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Outcome definitions for multidrug-resistant tuberculosis treated with shorter treatment regimens

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SUMMARY

OBJECTIVE: To assess whether the revised 2013 World Health Organization (WHO) definitions for multidrug-resistant tuberculosis (MDR-TB) treatment outcomes apply to shorter treatment regimens in low- and middle-income countries and to propose modified criteria.

METHODS: Criteria for 'failure' and 'cure' outcomes were assessed using data on 1006 patients enrolled in an observational study on the standardised 9–11 month shorter MDR-TB regimen in Africa.

RESULTS: Absence of conversion in the intensive phase, a WHO criteria for failure, was the worst performing criterion; reversion had low sensitivity and other criteria provided limited added value. Based on our study results, we propose new definitions for 'treatment failure' as treatment termination or the permanent discontinuation of ⩾2 anti-tuberculosis drugs due to 1) positive culture after ⩾6 months of treatment (except for one isolated positive culture) or 2) at least two consecutive grade ⩾2+ positive sputum smears after ⩾6 months of treatment if culture is not available; and for 'cure' as treatment completion without proof of failure AND two consecutive negative cultures taken ⩾30 days apart, one of which should be after 6 months of treatment.

CONCLUSION: The proposed new definitions are applicable to shorter regimens in low- and middle-income countries, and should also work for the newly recommended longer regimens.

KEY WORDS: MDR-TB; treatment; outcome; definition; shorter regimen

APPROPRIATE TREATMENT OF patients with tuberculosis (TB) reduces morbidity and mortality, and is crucial in stopping transmission of *Mycobacterium tuberculosis* in the community. Monitoring the outcome of anti-tuberculosis treatment is an essential component of the international TB control strategy.[1] TB treatment success in both drug-susceptible and drug-resistant patients is one of the top 10 criteria of the new End TB Strategy set by the World Health Organization (WHO).[2]

Outcome definitions for multidrug-resistant TB (MDR-TB) were initially proposed by Laserson,[3] and later adapted by the WHO in 2006.[4] Flaws in the definitions led Chiang et al. to propose a revised definition for 'treatment failure' in 2011.[5] Revised definitions were introduced in the 2013 updated WHO reporting framework for TB,[6] but challenges have limited their applicability and usefulness for meaningful comparisons. First, they were mainly developed for lengthy MDR-TB regimens, and are not directly applicable to shorter MDR-TB treatment regimens.[7] Reduced treatment duration and the increased efficacy of the shorter regimens render certain criteria in these definitions inappropriate or obsolete. Second, these definitions include bacteriological criteria based exclusively on culture or drug susceptibility testing (DST) results, which are not consistently available in many low- and middle-income countries (LMICs).

We used data from an observational study of the standardised 9–11 months shorter treatment regimen for MDR-TB conducted in nine countries in Africa (Benin, Burkina Faso, Burundi, Cameroon, Central African Republic, Côte d'Ivoire, Democratic Republic of Congo, Niger, Rwanda)[8] to assess the performance of the WHO definitions, test additional criteria and propose simplified definitions that would be appropriate for shorter regimens and feasible in LMICs.

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Table 1 WHO and study definitions of second-line treatment outcomes in RR-, MDR- and XDR-TB patients

WHO definitions	Study definitions
Cured: treatment completed as per the national policy without proof of failure AND ⩾3 consecutive culture samples that are negative after the intensive phase, taken ⩾30 days apart*	Cured: treatment completed as per the national policy without proof of failure AND ⩾3 consecutive cultures taken ⩾30 days apart are negative
Treatment completed: treatment completed as per the national policy without evidence of failure BUT no record that ⩾3 consecutive cultures taken ⩾30 days apart are negative after the intensive phase*	Treatment completed: treatment completed as per the national policy without evidence of failure BUT no record that ⩾3 consecutive cultures taken ⩾30 days apart are negative
Treatment failed: treatment terminated or need to permanently discontinue at least two anti-tuberculosis drugs due to: • lack of conversion† by the end of the intensive phase,* *or* • bacteriological reversion† in the continuation phase after conversion† to negative, *or* • evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, *or* • adverse drug reactions	Treatment failed: positive culture after ⩾6 months of treatment, except for isolated positive cultures (i.e., positive culture preceded by at least one and followed by ⩾2 negative cultures)
Died: patient who dies for any reason during the course of treatment	Idem
Lost to follow-up: patient whose treatment is interrupted for ⩾2 consecutive months	Idem
Not evaluated: patient for whom no treatment outcome is assigned (this includes cases that are transferred out to another treatment unit and whose treatment outcome is unknown)	Idem
Treatment success: sum of 'cured' and 'treatment completed'	Idem

