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Extension of the intensive phase reduces relapse but not failure in a regimen with rifampicin throughout

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SUMMARY

SETTING: Damien Foundation tuberculosis (TB) control projects in Bangladesh.

OBJECTIVE: To assess the effectiveness of extending the intensive phase (P1) of treatment by 1 month for patients who are smear-positive after 2 months of a 6-month regimen containing rifampicin (RMP) throughout.

DESIGN: Prospective operational study randomising P1 extension for new smear-positive cases with any number of acid-fast bacilli in the 2-month smear (2M+). Smear-defined failures and relapses underwent culture and drug susceptibility testing in addition to DNA sequencing of the *rpo*B gene before and after treatment.

RESULTS: Of 16 708 patients evaluated, 12 967 were smear-negative at 2 months (2M−); 1871 and 1870 2M+ were randomised to no extension or extension. Respectively 0.3% (95%CI 0.2–0.4), 1.2% (95%CI 0.7–1.8) and 2.0% (95%CI 1.4–2.8) smear- and culture-positive failures, and 1.2% (95%CI 1.0–1.4), 2.6% (95%CI 1.9–3.4) and 0.9% (95%CI 0.5–1.4) relapses were detected. Extension significantly reversed the relative risk (RR) of relapse of 2M+ vs. 2M− patients from 2.2 (95%CI 1.6–3.0) to 0.7 (95%CI 0.4–1.2). The RR for failure remained high, at 7.3 (95%CI 4.7–11.5) with and 4.2 (95%CI 2.5–7.2) without extension. More multidrug resistance was found after extension, but acquired RMP resistance was similar in all arms. The fair sensitivity of the 2-month smear for failure or relapse (40%) was offset by a very low positive predictive value (3%).

CONCLUSIONS: Extension of P1 is very inefficient with this 6-month regimen. Operational research should define appropriate algorithms allowing an earlier switch to the next higher regimen for those in need, using follow-up smears for screening.

KEY WORDS: tuberculosis; conversion; relapse; failure; drug resistance

EXTENSION of the intensive phase (P1) of antituberculosis (TB) treatment by 1 month in case of continued smear positivity at the end-of-phase follow-up continues to be widely practised in National Tuberculosis Programmes (NTP), although its effectiveness has never been demonstrated for regimens that contain rifampicin (RMP, R) throughout. We previously reported a significantly higher proportion of failure and relapse in patients who were smear-positive at 2 months (2M+) of the 8-month thioacetazone regimen, and its reduction to the same low level as in 2-month smear-negative patients (2M−) by extending P1 by 1 month.[1] However, in the opinion of many experts, extension of P1 might not be warranted for the 6-month regimen, with its more powerful continuation phase including RMP. At the time of our study, some countries had already omitted P1 extension on switching to the 6-month regimen while a new standard of care was being prepared.[2]

It is known that smear positivity at 2 months after the initiation of short-course chemotherapy correlates poorly with positive culture.[3] Cavities and extensive disease on chest X-ray, with the accompanying highly positive diagnostic smears, have been identified as risk factors for delayed smear conversion.[4–7] In the absence of extensive initial drug resistance or extremely poor treatment adherence, dead bacilli showing up in smears may then explain faster conversion in culture.[5–8] However, with continued excretion of viable bacilli, extension of P1 might in principle protect against relapse (particularly due to the sterilising effect of pyrazinamide [PZA, Z]), as well as against acquired resistance to the main drugs, RMP and isoniazid (INH, H)—the main role of ethambutol (EMB, E). This should then result in a reduction of failures and relapses after treatment.

