB = tuberculosis; OR = odds ratio; CI = confidence interval; SM = streptomycin; EMB = ethambutol.

Factors associated with sputum culture conversion

Of the factors analysed for association with sputum culture conversion in 580 patients, those patients with BMI <16 kg/m^2 and BMI 16–18 kg/m^2 were less likely to have sputum culture conversion (respectively OR 0.403, 95%CI 0.230–0.705; $P = 0.001$ and OR 0.519, 95%CI 0.279–0.967; $P = 0.039$) (Table 2). There was no significant difference in the progress of BMI during the intensive phase of treatment between culture non-converters ($n = 37$) and converters ($n = 574$) ($P = 0.097$).

Sputum culture conversion was not significantly different between HIV non-reactive and reactive patients ($n = 391$) (316/376, 84% vs. 11/15, 73%; $P = 0.272$) and in patients with and without associated illnesses ($n = 359$) (96/108, 89% vs. 207/251, 82%; $P = 0.124$).

Sputum culture conversion and treatment outcome

Of the 780 patients with information available on treatment outcome, 469 (393 cured + 76 treatment completed, i.e., 60%) had successful treatment outcomes. The remaining 311 included 135 (17%) who died, 43 (6%) failures, 128 (16%) LTFU, 3 (<1%) with treatment stopped and 2 (<1%) who switched to XDR-TB treatment. Culture conversion was observed in 70/135 (52%) who died and 70/128 (55%) LTFU.

Higher sputum conversion rates were observed in patients with successful treatment outcomes than those without treatment success (462/469, 99% vs. 183/311, 59%; $P < 0.0001$) (Table 3). The month of sputum culture conversion significantly differed between those with successful treatment outcomes and those without treatment success ($P = 0.011$). A higher proportion of those with successful treatment outcomes had culture conversion by month 3 than those without treatment success (330/462, 71% vs.117/183, 64%) (Table 3).

The ROC analysis of treatment success indicated that the area under the curve (AUC) was 0.544 (95%CI 0.504–0.583; $P = 0.036$) when the cut-off value was ⩽3 month of culture conversion, with a sensitivity of 71.4% (95%CI 67.1–75.5) and a specificity of 36.1% (95%CI 29.1–43.5).

DISCUSSION

We observed that 83% of the MDR-/RMP-resistant TB patients treated with the standardised regimen under PMDT had sputum culture conversion, which indicates that the remaining 17% non-converters

Table 3 Sputum culture conversion and treatment outcomes in multidrug-resistant/rifampicin-resistant pulmonary tuberculosis

	Successful treatment outcome				
	Yes		No		
Sputum culture conversion	Total	*n* (%)	Total	*n* (%)	*P* value
Sputum culture conversion ($n = 780$)	469		311		
Yes		462 (99)		183 (59)	<0.0001
No		7 (1)		128 (41)	
Month of sputum culture conversion ($n = 645$)	462		183		
3		330 (71)		117 (64)	0.011
4		86 (19)		36 (19)	
5		18 (4)		13 (7)	
6		12 (3)		5 (3)	
>6		16 (3)		12 (7)	

could potentially act as a source of transmission of disease in the community. This is a matter of concern, and all efforts should be made to improve the culture conversion rate. Culture conversion by months 3 and 6 of treatment was observed in respectively 57% and 79% of the MDR-TB patients. This is low compared to the culture conversion rates of respectively 84% and 87% at months 3 and 6 documented in a previous study of 38 patients with MDR-TB treated with a similar standardised regimen.[7] This may be due to the close supervision and monitoring procedures in the earlier study.[7] Prospective studies are needed to identify possible reasons for poor sputum conversion.

The median time to sputum culture conversion was 91.3 days in our study. This is longer than the median 60–78 days reported in earlier studies.[4,8,9] This could be attributed to the inability of our study to capture culture conversion that occurred within 3 months of treatment initiation, as the first follow-up sputum examination after initiating treatment was at 3 months under PMDT.

Patients with low BMI (<16 and 16–18 kg/m^2) were less likely to undergo culture conversion. This finding is consistent with a previous study from Indonesia among 212 MDR-TB patients, which documented that severely underweight patients (BMI <16 kg/m^2) had a longer time to initial conversion and a lower probability of sputum culture conversion within 4 months.[10] Similarly, a study from Georgia reported low culture conversion rates in MDR-TB patients with low BMI (<18.5 kg/m^2).[8] This underscores the importance of early diagnosis of MDR-TB by rapid tests, close monitoring of patients with low BMI by introducing more frequent sputum culture examinations, implementing infection control measures to prevent disease transmission and planning interventions accordingly.

Age, sex, sputum culture grading and previous treatment with second-line drugs were not associated with culture conversion in our study. Earlier studies have reported previous treatment for MDR-TB, high initial sputum culture colony count and female sex to be associated with longer culture conversion time.[4,10] Resistance to second-line drugs (fluoroquinolone, aminoglycoside), cavitation on chest radiograph, smoking and alcoholism have been reported to be negatively associated with culture conversion in previous studies.[3–6,8,10] We could not analyse the above-mentioned characteristics in our study due to non-availability of data in the treatment cards.

