TB Case Definitions
Revision May 2011

Table of contents

1. Background

TB and MDR-TB case and outcome definitions are essential for effective TB surveillance. They are necessary to provide consistent information on epidemiological trends and control programme performance. They are also used to guide treatment selection (e.g. MDR-TB treatment).

Standardised surveillance should allow the following activities to be consistently undertaken:

- evaluation of service performance including treatment outcomes through cohort analysis;
- monitoring of control efforts;
- identification of at-risk groups;
- detection of outbreaks;
- review and updating of guidelines and selection of treatment regimens;
- compliance with statutory requirements for reporting.

Conventional approaches to defining a case of TB and MDR-TB and classifying treatment outcomes depend on bacteriological methods (microscopy, culture, drug susceptibility testing). However, molecular methods for diagnosing TB that have been endorsed by WHO now exist. WHO has endorsed line probe assays for the detection of rifampicin resistance and (in late 2010) Xpert MTB/RIF for the simultaneous detection of TB and rifampicin resistance. Both can be used as stand-alone tests. Other molecular tests are in the pipeline.

These new molecular methods do not readily fit within the current case and treatment outcome definitions. Moreover, given significant growth in the TB diagnostics (both molecular and non-molecular technologies) pipeline it is conceivable that additional, stand-alone WHO-recommended diagnostics (WRD) may become available in the near future. As a consequence of these developments, case and treatment outcome definitions need to be revisited and updated. This revision and updating offers an opportunity to improve on current definitions, while also ensuring that any updated definitions will continue to apply when new tests become available.

This document highlights two options (labeled as Option 1 and Option 2) for case definitions and their core subcategories. It also presents two options (Option 1 and Option 2) for the definition of treatment outcomes, for MDR-TB and non MDR-TB separately. Option 1 is closest to existing case definitions, with relatively minor modifications (that bring added complexity) that accommodate new diagnostics. Option 2 is an alternative option with more substantive changes from existing case and treatment outcome definitions that bring greater simplicity.

After the presentation of the two alternative options, the main implications of adopting them are discussed. For example, both options require an adaptation of recording and reporting systems. While further disaggregations can easily be generated in countries with case-based or patient-based electronic recording and reporting system, it is also recognized that countries may require a prolonged transition from paper-based to electronic surveillance systems. **This document therefore presents a minimum set of**

essential dis-aggregations for a TB (including MDR-TB) surveillance system that are theoretically feasible for traditional paper-based TB surveillance systems.

The following points should also be stressed at the outset:

- **Case and treatment outcomes definitions are meant to be used primarily for surveillance purposes**;
- **The term "WRD" (WHO recommended diagnostics) is used throughout this document.** This is to avoid reference to any specific test but also to highlight the fact that WHO endorsement of new TB diagnostics will need to be test-specific for the foreseeable future. 'Blanket' approval of technologies (eg. all molecular tests) is not possible, given distinctly different performance results.

This document was prepared by a small writing group under the joint coordination of the TB Diagnostics and Laboratory Strengthening and the TB Monitoring and Evaluation units of the Stop TB Department of WHO.

2. Current WHO definitions of cases and treatment outcomes

Definite case of tuberculosis [1]. A patient with Mycobacterium tuberculosis complex identified from a clinical specimen, either by culture or by a newer method such as molecular line probe assay. In countries that lack the laboratory capacity to routinely identify M. tuberculosis, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.

Case of tuberculosis. A definite case of TB or one in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment. Any person given treatment for TB should be recorded as a case. Incomplete "trial" TB treatment should not be given as a method for diagnosis.

Cases of TB are also classified according to (see Annex):

- anatomical site of disease,
- bacteriological results (including drug resistance),
- history of previous treatment,
- HIV status of the patient.

Multi-drug resistant (MDR) TB is defined as TB caused by Mycobacterium tuberculosis resistant in vitro to the effects of isoniazid and rifampicin, with or without resistance to any other drugs [2].

Treatment outcomes, non MDR cases or MDR status not documented [1]:

- **Cure.** A patient whose sputum smear or culture was positive at the beginning of the treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion.
- **Completed.** A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion.
- **Treatment success** is the sum of cure and completed.
- **Failure.** A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive
- **Default.** A patient whose treatment was interrupted for 2 consecutive months or more.
- **Died.** A patient who dies for any reason during the course of treatment
- **Transfer out.** A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.

Some cases registered the previous year may be not evaluated for treatment outcomes; they should be added to denominators when computing proportions.

Treatment outcomes, MDR-TB [1, 2]

- **Cure**: MDR-TB patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.
- **Completed**: MDR-TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).
- **Died**: MDR-TB patient who dies for any reason during the course of MDR-TB treatment.
- **Failed**: Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events.
- **Default**: MDR-TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.
- **Transfer out**: MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.

3. Commentary on current WHO definitions of cases and treatment outcomes

3.1 Case definitions

"Definite cases" include smear-positive cases without formal species confirmation of *M. tuberculosis* through culture and identification. In many countries, including those in the European Union (EU), smear microscopy is not considered a confirmatory test because it detects all acid fast bacilli, including non-tuberculosis mycobacteria as well as a few non-pathogenic environmental bacilli. Furthermore, HIV-infected patients often shed non-tuberculosis acid fast bacilli.

Cases are further classified by the history of previous anti-TB treatment. Previously treated patients are more at risk of MDR-TB - and therefore, should be investigated for drug susceptibility. Such patients require a treatment regimen that differs from patients never previously treated.

A complication arises from the difference between (i) relapses and (ii) all other retreatments. Relapses occur after a period without TB and refer to *new TB episodes*. In contrast, other re-treatments (after failure or after default) are the continuation of a TB episode that requires *a change in the treatment regimen*. Changes in treatment regimen traditionally require re-registration. Relapses contribute to counts of incident episodes of TB while other re-treatments contribute to counts of prevalent cases.

The term relapse itself is not correct in the sense that so-called relapse cases include a mixture of a) true relapses and b) cases due to re-infection.

Besides classifying cases according to treatment history, cases are further disaggregated according to:

- HIV status
- MDR status
- anatomical site of disease. Case counts of extra-pulmonary cases are commonly reported but seldom interpreted in meaningful ways for policy decision making.

Current TB indicators and information systems do not capture information on groups with a high risk of TB. However, information on at-risk groups for MDR-TB is captured. Knowledge about at-risk groups can be used for policy decision-making on appropriate diagnostic and prevention interventions; these are of increasing relevance with the introduction of rapid diagnostic tools. The assessment of inequities in the burden of TB requires an appropriate disaggregation of groups defined according to geographical, social, or other determinants. There is currently no information on co-morbidities other than HIV reported in the WHO-recommended recording and reporting system [4].