* For 'Treatment failures', lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of the intensive phase as applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between the intensive and continuation phases, a cut-off of 8 months after the start of treatment is suggested to determine when the criteria for 'Cured', 'Treatment completed' and 'Treatment failure' start to apply.
† Conversion (to negative): if two consecutive cultures taken ⩾30 days apart are found to be negative; the specimen collection date of the first negative culture is used as the date of conversion. Reversion (to positive): if, after an initial conversion, two consecutive cultures taken ⩾30 days apart are found to be positive. For the purpose of defining 'Treatment failure', reversion is considered only if it occurs in the continuation phase.
WHO = World Health Organization; RR-TB = rifampicin-resistant tuberculosis; MDR-TB = multidrug-resistant TB; XDR-TB = extensively drug-resistant TB.

METHODS

World Health Organization definitions

WHO definitions apply to all patients with rifampicin-resistant TB (RR-TB), with (i.e., MDR-TB) or without concomitant isoniazid resistance or resistance to second-line drugs. They comprise six mutually exclusive outcomes: 'cured', 'treatment completed', 'treatment failure', 'died', 'lost to follow-up' and 'not evaluated' (Table 1). Definitions for 'cured', 'treatment completed' and 'treatment failure' are mutually dependent: the definition of 'cure' requires treatment completion without proof of failure with bacteriological evidence of cure. The definition for 'treatment completed' follows naturally from the last two definitions because it is defined as treatment completion without proof of failure, but also without bacteriological evidence of cure. 'Success' is defined as the sum of cured and treatment completed.[6]

Study definitions

Definitions used in the nine-country study were similar to the WHO definitions, except for definitions for 'cure' and 'treatment failure' (Table 1). Both definitions were based on culture alone, which is the current 'gold standard'.[9]

The criteria for cure comprised at least three successive negative cultures taken ⩾30 days apart at any time during treatment (i.e., not necessarily after the intensive phase, as required by the WHO definition). Negative cultures obtained during post-treatment follow-up were also accepted.

Study criteria for 'failure' comprised a positive culture after ⩾6 months of treatment, which is the maximum duration of the intensive phase of the shorter regimen.[10,11] Isolated positive cultures (i.e., a single positive culture, preceded by at least one and followed by at least two negative culture results) were not taken into account, as these are known to occur even in case of successful anti-tuberculosis treatment.[12]

'Culture conversion' was defined as at least two consecutive negative culture results not followed by a positive result obtained ⩾30 days apart, regardless of the culture result at baseline. If an isolated positive culture was obtained, 'definitive culture conversion' was considered to have occurred at the month of the first negative culture after the isolated positive culture.

Study data

Data on all 1006 adult patients with RR-TB included in the nine-country study were used. Treatment duration was 9–11 months, with a 4–6-month intensive phase (depending on microscopy results after 4 months), followed by a fixed 5-month continuation phase. The study protocol comprised initial (baseline) bacteriological examination of sputum specimens using smear, culture and DST against first- and second-line drugs. Bacteriological follow-up comprised quantified smear and culture testing performed every month during treatment, and every 6 months after treatment completion up to 24 months.

Table 2 Treatment outcomes of the 1006 patients enrolled in the nine-country study of shorter regimen according to study definitions

Treatment outcome	*n* (%)
Cured	749 (74.5)
Treatment completed	74 (7.4)
Death	79 (7.9)
Failure	60 (6.0)
Lost to follow-up	44 (4.4)
Total	1006 (100)

DST, which was performed by both National and the Supranational Reference Laboratories, was required for any positive culture obtained after 6 months. The exclusion criteria, regimen, technical details of DST and patient monitoring procedure have been described elsewhere.[8]

While smear microscopy was performed regularly, culture testing was irregular due to the difficult environment (reagent shortages, strikes, transport problems, irregular electricity supply). Rifampicin resistance was documented in 100% of the study patients, mostly using Xpert® MTB/RIF (Cepheid, Sunnyvale, CA, USA); initial DST results for other drugs were available for only 60% of the patients. Culture results 6 months and 12 months after treatment completion were available for respectively 67.8% and 57.2% of patients with treatment success; of these, some with a 'treatment completed' result were reclassified as 'cured' if three negative results had been obtained during the entire observation period. Treatment outcomes are presented in Table 2.