We report here the results of a prospective observational study on the extension of P1 of the standard

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2(3)EHRZ/4HR$_3$ regimen (RMP, INH, PZA and EMB daily for 2 or 3 months, followed by thrice-weekly RMP and INH). It was conducted under the Bangladesh NTP, involving the same Damien Foundation (DF) projects as in our first report, after the national treatment guidelines for new cases had been changed from the 8-month to the 6-month regimen.[9]

METHODS

All new smear-positive pulmonary TB patients registered in the 90 DF clinics of Greater Mymensingh and Greater Rajshahi Districts, Bangladesh, from 1 January 2006 to 30 June 2007 were eligible for enrolment. According to the NTP guidelines, the continuation phase was started when one morning sputum smear at 2 months of treatment was completely negative. Patients with any number of acid-fast bacilli (AFB) at 2 months (2M+) were randomly allocated to extension/no extension by administrative staff at project headquarters on an alternating basis via telephone communication with the clinic staff. Medical officers could exceptionally prescribe extension of P1 or switch patients to a regimen for multidrug-resistant TB (MDR-TB) treatment at any time in case of clinical deterioration or proof of MDR-TB.[10] The duration of the continuation phase remained at 4 months. Treatment was directly observed, using all possible providers, as described previously.[11] Follow-up for relapse was passive and the same for all arms, and patients were requested to report the recurrence of symptoms. Bacteriologically confirmed recurrence more than 2 years after the end of treatment was arbitrarily considered to represent re-infection.

Classification as a smear-positive new or relapse case was defined as any number of AFB found in one sputum smear, as per NTP guidelines. The definition of smear-based failure was at least 4 AFB/100 oil immersion fields (OIF) in sputum smears at the end of treatment (5th month onwards), without repeatedly negative smears afterwards. Two end-of-treatment smears were performed for all arms, at 5 and 6, or 6 and 7 months.

AFB examinations used the hot Ziehl-Neelsen method, as described previously.[12] All centres underwent continuous rechecking external quality assessment, and showed high concordance with the controllers (<1% false-positives and relative sensitivity ~95%). Sputum from failure and relapse cases was systematically cultured on Löwenstein-Jensen medium at the DF reference laboratory. Identification and drug susceptibility testing (DST) were performed at the Supranational TB Reference Laboratory in Antwerp, Belgium, using standard methods.[13,14] For failure and relapse cases, smear-positive sputum preserved in ethanol before and after treatment was tested by DNA sequencing, after amplification of the RMP resistance-determining core regions of the *rpo*B gene using previously described primers.[15] The identity of *Mycobacterium tuberculosis* pairs presenting a mutation in only one of its members was checked by standard fingerprinting techniques (15-loci mycobacterial interspersed repetitive unit-variable number tandem repeat analysis and spoligotyping).[15,16]

Study analysis in Epi Info 6.04d (Centers for Disease Control, Atlanta, GA, USA) used routine individual patient treatment and drug resistance databases, linked via unique treatment episode identifiers. Pearson's χ^2 test or Fisher's exact test were used for comparison of proportions. Exclusions included breach of protocol due to extension of P1 for 2M− cases, and regimen change before the 5th month.

The study was approved by the Bangladesh NTP and the Bangladesh Medical Research Council Ethical Review Committee. Informed consent was not requested, considering the changing standard of care, and as we feared that our patients would not be able to make a rational choice between the ill-defined or totally unknown risks of either approach without help from the clinic staff, leading to severe selection bias.

RESULTS

Of 17 815 new smear-positive patients enrolled in the study, 16 799 completed P1; the others did not due to early death, default, transfer out or other reasons (mainly non-start of treatment, Table 1). Of the 16 733 (99.6%) who underwent the end-of-P1 smear examination, 3748 (22.4%) were AFB-positive, of whom half were allocated to the extension arm and half to the no-extension arm (Table 2). A total of 25 patients (from both arms) were excluded from analysis: 11 2M− patients for whom P1 was extended and 14 who switched to another treatment regimen before the 5th month. This left 16 708 patients: 12 967 2M− (non-extended) and 1871/1870 2M+ without/with extension of P1. Respectively 249 and 241 of the 2M+ patients had high positive 2-month smears (≥1 AFB/field).

