

## 6. Technical Note

All 53 countries of the WHO European Region are included in tuberculosis surveillance activities coordinated by EuroTB (list of national Contact Points after title page). National surveillance institutions are responsible for the quality of data provided. The procedures, methods and definitions guiding EuroTB activities are those recommended by European experts, WHO and the International Union against Tuberculosis and Lung Disease (UNION) [1-4].

### 6.1 Reporting of tuberculosis cases, mortality, drug resistance and treatment outcome

#### TB case reporting and mortality

Since 1996 (reporting year 1995), data on TB notification for the previous calendar year have been collected annually. Reporting of case-based, anonymous data, in accordance with standardised specifications (see [www.eurotb.org](http://www.eurotb.org)), is preferred over aggregate reporting.<sup>1</sup> Individual data are now requested for the latest two years to allow for belated exclusion of cases included repeatedly or found not to have TB, as well as for updates of certain data including culture and treatment outcome. This may explain certain differences in data presented in the current report and those shown in previous years or in other publications.

Countries not reporting case-based records report notifications in standard, aggregate tables by age-group, sex, geographic origin, previous history of anti-TB treatment, site of disease, culture and sputum smear results. Following reception, EuroTB staff control data in liaison with the respective country. Since 1999, aggregate TB notification and outcome data have been collected and validated in collaboration with WHO personnel.

Tuberculosis mortality data were retrieved from the WHO Statistical Information System (WHOSIS) Mortality Database, available on Internet [5]. Both data coded under ICD9 and ICD10 were used. Population data for calculation of mortality rates were likewise downloaded from this site.

#### TB/HIV surveillance

Information on HIV sero-status of notified TB cases is collected by EuroTB in aggregate format only. Information on TB morbidity at AIDS diagnosis is obtained from case-based information on initial AIDS-indicative diseases reported to EuroHIV [6]. The

number of cases with HIV-associated TB obtained from both TB and AIDS notification is an underestimate. Testing and reporting of HIV sero-status of TB cases is incomplete. Moreover, TB episodes occurring after initial AIDS diagnosis are not reported to AIDS notification systems.

#### Drug resistance surveillance (DRS)

Since the reporting year 1998, the results of drug susceptibility testing (DST) from initial isolates of *M. tuberculosis* have been collected for isoniazid, rifampicin, ethambutol and streptomycin. In countries where DST results are matched with TB case notifications, DST information is collected as part of the individual data. When this is not possible, or when DRS data are not matched with TB case notifications (e.g. surveys), data are collected as aggregate tables by previous history of anti-TB treatment and by geographic origin (see [www.eurotb.org](http://www.eurotb.org)). Information on the organisation of DRS and on laboratory practices for DST is also collected using a standard form. Data from drug resistance surveys published by WHO are also included in this report [7].

#### Treatment outcome monitoring

Since the reporting year 2002, outcome data are collected for all cases in individual format by resubmission of an updated individual dataset for the year before the last (thus in 2006, outcome data were collected for TB cases notified in 2004). Alternatively, treatment outcome data are reported separately in tabular format (see [www.eurotb.org](http://www.eurotb.org)).

### 6.2 Data analysis and presentation

#### TB case reporting and mortality

While most countries reported data by November 2006, changes to the national totals of TB notifications shown in this report were allowed until end January 2007 and minor updates to data until 5 March 2007. Notification data were not adjusted for under- or over-reporting. Where relevant, particularly for countries in the EU & West, tables have been stratified by origin (national/foreign). The incomplete geographic coverage of notification data from certain countries has been noted in the report (see also below). For calculation of notification rates, country population denominators by age-group and sex were derived from United Nations statistics [8]. Population data for Montenegro (for 2005) and Serbia (since 1998) were supplied by the respective national Contact Points.

Mortality data for countries in which reporting completeness or estimated coverage was <80% in the latest available year (as reported by WHOSIS in March 2006) are not shown in Figure 2 but they are included in the Tables (identified in italics) and in the Country Profiles.

<sup>1</sup> By 2006, all countries of the EU & West and the Balkans except Bulgaria, Monaco, Montenegro, San Marino and Spain were reporting individual demographic and clinical data on TB cases to EuroTB, of which 30 countries also included data on drug-susceptibility testing and 24 on outcome. In contrast, no country in the East was reporting in individual format.

