UNDERSTANDING AND USING TUBERCULOSIS DATA

World Health Organization

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Acknowledgements

Indonesia, Iraq, Japan, Kenya, Latvia, Mozambique, the Netherlands, Niger, Nigeria, Peru, the Philippines, Romania, South Africa, Thailand, Uganda, the United Kingdom, the United States of America, Uzbekistan and Viet Nam.

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Introduction

Country health information systems provide a rich source of data on the burden of disease caused by tuberculosis (TB) and the effectiveness of programmatic efforts to reduce this burden, both of which are crucial for public health action. However, the available data are often underused, or not used at all. At least in part, this may reflect the absence of clear guidance on recommended approaches to the analysis of such data. This handbook is designed to address this gap through detailed practical examples of the analysis of TB surveillance data, in particular TB notification data, data from surveillance of anti-TB drug resistance, and mortality data compiled in national vital registration systems. It starts from the most basic kinds of analyses, and progresses to the description of more challenging topics such as the estimation of disease burden using multiple sources of evidence, including data from special surveys.

The handbook has seven major objectives:

1. To describe and explain how TB notification data can be analysed to understand TB epidemiology, including the distribution of disease geographically, by age and sex, and among specific population groups (Chapters 1, 2 and 3).
2. To describe and explain how TB notification data can be analysed to assess programme performance (including case detection and treatment success) and data quality (Chapters 1 and 2)
3. To describe and explain how genotyping data can be used to investigate an outbreak (Chapter 3).
4. To describe and explain how to analyse factors driving the TB epidemic at a country level, and how these affect (positively or negatively) trends in TB notifications and underlying TB incidence (Chapter 4).
5. To describe and explain how to analyse the burden of disease associated with drug-resistant TB and HIV-associated TB, and the associated programmatic responses that use surveillance data (Chapters 5 and 6).
6. To describe analyses of data from vital registration systems to estimate TB mortality (Chapter 7).
7. To demonstrate how to combine data from special surveys with surveillance data to understand trends in TB disease burden (Chapter 8) and to derive estimates of the burden of disease caused by TB.

Typical data sources that the handbook discusses and uses include:

1. Case-based or aggregated TB notification and treatment outcome data.
2. Results from facility audits or reviews of the quality of recorded data.
3. Laboratory data.
4. Results from drug resistance surveillance including drug resistance surveys.
5. Records from civil registration of vital statistics with cause of death data.
6. Results from mortality surveys.
7. Results from surveys of the prevalence of TB disease.
8. Results from inventory studies to measure TB under-reporting and, under certain circumstances, estimate incidence.

The handbook shows how to use these data sources, presents existing tools to analyse the quality of data and describes methods to estimate the burden of TB and related trends. Throughout the handbook, emphasis is also placed on the use of country-specific examples to illustrate how analyses can be carried out and results interpreted.

Chapters 1–2 should be accessible to most, if not all, readers and are designed to provide guidance on how to conduct certain analyses. Parts of Chapters 3–8 are intended primarily to provide an overview of more advanced types of analysis of surveillance data but do not provide detailed guidance on how to conduct these.

The handbook aims to help a broad target audience, including national TB programme (NTP) managers, monitoring and evaluation officers, researchers including epidemiologists and statisticians, and staff working with technical, financial and development agencies.

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Abbreviations

ACF	active case finding
BMI	body mass index
BMU	basic management unit
CDC	Centers for Disease Control and Prevention (US)
CI	confidence interval
DR-TB	drug-resistant TB
DST	drug sensitivity testing
HIV	human immunodeficiency virus
LGA	local government area
MDR-TB	multidrug-resistant TB
MIRU-VNTR	mycobacterium interspersed repetitive unit – variable number tandem repeat
NTIP	National Tuberculosis Indicators Project
NTP	national tuberculosis programme
NTR	national electronic TB register
OR	odds ratio
PPM	public–private & public–public mix
RFLP	restriction fragment length polymorphism
RVCT	revised report of verified tuberculosis
SOP	standard operating procedures
TB	tuberculosis

Chapter 1
Analysis of aggregated TB notification data

Audience:

General readers, but especially monitoring and evaluation officers, at any administrative level, working in national tuberculosis (TB) programmes (NTP).

Expected outcomes:

By the completion of this chapter, the reader should be able to understand:

- the importance of aggregated TB notification data in describing the epidemiology of TB and the programmatic implications for the NTP;
- how to analyse, report and interpret aggregated TB data by person, place and time;
- how to assess the quality of aggregated TB notification data;
- the advantages and limitations of aggregated TB notification data.

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1.1 Aggregated notification data: what are they?

Since the mid-1990s, a standardized system for paper-based recording and reporting of the number of individuals diagnosed with TB and their treatment outcomes have been used worldwide. Within this system, TB data are reported in aggregate form (i.e. the total number of cases account for the basic unit of recording) (1,2). Typically, health care staff record information about a patient's treatment history on individual TB treatment cards. Demographic, clinical and bacteriological information are collected for TB cases (individual episodes of TB disease) based on an internationally agreed common framework for recording and reporting.[a] These data are then transcribed into TB registers that list information for all cases treated within a particular health care facility and/or basic management unit (BMU).[b] Notification and treatment outcome data for all cases from the registers within a particular geographical area are then compiled and aggregated into reporting forms (2). These reports are sent to higher administrative levels (up to the national level), usually on a quarterly basis; reports can be paper-based or electronic (Box 1). At the national level, NTPs report on these aggregated data, which form the basis of analyses for annual reports. Details on individual cases are not known.

If notification data are collected electronically, it is important to properly select a data management software and prepare the database to allow the merging of multiple quarterly sub-national files into one national dataset. Numerous Excel spread sheets that may be easy to use at BMU level for data collection, are not effective at national level for monitoring and analysis of surveillance data. Notification data should be collected using a singular, uniform platform to facilitate data analysis. An example of using Epi Info™ software for national aggregated surveillance database is provided in Box 1.

Analysis of TB surveillance data is essential for programme evaluation, which helps guide decisions about case management and policy. It allows NTPs to monitor trends in the number and distribution of TB cases across the country. This enables NTPs to report on the country's TB epidemic and progress in reaching NTP goals and objectives. It also helps NTPs to develop targeted national strategies and funding plans.

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a.   The collection and analysis of a minimum set of variables (age or age group, sex, year of registration, bacteriological test results, history of previous treatment and type of disease) is also recommended as part of the WHO *Checklist of standards and benchmarks for case-based TB surveillance data* (http://www.who.int/tb/publications/standardsandbenchmarks/en/, accessed 19 July 2014).

b.   A basic management unit (BMU) is defined in terms of management, supervision and monitoring responsibility. A BMU for a national TB programme may have several treatment facilities, one or more laboratories and one or more hospitals. The defining aspect is the presence of a manager or coordinator who oversees TB control activities for the unit and who maintains a master register of all TB patients being treated. This register is used to monitor the programme and report on indicators to higher administrative levels. Typically, the units correspond to the government's second sub-national administrative division, which might be called, for example, a district or county. It is internationally recommended that a BMU cover a population of between 50 000 and 150 000, or of up to 300 000 for large cities. (Source: *Compendium of indicators for monitoring and evaluating national tuberculosis programmes*. (http://www.who.int/tb/publications/tb_compendium_of_indicators/en/, accessed 10 December 2013).

In this chapter, different methods to analyse aggregated TB surveillance data are described. These analytical approaches primarily focus on assessing the distribution of case notification rates (number of cases per 100 000 population) among sub-national areas, among different population groups (e.g. by age and sex), and trends. In order to conduct these analyses, a recommended minimum set of variables is needed, which includes age (or age group), sex, year of registration, bacteriological test results, history of previous treatment, type of disease and geographic region (*4*). The limitations of aggregated data will also be covered along with discussion on data quality indicators and data validation methods specific to surveillance systems that only use aggregated TB data.

BOX 1
Electronic aggregated TB surveillance database (example from Nigeria)

In Nigeria, the National Aggregated TB Surveillance System has been developed and installed to collect TB surveillance data at the local government area (LGA) and national levels. The database includes several sections that correspond to WHO-recommended reporting form guidelines (*1*). The database interface visually follows the design and sequence of data entry paper forms. All recommended variables – including age group, sex, period of time, bacteriological results, history of previous treatment, type of disease and geographic region – are in the database. Monitoring and analysis of trends in the number and distribution of TB cases can be conducted effectively and in a timely way at the LGA, state and national levels in Nigeria.