Table 1 Details of enrolment and sputum smear status at 2 months

	Patients *n*
Enrolled	17 815
Did not complete Phase I	
Died	464
Defaulted	376
Transferred	149
Other	27
Ended Phase I	16 799
2-month smear*	
Not performed	66
Performed	16 733
2M− (% of known)	12 985 (77.6)
2M+ (% of known)	3 748 (22.4)

*2M− = negative smear at 2 months; 2M+ = positive smear at 2 months (any number of acid-fast bacilli).

Table 2 Patients evaluated and smear-defined unfavourable bacteriological outcome by arm and smear status at 2 months

	Arm and smear status at 2 months			
	2M− *n*	2M+, no extension *n*	2M+, extension *n*	Total cohort *n*
Patients reaching the end of Phase 1	12 985	1874	1874	16 733
Excluded				
2M− extended	11			11
Early switch	7	3	4	14
Evaluated	12 967	1871	1870	16 708
No end-of-treatment smear	129	58	51	238
Failed (%, 95%CI)	74 (0.6, 0.45–0.72)	104 (5.6, 4.56–6.69)	109 (5.8, 4.81–6.99)	287 (1.7, 1.53–1.93)
RR (95%CI) vs. 2M−		9.7 (7.3–13.1) $P < 0.000001$	10.2 (7.6–13.7) $P < 0.000001$	
RR (95%CI) vs. 2M+ extended		0.95 (0.7–1.2) NS		
Relapsed (%, 95%CI)	219 (1.7, 1.47–1.93)	62 (3.3, 2.55–4.23)	27 (1.4, 0.95–2.09)	308 (1.8, 1.64–2.06)
RR (95%CI) vs. 2M−		2.0 (1.5–2.6) $P < 0.00001$	0.9 (0.6–1.3) NS	
RR (95%CI) vs. 2M+ extended		2.3 (1.5–3.6) $P < 0.001$		

2M− = negative smear at 2 months; 2M+ = positive smear at 2 months (any number of acid-fast bacilli); CI = confidence interval; RR = relative risk; NS = non-significant.

Table 2 also shows smear-defined failure and relapse outcomes by 2-month smear and extension status, with 95% confidence intervals (CIs). Only 1% of 2M− and about 3% of both 2M+ arms did not undergo end-of-treatment smear examination. Failure was declared for 0.6% of the 2M− patients compared to respectively 5.6% and 5.8% of the 2M+ patients without and with P1 extension, and there were respectively 1.7%, 3.3% and 1.4% smear-defined relapses. The relative risk (RR) of failure was significantly higher for both 2M+ arms (9.7–10.2 compared to 2M−), and was unaffected by extension (RR non-extended vs. extended 0.95, 95%CI 0.7–1.2). The RR of relapse differed significantly between the two 2M+ arms, at 2.0 (95%CI 1.5–2.6) without and 0.9 (95%CI 0.6–1.3) with extension. Among the 2M+ arms, non-extension of P1 carried an RR of relapse of 2.3 (95%CI 1.5–3.6, $P < 0.001$).

Respectively 20% and 10% of smear-positive failures and relapses did not undergo culture; these were similarly distributed over the study arms (Table 3). Of 231 failure and 277 relapse cultures performed, 312 (61%) were positive for *M. tuberculosis*, while 178 remained negative and some were contaminated or grew environmental mycobacteria (details not shown). Culture-confirmed failures occurred in respectively 0.3%, 1.2% and 2.0% of the 2M−, 2M+ non-extended and 2M+ extended patients. The RR of 2M+ vs. 2M− remained highly significant and similar in both 2M+ arms (4.2 and 7.3), although there was a suggestion of reduced risk due to non-extension (RR of non-extension vs. extension 0.6,

Table 3 Culture-defined unfavourable bacteriological outcome by arm and smear status at 2 months