Data analysis

Taking culture results obtained during treatment or follow-up as the reference standard, we used study definitions to determine the sensitivity, specificity, positive predictive value (PPV) and negative predictive value (NPV) of the WHO criteria for treatment failure and cure.

'Additional acquired resistance' was defined as resistance to fluoroquinolones or second-line injectables in a sample taken $\geqslant 4$ months after treatment in a patient who was initially susceptible. 'Need to replace at least two drugs due to adverse drug reactions' was defined as permanent discontinuation of at least two drugs as the study protocol did not provide for drug replacement.

Criteria for failure were evaluated among the 883 patients who completed $\geqslant 6$ months of treatment (excluding deaths and loss to follow-up). The criteria for cure were evaluated among the 823 patients with treatment success as per the study definition.

The performance of other criteria for failure based on smear results and of a modified definition for cure were also assessed by comparing with the study definitions (reference).

RESULTS

Definition of treatment failure

Each WHO criterion for treatment failure and the definition combining all four criteria are given in Table 3. While Criteria 1 and 2 are mutually exclusive, the other two are not. For example, a patient may revert in the continuation phase (thereby meeting Criterion 2) and also demonstrate acquired resistance (thereby meeting Criterion 3).

According to Criterion 1 (i.e., lack of culture conversion by the end of the intensive phase), 29/60 patients were study failures (48% sensitivity); 203/823 patients with treatment success (75% specificity) were identified. Most patients with treatment success (138/203) had <2 culture results available (in addition to the baseline result) during the intensive phase. PPV in the study cohort was thus low (13%). A substantial number of patients with later confirmed treatment success (105/823, 13%) converted after the end of the intensive phase (Figure).

Criterion 2 (bacteriological reversion in the con-

Table 3 RR-TB patients who met the 2013 WHO criteria for failure among study failures ($n = 60$) and study successes ($n = 823$) and the performance of WHO criteria for failure with reference to the study definition of failure*

WHO criteria for failure	Failure ($n = 60$) *n* (%)	Success ($n = 823$) *n* (%)	Performance ($n = 883$) Sensitivity %	Specificity %	PPV %	NPV %
1 Lack of culture conversion by the end of the intensive phase	29 (48)	203 (25)	48	75	13	95
2 Reversion in continuation phase after two negative cultures in the intensive phase	9 (15)	0	15	100	100	94
3 Additional acquired resistance†	9 (15)	1 (0)	15	99.9	90	94
4 Need for permanent replacement of $\geqslant 2$ drugs‡ due to adverse drug reactions	0	0	0	100	—	93
Any one of the four criteria stated above§	40 (67)	203 (25)	67	75	17	97

* Failure defined by culture positivity at Month 6 of treatment, except for isolated positive cultures (i.e., culture preceded by $\geqslant 1$ and followed by $\geqslant 2$ negative cultures).
† Acquired resistance to fluoroquinolones or to second-line injectable drugs on a sample tested $\geqslant 4$ months after the start of treatment, when baseline drug susceptibility testing showed initial susceptibility and strains were not proven to be different using genotyping methods.
‡ Permanent discontinuation of $\geqslant 2$ drugs. As per the study protocol, drugs were not replaced, instead the entire regimen was changed in case of failure.
§ Criteria 1 and 2 are mutually exclusive, but the other two are not, e.g., a patient may have reverted in the continuation phase (thereby meeting Criterion 2) and also demonstrated acquired resistance (thereby meeting Criterion 3).
RR-TB = rifampicin-resistant tuberculosis; WHO = World Health Organization; PPV = positive predictive value; NPV = negative predictive value.