The complete database includes three electronic pages. An example of the first page of the database at the LGA level is shown below.

1.2 Assessment and assurance of the quality of aggregated TB notification data

Factors determining data quality are diverse (e.g. accuracy, precision, plausibility, consistency and validity), but data are only as good as the system in which they are captured and reported. In the case of TB surveillance, data cannot accurately depict the current TB burden in a country if the surveillance system collects incomplete, inconsistent or incorrect information. As a result, the assessment of data quality is really an assessment of the quality of methods used to collect the data. Assessing the quality of notification data thus highlights the strengths and weaknesses of the TB surveillance system and reveals how well these data provide an accurate measure of the national TB burden and its trends over time.

TABLE 1
Standards used in the *Checklist of standards and benchmarks for TB surveillance and vital registration system*

Data quality
1. Case definitions are consistent with WHO guidelines
2. TB surveillance system is designed to capture a minimum set of variables for all reported TB cases
3. All scheduled periodic data submissions have been received and processed at the national level
4. Data in quarterly reports (or equivalent) are accurate, complete and internally consistent *(For paper-based systems only)*
5. Data in national database are accurate, complete, internally consistent and free of duplicates *(For electronic case-based or patient-based systems only)*
6. TB surveillance data are externally consistent
7. Number of reported TB cases is internally consistent over time
Coverage
8. All diagnosed cases of TB are reported
9. Population has good access to health care
Vital registration
10. Vital registration system has high national coverage and quality
DR-TB, TB/HIV and children
11. Surveillance data provide a direct measure of drug-resistant TB in new cases
12. Surveillance data provide a direct measure of the prevalence of HIV infection in TB cases
13. Surveillance data for children reported with TB are reliable and accurate, and all diagnosed childhood TB cases are reported

The World Health Organization (WHO) *Checklist of standards and benchmarks for TB surveillance and vital registration system* provides a systematic approach to assess the quality of

national TB surveillance systems, including, among other things, methods for analysing the quality of notification data (Table 1). Detailed information on how to do the assessment of the TB surveillance system can be found in the accompanying user guide[c] (examples on the application of the checklist's TB surveillance data quality standards can be found in Annex 1).

Data validation at data entry

Different methods can be used to validate data during data collection, aggregation, entry and verification procedures. An example of data validation at the level where data are entered is a manual inspection of TB registers before data are entered in an aggregated form. This includes checking for duplicate registration of the same patient at different facilities, data consistency within records (e.g. cure as treatment outcome for a smear-negative patient), and completeness of all required fields per record. In addition, electronic checks can be included with the data entry form (see Box 2).

BOX 2
Data validation at the time of electronic data entry (example from Nigeria)

To expedite electronic data entry and validation at the time of data collection, numerous data checks (or check-codes) can be created and added to the data entry form. The Nigeria electronic aggregated TB surveillance database (see Box 1) is an example of a system with these automatic data checks.

For instance, in this system when the case counts are entered for sex-specific age groups, the total number of smear-positive cases for males and for females are then calculated automatically (Box 1, block 2a and block 1). If the calculated total differs from the entered total number of smear-positive cases (compare block1 to block 2a), the following error message is generated:
"Number of New Smear Positive TB Cases (block1) should be = Total Male + Total Female (block 2a) - Check your data!"

Another way the Nigerian system validates data at the time of data entry is by ensuring certain fields have data entered. That is, the data entry clerk cannot move to the next field until the required field is entered. In the Nigeria database, these fields are State, LGA, year and quarter of aggregated data. Similarly, the system uses predefined drop down lists for Zone, State, LGA and facility type to avoid mistyping and to ensure valid values.

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c.   The checklist and user guide are available on the website of the WHO Global Task Force on TB Impact Measurement: http://www.who.int/tb/publications/standardsandbenchmarks/en/

Data validation after data entry

Utilizing data validation at entry will minimize and help correct mistakes that could be made by human error and ensure the correctness and plausibility of the aggregated data. Additional validation can be done at the regional or national levels. This should include checking for missing data (e.g. did all basic units send aggregated data for each quarter in the year?). It is only after conducting these initial data validation steps that more detailed data quality analyses should be undertaken. Examples of validation for aggregated data (Box 3) include ensuring consistency between the total number of TB cases and: i) the sum of new and retreated cases; ii) the sum of TB cases among males and females; and iii) the sum of TB cases that are grouped by patient age. In a system with an electronic aggregated database, computer-assisted checks during and after data entry can be used to detect data quality problems and correct them.

BOX 3
Data cleaning and preparing for analysis

As soon as aggregated data are entered into the database, several additional data quality checks can be used to ensure that data are complete and ready for analysis (e.g. identify duplicate entries for a facility and missing or inconsistent values). For example:

- **Check for duplicate records.** If duplicate records of aggregated data per facility or district are identified, carefully investigate the case by checking data from each duplicate record, including paper forms. Identify the reason and fix errors leading to the duplication. Although in some systems, duplicate records will be identified during data entry.

- **Check for missing values.** In systems relying on aggregated data, missing information is usually due to human error at the time of data entry or missing data on paper forms. It is important to remember that an aggregated count of zero cases (zero reporting) is different from a missing value, and this should be noted accordingly. If possible, original paper-based data sources should be used to check and populate missing values.

- **Check for consistency among electronic data.** Use available electronic data analysis tools to check if the total number of TB cases among age groups is equal to total number of TB cases. Use the original data source to fix any inconsistencies that are identified. Note that in some systems, most inconsistencies will be identified during data entry (Box 2).

1.3 Analysis of aggregate data

Rationale for analysis of trends

A complete analysis of surveillance data involves an investigation of changes in rates over time, followed by attempts to understand their underlying causes. Interpretation of trends in TB burden is an essential part in evaluating a country's performance on TB control and prevention.

When trends are considered inconsistent (i.e. notification rates change rapidly or unpredictably) NTP managers should look for the possible causes.[d] Reasons for rapid changes or inconsistent trends in the case reports should be investigated. For example, could unexpected inconsistencies represent true changes in the TB epidemic or could they be the result of changes in other TB determinants (i.e. urbanization, socioeconomic situation, implementation of health insurance schemes, or specific TB control activities)? In other considerations, could these unexpected inconsistencies in trends be primarily a result of changes in case definitions or in the recording and reporting system (i.e. changes in the structure, coverage or performance of the notification system)? While searching for the reasons behind inconsistent trends, it is essential to first check for errors in data and correct them at all levels. This helps ensure the trends are not attributable to inaccurate data. This is why it is also very important to validate the quality of the data being collected. However, assessing trends can also be a way to reveal possible problems with data quality. The following section explores trend analyses, related to patients (or people), place, and time.

When an NTP reports on the number of TB cases for a given year, data are usually reported for the whole country for a calendar year (January to December). In some instances, the same data are reported for sub-national levels (e.g. provinces or states). National level data by patient age and sex, treatment history, site of disease and bacteriological results are reported annually to the WHO Global TB Programme annually in order to provide a current overview of the global TB situation.[e]

However, from a country perspective it is also important to track the national and sub-national trends in the number and distribution of TB cases, which involve more detailed analysis than

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d.   Examples of inconsistent trends could include a change of more than 4% in case notifications, or a sudden and unexpected change in sex and age disaggregation.

e.   An annual report is produced that provides the latest information and analysis about the TB epidemic and progress in TB care and control at the global, regional and country levels. It is based primarily on data reported by WHO Member States in annual rounds of Global TB data collection. In 2013, a total of 197 countries and territories that collectively have more than 99% of the world's TB cases reported data (http://www.who.int/tb/country/en/index.html, accessed 14 July 2014).

the national data reported to WHO. This demonstrates whether the TB situation is improving, worsening or showing no change. As such, the NTP should regularly evaluate whether or not there are inconsistencies in TB trends, and whether changes in programmatic strategies are required to address these trends. Once again, the data must be of the highest quality to reflect the current situation for the most reliable interpretation.