	Arm and smear status at 2 months			
	2M−	2M+, no extension	2M+, extension	Total cohort
Evaluated, *n*	12 967	1871	1870	16 708
Failures (smear-positive*), *n*	74	104	109	287
Failures with no culture done, *n* (%)	14 (18.9)	22 (21.2)	20 (18.3)	56 (19.5)
Culture-positive (% of arm; 95%CI)	36 (0.3; 0.19–0.38)	22 (1.2; 0.74–1.77)	38 (2.0; 1.44–2.78)	96 (0.6; 0.47–0.70)
RR (95%CI) vs. 2M−		4.2 (2.5–7.2) $P < 0.000001$	7.3 (4.7–11.5) $P < 0.000001$	
RR (95%CI) vs. 2M+ extended		0.6 (0.3–1.0) $P = 0.05$		
Relapses (smear-positive*), *n*	219	62	27	308
Relapses with no culture done, *n* (%)	24 (11.0)	4 (6.5)	3 (11.1)	31 (10.1)
Culture-positive (% of arm; 95%CI)	152 (1.2; 0.99–1.37)	48 (2.6; 1.90–3.39)	16 (0.9; 0.49–1.39)	216 (1.3; 1.13–1.48)
RR (95%CI) vs. 2M−		2.2 (1.6–3.0) $P < 0.00001$	0.7 (0.4–1.2) NS	
RR (95%CI) vs. 2M+ extended		3.0 (1.7–5.3) $P < 0.0001$		

* Smear-positive = defining failure or relapse.
2M− = negative smear at 2 months; 2M+ = positive smear at 2 months (any number of acid-fast bacilli); CI = confidence interval; RR = relative risk; NS = non-significant.

95%CI 0.3–1.0, $P = 0.05$). There were respectively 1.2%, 2.6% and 0.9% culture-confirmed relapses. As for smears, the RR of 2M+ was significantly reduced by the extension of P1 (from 2.2 to 0.7 compared to 2M−, RR of non-extension = 3.0). For failures in particular, only a fraction could thus be confirmed by culture. However, extrapolation for non-performed cultures, applying arm-specific positivity rates, did not perceptibly change the RR of non-extension: failure remained at 0.6, while relapse decreased to 2.8 (details not shown).

Table 4 shows the drug resistance profiles of the failure and relapse strains. Pan-susceptible strains (or those resistant only to streptomycin) comprised 65% and 59% of the 2M− and 2M+ non-extended cases compared to 21% of the 2M+ extended cases. MDR-TB strains were responsible for this difference, making up 20% of the 2M−, 29% of the 2M+ non-extended and 66% of the 2M+ extended cases. Only the 2M+ extended rates differed significantly from both other arms ($P < 10^{-4}$ to 10^{-6}). As a percentage of the patients in the arm, MDR-TB represented 0.3%, 1.1% and 1.7% of the 2M−, 2M+ non-extended and 2M+ extended at the time of failure or relapse. This prevalence was significantly lower for the 2M− cases, but it did not differ between the 2M+ arms ($P = 0.12$). Strains isolated from patients who experience recurrent TB more than 2 years after the end of treatment showed an even higher proportion of pan-susceptible strains (83%) and a lower proportion of MDR-TB (5%).

Table 5 shows the result of *rpo*B DNA sequencing of pairs of samples before treatment and at the time of failure or relapse. DNA amplification and sequencing were successful for respectively 40, 97 and 81 pairs from the 2M−, 2M+ non-extended and 2M+ extended arms. In each arm, one pair yielded indeterminate results (*M. tuberculosis* before but environmental mycobacteria after treatment or the reverse; or *rpo*B mutation before but wild-type after). The same mutation was found before and after treatment in respectively 3, 11 and 13 pairs of the 2M−, 2M+ non-extended and 2M+ extended arms, while respectively 31, 77 and 57 pairs showed wild-type DNA before and after. Mutations that were not observed before treatment were detected in respectively 5, 8 and 10 pairs, but fingerprinting showed the same strain in only 5, 5 and 6 of these (a total of 16 cases with acquired RMP). Excluding strain mismatches, acquired RMP resistance was seen in 13.9%, 6.1% and 9.5% of those 'at risk' with wild-type DNA before treatment. This accounted for 62.5%, 26.3% and 26.1% of all *rpo*B mutations detected after treatment among the 2M−, 2M+ non-extended and 2M+ extended cases, respectively. The differences were non-significant.