### TB/HIV surveillance

Information on HIV sero-status of TB cases is incomplete in many countries. HIV prevalence is calculated as the percentage of all TB cases reported known to have a positive test, which may thus result in an under-estimated HIV prevalence. AIDS data for the latest year are presented by year of report. The number of AIDS cases with TB as initial AIDS indicative disease, expressed as a proportion of total TB cases notified in the same year, is used to give a conservative estimate of HIV-associated TB. Time trends in numbers of AIDS-defining TB cases are presented by year of diagnosis adjusted for reporting delays [9].

### Drug resistance surveillance

Data on the result of DST for isoniazid, rifampicin, ethambutol and streptomycin at the start of treatment are reported as "susceptible" or "resistant". Proportions of drug-resistant cases are calculated using as a denominator cases with available DST results for at least isoniazid and rifampicin. If 90% of these cases or more had results for ethambutol and streptomycin, DST results for the latter antibiotics are also shown. DRS methodology varies across countries. Initial DST results may be collected routinely for all culture positive TB cases notified, or for cases included in specific surveys or diagnosed in / referred to selected laboratories. Geographic coverage of DRS is partial in some countries. The representativeness of diagnostic DST data depends on the routine use of culture and DST at TB diagnosis. On the basis of differences in geographic coverage and on underlying laboratory practices, DRS data are analysed and presented in two groups:

#### **Group A:**

- nationwide data matched to TB case notification in countries using culture routinely (50%+ of cases reported as culture positive in 2005) and DST results for isoniazid and rifampicin are available for the majority of culture positive cases (80%+ in 2005)

or

- data from laboratory networks or surveys using sampling methods considered nationally representative;

#### **Group B:**

- data with incomplete or undefined geographic coverage;

- diagnostic DST data from countries where:

- culture and DST are routinely used but conditions for being in group A above are not met (<50% culture confirmation or <80% culture positive cases with DST results)

or

- diagnostic DST results are provided from selected laboratories or areas.

Data in Group A are considered representative of the national situation and comparable across countries, whereas data in Group B are not considered representative.

Time-trends were considered statistically significant if Chi-squared test for linear trend has a P value <0.05.

### Treatment outcome monitoring

Treatment outcome data are now collected for all cases in case-based format or in aggregate tables. Cases eligible for outcome analysis (cohorts) are expected to include all definite pulmonary TB cases notified in the calendar year of interest, after exclusion of cases with final diagnosis other than TB as well as cases found to have been reported more than once. In countries reporting individual data, the cohort is defined on the basis of the new dataset updated following initial notification (see above). In countries reporting aggregate outcome data, completeness of cohorts is assessed by comparing the total number of cases included in TOM cohorts with those initially notified as pulmonary culture or smear positive depending on the type of cohort.

On the basis of available information, TOM data are presented in two groups:

- **Group A**, cohorts including at least 90% of definite pulmonary TB cases notified, considered as country-representative and complete
- **Group B**, cohorts including less than 90% of TB cases initially notified, or from selected areas, or for which data for assessing completeness of TOM cohorts were not available. In this report, if the total of Defaulted, Transferred and Unknown exceeds 35% of cases included in the cohort, data are included under Group B.

'DOTS areas' as used in this report refer to units within the country adopting the WHO-recommended strategy to control TB.

### Geographic areas

The 53 countries of the WHO European Region have been grouped into geographic areas, based on epidemiological and geo-political features (map on cover page):

- the European Union and West (EU & West): the 27 Member States of the EU in 2007 plus Andorra, Iceland, Israel, Monaco, Norway, San Marino and Switzerland.
- the Balkans: Albania, Bosnia & Herzegovina, Croatia, the Former Yugoslav Republic of Macedonia, Montenegro, Serbia and Turkey.
- the East: 12 countries of the former Soviet Union - Armenia, Azerbaijan, Belarus, Georgia, Kazakhstan, Kyrgyzstan, Republic of Moldova, Russian Federation, Tajikistan, Turkmenistan, Ukraine and Uzbekistan.

The respective total populations of the three areas in 2005 were 510, 95 and 278 million.

TB notifications from Greenland and Kosovo in 2005 are footnoted in Table 1 and in the Country Profiles of Denmark and Serbia respectively, but are not included in the totals of the latter countries or of the WHO European Region. Data for the part of Cyprus outside the government-controlled area, for Abkhazia and for Southern Ossetia were not available.