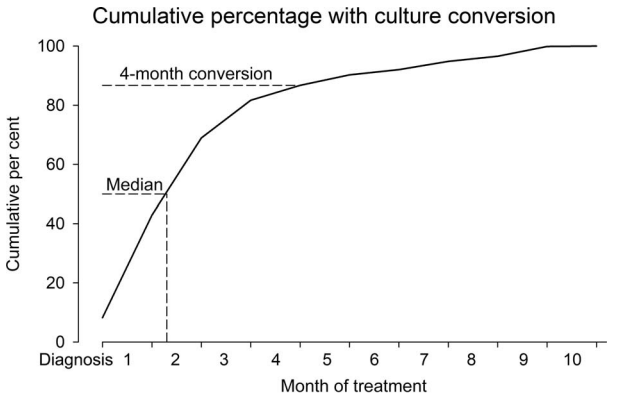

Figure Month of culture conversion* among patients with treatment success in a nine-country study ($n = 792$).† *Defined by ⩾2 consecutive negative culture results on a specimen taken ⩾30 days apart not followed by a positive one during treatment, regardless of culture result at baseline. If an isolated positive culture (i.e., a positive culture preceded by ⩾1 and followed by ⩾2 negative cultures) was obtained, definite culture conversion was considered to have occurred when the first negative culture after the isolated positive culture was obtained. †Definite conversion in 792/823 patients with treatment success but no conversion in 31.

tinuation phase) had a specificity of 100%, and thus a PPV of 100%. However, only nine of the 60 study failures (15% sensitivity) were identified based on this criterion because those who had only one positive culture in the continuation phase and those with no conversion during the intensive phase were missed.

Eleven patients developed additional acquired resistance (Criterion 3), nine of whom failed treatment, one was lost to follow-up after 5 months and one had treatment success. The specificity was 99.9% and PPV was 90%.

In three patients, ⩾2 drugs had to be replaced due to adverse drug reactions (Criterion 4) during the intensive phase. None had treatment failure according to the study definition (0% sensitivity) and none had treatment success: two died and one was lost to follow-up (100% specificity).

Application of the WHO definition criteria according to which patients meeting any of these four criteria were declared failures resulted in the correct identification of 40/60 study failures (67% sensitivity) and incorrect identification as failures of 203/823 patients, who subsequently experienced treatment success (75% specificity). Fifteen patients with unsuccessful outcomes (10 deaths, five lost to follow-up) met at least one of the first three criteria for failure.

The various combinations of smear results recorded ⩾2 months after the end of the intensive phase, i.e., after 6 months of treatment (or 7–8 months in case of a prolonged intensive phase) as compared with the study definition for treatment failure are given in Table 4. The criterion based on at least two consecutive grade ⩾2+ positive smears resulted in misclassification of only four of the 823 successes and detection of 10 of the study failures (17% sensitivity); this criterion had the highest specificity (99.8%).

Definitions for cure

The WHO definition criterion for cure (three negative cultures in the continuation phase) was 100% specific, but led to identification of only 592/749 patients considered to be cured as per the study definition (79% sensitivity). The PPV was 100%; however, the NPV for the 823 successes was very low (32%).

The definition criterion for cure requiring only two negative culture results, one of which was obtained after 6 months of treatment, led to the identification of 697 cured patients (93% sensitivity) and reclassification as cured of 15/74 patients who had been classified as 'treatment completed' according to the study definition (80% specificity). However, there was no change in the overall number of treatment successes.

DISCUSSION

The WHO outcome criteria for failure and cure proved impractical and inadequate when applied to our large cohort of MDR-TB patients treated with the shorter regimen. The worst-performing failure criterion was the first (lack of conversion), leading to a high proportion of false identification of 'failures' in patients with proven cure. This was because conversion had to be achieved by the end of the intensive phase. At the time this criterion was established,

Table 4 RR-TB patients who met the criteria for failure based on smear positivity among study failures ($n = 60$) and study successes ($n = 823$), and the performance of these criteria with reference to the study definition for failure*

Criterion #	Proposed definitions	Failure ($n = 60$) n (%)	Success ($n = 823$) n (%)	Performance ($n = 883$) Sensitivity %	Sensitivity %	Sensitivity %	Sensitivity %
1	One positive smear (⩾1+) at Month 6†	41 (68)	91 (11)	68	89	31	97
2	Two consecutive positive smears (⩾1+) at Month 6†	38 (63)	60 (7)	63	93	39	97
3	One positive smear (⩾2+) at Month 6†	24 (40)	13 (2)	40	98	65	96
4	Two consecutive positive smears (⩾2+) Month 6†	10 (17)	4 (0)	17	100	71	94

* Failure defined by culture positivity at Month 6 of treatment, except for isolated positive cultures (i.e., culture preceded by ⩾1 and followed by ⩾2 negative cultures).
† 2 months after the end of the intensive phase, i.e., after 6 months (in case of a 4-month intensive phase), 7 months (in case of a 5-month intensive phase) or 8 months (in case of a 6-month intensive phase).
RR-TB = rifampicin-resistant tuberculosis.