In four of the 16 cases with acquired resistance, cultures remained negative, while MDR-TB was detected in 11/12 isolates (details not shown). The twelfth isolate, with *rpo*B mixed wild-type/Asp516Tyr on sequencing, showed only INH resistance phenotypically.

No suspected adverse events were recorded during

Table 4 Drug resistance profiles at time of failure or relapse by sputum smear status and intensive phase extension at 2 months

	Failure or recurrence within 2 years				
Resistance profile	2M− ($n = 179$)	2M+, no extension ($n = 68$)	2M+, extension ($n = 47$)	Total ($n = 294$)	Recurrence >2 years ($n = 41$)
Susceptible* or S resistant					
n	116	40	10	166	34
% strains	64.8	58.8	21.3	55.9	82.9
% arm	0.9	2.1	0.5	1.0	
H or HS resistant					
n	20	6	5	31	5
% strains	11.2	8.8	10.6	10.4	12.2
% arm	0.2	0.3	0.3	0.2	
HE or HES resistant					
n	1	1	0	2	0
% strains	0.6	1.5		0.7	
% arm	0.01	0.1		0.01	
R or RS resistant					
n	6	1	1	8	0
% strains	3.4	1.5	2.1	2.7	
% arm	0.05	0.1	0.05	0.05	
MDR					
n	36	20	31	87	2
% strains	20.1	29.4	66.0	29.3	4.9
% arm	0.3	1.1	1.7	0.5	

*Susceptible to isoniazid, rifampicin, streptomycin and ethambutol.
2M− = negative smear at 2 months; 2M+ = positive smear at 2 months (any number of acid-fast bacilli); S = streptomycin; H = isoniazid; E = ethambutol; R = rifampicin; MDR = multidrug-resistant (resistant to at least H and R).

Table 5 *rpo*B sequences before treatment and at time of failure or relapse, by smear status and extension of intensive phase at 2 months

	2M−	2M+, no extension	2M+, extension
Number of failures/relapses (smear-defined)	293	166	136
Pairs tested, *n*	40	97	81
Uninterpretable	1	1	1
Mutation/mutation	3	11	13
Wild-type/wild-type	31	77	57
Wild-type/mutation	5	8	10
Acquired rifampicin resistance			
n	5	5	6
% of those at risk (95%CI)	13.9 (4.7–29.5)	6.1 (2.0–13.7)	9.5 (3.6–19.6)
% of those resistant (95%CI)	62.5 (24.5–91.5)	26.3 (11.0–58.7)	26.1 (12.6–56.6)

2M− = negative smear at 2 months; 2M+ = positive smear at 2 months (any number of acid-fast bacilli); CI = confidence interval.

P1 for 94% of the patients without vs. 92% with extension (details not shown). There was a two-fold higher incidence of joint pain (4.3% vs. 2.2%) and peripheral neuritis (0.2% vs. 0.1%) among those with P1 extended, and slightly more jaundice (0.5% vs. 0.4%). Only joint pain was significantly more frequent (RR 1.9, 95%CI 1.5–2.5). Minor adverse events (rashes, vomiting) occurred at the same low frequency, and no other serious adverse events were registered. As usual, under field conditions, these events were recorded based on symptoms only.

Table 6 shows the sensitivity, specificity and predictive value for failure and relapse of the 2-month smear. A positive 2-month smear predicted smear-only defined failures plus relapses with 50.8% sensitivity, at 78.7% specificity, while for those defined by both smear and culture these values were respectively 39.7% and 77.9%. While the predictive value of a negative smear was high (97.7%/98.6%), that of a positive smear was extremely low (8.1%/3.3%).