3.2 Treatment outcomes

Treatment outcomes have traditionally been recorded for smear-positive cases (with more recent efforts to record outcomes for new pulmonary smear-negative and extra-pulmonary cases), disaggregated by treatment history. With the introduction of the Stop TB Strategy, an increasing number of countries report treatment outcomes for smear-negative cases, HIV-positive cases and the subset of MDR-TB cases on second-line anti-TB drugs that are reported to National TB Programmes. In smear negative cases, there is no “cured” outcome category.

In current WHO policy guidance on the use of WRD Xpert MTB/RIF, smear microscopy and/or culture may be replaced with Xpert MTB/RIF for initial diagnosis in defined high-risk patient groups [6]. A large proportion of Xpert MTB/RIF-positive patients will be found smear-negative at the time of diagnosis, as a result of the greater sensitivity of Xpert MTB/RIF to detect *M. tuberculosis* bacilli. Given that molecular tests also detect DNA from nonviable organisms, it is currently recommended that treatment follow-up not be done with Xpert MTB/RIFWRD but with smear microscopy and/or culture.

Treatment outcome definitions for MDR-TB cases who are “cured” or “failed” are exceptionally complicated. They have limited usage for the clinician as they need to be applied retrospectively and cannot be usefully applied for patient decision making. The computation of MDR-TB treatment outcomes requires case-based computerized information systems (unless the analyzed cohort of patients is only comprised of a few records that can be examined manually). The lack of bacteriological information at different endpoints, which is a frequent occurrence, makes these definitions difficult to apply. They cannot be applied to treatment regimens shorter than 12 months.

Current case definitions reflect additions made as the world transitioned from DOTS to the Stop TB Strategy, resulting in the introduction of many sub-categories.

4. Updated case definitions

4.1 Option 1

Option 1 is illustrated in Figure 1 and further explained in Table 1. Minimal changes are proposed. Current case definitions are extended with additional subcategories and disaggregations to accommodate WRD.

Figure 1. Case definitions, option 1

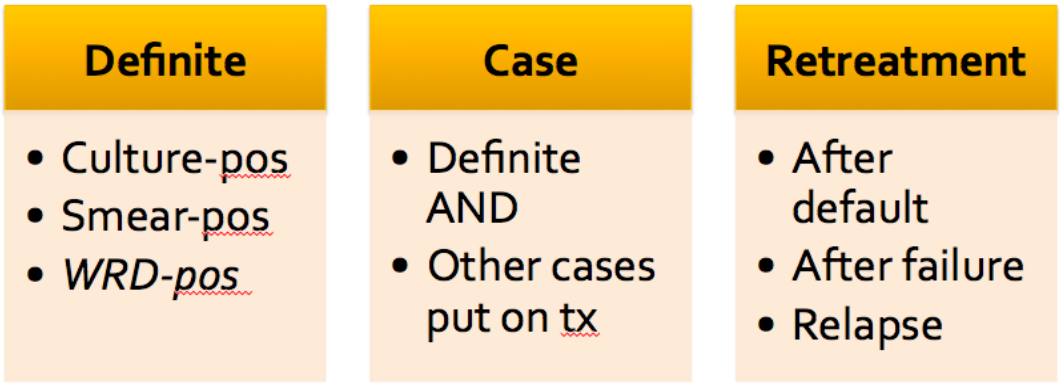

Table 1: Case definitions and disaggregations, Option 1

Category	Definition	Disaggregated by**	and by
Definite	A patient with *Mycobacterium tuberculosis* complex identified from a clinical specimen, either by culture or by new WRDs In countries that lack the laboratory capacity to routinely identify *M. tuberculosis*, a pulmonary case with one or more initial sputum smear examinations positive for acid-fast bacilli (AFB) is also considered to be a "definite" case, provided that there is a functional external quality assurance (EQA) system with blind rechecking.	• Smear • WRD • HIV*	• AgeX sex • ageX sex • ART; CPT
Case	A definite TB case or a case in which a health worker (clinician or other medical practitioner) has diagnosed TB and has decided to treat the patient with a full course of TB treatment.	• Smear neg, extra-pulm. • HIV* • Age	• Sex • ART • CPT • Sex
Retreatment	• Returning after default • Retreated after treatment failure • relapse	• Smear • WRD • MDR	

***** WHO-recommended Rapid Diagnostics

** HIV results are recorded as part of treatment outcomes

Implications of adopting Option 1

Case definitions are blurred and inconsistent over time. The criteria for "definite cases" include diagnostic tests with widely varying performance characteristics. Meaningful comparisons among countries and within countries over time require the disaggregation of definite cases by smear, culture or WRD result. In settings where smear examination (and/or culture) is not be performed because WRDs are available for diagnosis, time-series will become very difficult to interpret. This is because existing WRDs are considerably more sensitive than direct smear microscopy. In settings were definite cases were mostly smear-positive cases, the addition of WRD positive cases in the "definite case" category will result in an increase in numbers and rates.

The gradual introduction of new diagnostic tools (rather than immediate full coverage) as recommended by WHO complicates the monitoring of trends in case detection until full coverage has been achieved.

Paper-based recording and reporting. Forms and registers need to be adapted. New subcategories are introduced (notably, definite cases by WRD status, further disaggregated by ageXsex), significantly increasing the complexicity of the currently recommended paper-based recording and reporting [4].

4.2 Option 2

Option 2 is illustrated in Figure 2 and further explained in Table 2. Categories are more rigorously defined; allowing consistent monitoring of time series. Proposed categories are similar to the current definitions used in the EU (see Annex).

