microangiopathy: a clinical analysis of 30 autopsy cases. *Intern Med* 2013;52:1317–1323.
3. von Herbay A, Illes A, Waldherr R, Otto HF. Pulmonary tumor thrombotic microangiopathy with pulmonary hypertension. *Cancer* 1990;66:587–592.
4. McCabe JM, Bhave PD, McGlothlin D, Teerlink JR. Running from her past: a case of rapidly progressive dyspnea on exertion. *Circulation* 2011;124:2355–2361.
5. Gavin MC, Morse D, Partridge AH, Levy BD, Loscalzo J. Clinical problem-solving: breathless. *N Engl J Med* 2012;366:75–81.

How Do the New Definitions for Multidrug-Resistant Tuberculosis Treatment Outcomes Really Perform?

To the Editor:

Bastard and colleagues (1) compare treatment outcomes of 1,455 patients with multidrug-resistant tuberculosis enrolled on second-line treatment in the period 2001–2009, applying the 2008 and 2013 World Health Organization treatment outcome definitions.

Their most significant finding is that the 2013 definitions lead to a much higher reported failure rate (37.9% vs. 11.3%). One of their explanations is the reclassification of successfully treated patients under 2008 definitions as failures under 2013 definitions. Bastard and colleagues suggest that this is a reflection of ineffective treatment and state that the 2013 definitions give a better indication of the reality.

We share the conclusion that a positive culture at 6 months is a strong warning for potential treatment failure. However, to our understanding, the reported shift from success to failure may largely be explained by the choice for a 6-month cutoff point for sputum culture conversion. The 2013 definitions (2) propose an 8-month cutoff for regimens in which no maximum duration of the intensive phase is defined or without a clear distinction between the intensive and continuation phases. This is applicable to this cohort receiving individualized treatment. The choice of an 8-month cutoff is justified by a metaanalysis of data from 9,153 patients with multidrug-resistant tuberculosis (3) showing that, per the 2008 definitions, a duration of the initial phase of 7.0–8.4 months corresponded to a higher likelihood of successful treatment than a duration of 5.5–6.9 months.

We invite the authors to reassess the treatment outcomes in their cohort, applying the 8-month cutoff, to assess whether this would lead to higher cure and success rates resulting from expectedly higher conversion rates after 8 than after 6 months.

Another point we would like to highlight in the 2013 definitions is the addition of "a change of two or more drugs, due to adverse drug reactions (ADRs)" to criteria for failure, regardless of the bacteriological status of the patient. The aim of the World Health Organization reporting framework is not to compare specific regimens but, rather, to evaluate programmatic performance; that is, the outcome of an algorithm consisting of a series of diagnostic and treatment decisions. If these decisions include a change of regimen for patients with ADRs, this should be allowable and be captured as (adequate) programmatic performance. Therefore, we propose to World Health Organization that a regimen change of two or more drugs as a result of ADRs should not be an automatic disqualifier for treatment success.

We also request that the authors make an assessment of the effect of inclusion and exclusion of the criterion "regimen change of at least 2 drugs due to ADRs" as a failure-defining criterion.

We thank the authors in advance for their valuable efforts in highlighting important issues in applying the revised reporting definitions. ■

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References

1. Bastard M, Bonnet M, du Cros P, Khamraev AK, Hayrapetyan A, Kimenye K, Khurkhumal S, Dlamini T, Telnov A, Sanchez-Padilla E, *et al*. Revised definitions of multidrug-resistant tuberculosis treatment outcomes: closer to the reality? *Am J Respir Crit Care Med* 2015;191: 355–358.
2. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision. Geneva: World Health Organization; 2013 [accessed 2015 Oct 3]. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
3. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, Becerra MC, Benedetti A, Burgos M, Centis R, *et al*.; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012;9: e1001300.

Reply

From the Authors:

Gebhard and colleagues rightly underline that the 2013 World Health Organization definitions (1) of multidrug-resistant tuberculosis treatment outcomes propose a cutoff at 8 months for culture conversion when no maximum duration of intensive phase is defined.

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Table 1. Treatment Outcomes of Multidrug-Resistant Tuberculosis Patients Using the 2008 and 2013 World Health Organization Definitions with a 6- and 8-Month Cutoff (N = 1,455)

	2008 WHO Definitions		2013 WHO Definitions, 6-mo Cutoff		2013 WHO Definitions, 8-mo Cutoff	
Outcome	**N**	**%**	**N**	**%**	**N**	**%**
Cure	505	34.7	511	35.1	501	34.4
Treatment completed	303	20.8	106	7.3	134	9.2
Success	808	55.5	617	42.4	635	43.6
Death	127	8.7	60	4.1	62	4.3
Failure	165	11.3	551	37.9	529	36.4
Lost to follow-up*	333	22.9	211	14.5	213	14.6
Not evaluated†	2	1.6	16	1.1	16	1.1

Definition of abbreviation: WHO = World Health Organization.
*"Defaulter" in the 2008 definitions.
†Transferred "out" or "still on treatment" in the 2008 definitions.

As suggested by Gebhard and colleagues, we retrospectively assessed the treatment outcomes using an 8-month cutoff for sputum culture conversion (2). As shown in Table 1, no significant difference was observed in the success and failure rates between the 6- and 8-month cutoffs. Indeed, the proportion of failure was 37.9% using a 6-month cutoff and 36.4% using an 8-month cutoff, whereas the proportion of success was 42.4 and 43.6%, respectively. Interestingly, the cure rate was even slightly lower with the 8-month cutoff, as 10 patients had one of their three negative cultures required to meet the definition of "cure" between the sixth and eighth months of treatment.

As the 2013 definition was applied retrospectively to our data, it was not possible in our analysis to identify "changes of at least 2 drugs in the regimen due to adverse events." We could only identify patients for whom the treatment was "terminated because of serious adverse event," which resulted in a potential underestimation of the number of failures. Removing these 43 patients from the analysis as suggested by Gebhard and colleagues would have resulted in a proportion of failure of 34.4% (486/1412).

In conclusion, changing the cutoff for culture conversion to 8 months and removing the patients with treatment "terminated because of serious adverse event" did not change significantly the multidrug-resistant tuberculosis treatment outcomes, highlighting the poor efficacy of the current regimen. We also think that a 6-month cutoff for culture conversion is more appropriate programmatically to have time to receive culture results to be able to make the decision on a potential treatment change at 8 months, which is the recommended duration of the intensive phase based on the metaanalysis by Ahuja and colleagues (3). ■

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References

1. World Health Organization. Definitions and reporting framework for tuberculosis: 2013 revision. Geneva: World Health Organization; 2013 [accessed 2015 Apr 13]. Available from: http://apps.who.int/iris/bitstream/10665/79199/1/9789241505345_eng.pdf
2. Bastard M, Bonnet M, du Cros P, Khamraev AK, Hayrapetyan A, Kimenye K, Khurkhumal S, Dlamini T, Telnov A, Sanchez-Padilla E, *et al*. Revised definitions of multidrug-resistant tuberculosis treatment outcomes: closer to the reality? *Am J Respir Crit Care Med* 2015;191:355–358.
3. Ahuja SD, Ashkin D, Avendano M, Banerjee R, Bauer M, Bayona JN, Becerra MC, Benedetti A, Burgos M, Centis R, *et al*.; Collaborative Group for Meta-Analysis of Individual Patient Data in MDR-TB. Multidrug resistant pulmonary tuberculosis treatment regimens and patient outcomes: an individual patient data meta-analysis of 9,153 patients. *PLoS Med* 2012;9:e1001300.