Reported number of TB cases[f] over time (i.e. time-series notifications, of aggregate data at the national and sub-national level) can provide very important information. As well as the total numbers, such data can also indicate who is getting TB (e.g. males or females), what type of TB disease they are getting (e.g. pulmonary or extrapulmonary), at what stage in life they are getting TB (e.g. young or older people), and where they live (e.g. the geographical distribution of cases). The description of aggregated data by person, place and time are key activities that are required to describe a country's epidemiological situation, and whether there are considerable trends in these distributions.

1.4 Examples of analysis of trends

Notifications by time

Interpretation of trends in case notifications requires looking for reasons for the changes. To demonstrate how notification rates over time can be analysed and interpreted, the examples of England and Wales, Bangladesh and Indonesia are explored below. Together, these examples highlight that in-depth knowledge of the country, the NTP with its programmatic approach and TB surveillance system are integral to correctly interpreting a country's epidemiological situation.

England and Wales

England and Wales have documented notification rates for nearly 100 years with high quality, reliable data (Figure 1). Plotting the number of TB cases reported each year over time has allowed the NTP to observe the gradual decline in TB cases over the past century. The fastest declines of around 10% per year occurred in the post-1945 period that were attributed to improvements in living conditions combined with rapid economic growth and the introduction of effective chemotherapy, the Bacillus Calmette–Guérin (BCG) vaccine, pasteurization and universal access to health care.[g]

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f.　In this chapter, examples utilize country data of all notified TB cases unless otherwise specified. Some surveillance systems may have limited data available therefore it may be warranted to use just the number of new and relapse notifications, or even smear-positive TB notifications.

g.　*1913–1982 Statutory Notifications of Infectious Diseases (NOIDS); 2010–2011 Enhanced Tuberculosis Surveillance (ETS)*. Prepared by: TB Section, Health Protection Services–Colindale, UK.

FIGURE 1
TB case (all forms) notification, England and Wales (1913–2011).
Source: **Public Health England (TB section)**
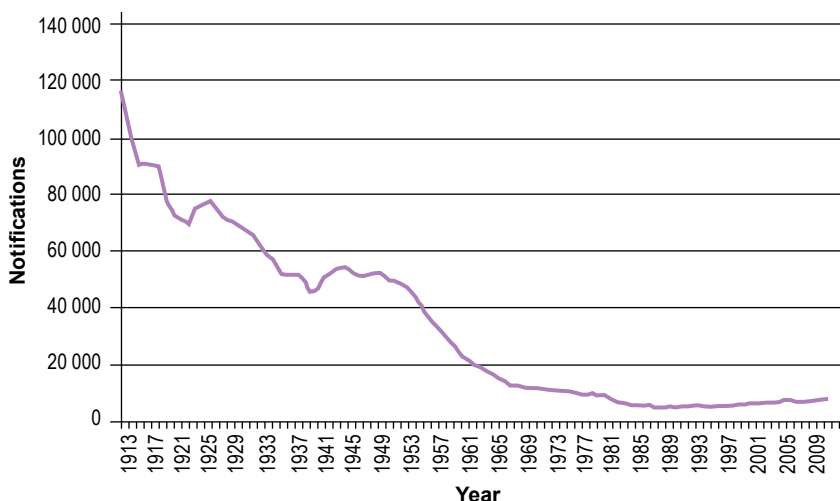
Bangladesh

The total notifications of new and relapse TB cases in Bangladesh from 2000 to 2012 show an increase in the number of reported cases over time (Figure 2). Specifically, there is a sharp rise in cases from 2004 to 2006, before a period of very little change in subsequent years. The NTP reported an increase in annual total notifications of approximately 25% from 2004 to 2005. This corresponds to an absolute increase of 24 000 patients. Figure 2 demonstrates another increase of 18%, or 22 000 patients, observed from 2005 to 2006. Previously, the same magnitude of change was observed over five years (2000–2004). Could this rise in cases over time be a true reflection of the TB epidemic in Bangladesh, or are there other reasons that can account for this trend? Discussion with the NTP revealed that in the middle part of the decade, the NTP launched an effort to improve case-finding and implemented measures to engage health care providers from other sectors (e.g. the private sector) in TB programme case-finding and treatment. As a result, the sharp rise in TB case notification can be attributed to programmatic changes, and is not considered a true increase in the incidence of TB in the country.

FIGURE 2
The total number of notifications of new and relapse TB cases as reported by the NTP of Bangladesh to WHO (2000–2012).
Source: **WHO Global TB report 2013**
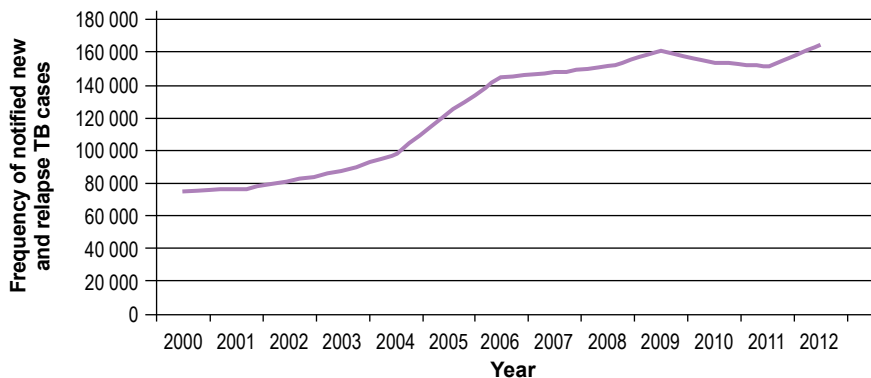
Indonesia

The effective implementation of DOTS at a national scale can also result in an increase in case notifications. This is seen in Indonesia, where data show a characteristic rise in notifications following implementation and DOTS at national scale in the late 1990s, when the DOTS programme began (Figure 3). In addition, an increasing trend in case detection was observed from 2009 to 2011, after a period of stagnation between 2006 and 2008. The researchers reviewed the potential reasons for this and found that the increase was mainly due to: i) a rising trend in patients who were investigated for TB symptoms; ii) an increase in notifications by hospitals and lung clinics as a result of enhanced hospital-DOTS linkages; and iii) increased coverage of microscopy services for the detection of smear-positive TB cases and readily available first-line treatment at health centres and hospitals. Data from the provincial level further supports the rise in notifications with an increase in the number of symptomatic individuals evaluated over the past decade (Figure 4).

The above examples each highlight that in-depth knowledge of the NTP and its TB surveillance system is integral to correctly interpreting a country's epidemiological situation as described through their routine data.

FIGURE 3
The total number of notifications of new and relapse TB cases as reported by the NTP of Indonesia to WHO (1990–2012).
Source: WHO Global TB report 2013
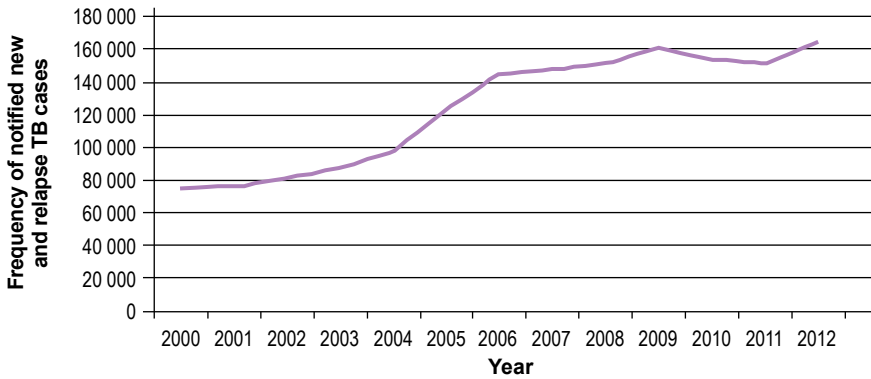
FIGURE 4
Provincial and national (graph 100_Indonesia) level time-series of suspect evaluation rate during the period 1990–2011.
Source: Indonesia NTP

Notifications by age

It is known that the incidence of TB varies with age. In Africa, TB primarily affects ado-lescents and young adults. However, in countries where TB has gone from high to low incidence, such as the United States, TB is mainly a disease of older people, or of the immunocompromised.