Figure 2. Case definitions, option 2

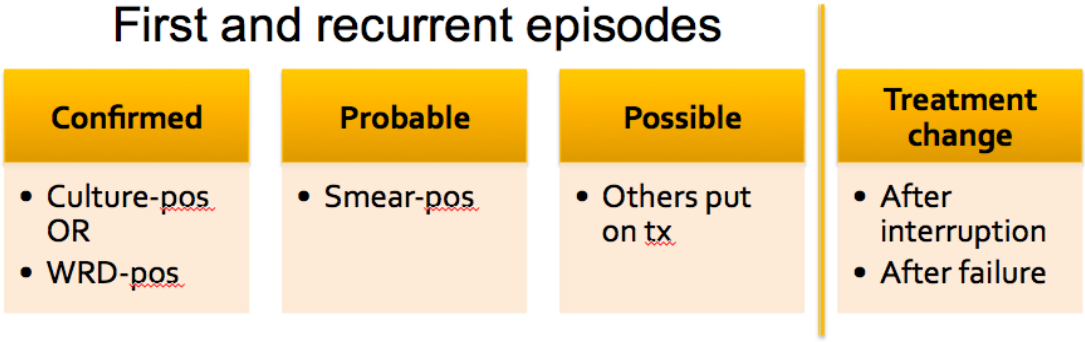

Table 2: Case definitions, option 2

Category		Definition	Disaggregated by*	and by
New TB episodes (first and recurrence episodes)	**Confirmed**	a culture positive for *Mycobacterium tuberculosis*, or, WRD test positive	MDR status (pos, neg, unknown) recurrence	-HIV status (pos, neg, unknown) -Recurrence -Age groups (0-14, 15-49, 50+) -Sex -ART -CPT
	Probable	At least one sputum specimen positive for acid fast bacilli (from a quality assured microscopy center)	recurrence	
	Possible	Unconfirmed TB case put on a full course of TB treatment by a qualified physician or health worker	recurrence	
Treatment change		-Returning after default -re-registered due to treatment failure*	-Confirmed, -probable, -possible	MDR HIV

* Recording may occur on the same year as the year of registration

Probable cases include pulmonary smear positive cases and extra-pulmonary cases with positive microscopy from a specimen.

All cases, confirmed, probable and possible, should be reported.

Recurrent cases (formerly “relapse cases”) have been treated for tuberculosis in the past and been declared successfully treated (cured/treatment completed) at the end of their treatment regimen. Recurrent cases include relapses due to the same *Mycobacterium tuberculosis* strain as for the previous episode as well as new episodes of TB due to reinfection. Since recurrences may occur a few weeks after successful treatment of a previous episode, it is possible for some recurrence cases to be reported in the same year as the year of registration for the previous episode.

All new and recurrent cases are the sum of confirmed, probable and possible cases. All new and recurrent cases are disaggregated by HIV status and ageXsex.

Treatment changed cases include re-registered patients returning after default and patients put on a new treatment regimen and re-registered due to failure of the current treatment regimen.

Confirmed MDR-TB case has a drug susceptibility test showing resistance to Rifampicin and Isoniazid.

Probable MDR-TB case has an NMT test positive for Rifampicin resistance or a test showing Rifampicin resistance in a patient with high risk of harbouring R resistant organisms [1, 2, 5]. Individual risk assessment will become increasingly important with the advent of Xpert MTB/RIF, as outlined in WHO policy recommendations on use of the assay.

In settings or patient groups where rifampicin resistance is rare, probable MDR-TB cases need a second, alternative test to confirm rifampicin resistance [5].

Implications of adopting Option 2

One important reason to classify cases on a scale from possible to confirmed is to indicate clearly the level of diagnostic certainty among notified TB cases. It is expected that the proportion of **confirmed cases** increases over time or does not diminish (it is acknowledged that a small number of confirmed and probable cases may have laboratory results without clinical evidence of disease; however, this problem can be overcome by ensuring that laboratory results are quality assured and that laboratory cross-contamination is minimized).

The **possible case category** allows monitoring of bacteriologically unconfirmed cases, including most extra-pulmonary cases. Pulmonary cases are no longer distinguished from extra-pulmonary cases. As HIV testing in TB patients becomes more widely performed, there is no longer a great need to disaggregate cases by disease site.

All possible cases, including pediatric cases, should be properly investigated in order to limit the risk of over-diagnosis and unnecessary treatment.

Implications for paper-based recording and reporting. Forms and registers need to be adapted. In a transition period, the following changes to the 2006 WHO recording and reporting system [4] may be made (with required training of personnel):

1. WRDs should feature as one of the tests in test request forms [4]
2. Culture and WRD results may be indicated in the comments section of the treatment card
3. Culture and WRD results may be indicated in the remarks section of the Basic Management Unit TB Register
4. Quarterly report form needs to be adapted, to introduce indicators based on WRD results and disaggregate cases between confirmed, probable and possible and update ageXsex cells

4.3 Comparison of the number of categories for which cases are reported in Option 1 and Option 2

Table 3 shows the number of case categories and their core disaggregations in Option 1 and Option 2.

Table 3: Comparison of the number of case categories and subcategories, Options 1 and 2

	Categories	Sub-categories
Option 1	7	53
Option 2	5	37

5. Treatment outcomes

5.1 Option 1

Option 1, which extends and adapts current outcome categories, is presented and explained in Table 4.

5.1.1 Non MDR-TB cases

Non MDR-TB cases may include cases with resistance to one or several anti-TB drugs.

Table 4: Definition of treatment outcomes for non MDR-TB, Option 1

Outcome	Definition	Comment
Cured*	A patient whose sputum smear or culture was positive at the beginning of treatment but who was smear- or culture-negative in the last month of treatment and on at least one previous occasion	Disaggregated by • Smear-pos or Culture-pos • HIV-pos • New • Retreatment
Completed	A patient who completed treatment but who does not have a negative sputum smear or culture result in the last month of treatment and on at least one previous occasion	As above, plus** • WRD-pos • Smear-neg and culture-neg (if culture done) • *Males* • *Females* • *Children*
Failed	A patient whose sputum smear or culture is positive at 5 months or later during treatment. Also included in this definition are patients found to harbour a multidrug-resistant (MDR) strain at any point of time during the treatment, whether they are smear-negative or -positive	Ditto
Died	A patient who dies for any reason during the course of treatment	ditto
Defaulted	A patient whose treatment was interrupted for 2 consecutive months or more without medical approval.	ditto
Transferred out	A patient who has been transferred to another recording and reporting unit and whose treatment outcome is unknown.	ditto
Not evaluated	Treatment outcome not documented	ditto

* Restricted to cohorts smear and/or culture positive at onset of treatment

** Disaggregation by Sex and Children proposed in addition to the minimal MDR indicators (see Annex) in countries with case-based or patient-based electronic recording and reporting systems.

Monitoring treatment efficacy requires systematic smears and culture (if available).

Implications of adopting Option 1

Forms need to be adapted to incorporate the new disaggregations, resulting in significantly more complexity. Outcomes for WRD-positive need to be compiled separately. **Definitions are not streamlined** with outcome definitions for MDR-TB patients (see sub-section 6.1.2).