In 2006, Montenegro and Serbia became separate states following the division of the country to which they previously belonged. Bulgaria and Romania joined the EU in 2007 and are included under EU & West in this report. In Table 1, distinction is made between the 15 countries which made up the EU until 2003 and the 12 which joined since 2004.

The template used for maps in this report was adapted from the map of the WHO European Region located at the WHO EURO website ([www.euro.who.int](http://www.euro.who.int)).

### 6.3 Definitions

#### TB case definition for surveillance

##### *Definite TB case*

- in countries where laboratories able to perform culture and identification of *M. tuberculosis* complex are routinely available, a definite case is a patient with culture-confirmed disease due to *M. tuberculosis*, *M. africanum* or *M. bovis* (excluding *M. bovis* BCG);
- in countries where routine culturing of specimens is not feasible, patients with sputum smear positive for acid-fast bacilli (AFB) are also considered as definite cases.

##### *Other-than-definite TB case*

A patient meeting the two following conditions:

- a clinician's judgement that the patient's clinical and/or radiological signs and/or symptoms are compatible with tuberculosis,  
and
- a clinician's decision to treat the patient with a full course of anti-tuberculosis treatment.

#### Previous anti-TB treatment status

##### *Never treated case*

A case who never received drug treatment for active TB in the past, or who received anti-TB drugs for less than one month.

##### *Previously treated case (retreated case)*

A case who was diagnosed with TB and received treatment with anti-TB drugs (excluding preventive therapy) for at least one month.

#### Site of disease

##### *Pulmonary case*

A case with TB affecting the lung parenchyma, the tracheo-bronchial tree or the larynx.

##### *Extra-pulmonary case*

A case with TB affecting any site other than pulmonary (see above). Pleural TB and intra-thoracic lymphatic TB by themselves are considered as extra-pulmonary.

#### Notes

- The above definitions conform to the European Commission's definitions for tuberculosis surveillance [4]. Cases with laryngeal TB are included with pulmonary for surveillance purposes;
- All definite and other-than-definite TB cases notified in the calendar year of interest should be reported to EuroTB and are included in the totals presented in this report. Cases should be notified only once in a given calendar year;
- Never treated cases are commonly referred to as "new" cases although this term should not be considered to indicate "incidence" in the strict epidemiological sense. Among retreated cases, relapses (cases having bacteriologically positive TB who had previously completed treatment for tuberculosis) are included in notifications in all countries whereas cases retreated after failure or after default or chronic cases are variably included in notifications across countries. In countries where information on previous anti-TB treatment is incomplete or not available, information on whether or not TB had been previously diagnosed is used as a proxy (as in Table 12);
- Cases with disseminated tuberculosis (i.e. tuberculosis involving more than two organ systems or the isolation of *M. tuberculosis* complex from blood) are classified as pulmonary if the lung parenchyma, the larynx or the tracheo-bronchial tree are involved, and as extra-pulmonary otherwise. Miliary tuberculosis is included under pulmonary (shown separately from respiratory in analysis of mortality, see Table 32). In individual data, detailed information is collected on the major site and one minor site of disease. A pulmonary localisation when present is always classified as the major site. In contrast to the recommended pulmonary classification, under the respiratory classification pulmonary cases as well as cases with pleural and intra-thoracic lymphatic TB are classified as 'respiratory' cases, and cases with another localisation as 'extra-respiratory'.

#### Geographic origin

The geographic origin of TB cases is classified according to place of birth (born in the country / foreign born) or, if unavailable, citizenship (citizen / non citizen). In Denmark, the place of birth of the parents is also used in classifying origin (similarly in the Netherlands for time-trend data shown in Table 6 and in the Country Profile). The country or continent of origin is included in individual data. The term "national" as used in this report refers to cases born in, or having citizenship of, the country of report.

## Drug resistance

*Resistance among cases never treated:* it indicates primary drug resistance due to infection with resistant bacilli.

*Resistance among cases previously treated:* this usually indicates acquired drug resistance emerging during treatment as a consequence of selection of drug-resistant mutant bacilli. It can also result from exogenous re-infection with resistant bacilli.

*Combined resistance:* overall resistance in the population regardless of prior treatment [7].

*Multi-drug resistance (MDR):* resistance to at least isoniazid and rifampicin.

*Extensive drug resistance (XDR):* resistance to (1) at least isoniazid and rifampicin (i.e. MDR) and (2) resistance to a fluoroquinolone and (3) resistance to one or more of the following injectable drugs: amikacin, capreomycin, or kanamycin [10].