Thus, in describing the epidemiology of TB, it is important to observe the distribution of TB cases by age group. This information helps inform the NTP what age group is experi-encing the highest burden of TB and who to target for intervention. Several case studies from a range of countries are presented below.

South Africa

In South Africa, case notification rates were calculated for each age group based on all notified TB cases and the estimated population in 2012 (Figure 5). In this example, we compare the absolute number of notified TB cases within each age group to the notifica-tion rate (number of cases per 100 000 population) for each age group. Both indicators are important measures for public health officials in terms of understanding the burden of disease. In South Africa, the age distribution of absolute numbers of cases is slightly different from the age distribution of notification rates. For example, the highest number of absolute cases is in the 25–34 year age group, while the notification rate is highest in the 35–44 year age group. Also, the notification rate among people aged over 65 years is quite high, while the absolute number of cases is the lowest in this age group. Given that countries have different population age structures, such an adjustment also allows for between-country comparisons, if required.

In addition, if we break down the national case notification rate (567/100 000 in South Africa in 2012) by age groups, high variations of rate between age groups become visible. The notification rate is high in infants before declining in 5–14 year olds; then it rises to a peak in the 35–44 year age group, before declining again in the older age groups. This pattern is quite typical of TB in a country that is highly endemic, and where the majority of cases are in the general working population (in South Africa, this is partly due to the highest HIV prevalence in this age group). This pattern also reflects the NTP's ability to diagnose and notify childhood TB cases.

FIGURE 5
Derivation of case notification rate by age group in South Africa (2012). A) Absolute number of cases by age group; B) Population distribution; C) Case notification rate (number of cases per 100 000 population). *Source:* WHO Global TB report 2013 and the 2012 revision of the World Population Prospects (United Nations Population Division).

A
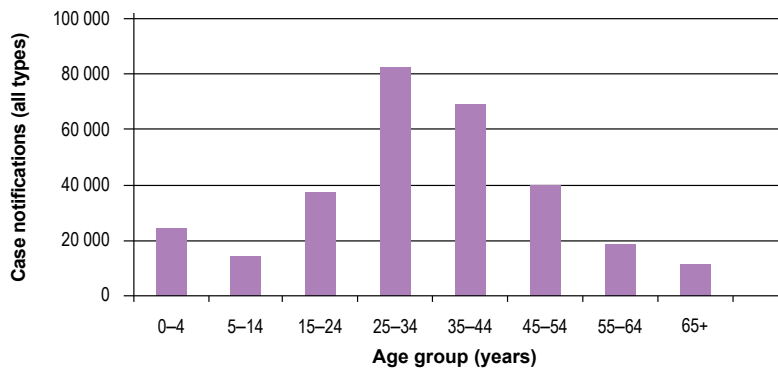
B
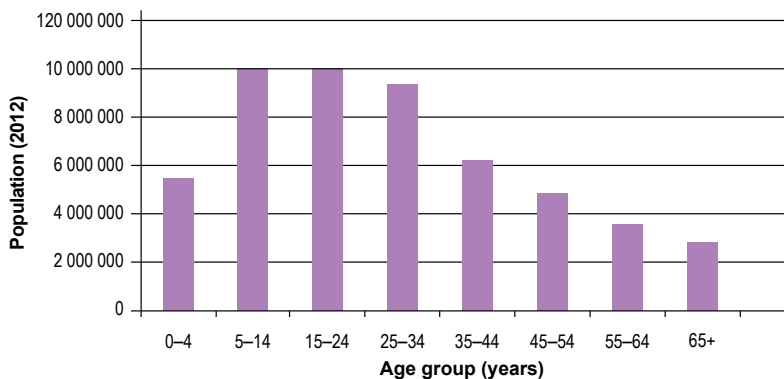
C
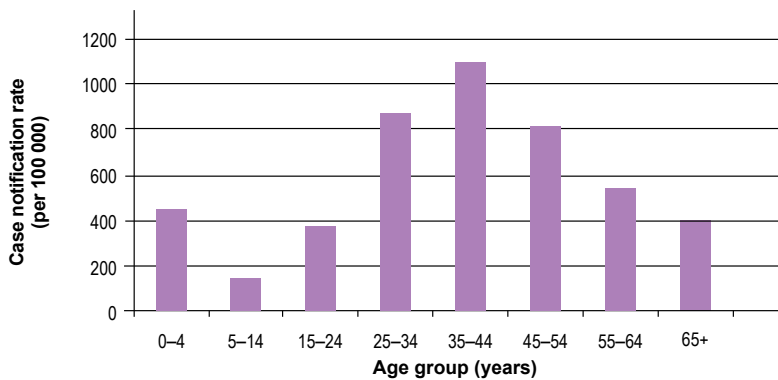
Cambodia

By comparison, we can see that for Cambodia the notification rates increases with age, with the oldest age groups having the highest rates (Figure 6). As TB prevention, diagnostics and treatments improve, there is generally a shift in the highest notification rate of TB from the younger to the older age groups, due to declining infection rates over time, which results in a decline in notification rate among younger age groups. However, zero case notification among 0–4 and 5–14 age groups could also reflect problems with either diagnosing or reporting childhood TB cases to the NTP.

FIGURE 6
Case notification (all types) rate (per 100 000) by age group from Cambodia NTP, 2012. *Source:* **WHO Global TB report 2013**
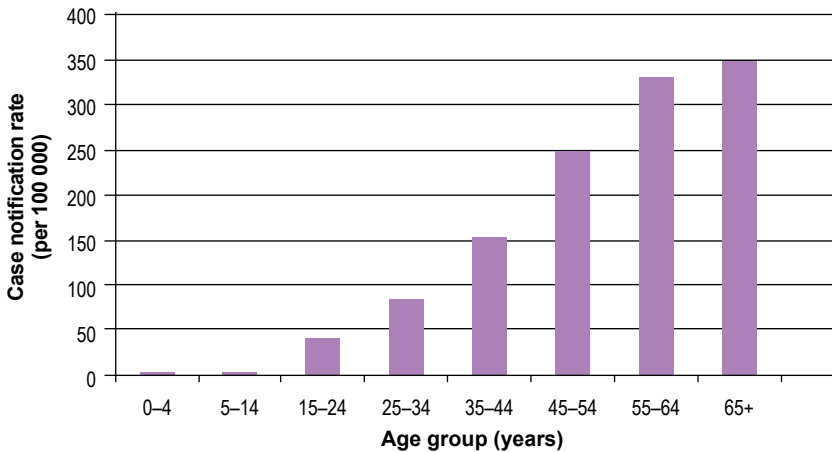
Japan

Aggregated data from case-based surveillance systems[h] can also provide important information about TB burden. Japan provides a good example of how the peak in TB notification rates from younger to older age groups shifts as TB prevention, care and treatment services expand and improve (Figure 7). From 1962 to 2011, notification rates in Japan significantly declined in all age groups, and the change in the rate of decline decreased as age increases. It means that a greater proportion of TB cases shifted from the younger to the older age groups with time. According to the expectation that the aging of the population has resulted in less childhood TB relative to adult TB, this data clearly high-

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h.   Case-based surveillance data contain records for which an episode of TB and associated treatment information is the unit of analysis (see Chapter 2).

lights the rapid rate of decline in notification rates among children from birth to the age of 14. This observation is a proxy for the declining spread of TB in the community, thus providing evidence that with an improved TB programme, transmission of TB infection in the community can also be reduced.

The aggregated data also capture specific changes in the TB surveillance system in Japan. From 1987, the NTP started using the "80 years or more" category and introduced the "90 years and more" category in 2003.