5.1.2 MDR-TB cases

Table 5: Definition of treatment outcomes for MDR-TB, Option 1

Outcome	Definition	Comment
Cured	MDR-TB patient who has completed treatment according to programme protocol and has at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment. If only one positive culture is reported during that time, and there is no concomitant clinical evidence of deterioration, a patient may still be considered cured, provided that this positive culture is followed by a minimum of three consecutive negative cultures taken at least 30 days apart.	This current definition can only be applied to patients treated for more than 12 months Disaggregation by*: ● All MDR ● XDR+ ● HIV+ ● *Males* ● *Females* ● *Children*
Completed	MDR-TB patient who has completed treatment according to programme protocol but does not meet the definition for cure because of lack of bacteriological results (i.e. fewer than five cultures were performed in the final 12 months of treatment).	ditto
Failed	Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12 months of therapy are positive, or if any one of the final three cultures is positive. (Treatment will also be considered to have failed if a clinical decision has been made to terminate treatment early because of poor clinical or radiological response or adverse events.	ditto
Died	MDR-TB patient who dies for any reason during the course of MDR-TB treatment.	ditto
Defaulted	MDR-TB patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.	ditto
Transferred out	MDR-TB patient who has been transferred to another reporting and recording unit and for whom the treatment outcome is unknown.	ditto

* Disaggregation by Sex and Children proposed in addition to the minimal MDR indicators (see Annex) in countries with case-based or patient-based electronic recording and reporting systems.

Culture and DST are required at the onset of MDR-TB treatment. Definitions are very complicated and cannot be applied to patients treated with MDR regimen lasting 12 months or less.

5.2 Option 2

5.2.1 Non MDR-TB cases

Option 2 for non-MDR-TB cases is illustrated in Table 6. Outcome categories are streamlined to include five categories only, and the term "default" is replaced with "interrupted".

Table 6: Treatment outcome definitions for non MDR-TB cases, Option 1

Outcome	Definition	Comment
Cured	Patient with no signs of continued active disease whose treatment was successfully completed and bacteriological success demonstrated	Disaggregate by** ● New episode ● Treatment changed ● HIV+ ● *Males* ● *Females* ● *Children*
Failed	Patient with clinical and/or bacteriological signs of continued active disease or deterioration requiring a treatment change	Ditto
Interrupted*	A patient whose treatment was interrupted for 2 consecutive months or more for any reason without medical approval	ditto
Died	A patient who dies for any reason during the course of treatment	ditto
Not evaluated	A patient whose treatment outcome is unknown (includes former “transfer out”)	ditto

* New terminology, preferred over “default”

**Cross tabulation HIV status X treatment history not required. Disaggregation by Sex and Children proposed in addition to the minimal MDR indicators (see Annex) in countries with case-based or patient-based electronic recording and reporting systems.

Implications of adopting Option 2

Definitions are simplified, with the former cure and treatment completed merged. **Bacteriological follow-up is required** for appropriate patient monitoring. The “transfer out” category is merged with “not evaluated”. Patients may still be transferred between treatment units, a **TB referral form will be needed in countries using paper-based TB information systems**.

5.2.2 MDR-TB cases

Option 2 for MDR-TB cases is illustrated in Table 7. Outcome categories are streamlined to include five categories only, and the term "default" is replaced with "interrupted". Definitions for the categories "cured" and "failed" are simplified.

Table 7: Treatment outcome definitions for MDR-TB cases, Option 2

Outcome	Definition	Comment
Cured	MDR-TB patient with no signs of continued active disease whose treatment was successfully completed and bacteriological success demonstrated	Disaggregate by** • All MDR • HIV+ • XDR • *Males* • *Females* • *Children*
Failed	MDR-TB patient with clinical and/or bacteriological signs of continued active disease or deterioration requiring a treatment change or early termination*	ditto
Died	MDR patient who dies for any reason during the course of MDR-TB treatment.	ditto
Interrupted	MDR patient whose treatment was interrupted for two or more consecutive months for any reason without medical approval.	ditto
Not evaluated	MDR patient for whom the treatment outcome is unknown (includes former “transfer out”)	ditto

* This includes patients whose regimens had to be drastically changed (e.g. at least two drug classes) due to serious drug adverse effects.
**Disaggregation by treatment history not required. Disaggregation by Sex and Children, with disaggregated indicators for Interruption and No evaluation, proposed in addition to the minimal MDR indicators (see Annex) in countries with case-based or patient-based electronic recording and reporting systems.

Implications of adopting Option 2

Outcome definitions greatly simplified, with many fewer disaggregations required compared with the current recommended system. The **loss of information will be compensated by improved data quality** as definitions and computations are simplified, and easier to understand indicators.

No revision of current treatment guidelines for non-MDR and for MDR cases is required.

5.3 Comparison of the number of categories for treatment outcomes, Option 1 and Option 2

Table 8 shows the number of categories and their core disaggregations for which treatment outcomes would be reported in Option 1 and Option 2.

The number of additional disaggregations when outcomes are disaggregated by men, women and children is shown in brackets.

Table 8: Comparison of the number of core categories and subcategories for treatment outcomes, Options 1 and 2

	Core categories	Sub-categories
Option 1		
non-MDR	7	40 (58)
MDR	7	21 (42)
Option 2		
non-MDR	5	15 (30)
MDR	5	15 (30)

6. Questions to the group

1. Are there further simplifications that can be recommended in the classification of case definitions?
2. Are there further simplifications that can be recommended in the classification of treatment outcomes?
3. Should deaths (as treatment outcome) be disaggregated into deaths due to TB and deaths not due to TB?

References

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ANNEXES

A - Case definitions

Latest WHO case definitions - Treatment Guidelines 4th edition:

http://www.who.int/tb/publications/tb_treatmentguidelines/en/index.html

Defining the site is important for recording and reporting purposes and to identify the more infectious patients – those with pulmonary involvement (who will be further subdivided by smear status – see section 2.5 below).

Pulmonary tuberculosis (PTB) refers to a case of TB (defined above) involving the lung parenchyma. Miliary tuberculosis is classified as pulmonary TB because there are lesions in the lungs. Tuberculous intrathoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of pulmonary TB.

Extrapulmonary tuberculosis (EPTB) refers to a case of TB (defined above) involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges. Diagnosis should be based on at least one specimen with confirmed M. tuberculosis or histological or strong clinical evidence consistent with active EPTB, followed by a decision by a clinician to treat with a full course of tuberculosis chemotherapy. The case definition of an EPTB case with several sites affected depends on the site representing the most severe form of disease. Unless a case of EPTB is confirmed by culture as caused by M. tuberculosis, it cannot meet the "definite case" definition.