Culture conversion was similar in patients who were non-reactive and reactive for HIV. No difference in the proportion of sputum culture conversion between HIV-infected and non-infected MDR-TB cohorts treated with individualised treatment regimens was reported in a previous study in Botswana.[9] In our study, patients with or without associated illnesses had similar sputum culture conversion rates. DM was the associated illness in 79% of patients in our study. An earlier study reported similar rates of culture conversion among patients with MDR-TB and DM compared to patients with MDR-TB only.[8]

Our study has shown high sputum culture conversion rates in patients with successful treatment outcomes. A previous study from Latvia reported worse treatment outcomes in patients who failed to sputum convert within 2 months.[4] A positive association of sputum culture conversion at 6 months and culture conversion at 2 months in HIV-negative patients with treatment success was reported in an earlier study.[3] We observed that month 3 culture conversion had moderate sensitivity and poor specificity for treatment success. This implies that sputum culture conversion and month of culture conversion could indicate treatment success in MDR-/RMP-resistant TB patients.

The limitations of the study include inability to capture data on sputum culture conversion that occurred within 3 months of treatment initiation. As this study was record-based, data on a minimum of two consecutive sputum specimens were used to classify converters and non-converters due to missing information. The missing data precluded the inclusion of all patients and variables for the factors associated with culture conversion analysis.

In conclusion, our analysis shows that nearly 79% of MDR-/RMP-resistant TB patients achieve sputum culture conversion by month 6 of treatment and that

sputum culture conversion affects successful treatment outcomes. Patients with low BMI need to be closely monitored. Further studies are required to understand patient and health system-related factors that influence sputum culture conversion and treatment outcomes in drug-resistant TB patients treated under PMDT.

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Conflicts of interest: none declared.

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RESUME

CADRE : La conversion de la culture de crachats dans la tuberculose pulmonaire multirésistante (TB-MDR) est cruciale en matière de décisions thérapeutiques et de transmission de la maladie.

OBJECTIF : Identifier les facteurs associés à la conversion de la culture de crachats, déterminer le délai de conversion de la culture et l'impact de la conversion de la culture sur la réussite du traitement dans la TB-MDR/résistante à la rifampicine (RMP).

MÉTHODE : Analyse rétrospective des données contenues dans les cartes de traitement et les registres de patients atteints de TB-MDR/résistante à la RMP, mis sous traitement dans le cadre du Programme national de lutte contre la TB révisé, dans le Bengale de l'Ouest et le Kerala entre janvier 2009 et décembre 2011. Les proportions ont été calculées et une analyse de régression logistique a été effectuée.

RÉSULTATS : Sur 836 patients, 787 ont été analysés, dont 651 (83%) ont eu une conversion de culture : 57%, 73% et 79% au cours du 3e, 4e et 6e mois de traitement, respectivement. Le délai médian de conversion de la culture a été de 91,3 jours. Les patients qui avaient un indice de masse corporelle (BMI) inférieur à 16 kg/m^2 (OR 0,403 ; $P = 0{,}001$) et entre 16 et 18 kg/m^2 (OR 0,519 ; $P = 0{,}039$) ont été moins susceptibles d'avoir une conversion de culture. Un taux élevé de conversion de culture a été observé chez les patients dont le traitement a eu un bon résultat comparés à ceux dont le traitement n'a pas été efficace (462/469, 99% contre 183/311, 59% ; $P < 0{,}0001$).

CONCLUSION : Un BMI faible est associé à une conversion de culture de crachats médiocre chez les patients atteints de TB-MDR/résistante à la RMP. La conversion de la culture semble avoir un impact sur le bon résultat du traitement.

RESUMEN

MARCO DE REFERENCIA: La conversión del cultivo del esputo en los casos de tuberculosis multirresistente (TB-MDR) pulmonar es un aspecto importante en las decisiones relacionadas con el tratamiento y en la interrupción de la transmisión de la enfermedad.

OBJETIVO: Reconocer los factores que se asocian con la conversión del cultivo de esputo, definir el lapso hasta la conversión y analizar la repercusión de la misma en el éxito terapéutico de los casos de TB-MDR, y los casos esistente a rifampicina (RMP).

MÉTODO: Se llevó a cabo un análisis retrospectivo de los datos obtenidos de las tarjetas de tratamiento y los registros de los pacientes con diagnóstico de TB-MDR y pacientes resistente a RMP, que iniciaron tratamiento en el marco del Programa Nacional Revisado contra la Tuberculosis en Delhi, Bengala Occidental y Kerala de enero del 2009 a diciembre del 2011. Se calcularon las proporciones y se realizó un análisis de regresión logística.

RESULTADOS: De los 836 pacientes que iniciaron tratamiento, se analizaron 787, de los cuales 651 obtuvieron la conversión del esputo, un 57% al tercer mes, un 73% al cuarto mes y un 79% al sexto mes de tratamiento. La mediana del tiempo hasta la conversión del cultivo fue 91,3 días. Fue menos probable que lograran la conversión del cultivo los pacientes con un índice de masa corporal (BMI) <16 kg/m^2 (OR 0,403; $P = 0{,}001$) y de 16–18 kg/m^2 (OR 0,519; $P = 0{,}039$). Se observó una alta tasa de conversión en los pacientes con desenlaces terapéuticos favorables, en comparación con los pacientes sin tratamiento exitoso (462/469, 99% contra 183/311, 59%; $P < 0{,}0001$).

CONCLUSIÓN: Un bajo BMI se asocia con deficiente conversión del cultivo de esputo en los pacientes con TB-MDR pulmonar, y pacientes resistente a RMP. La conversión del cultivo influye en el éxito terapéutico.