FIGURE 7
TB case notification rates in Japan (1962–2011). The log-scale for the Y-axis is used to demonstrate the rapid decrease in TB rates.
Source: **Japan NTP annual report 2012.**
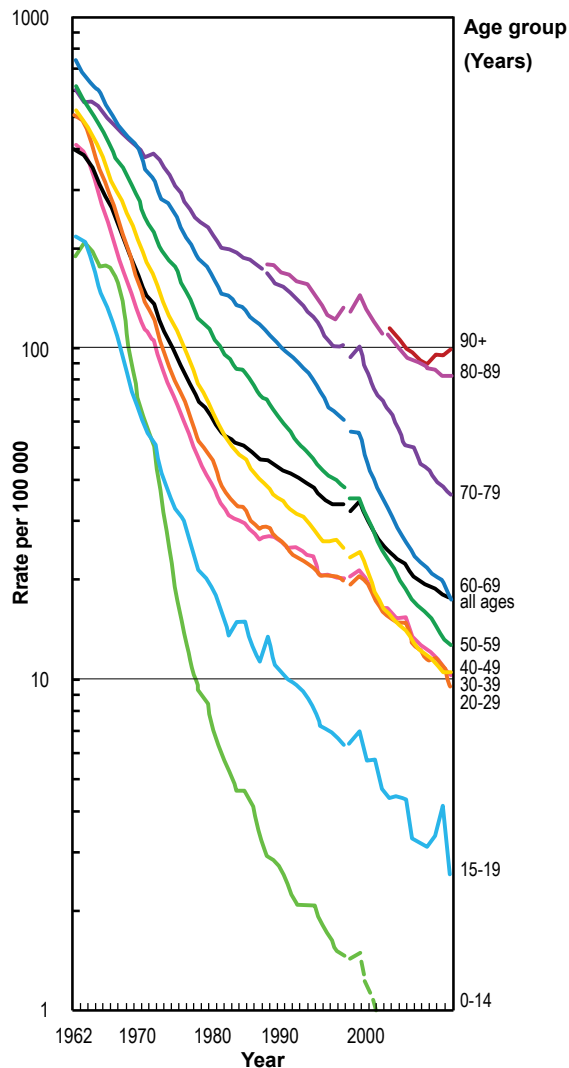
In addition, the TB case definition was amended in 1998 to exclude individuals with non-tuberculosis mycobacteria diagnoses, therefore only those with *Mycobacterium tuberculosis* diagnoses were classified as cases. Another notable change in the trend of TB notifications was observed in 1999, whereby the NTP declared a national TB emergency and thus with greater awareness in the general population and among health providers, more cases were diagnosed and notified.

Notifications by sex

Based on current global TB notifications (2012), the global male-to-female ratio for all new cases (all types of TB) is 1.6, with substantial variation between countries (Figure 8). Although most countries have a sex ratio for new cases that is greater than one, which means there are more males than females being notified, there are a few countries (e.g. Afghanistan, Pakistan, Papua New Guinea) where the overall male-to-female ratio for new cases is less or equal to one, which means they have fewer male than female patients being notified.

FIGURE 8
Male-to-female ratio of notified new TB cases (all types) from 193 countries with available sex-disaggregated data, 2012.
Source: **WHO Global TB Report 2013**
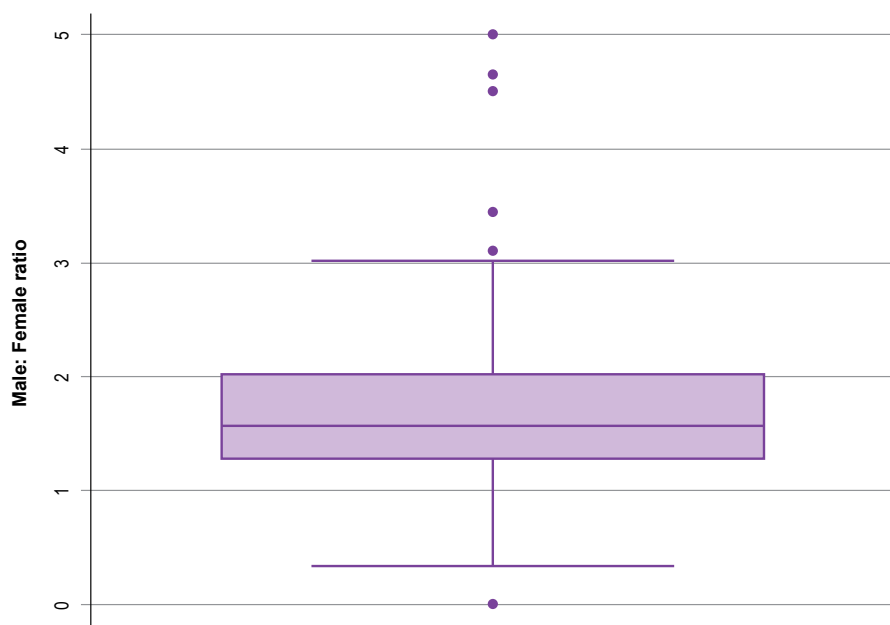
If the male-to-female ratio is observed over time at the national level, it can help assess the internal consistency[i] of the NTP's surveillance system. 'Internal consistency' is one of the data quality standards from the *WHO Checklist of standards and benchmarks for TB surveillance and vital registration system* that can be used to assess the data of NTP routine surveillance systems (Annex 1). To assess the internal consistency of the surveillance system, the minimum set of variables should be examined over time looking for any substantial differences that require an explanation. Ratio of male-to-female cases is one of the suggested indicators for the examination. For example, in Uganda the NTP analysed the change in the male-to-female ratio of TB cases from 2008 to 2012 (Table 2). Each year there was a modest increase in the proportion of males diagnosed with and treated for TB. Since the changes between each year were minor, this analysis suggests that the data have good internal consistency. However, in a five-year span, the change in the ratio could be considered substantial: 1.47 to 1.64, or 11.6%. As such, it would be beneficial for the NTP to look further into why this ratio was increasing over time.

TABLE 2
The ratio of male to female TB cases in Uganda, 2008–2012.

Year	Male to female ratio (All new and recurrent cases)
2008	1.47
2009	1.52
2010	1.58
2011	1.63
2012	1.64

When we further stratify notification data from Uganda (2012) by age group and sex (Figure 9), we can see that although the rates in male and female children (0–14 years) are the same, a clear disparity between the sexes becomes more obvious in the older age groups beyond children and adolescents. The greatest difference in male-to-female cases occurs in the 35 to 54 year age group. Possible hypotheses for this situation may include: i) that women were less likely to seek health care as they got older or were underdiagnosed when they did seek health care; ii) that men became more likely to seek health care and thus comprise a greater percentage of the TB cases; or iii) that epidemiologically, there was a real increase in men (or decrease in women[j]) who developed TB in Uganda over these years.

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i. 'Internal consistency' refers to surveillance system indicators that can be reproduced and compared over time (Annex1).
j. The prevalence of HIV is higher in women (15-49 years) than in men in Uganda (UNAIDS 2014), however the prevalence of TB is higher in men. It could be hypothesized that HIV-positive women in Uganda are more likely to come from the wealthiest quintile, who are therefore more likely to be on antiretroviral therapy, therefore they may be less vulnerable to TB despite the higher HIV prevalence. See Chapters 4 and 6 for more details of factors driving the TB epidemic.

FIGURE 9
All types TB case notification rate (per 100 000) by age group and sex in Uganda, 2012. *Source:* **NTP Uganda**
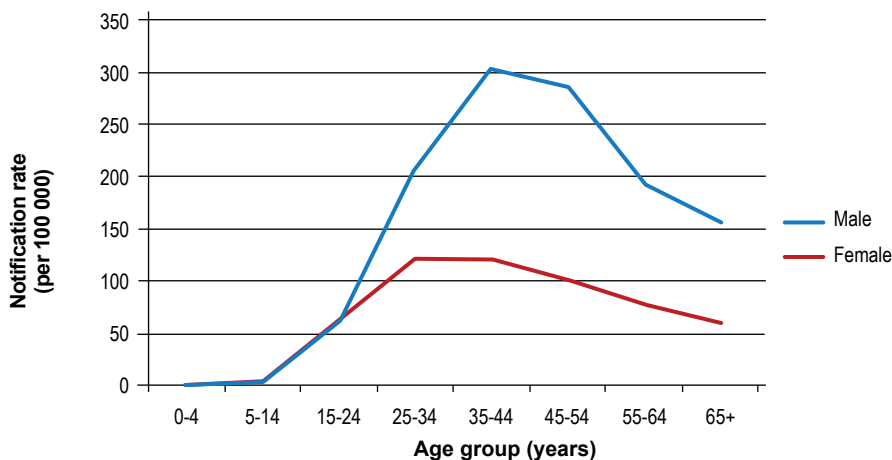
Notifications by place

Another valuable approach to analysis of surveillance data is to look at variations in the notified cases across geographic areas within the country. As we have seen so far, aggregated national data can be used to describe the overall epidemiological situation, but the burden of TB is usually not equally distributed throughout the population. Therefore, sub-national data can also be used strategically to inform policy, programmes and specific activities to help allocate resources where they are needed the most.