Bacteriology refers to the smear status of pulmonary cases and the identification of M. tuberculosis for any case by culture or newer methods. A case of pulmonary TB is considered to be smear-positive if one or more sputum smear specimens at the start of treatment are positive for AFB (provided that there is a functional EQA system with blind rechecking). In countries without functional EQA, the definition from the third edition of these guidelines applies: a smear-positive pulmonary TB case was defined as one with:

a. two or more initial sputum smear examinations positive for AFB, or
b. one sputum smear examination positive for AFB plus radiographic abnormalities consistent with active PTB as determined by a clinician, or
c. one sputum smear positive for AFB plus sputum culture-positive for M. tuberculosis.

The definition of a **new sputum smear-positive pulmonary** TB case is based on the presence of at least one acid fast bacillus (AFB+) in at least one sputum sample in countries with a well functioning EQA system. (See www.who.int/tb/dots/laboratory/policy/en/index1.html.)

Smear-negative PTB cases should either:

A. have sputum that is smear-negative but culture-positive for M. tuberculosis:

- a case of pulmonary TB is considered to be smear-negative if at least two sputum specimens at the start of treatment are negative for AFB1 in countries with a functional EQA system, where the workload is very high and human resources are limited (see http:///www.who.int/tb/dots/laboratory/policy/en/index2.html);

- in all settings with an HIV prevalence of >1% in pregnant women or ≥5% in TB patients, sputum culture for M. tuberculosis should be performed in patients who are sputum smear-negative to confirm the diagnosis of TB.

OR

B. meet the following diagnostic criteria:

- decision by a clinician to treat with a full course of anti-TB therapy; and
- radiographic abnormalities consistent with active pulmonary TB and either:
- laboratory or strong clinical evidence of HIV infection or:
- if HIV-negative (or unknown HIV status living in an area of low HIV prevalence), no improvement in response to a course of broad-spectrum antibiotics (excluding anti-TB drugs and fluoroquinolones and aminoglycosides).

Pulmonary TB cases without smear results are no longer classified as smear-negative; instead, they are recorded as “smear not done” on the TB register and on the annual WHO survey of countries.

For patients suspected of having EPTB, specimens should be obtained from the suspected sites of involvement (Standard 3 of the ISTC). Where available, culture and histopathological examination should also be carried out. Additionally, a chest X-ray and examination of sputum may be useful, especially in persons with HIV infection.

At the time of registration, each patient meeting the case definition is also classified according to whether or not he or she has previously received TB treatment and, if so, the outcome (if known). It is important to identify previously treated patients because they are at increased risk of drug resistance, including MDR-TB. At the start of therapy, specimens should be obtained for culture and DST from all previously treated patients.

New patients have never had treatment for TB, or have taken anti-TB drugs for less than 1 month. New patients may have positive or negative bacteriology and may have disease at any anatomical site.

Previously treated patients have received 1 month or more of anti-TB drugs in the past, may have positive or negative bacteriology and may have disease at any anatomical site. They are further classified by the outcome of their most recent course of treatment as

- relapse if the previous outcome was cured or treatment completed
- failure
- default
- transfer in if the patient was transferred to another unit for treatment continuation
- other if the patient does not fit in the above categories or treatment history is unknown

Patients whose sputum is smear-positive at the end of (or returning from) a second or subsequent course of treatment are no longer defined as “chronic”. Instead, they should be classified by the outcome of their most recent retreatment course: relapsed, defaulted or failed.

USA case definitions

http://www.cdc.gov/mmwr/PDF/rr/rr4610.pdf

Tuberculosis (Revised 9/96). Clinical description

A chronic bacterial infection caused by Mycobacterium tuberculosis, characterized pathologically by the formation of granulomas. The most common site of infection is the lung, but other organs may be involved.

Clinical case definition

A case that meets the following criteria:

- A positive tuberculin skin test
- Other signs and symptoms compatible with tuberculosis (e.g., an abnormal, unstable [i.e., worsening or improving] chest radiographs, or clinical evidence of current disease)
- Treatment with two or more antituberculosis medications
- Completed diagnostic evaluation

Laboratory criteria for diagnosis

- Isolation of M. tuberculosis from a clinical specimen* or
- Demonstration of M. tuberculosis from a clinical specimen by nucleic acid amplification test,

or

- Demonstration of acid-fast bacilli in a clinical specimen when a culture has not been or cannot be obtained

Case classification

Confirmed: a case that meets the clinical case definition or is laboratory confirmed

Comment. A case should not be counted twice within any consecutive 12-month period. However, cases in which the patients had previously had verified disease should be reported again if the patients were discharged from treatment. Cases also should be reported again if patients were lost to supervision for >12 months and disease can be verified again. Mycobacterial diseases other than those caused by M. tuberculosis complex should not be counted in tuberculosis morbidity statistics unless there is concurrent tuberculosis.

European case definitions

European Union Commission. 2008/426/EC: Commission Decision of 28 April 2008 amending Decision 2002/253/EC laying down case definitions for reporting communicable diseases to the Community network under Decision No 2119/98/EC of the European Parliament and of the Council (notified under document number C(2008) 1589). OJ L 159, 18.06.2008, p. 46.

Clinical Criteria

Any person with the following two:

- Signs, symptoms and/or radiological findings consistent with active tuberculosis in any site

AND

- A clinician's decision to treat the person with a full course of anti-tuberculosis therapy

OR

A case discovered post-mortem with pathological findings consistent with active tuberculosis that would have indicated anti-tuberculosis antibiotic treatment had the patient been diagnosed before dying

Laboratory Criteria

Laboratory criteria for **case confirmation**
At least one of the following two:

- Isolation of Mycobacterium tuberculosis complex (excluding *Mycobacterium bovis*-BCG) from a clinical specimen
- Detection of M. tuberculosis complex nucleic acid in a clinical specimen AND positive microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy

Laboratory criteria for a **probable case**
At least one of the following three:

- Microscopy for acid-fast bacilli or equivalent fluorescent staining bacilli on light microscopy
- Detection of M. tuberculosis complex nucleic acid in a clinical specimen
- Histological appearance of granulomata

Case Classification

A. Possible case

Any person meeting the clinical criteria

B. Probable case

Any person meeting the clinical criteria and the laboratory criteria for a probable case

C. Confirmed case

Any person meeting the clinical and the laboratory criteria for case confirmation

Australia case definitions

http://www.health.gov.au/internet/main/publishing.nsf/content/0292695507F152A7CA256F1900038E0D/$File/tb-casedef.pdf

Reporting

Only confirmed cases should be notified.