## Treatment outcome

### *Cohort*

TB cases notified in the calendar year of interest, after exclusion of cases with final diagnosis other than TB or cases found to have been reported more than once.

### Notes:

- 1) since 2002 cohorts, individual outcome data have been collected for all TB cases;
- 2) up to 2003 cohorts, only aggregate data on definite pulmonary cases were collected. Since 2004 cohorts, aggregate data are also collected for all types of extra-pulmonary and retreated cases.

### *Period of observation*

Cases are observed until meeting the first outcome, for a maximum of 12 months after the start of treatment.

### *Outcome categories*

Since 2001 cohorts, outcome categories are those internationally recommended - with two additional categories "still on treatment at 12 months", and "unknown" [3, 11]

*Cured:* Treatment completion and:

- culture becoming negative on samples taken at the end of treatment and on at least one previous occasion
- or
- in countries where sputum smear positive cases are classified as definite cases sputum microscopy becoming negative for AFB at the end of treatment and on at least one previous occasion.

*Completed:* Treatment completion and does not meet the criteria to be classified as cure or treatment failure

*Failed:* Culture or sputum smear remaining positive or becoming positive again 5 months or later into the course of treatment.

*Died:* Death before cure or treatment completion irrespective of cause.

*Defaulted:* Treatment interrupted for 2 months or more, not resulting from a decision of the care provider or patient lost to follow-up for 2 months or more before the end of treatment, except transferred.

*Transferred:* Patient referral to another clinical unit for treatment and information on outcome not available

*Still on treatment:* Patient still on treatment at 12 months and who did not meet any other outcome during treatment. It includes patients with:

- initial treatment changed due to polyresistance (i.e. resistance to at least two first line drugs) on the isolate taken at the start of treatment.
- treatment prolonged because of side effects / complications, initial regimen planned for > 12 months
- information on the reasons for being still on treatment not available

*Unknown:* Information on outcome not available, for cases not known to have been transferred

In this report:

- "Success" refers to the combined ratios of cured and completed
- "Loss to follow up" is the combination of defaulted, transferred and unknown.

## **6.4 References**

1. Rieder H, Watson J, Raviglione M, et al. Surveillance of tuberculosis in Europe. Recommendations of a Working Group of the World Health Organization (WHO) and the European Region of the International Union Against Tuberculosis and Lung Disease (IUATLD) for uniform reporting on tuberculosis cases. *Eur Respir J* 1996; 9:1097-1104.
2. Schwoebel V, Lambregts-van Weezenbeeck CSB, Moro ML, et al. Standardisation of antituberculosis drug resistance surveillance in Europe. Recommendations of a World Health Organization (WHO) and International Union Against Tuberculosis and Lung Disease (IUATLD) Working Group. *Eur Respir J* 2000; 16: 364-371.
3. Veen J, Raviglione M., Rieder HL, et al. Standardised tuberculosis treatment outcome in Europe. *Eur Respir J* 1998; 12: 505-510.
4. 2002/253/EC. COMMISSION DECISION (19 March 2002) 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.

5. WHO Statistical Information System (WHOSIS). WHO Mortality Database. Update 17 November 2006 ([www3.who.int/whosis/](http://www3.who.int/whosis/)). Last accessed 18 February 2007.
6. EuroHIV and the national coordinators for tuberculosis surveillance in the WHO European Region. European Non-Aggregate AIDS Data Set (ENAADS). EuroHIV, Institut de veille sanitaire, Saint-Maurice, France. Update December 2005 (accessed December 2006).
7. World Health Organization. Anti-tuberculosis Drug Resistance in the World. 3<sup>rd</sup> global report. WHO, Geneva, Switzerland 2004. WHO/HTM/TB/2004.343.
8. United Nations Population Division. Annual Populations 1950-2050 (The 2004 Revision), United Nations, New York, 2005.
9. EuroHIV. HIV/AIDS Surveillance in Europe. End-year report 2005. Saint-Maurice, France: Institut de veille sanitaire, 2006. No 73.
10. World Health Organization. Case definition for extensively drug-resistant tuberculosis. Weekly Epidemiol Rec 2006 Oct 20;81(42):408. ([www.who.int/wer/2006/wer8142.pdf](http://www.who.int/wer/2006/wer8142.pdf))
11. Falzon D, Scholten J, Infuso A. Tuberculosis outcome monitoring - is it time to update European recommendations? Eurosurveillance 2006; 11 (3):20-5.