DISCUSSION

The latest guidelines of the World Health Organization as well as those of the International Union Against Tuberculosis and Lung Disease no longer recommend extending the intensive phase of treatment in case of non-conversion of sputum smears at the end of the phase.[16,17] Our study supports this change from longstanding practice by showing that extending the intensive phase does not prevent treatment failure or acquired RMP resistance. Relapse was significantly reduced, but total treatment duration increased, which is known to inversely affect relapse rates.[18] Extending the continuation phase for patients who are positive at 2 months might thus have the

Table 6 Sensitivity, specificity and predictive values of the 2-month smear in predicting failure and/or relapse, as defined by positive smear only or by positive smear and culture

	Failure			Relapse			Failure + relapse		
	Yes	No	Total	Yes	No	Total	Yes	No	Total
Smear-defined									
2-month smear, *n*									
Positive	213	3528	3741	89	3652	3741	302	3439	3741
Negative	74	12893	12967	219	12748	12967	293	12674	12967
Total	287	16421	16708	308	16400	16708	595	16113	16708
Sensitivity, %	74.2			28.9			50.8		
Specificity, %	78.5			77.7			78.7		
PPV, %	5.7			2.4			8.1		
NPV, %	99.4			98.3			97.7		
Smear- and culture-defined									
2-month smear, *n*									
Positive	60	3681	3741	64	3677	3741	124	3617	3741
Negative	36	12931	12967	152	12815	12967	188	12779	12967
Total	96	16612	16708	216	16492	16708	312	16396	16708
Sensitivity, %	62.5			29.6			39.7		
Specificity, %	77.8			77.7			77.9		
PPV, %	1.6			1.7			3.3		
NPV, %	99.7			98.8			98.6		

PPV = positive predictive value; NPV = negative predictive value.

same effect, but this hypothesis could not be tested with our study design. However, it is supported by the 12-fold reduction in prevalence of relapse strains found to be susceptible, or with resistance easily overcome by the HR combination after extension (13 vs. 163 among the non-extended, details not shown). Initial smear grading, associated with extensive disease, cavities and low body mass index, has been identified as a main determinant of delayed conversion and relapse.[7,19] The proportion of smears with >10 AFB/OIF at the time of diagnosis, 39% among the 2M− patients but 64%/66% among the 2M+ patients without/with PhI extension, confirms these reports. The conclusions of a recent review can also be confirmed: the 2-month smear was fairly sensitive, but had a dismally low predictive value for failure and relapse outcome.[2]

The high proportion of non-converters (>22%) is also explained by the long tradition of careful microscopy with continuous quality assurance in the DF projects, and by the low cut-off used (any number of AFB). In our study on the 8-month regimen, patients with <4 AFB/100 fields were recorded as smear-negative (and were not eligible for extension), explaining the slightly higher conversion rates reported there.[1] The two studies were otherwise fully comparable as regards setting and the definitions used (same project, similar proportions of high-positive diagnostic smears, human immunodeficiency virus infection virtually absent). It is thus surprising that the more powerful 6-month regimen did not perform better than the 8-month regimen, with similar smear-based failure plus relapse rates (2.3% vs. 3.0%, 8.9% vs. 8.2% and 7.3% vs. 3.1% among respectively 2M−, 2M+ non-extended and 2M+ extended cases). Smear- and culture-defined rates were lower, but were again comparable between the two studies (1.5% vs. 1.9%, 3.8% vs. 3.7% and 2.9% vs. 1.6%). Higher MDR-TB rates since the introduction of the 6-month regimen is a possible explanation, supported by our continuous monitoring of drug resistance among retreatment cases (data not shown).[13]