Confirmed case

A confirmed case requires a diagnosis accepted by the Director of Tuberculosis Control (or

equivalent) in the relevant jurisdiction, based on either:

Laboratory definitive evidence OR clinical evidence.

Laboratory definitive evidence

1. Isolation of Mycobacterium tuberculosis complex (M. tuberculosis, M. bovis or M. africanum, excluding M bovis var BCG) by culture

OR

2. Detection of M. tuberculosis complex by nucleic acid testing EXCEPT where this is likely to be due to previously treated or inactive disease.

Clinical evidence

A clinician experienced in tuberculosis makes a clinical diagnosis of tuberculosis, including

clinical follow-up assessment to ensure a consistent clinical course.

B - Core indicators

The following table lists current core TB indicators.

Disaggregation of TB case counts	Reason for requesting it	Problems
all TB cases by HIV	monitor impact of HIV on TB, assess ART needs	Usable to monitor impact of HIV on TB only if a high proportion of cases have an HIV status recorded
confirmed cases by MDR	monitor burden of MDR; monitor care performance; assess SLD needs	Usable to monitor the burden of MDR only if a high proportion of cases have an MDR status recorded
confirmed cases by diagnostic method (smear, culture, WRD,...)	smear pos case counts have been reported for many years (except for EU)	As approved diagnostic methods increase, reporting complications will also increase
extra-pulmonary	counts have been reported for many years	not much is done with those counts - if anything at all
relapse cases	a different treatment regimen is needed	unreliable: mis-classification of treatment history is extremely common
cases re-registered for - return after default - failure of an ongoing treatment	a different treatment regimen is needed	re-registration is only an administrative procedure, it concerns the same episode of TB gone bad
cases with unknown treatment history		this is a very problematic category
retreatment for other reasons (than return after default or failure of ongoing treatment)		really needed?
foreign born	a determinant of trends in TB in many high-income countries	irrelevant to HBCs and to most low and middle-income countries
prisoner	a high-risk group in low and middle-income countries	
health staff	a high-risk group in low and middle-income countries, used in comparison with	

	case notification rates, to monitor impact of infection control	
GLC cases	relevant to GLC administrative procedures	a definite complication, irrelevant to overall programme monitoring unless all MDR cases are "GLC cases"
all cases, tested for HIV	a programmatic indicator, used as a denominator to measure the burden of HIV in TB	
all cases, on ART	a programmatic indicator, measures adherence to standards	
all cases, on CPT	a programmatic indicator, measures adherence to standards	of lesser importance compared with "all cases, on ART"

Treatment outcomes are currently reported to WHO for the following categories of patients

Patient category	**Reason for requesting it**	**Problems**
smear positive	allows to determine the cure rate	cure rate not used as much as treatment success rate
new cases not smear positive	measures the outcome in about 50% of cases	cure rate cannot be measured
retreatment cases	prognosis less favorable, higher likelihood of drug resistance	cure rate not used as much as treatment success rates, very disparate group making comparisons over time or between settings very difficult to interpret
smear pos, HIV-positive		
not smear pos, HIV-positive		No information on anti-retroviral treatment (ART)
retreatment, HIV-positive		no information on ART
MDR, GLC programme		GLC standards should be applied nationwide. In contrast, the disaggregation of

		outcomes by DOTS versus non-DOTS is no longer requested

	MDR-TB indicator [6]	**Disaggregation**	**Reason for requesting it & problems**
Detection	TB patients with result for isoniazid and rifampicin DST	By risk category in national policy	Coverage of testing for target groups
	Confirmed MDR-TB cases detected among TB patients tested for isoniazid and rifampicin DST	By risk category in national policy	Yield of DR in different target groups
	Confirmed MDR-TB cases tested for susceptibility to fluoroquinolone and second-line injectable	None	Appropriateness of (individualized) 2nd line regimen
	Delay in diagnosis of MDR-TB	None	Monitor delay over time for Q of care; need linkage between basic & MDR TB registers for certain risk categories
Enrollment	MDR-TB cases (suspected or confirmed) enrolled on MDR-TB treatment	Age (<15y<) & Sex	Access to treatment
	Confirmed MDR-TB cases enrolled on MDR-TB treatment regimen	HIV/TB on ART or not on ART	Access to treatment; disaggregation arduous
	Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen	None	Definition of an XDR regimen
	Delay in start of MDR-TB treatment	None	Monitor delay over time for Q of care