Examining case notification rates for each sub-national level (e.g. provincial or district level) is particularly useful to understand how the burden of TB differs within a country. To undertake this assessment, total case notifications for each sub-national level are divided by the population for each respective area. Visualization of sub-national rates as simple maps, using different colours to indicate different levels of case notification rate, can show nationwide variation quite clearly.[k] For example, in Cambodia it is clear that the north east provinces have lower TB notification rates than the rest of the country (Figure 10). These rates may reflect the true TB burden in the region, or they may indicate low levels of health care access in areas with low population density. Conversely, the highly populated areas have higher TB notification rates, which could be due to real differences in TB infection and disease or the result of better access to health care in those areas. This is in contrast to China, where the heavily populated and richer urbanized areas in the

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k.   These maps were created using Quantum GIS. A free, cross-platform, open-source (GIS) application for desktop computers that provides data viewing, editing and analysis capabilities (http://www.qgis.org).

eastern part of the country have a lower notification rate than in western regions, where access to health care is low and rural areas are sparsely populated (Figure 11). In Thailand, there are also higher notification rates in major cities as well as in provinces with high cross-border migration (Figure 12). Similarly, in Cambodia, high TB notification rates are also noted in provinces that share border crossing areas with Viet Nam and Thailand. Likewise, in Mozambique, higher notification rates can be seen in the country's more heavily populated southern districts that border Swaziland and South Africa, as well as the larger cities along the coastline (Figure 13).

Other routinely collected data can be visualized and compared at the sub-national level. In Mozambique, examples include the proportion of TB notifications that occur among children less than 15 years of age (Figure 14), and the proportion of TB notifications that are extrapulmonary cases (Figure 15). Even within one country, we can see high variation by province, which is likely a function of clinical diagnostic abilities, health care access and quality of the provincial surveillance system to capture cases rather than a true difference in the burden of childhood TB and extrapulmonary disease by place.

Although beyond the scope of this handbook, it is important to note that if population and socioeconomic data are available, further analyses can determine relationships between demographic variability and TB burden (e.g. how does TB case notification compare between the rich urban, poor urban, rich rural and poor rural populations?).

FIGURE 10
TB notification rate (all forms) by province; Cambodia, 2011.
Source: **Cambodia NTP annual report 2012**

Case notification rate per 100 000
- 0 – 87
- 88 – 169
- 170 – 273
- 274 – 366
- 367 – 554
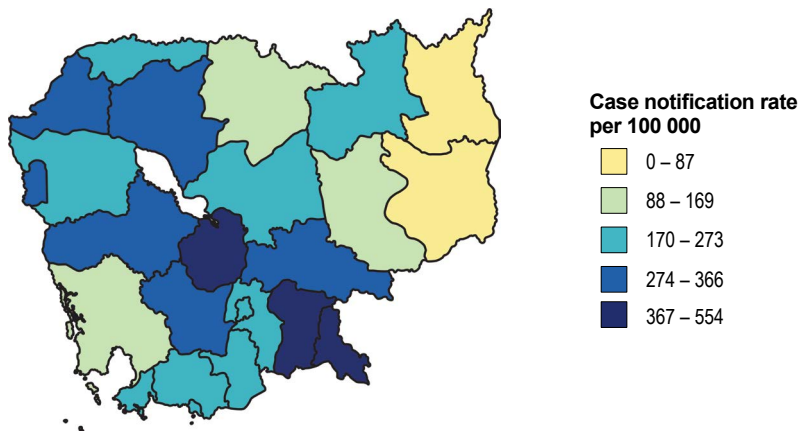
FIGURE 11
TB notification rate (all forms) by province; China, 2010.
Source: **China MOH, China ten years national tuberculosis program evaluation report (2001–2010), 2011, Military Medicine and Science, Beijing**
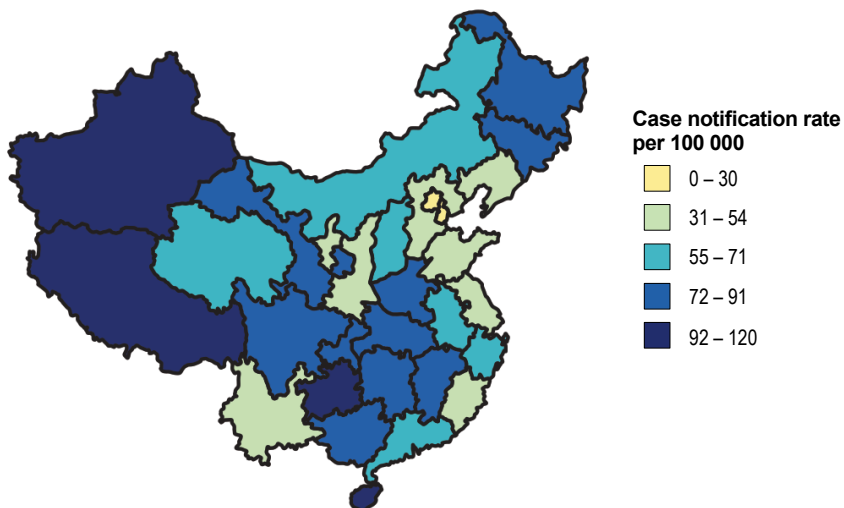
FIGURE 12
TB notification rate (all forms) by province; Thailand, 2012.
Source: **Thailand NTP**
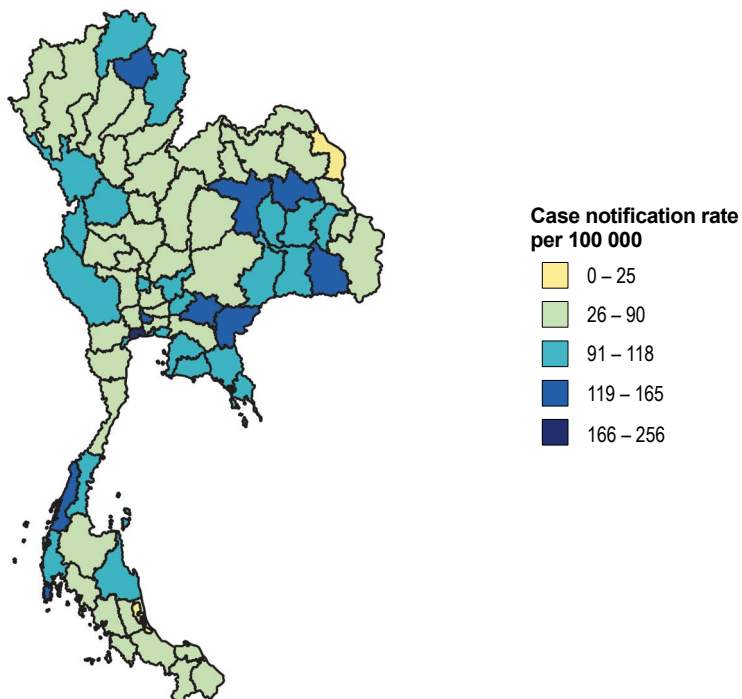
FIGURE 13
TB notification rate (all forms, new cases) by district; Mozambique, 2012. *Source:* **Mozambique NTP**
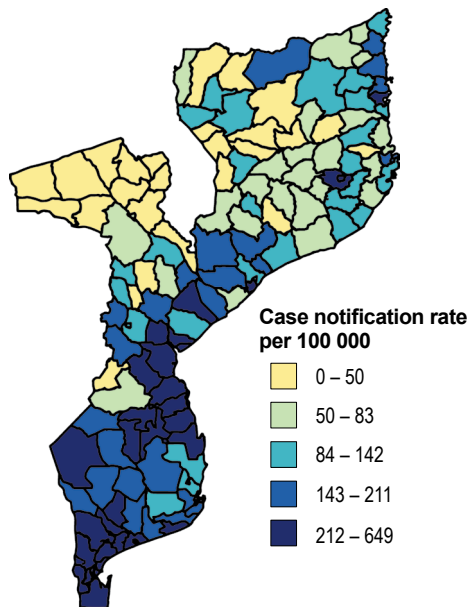
FIGURE 14
Proportion of childhood TB notifications (all forms, new cases) out of all notifications by province; Mozambique, 2012.
Source: **Mozambique NTP**
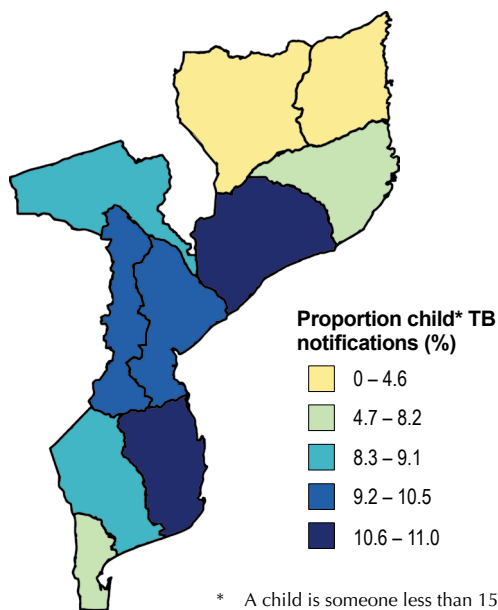
* A child is someone less than 15 years of age.