Contrary to widespread belief, extension of the intensive phase did not protect against acquired resistance, nor was there any suggestion of reduced risk. More MDR-TB was found among post-treatment strains of 2M+ patients with than without extension (non-significant), and more among both 2M+ than 2M− patients. Molecular analysis of sputum pairs before and after treatment showed no difference in incidence of newly acquired RMP resistance mutations between the arms. Initial MDR-TB as a determinant of delayed conversion at 2 months explains the difference in post-treatment rates between the 2M+ and 2M− groups (but not between both 2M+ arms), and also that acquired resistance was proportionally far more frequent among 2M− post-treatment strains. Resistance may thus be acquired early during the intensive phase, when large numbers of bacilli are present. Highly positive 2-month smears may then indicate presence of MDR-TB, which is unaffected by the extension of treatment, while patients with low-positive smears will not acquire resistance readily in the continuation phase, as these represent dead bacilli or too small a bacillary population to produce RMP-resistant mutants. However, we could not test specimens at the end of the intensive phase to support this hypothesis.

Our study has some limitations: relapse follow-up was passive and probably incomplete. This may not have affected one arm more than another. The arbitrary distinction between relapse and re-infection used a 2-year cut-off after cure or completion, thus equalising the follow-up period for different treatment durations. This cut-off seemed justified considering the low prevalence of resistance among recurrences classified as re-infection, which was closer to the prevalence among our new cases.[20]

As is usual in NTPs, declaration of failure and relapse was based mainly on sputum smears, and no cultures were performed for smear-negatives at the end of treatment. However, culture coverage was high for routine conditions. Cultures performed at the time of failure yielded *M. tuberculosis* in only 60%, 27% and 43% of the 2M−, 2M+ non-extended and 2M+ extended arms. In contrast, 78% of relapses yielded a positive culture. These substantially different proportions suggest that losses due to transport delay and inadequate culture quality are only part of the reason. Excretion of non-viable bacilli and false declaration of failure based on careful microscopy may be the main reason, particularly among the 2M+ non-extended cases, as reported earlier.[21,22] Extrapolations for non-performed or failed cultures showed that study findings would not have changed.

CONCLUSIONS

Treatment failure and acquired RMP resistance cannot be prevented by a 1-month extension of the intensive phase of a 6-month regimen with RMP throughout in case of positive smears at 2 months. It is possible that the reduced relapse rate could also have been obtained by extending the continuation phase. This would reduce costs, adverse events and the risk of amplifying resistance by continued use of EMB and PZA if MDR-TB is present. However, an early change to second-line treatment would be necessary for MDR-TB patients. Treatment monitoring at the usual intervals using AFB smear examination should be continued for screening. Non-converters at 2 or 3 months and those reverting to positive should then be referred for tests with high predictive value for RMP resistance: the Gene Xpert assay, for example, which would also detect DNA from dead AFB of uncertain significance, or vital staining with

fluorescein-diacetate using light-emitting diode fluorescence microscopy,[23] which would also detect susceptible bacilli in non-adherent patients. Future studies should investigate the value of such techniques in terms of accuracy and predictive values at specific times of treatment, the feasibility of whole population coverage, cost and long-term sustainability.

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RÉSUMÉ

CONTEXTE : Projets de lutte antituberculeuse de la Fondation Damien au Bangladesh.

OBJECTIF : Evaluer l'efficience de la prolongation de la phase intensive pendant 1 mois chez les patients dont les frottis sont positifs à 2 mois d'un régime de 6 mois contenant la rifampicine (RMP) pendant tout le traitement.

SCHÉMA : Etude opérationnelle prospective avec randomisation de la prolongation de la phase intensive chez les cas à bacilloscopie positive dont le frottis à 2 mois comporte n'importe quel nombre de bacilles acido-résistants (2M+). On a réalisé chez le échecs et rechutes déterminés par les frottis, une culture et des tests de sensibilité ainsi que le séquençage du gène *rpo*B avant et après leur traitement.