MDR-TB treatment comprised an 8-month intensive phase.[13,14] With the shorter regimen, however, definite conversion was possible after 6 months (i.e., the longest possible duration of the intensive phase in the shorter regimen) in a substantial proportion of patients with confirmed cure (13%). Second, this criterion requires numerous culture results, which were very difficult to obtain in LMICs within the 4-month intensive phase period. This also affects the performance of the 'reversion' criterion because it requires at least two positive cultures within the short continuation phase (5 months). Poor laboratory capacity, sputum transportation problems and lack of timely results are huge challenges to the currently recommended requirement of monthly culture results.[15] The study criterion for 'treatment failure' (at least one positive culture after 6 months of treatment, with the exception of isolated positive cultures) could be a reasonable alternative, as it captures both early failures due to the absence of conversion and later reversions.

Criteria 3 and 4 for failure are highly specific but provide very limited added value. In our cohort, nine of the 11 patients with acquired resistance failed treatment according to our definition (positive culture after 6 months), one was cured and the remaining patient was lost to follow-up. Because acquired resistance is usually observed in culture samples that are positive during the continuation phase, most patients satisfying this criterion already meet the bacteriological criterion for failure. Availability of molecular DST methods could, in theory, allow earlier detection of acquired resistance in direct specimens, but their clinical importance is uncertain because inconsistent DST results may be more frequent in LMICs.[15] Very few patients in our cohort required at least two drugs to be replaced due to adverse drug reactions. Even if it is argued that the three patients for whom two drugs were discontinued would have failed treatment, they died or were lost to follow-up before it was possible to modify their treatment.

We found that a criterion for failure based on smear results (at least two grade $\geqslant$2+ positive smears after 6 months) had very high specificity. Although application of this criterion led to the identification of only a few of the true failures, all but four of these patients identified using positive smears failed treatment because they were culture-positive after 6 months. Since smear microscopy and accurate smear grading can be performed in most peripheral laboratories and results are rapidly available, this additional criterion could be an early indicator for a change in regimen if culture results are not available.

While the WHO definition criterion for cure has theoretical and intuitive appeal, its applicability was also limited due to the difficulty in obtaining the required number of culture results within the short continuation phase (5 months) of the shorter regimen. Culture conversion occurred early in many patients treated with the shorter regimen (69% before Month 2). It is therefore more realistic to require three consecutive negative cultures without necessarily restricting these to the continuation phase. Further attempts to reduce the required number of negative cultures during treatment to two, including one after 6 months of treatment, would only marginally reduce its performance, while enabling a much larger application in LMICs.

We therefore propose modified definitions for 'treatment failure' and 'cure' based on our study definitions, including an additional criterion for failure based on sputum smear microscopy and a relaxation of the criteria for cure. The third and fourth criteria of the WHO definition for failure should not be retained because they have little relevance and offer very limited added value. Our proposed new definitions are given in Table 5. Ideally, their application requires monthly sputum smear testing and only a minimum of three culture samples during treatment (one at baseline, a second at the end of the intensive phase and a third after 6 months of treatment or later). These are essential to detect failure and prove bacteriological cure. If a culture is positive after 6 months, additional cultures are recommended to either confirm failure or prove that the positive culture is an isolated one.

Our analysis had some limitations. We used current study definitions as the reference standard, and this may be challenged. Culture results for several patients were missing during treatment, which limited our ability to determine outcomes. However, inclusion of all negative culture results during follow-up in the study definition criteria reinforced the validity of the reference standard. Negative culture results obtained after treatment completion helped confirm cure in a substantial proportion of cohort patients.

CONCLUSION

Our proposed definitions are a clear improvement over the WHO definitions for many LMICs if the shorter regimen is used. In similar settings, these would also apply to the longer regimen recently recommended by the WHO in the revised guidelines for MDR-TB treatment, particularly regimens without injectable drugs.[16–18] However, further research would be needed to evaluate this hypothesis. National TB programmes and clinicians in LMICs face immense difficulties in MDR-TB management due to limited laboratory capacity, poor quality of data on treatment outcomes at both the national and international levels and lack of reliable cure rates. The potential benefits of a simple, feasible (yet accurate and reliable) definition of treatment outcomes are likely to be considerable.