FIGURE 15
Proportion of extrapulmonary TB notifications (new cases) out of all notifications by province; Mozambique, 2012.
Source: **Mozambique NTP**

Proportion of
extrapulmonary TB (%)

- 0 – 6.7
- 6.8 – 9.5
- 9.6 – 10.71
- 10.8 – 13.4
- 13.5 – 24.0
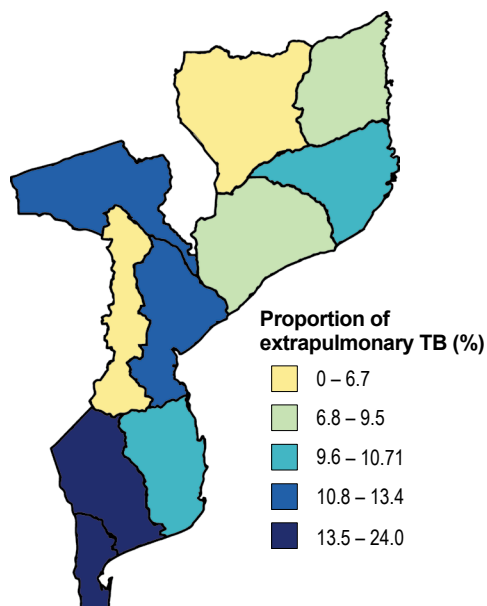
Notifications by place and time

Trends can be observed in relation to place by person and time. For example, one can assess trends in age- and sex-specific notification rates in sub-national regions. If this can be undertaken in relation to a detailed analysis of the routine recording and reporting system, this may allow the NTP to improve its understanding of TB epidemiology and shortcomings of routine TB surveillance.

Ghana

Examination of sub-national TB notification rates in Ghana from 2008 to 2012 identifies much variation between regions (Figure 16). On average, Greater Accra has the highest rates while the Northern Region consistently has the lowest rates. If just the national rates were observed, such variation would be missed and the TB epidemic over generalized.

FIGURE 16
TB Case (all forms) notification rate by region, Ghana (2008–2012).
Source: **Ghana NTP**
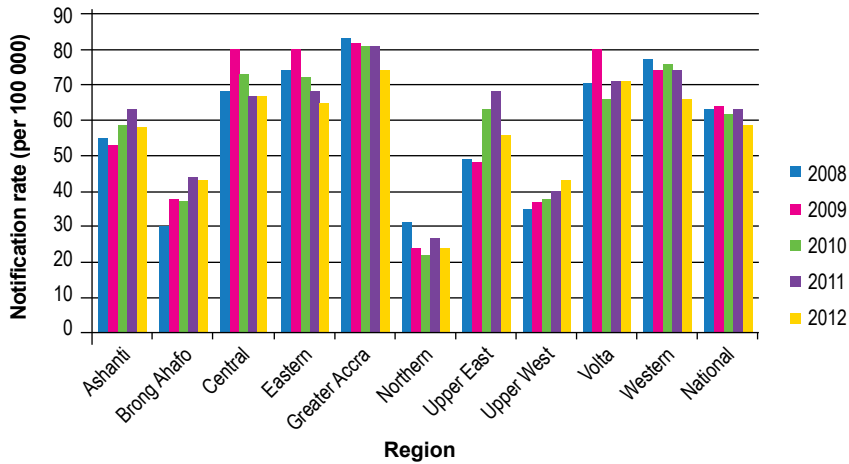
The variation within each region from 2008 to 2012 can also be observed. It appears that there were large unexpected increases in TB case rates in Brong Ahafo from 2008 to 2012 and in Upper East Region from 2009 to 2010. These changes can be even more useful if the percentage change in TB case rates between subsequent years is calculated (Figure 17). This can be done by using the following formula, in which '*year i*' corresponds to the first year of interest and '*year i+1*' corresponds to the subsequent year:

$$\textit{Percentage change per year} = \frac{\textit{Rate (year i)} - \textit{Rate (year i + 1)}}{\textit{Rate (year i)}} \times 100$$

Calculating the percentage change is an internal consistency check for data quality. When large percentage changes are observed between years, it is important to identify possible reasons for these discrepancies. Are these fluctuations occurring because of natural changes or are there programmatic or human-based errors that are artificially affecting the surveillance data? Weak systems that have a large discrepancy (e.g. more than 10% change), are more likely due to issues related to reporting and recording errors rather than a true change in the number of cases in that region.[I]

I.   In high-performing surveillance systems, large year-to-year fluctuations may exist where there are few TB cases initially.

FIGURE 17
TB Case (all forms) notifications: percentage change by year for each region, Ghana (2008–2012). *Source:* **Ghana NTP**
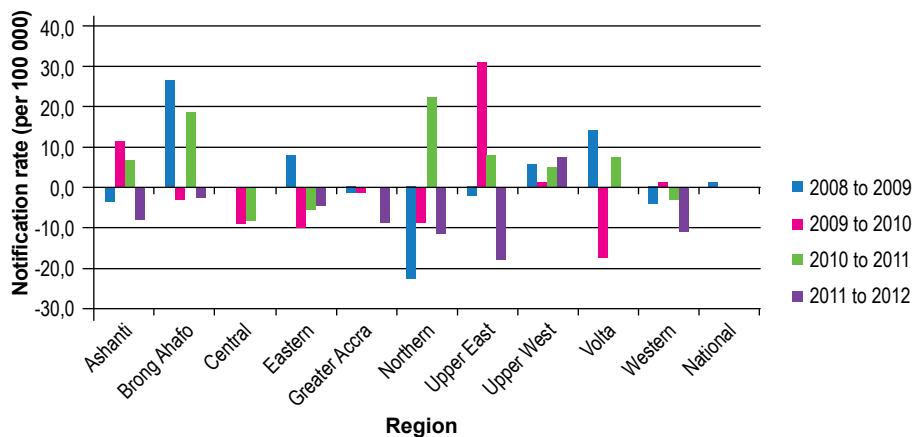
The assessment of Ghana's NTP surveillance system using the WHO Standards and benchmarks checklist found that data in quarterly reports were not internally consistent and in some instances inaccurate and incomplete. Extensive data quality audits identified that only 11 out of 29 BMUs selected across four regions had total TB cases in the quarterly NTP reports matching the number of cases in the BMUs TB register. A further 11 BMUs were found to be under-reporting and seven BMUs were over-reporting TB cases. Such discrepancies are related to the wide fluctuation in the percentage change of notification rates observed in certain regions. Consequentially, the NTP has since strived to increase overall data quality by placing greater focus on the correct use of revised data collection tools, facilitating more frequent training, implementing standard operating procedures (SOPs), and holding more regular supervisory monitoring visits and quarterly data quality audits.