RÉSULTATS : Sur les 16 708 patients évalués, les frottis ont été négatifs à 2 mois chez 12 967 (2M−). On a randomisé les 2M+ vers l'absence de prolongation (n = 1871) ou vers la prolongation (n = 1870). On a détecté des échecs positifs au frottis et à la culture respectivement chez 0,3% (IC95% 0,2–0,4) des 2M−, chez 1,2% (IC95% 0,7–1,8) des 2M+ sans prolongation et 2,0% (1,4–2,8) chez les 2M+ avec prolongation. La prolongation a abaissé significativement le risque relatif (RR) de rechute chez les 2M+ de 2,2 (IC95% 1,6–3,0) à 0,7 (IC95% 0,4–1,2). Le RR d'échec est resté élevé (7,3 ; IC95% 4,7–11,5 avec prolongation et 4,2 ; IC95% 2,5–7,2 sans prolongation). On a observé un plus grand nombre de multirésistance après prolongation, mais la résistance acquise à la RMP a été similaire dans tous les bras. La sensibilité relativement satisfaisante du frottis à 2 mois pour ce qui concerne les échecs ou les rechutes (40%) est effacée par une valeur prédictive positive trop faible (3%).

CONCLUSIONS : Dans ce régime de 6 mois, la prolongation de la phase intensive est très inefficiente. La recherche opérationnelle devrait déterminer les algorithmes appropriés permettant de changer plus tôt à un régime plus puissant pour ceux qui en ont besoin, tout en utilisant les frottis de suivi pour leur dépistage.

RESUMEN

MARCO DE REFERENCIA: Los proyectos de la Damien Foundation de control de la tuberculosis en Bangladesh.

OBJETIVO: Evaluar la eficacia de prolongar de 1 mes la fase intensiva del tratamiento antituberculoso en pacientes cuya baciloscopia permanece positiva a los 2 meses de recibir una pauta que comporta la rifampicina (RMP) durante todo el tratamiento.

MÉTODO: Estudio operativo prospectivo, en el cual se practicó en forma aleatoria una prolongación de la fase intensiva del tratamiento en los casos nuevos bacilíferos que presentaron una baciloscopia positiva de cualquier grado en el control a los 2 meses de tratamiento (2M+). En los casos de recaída y fracaso terapéutico definidos por el resultado de la baciloscopia, se practicaron cultivos y pruebas de sensibilidad antes y después del tratamiento, además de la secuenciación del gen *rpo*B.

RESULTADOS: De los 16 708 pacientes que se examinaron, 12 967 presentaron una baciloscopia negativa a los 2 meses (2M−) y a los demás se atribuyó en forma aleatoria la prolongación de la fase intensiva (n = 1870) o la continuación del tratamiento inicial (n = 1871). Se detectaron fracasos confirmados por cultivo en 0,3% de los 2M− (IC95% 0,2–0,4), en 1,2% de los 2M+ sin prolongación (IC95% 0,7–1,8) y en 2,0% de 2M+ (IC95% 1,4–2,8) y las recaídas fueron de 1,2% (IC95% 1,0–1,4), 2,6% (IC95% 1,9–3,4) y 0,9% (IC95% 0,5–1,4), respectivamente. Tomando como referencia los 2M−, la extensión revirtió en forma significativa el riesgo relativo (RR) de recaída en los 2M+ sin extensión (2,2; IC95% 1,6–3,0) a 0,7 cuando se prolongó la fase intensiva (IC95% 0,4–1,2). El RR de fracaso permaneció alto con la prolongación 7,3 (IC95% 4,7–11,5) o sin ella 4,2 (IC95% 2,5–7,2). Se encontraron más casos de multidrogorresistencia después de la prolongación, pero la resistencia adquirida a RMP fue equivalente en todos los grupos. La adecuada sensibilidad de la baciloscopia a los 2 meses como indicador de fracaso o recaída (40%) se debilitó por un valor pronóstico positivo demasiado bajo (3%).

CONCLUSIÓN: La prolongación de la fase intensiva es muy ineficiente en el marco de esta pauta de 6 meses de tratamiento antituberculoso. Sería importante definir mediante investigación operativa los algoritmos adecuados que permitan un cambio más temprano hacia la pauta superior en los pacientes que lo precisen, con base en las baciloscopias de control.