Table 5 Proposed definitions for MDR-TB treatment outcome with the shorter regimen

Outcome	Definition
Cure	Treatment completed without evidence of failure AND 2 consecutive negative cultures* taken ⩾30 days apart, one of them after 6 months of treatment
Treatment completed	Patient who has completed treatment without evidence of failure BUT who does not meet the criteria for cure
Failure	Treatment termination or need for permanent regimen change of ⩾2 drugs due to: • ⩾1 positive culture after ⩾6 months of treatment, except for isolated positive culture (i.e., a positive culture preceded by at least one and followed by ⩾2 negative cultures) • ⩾2 consecutive grade ⩾2+ sputum smears after 6 months of treatment (if cultures are not available)†
Died	Patient who died for any reason during the course of treatment
Lost to follow-up	Patient whose treatment was interrupted for ⩾2 consecutive months
Not evaluated	Patient for whom no treatment outcome is assigned (this includes cases who are transferred out to another treatment unit and whose treatment outcome is not known)
Treatment success	Sum of 'cured' and 'treatment completed'

* A minimum of three cultures should be performed: one before treatment initiation (M0), one at the end of intensive phase (M4, M5 or M6 if the intensive phase is prolonged) and one after 6 months of treatment. Additional specimens should be requested in case of one positive culture after 6 months to either confirm failure or prove that a positive culture is isolated.

† Smears should be performed on sputum specimen taken before initiation of treatment (M0), and then monthly (M1, M2, M3, M4, M5, M6, M7, M8, M9, and possibly M10 and M11 if the intensive phase is prolonged). Smears should be performed on two specimens at M4, and M5 if positive at M4, to allow the physician to decide whether the intensive phase should be prolonged. Results are classified as rare = 1–9 AFB/100 fields; 1+ = 10–99 AFB/100 fields; 2+ = 1–9 AFB/field; 3+ = ⩾10 AFB/field.

MDR-TB = multidrug-resistant tuberculosis; M = month; AFB = acid-fast bacilli.

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Conflicts of interest: none declared.

References

1 World Health Organization. Framework for effective tuberculosis control. WHO/TB/94.179. Geneva, Switzerland: WHO, 1994.
2 World Health Organization. Implementing the End TB Strategy: the essentials. WHO/HTM/TB/2015.31. Geneva, Switzerland: WHO, 2015.
3 Laserson K F, Thorpe L E, Leimane V, et al. Speaking the same language: treatment outcome definitions for multidrug-resistant tuberculosis. Int J Tuberc Lung Dis 2005; 9: 640–645.
4 World Health Organization. Guidelines of the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2006.361. Geneva, Switzerland: WHO, 2006.
5 Chiang C Y, Van Deun A, Trébucq A, Heldal E, Caminero J A, Aït-Khaled N. Treatment of multidrug-resistant tuberculosis: definition of the outcome 'failure'. Int J Tuberc Lung Dis 2011; 15: 4–5.
6 World Health Organization. Definitions and reporting framework for tuberculosis–2013 revision. WHO/HTM/TB/2013.2. Geneva, Switzerland: WHO, 2013.
7 World Health Organization. WHO treatment guidelines for drug-resistant tuberculosis (2016 update). WHO/HTM/TB/2016.04. Geneva, Switzerland: WHO, 2016.
8 Trébucq A, Schwoebel V, Kashongwe Z, et al. Treatment outcome with a short multidrug-resistant tuberculosis regimen in nine African countries. Int J Tuberc Lung Dis 2018; 22: 17–25.
9 Mitnick C D, White R A, Lu C, et al. Multidrug-resistant tuberculosis treatment failure detection depends on monitoring interval and microbiological method. Eur Respir J 2016; 48: 1160–1170.
10 Van Deun A, Aung K J M, Halim M A, et al. Short, highly effective, and inexpensive standardized treatment of multidrug-resistant tuberculosis. Am J Respir Crit Care Med 2010; 182: 684–692.
11 Aung K J M, Van Deun A, Declercq E, et al. Successful '9-month Bangladesh regimen' for multidrug-resistant tuberculosis among over 500 consecutive patients. Int J Tuberc Lung Dis 2014; 18: 1180–1187.
12 Fox W, Ellard G A, Mitchison D A. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council Tuberculosis Units, 1946–1986, with relevant subsequent publications. Int J Tuberc Lung Dis 1999; 3 (Suppl 2): S231–S279.
13 Ahuja S D, Ashkin D, Avendano M, et al. Multidrug-resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. PLOS Med 2012; 9: e1001300.
14 World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. WHO/HTM/TB/2014.11. Geneva, Switzerland: WHO, 2014.
15 Kim S J. Drug susceptibility testing in tuberculosis: methods and reliability of results. Eur Respir J 2005; 25: 564–569.
16 World Health Organization. Introduction of bedaquiline for the treatment of multidrug-resistant tuberculosis at country level. Implementation plan. WHO/HTM/TB/2014.11. Geneva, Switzerland: WHO, 2015.
17 World Health Organization. Rapid communication: Key changes to treatment of multidrug- and rifampicin-resistant tuberculosis (MDR/RR-TB). WHO/CDS/TB/2018.18. Geneva, Switzerland: WHO, 2018. http://www.who.int/tb/publications/2018/WHO_RapidCommunicationMDRTB.pdf?ua=1. Accessed February 2019.
18 World Health Organization. WHO treatment guidelines for multidrug- and rifampicin-resistant tuberculosis, 2018 update. WHO/CDS/TB/2018.15. Geneva, Switzerland: WHO, 2018.