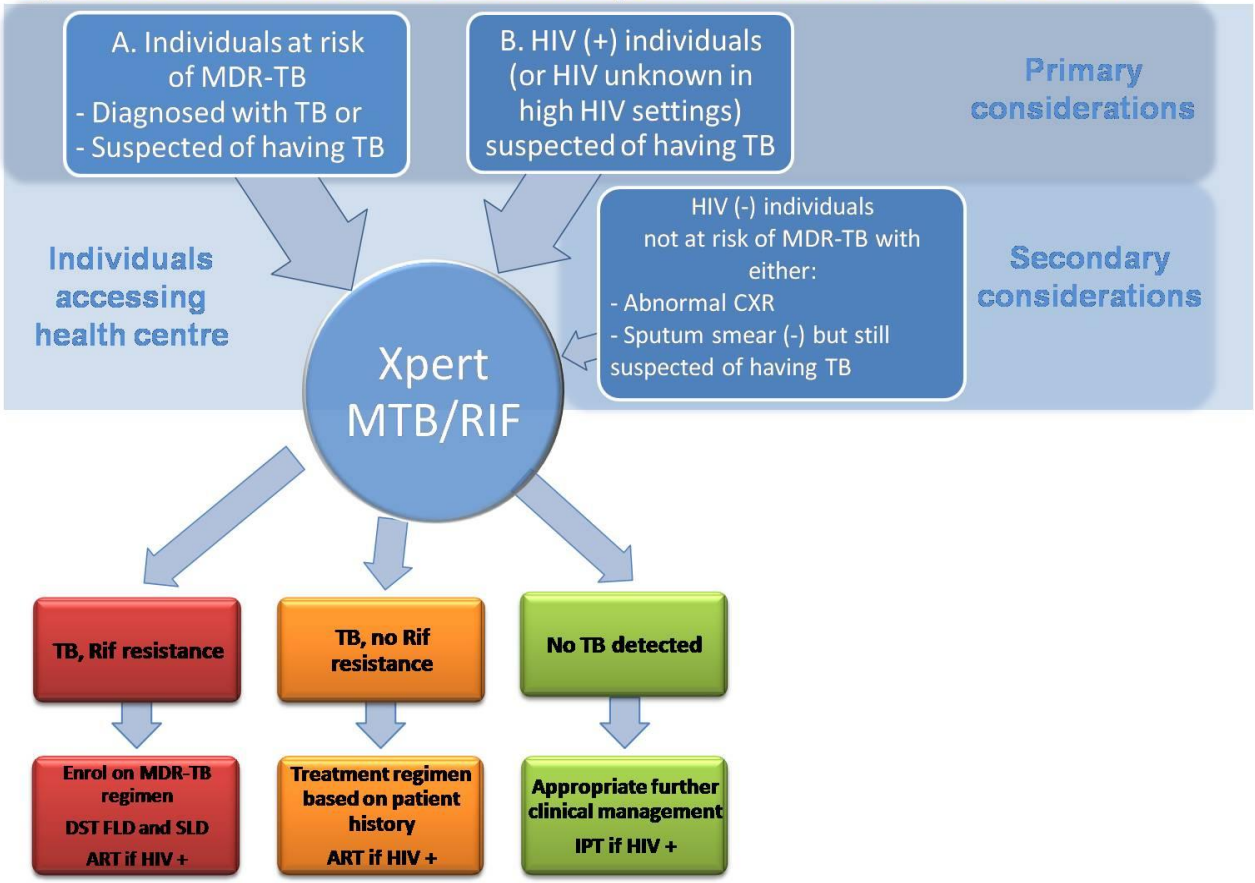
	MDR-TB indicator [6]	Disaggregation	Reason for requesting it & problems
Interim results	MDR-TB cases on MDR-TB treatment regimen with negative culture by six months	None (pulmonary cases only)	Rough idea of conversion and proxy for success; simplified from previous version
	MDR-TB cases on MDR-TB treatment regimen who died by six months	None	Monitor early deaths
	MDR-TB cases on MDR-TB treatment regimen who defaulted by six months	None	Monitor early interruptions
	Patients on MDR-TB treatment regimen found not to have MDR	None	Specificity of criteria applied to start SLD Rx; can be "sensitive" for NTP to report
	Patients on XDR-TB treatment regimen found not to have XDR	None	Specificity of criteria applied to start XDR Rx; can be "sensitive" for NTP to report
Final outcomes	MDR-TB cases on MDR-TB treatment regimen with an outcome cured	MDR/XDR/HIV+*	Monitor success
	… completed	MDR/XDR/HIV+*	Monitor success
	… died	MDR/XDR/HIV+*	Monitor mortality
	… failed	None	Monitor failure of regimen; case definition arduous
	… defaulted	None	Monitor case holding
	MDR-TB cases on MDR-TB treatment regimen with no outcome assigned (transferred, still on treatment or unknown).	None	Monitor the quality of data (comprehensiveness)

* disaggregation applies only when frequency of cases in each subgroup is sufficiently high (see ref. document)

C. Diagnostic algorithm using Xpert MTB/RIF [5]

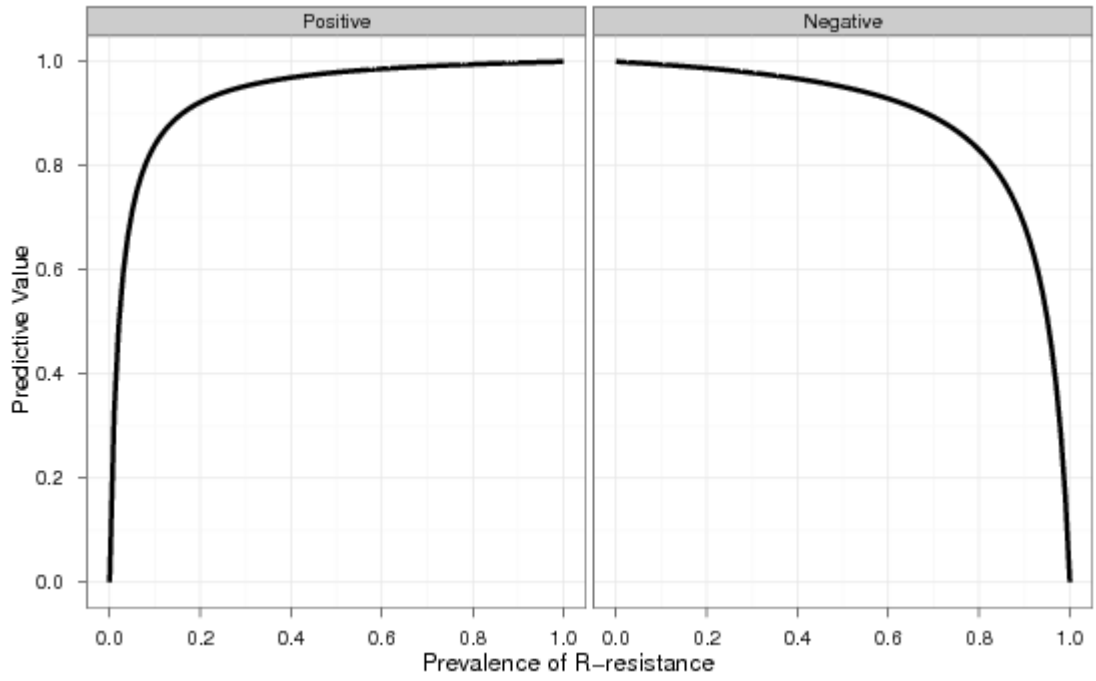
The decision for performing the Xpert MTB/RIF test should be taken through a **risk assessment** of each individual approaching the health centre following the considerations described below (Figure 1). One sputum specimen should be collected and be tested with Xpert MTB/RIF. Patients should be instructed and supported in the collection of a good quality sputum specimen.

Figure 1 .Selection of individuals to test with Xpert MTB/RIF based on risk assessment



D- Predictive values of Xpert MTB/RIF for the diagnosis of MDR-TB

Xpert MTB/RIF sensitivity and specificity for the diagnosis of Rifampicin resistance are assumed equal to 0.95 and 0.98, respectively [*5*].



Predictive values of Xpert MTB/RIF for the diagnosis of MDR-TB depend on Xpert MTB/RIF's sensitivity and specificity to diagnose Rif-resistance, the prevalence of rifampicine resistance and the conditional probability of INH-resistance given Rifampicin resistance:

$$\Pr\left(H^+, R^+ \mid Xp^+, m, r\right) = \Pr\left(R^+ \mid Xp^+, r\right) \times \Pr\left(H^+ \mid R^+\right) \qquad (1)$$

where μ indicates the prevalence of MDR-TB (resistance to H and R are denoted H^+ and R^+, respectively), and $\Pr(R^+ \mid Xp^+, \rho)$ denotes the predictive value of a Positive Xpert MTB/RIF test (positive for R-resistance) given prevalence of R-resistance ρ.