RÉSUMÉ

OBJECTIF : Evaluer dans quelle mesure les définitions des résultats du traitement de la tuberculose multirésistante (TB-MDR) révisées par l'Organisation Mondiale de la Santé (OMS) en 2013 s'appliquent aux protocoles plus courts dans les pays à revenu faible et moyen et proposer des critères modifiés.

MÉTHODE : La performance des critères d'échec et de guérison a été évaluée grâce aux données de 1006 patients enrôlés dans une étude d'observation du protocole standard plus court de 9 à 11 mois pour la TB-MDR en Afrique.

RÉSULTATS : Dans la définition OMS de l'échec, l'absence de conversion pendant la phase intensive a été le critère le moins performant, la réversion a eu une faible sensibilité et les autres critères ont eu peu de valeur ajoutée. Ces résultats nous ont amené à proposer de nouvelles définitions: 'échec', défini comme traitement arrêté ou besoin de modification permanente du protocole portant sur au moins deux médicaments anti-tuberculeux à cause de 1) culture positive après ⩾6 mois de traitement (sauf en cas de culture positive isolée), ou 2) au moins deux frottis de crachats consécutifs positifs avec une grade ⩾2+ après ⩾6 mois de traitement (si les cultures ne sont pas disponibles) ; et guérison, définie comme traitement achevé sans signe d'échec ET deux cultures consécutives négatives à au moins 30 jours d'intervalle, dont une après 6 mois de traitement.

CONCLUSION : Les nouvelles définitions proposées sont applicables aux protocoles plus courts dans les pays à revenu faible et moyen et devraient également être valables pour les protocoles plus longs récemment recommandés.

RESUMEN

OBJETIVO: Evaluar la conveniencia de las definiciones de desenlace terapéutico de la tuberculosis multirresistente (TB-MDR), revisadas por la Organización Mundial de la Salud (OMS) en el 2013, cuando se utilizan esquemas terapéuticos más breves en los países de ingresos bajos y medianos y proponer criterios modificados.

MÉTODO: Se evaluó la pertinencia de los criterios de fracaso y curación a partir de los datos de 1006 pacientes incluidos en un estudio observacional del esquema estandarizado antituberculoso más breve de 9–11 meses de TB-MDR, realizado en África.

RESULTADOS: En la definición de fracaso de la OMS, el criterio con el desempeño más deficiente fue la falta de conversión del cultivo (a negativo) durante la fase intensiva; la reversión (a positivo) exhibió una sensibilidad baja y otros criterios ofrecieron escaso valor añadido. Estos resultados llevaron a proponer las siguientes nuevas definiciones: 'fracaso' definido como tratamiento suspendido o necesidad de un cambio permanente de por lo menos dos fármacos antituberculosos debido a: 1) cultivo positivo después de ⩾6 meses de tratamiento (con la excepción de un cultivo positivo aislado); o 2) por lo menos dos baciloscopias de esputo con resultado positivo de ⩾grado 2+, después de ⩾6 meses de tratamiento (cuando no se cuenta con cultivos); y 'curación' como tratamiento completo sin evidencia de fracaso Y dos cultivos consecutivos negativos, como mínimo con 30 días de intervalo y uno de ellos después de 6 meses de tratamiento.

CONCLUSIÓN: Las nuevas definiciones propuestas se pueden aplicar a los tratamientos más breves en los países de ingresos bajos y medianos y también serían útiles para los esquemas más prolongados recomendados recientemente.