Figures 1 and 2 below show the predictive values of Xpert MTB/RIF for the diagnosis of TB as determined from the Global Drug Resistance project over the period 1994–2010, which includes 445 country-year data points for Drug Resistance (DR) in new cases and 383 country-year data points for DR in retreatment cases. Positive predictive values of Xpert MTB/RIF to diagnose MDR-TB increase with the prevalence of MDR-TB, and therefore, are relatively higher in cases re-registered for a treatment change. Among

other predictors of positive predictive value is the prevalence of HIV in TB. In settings with high HIV prevalence, R-resistance seems to appear alone (without H-resistance) more often, having a detrimental effect on the performance of Xpert MTB/RIF to diagnose MDR-TB.

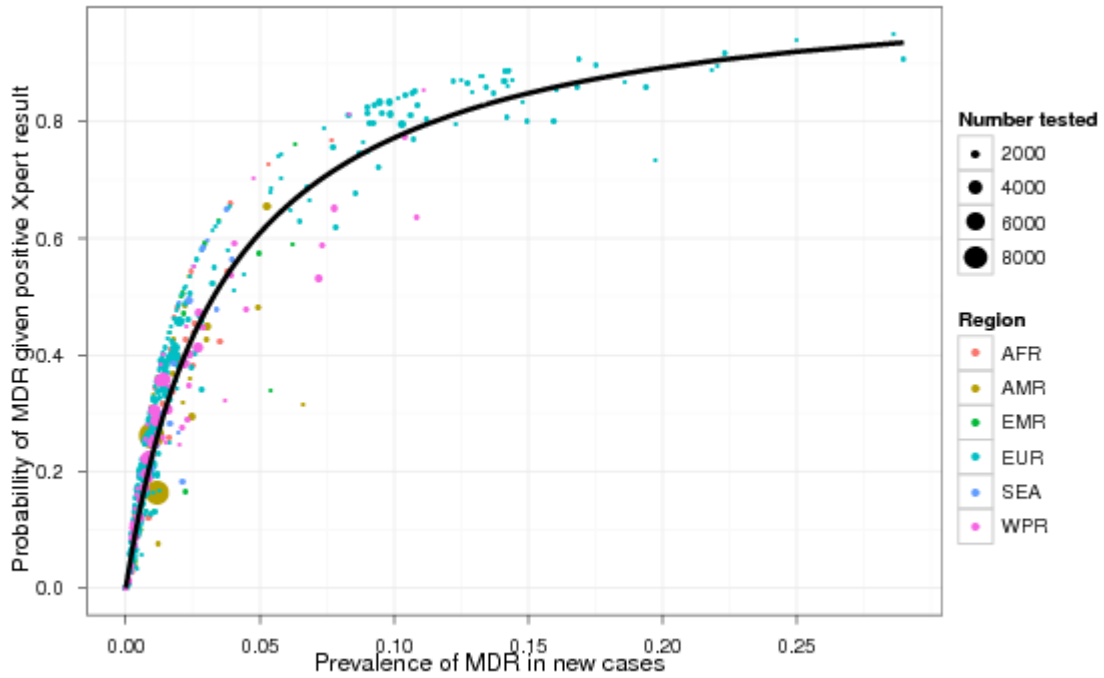


Figure 1. Predictive values of Xpert MTB/RIF for the diagnosis of MDR-TB in patients with no history of prior treatment, Global Drug Resistance Surveillance Project 1994–2010. The solid line shows fitted values using equation (1).

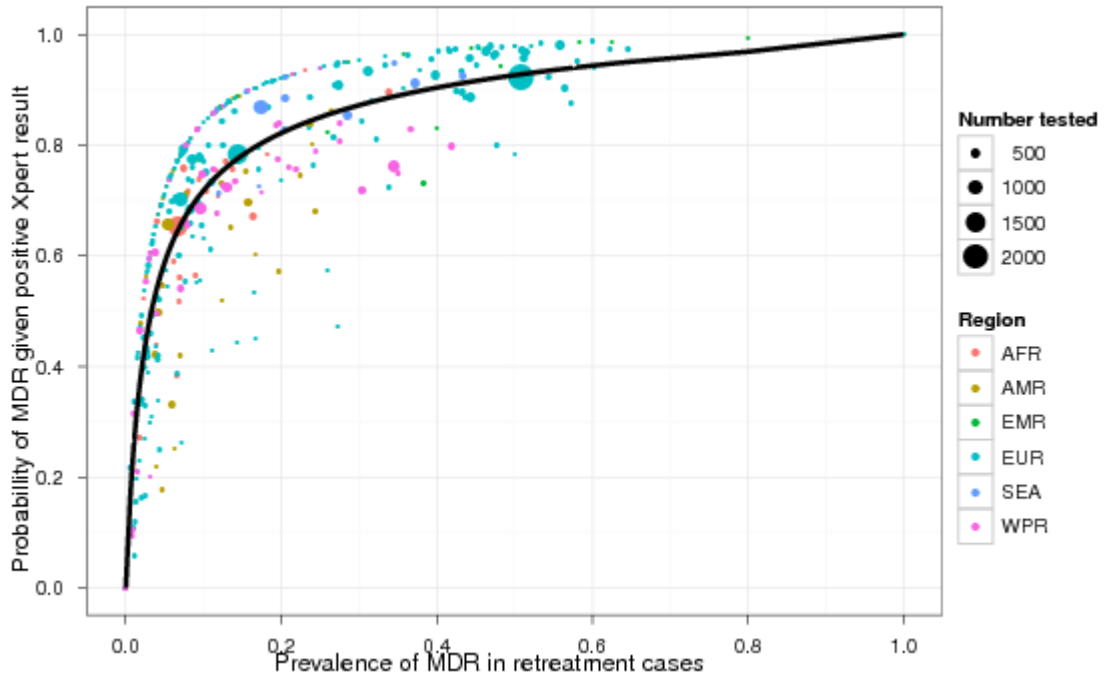


Figure 2. Predictive values of Xpert MTB/RIF for the diagnosis of MDR-TB in retreatment patients. Global Drug Resistance Project 1994–2010. The solid line shows fitted values using equation (1).