Uganda

Examination of TB cases by gender at the provincial level in Uganda during 2008–2012 shows considerable variation (Figure 18). For all regions, more male than female cases were reported, however, the proportion of all male cases also varied between regions. There also appeared to be inconsistencies that need to be addressed to improve the quality of data in the surveillance system. For example, the North West and Kampala provinces saw greater inconsistencies in such reporting as noted by large fluctuations in the percentage of notified TB cases that were male from 2010–2011 and 2011–2012, respectively. The reasons for these inconsistencies need to be identified and similar patterns in inconsistencies should be sought among other variables to understand the issues that need to be addressed to improve data quality.

FIGURE 18
The proportion of reported TB cases that were male by TB reporting zone, Uganda, 2008–2012. *Source:* **Uganda NTP**
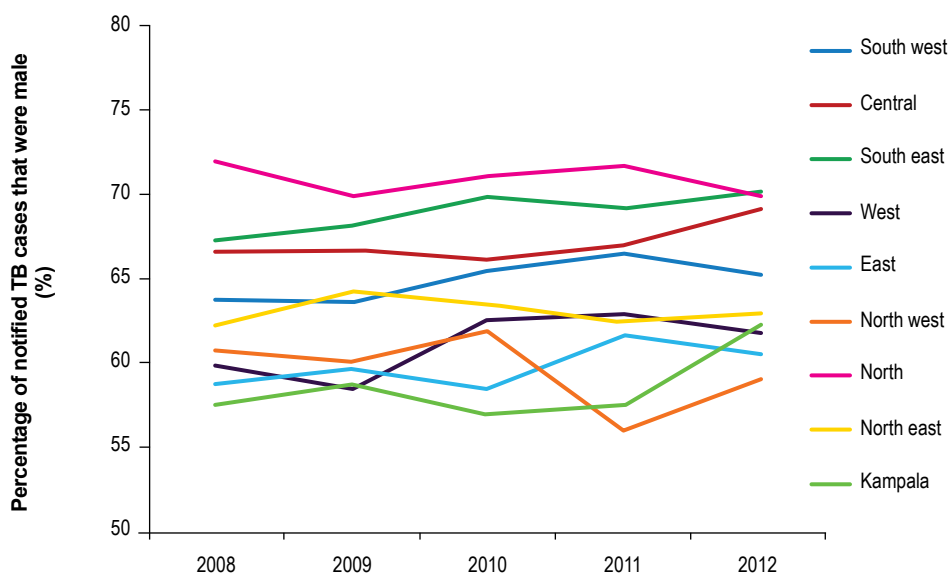
Reasons for changes in notification rates over time

There could be many reasons for changes in notification rates, including: natural causes (e.g. an increase in migration or a localized epidemic); programmatic causes (e.g. a shift to focus on the detection of childhood TB); or, unknown causes. Often changes in rates should be attributed to issues with the surveillance system and data quality unless otherwise proved. Answering the following questions can assist in determining the reasons behind substantial variations in the data:

- Were there any significant events in the community that could have naturally affected the burden of TB (e.g. influx of refugees)?
- Were there any significant events in the community that could have affected access to health care positively or negatively (e.g. war, natural disaster, introduction of a universal health insurance programme, construction of new health centres or hospitals)?
- Were there any significant changes to the surveillance system during the time period (e.g. change in reporting forms, or a change in staffing)? These changes could have resulted in problems with data quality (e.g. different interpretations of definitions or slow adoption of new forms, or they could have artificially increased or decreased TB indicators because of widespread adaptation of new definitions or new reporting methods).

- Were there any significant changes to the TB or health outreach programmes during the period of interest (e.g. an increase in health workers)? Was there an increase in health communication programmes on TB or an increased focus on childhood TB? Was there a new effort to reach particularly vulnerable population known to be at risk for TB?

If research determines that the observed changes are related to the reporting system and do not really reflect an increase in TB, it is important to identify the root of the problem along with solutions that address it.

1.5 Limitations of aggregated notification data

Aggregated reports have several limitations over case-based collection of notification data (*1*). The main limitations are:

1. Aggregate reports are usually based on manual case counts from multiple paper-based records on a quarterly basis. This is an intensive process that can lead to mistakes, yet there is often no built-in mechanism for identifying and correcting mistakes. As a result, collection and reporting of aggregate data from all health facilities to TB data management units at district, regional and national levels is time-consuming, resulting in delays in compilation, analysis and identification of trends in notified TB cases and treatment outcomes. Furthermore, manual handling of data often results in transcription mistakes as the information is transferred from one form to another.

2. As it is labour-intensive to transcribe and compile case-based information into aggregate reports, only limited information can be collected in these systems. The standard data collected are: sex, age groups, treatment history, disease site (pulmonary or extrapulmonary), and bacteriological status at diagnosis. Treatment outcomes are collected usually only by treatment history.

3. Analysis of aggregated data is complicated and reporting options are limited. It is especially important because of increasing needs in the collecting and reporting of comprehensive information related to diagnosis and treatment of DR-TB.

4. Data on individual cases or patients are not readily available above the health facility level. Therefore, access to case-based data is restricted for programme directors and policy-makers, who are required to make informed programmatic assessments (e.g. diagnostic and treatment management of patients).

5. It is not possible to link aggregate data to other databases. This minimizes the scope, potential and utility of the TB data collected in the system, and reduces the research, programmatic and policy linkages that could be made if case-based data were used.

Overall, a case-based TB surveillance system allows for more detailed, extensive and timely collection and analysis of information. As a result, several countries – including Indonesia, Kenya and Viet Nam – are in the process of moving from paper-based, aggregate TB sur-veillance systems to electronic, case-based systems. In some countries, these systems need to be created, while in others they are incorporated into pre-existing electronic reporting systems for other infectious diseases. Examples of these systems are illustrated in the WHO guide on *Electronic recording and reporting for tuberculosis care and control* (*1*) as well as details on how to select, design, implement and maintain such systems.

1.6 Summary

NTPs are encouraged to routinely analyse their own data. This chapter explains and demon-strates methods by which the NTP can use aggregate data that are routinely collected in a TB surveillance system. Simple descriptive data analysis, assuming the data are of high quality, can help the NTP to describe 'who, what, when and where' of TB in the commu-nity. These analyses can then generate hypotheses and further exploratory studies to answer 'how' and 'why' the situation currently exists. The NTP can also use their data and specific data analyses to assess the quality of the data collected through the surveillance system and determine if it truly represents the current TB situation in their country. While the focus of this chapter has been on case notification data, other indicators, such as aggregate mortality data or successful TB treatment outcome, could also be used for similar analysis. Despite the utility of aggregate data, it is limited in a considerable number of ways. It is important to recognize these limitations and, if possible, strive to develop or adapt a case-based surveil-lance system, which would allow for more robust analyses.

BOX 4
Data analyses that can be undertaken by national TB programmes

- Collect national notification data and plot case notifications (all types, smear positive, depending on data availability) by year.

- For the most recent year, plot the age distribution of case notifications (all types or smear-positive TB cases). Can this be done for the previous five years too? Describe what you have plotted. What does it mean?

- Is your notification data broken down by age? If so, create the notification rate and plot by age group. Can this be done for the previous five years too? Describe what you have plotted. What does it mean?

- What proportion of all TB notifications is in children less than 15 years? Is the proportion the same for previous years too?

- Is your notification data broken down by sex? If so, create the notification rate and plot by sex. Can this be done for the previous five years too? Can this be done by age group as well? Describe what you have plotted. What does it mean?

- Do you have notification and population data at the sub-national level (e.g. province)? If so, create sub-national notification rates and compare them. Describe the variation in rates. Also, calculate sub-national notification rates by age or sex and then compare the distributions and time trends. What do these all mean?

- Can the same analyses be performed with other indicators too (e.g. mortality or successful treatment outcome data)?

- Decide on the best means of interpreting this information.

References

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3.   Checklist of standards and benchmarks for case-based TB surveillance data. Geneva: World Health Organization; 2014. Available at: http://apps.who.int/iris/bitstream/10665/112673/1/9789241506724_eng.pdf?ua=1
4.   Worker's manual on the management of tuberculosis and leprosy diseases - 5th edition. Federal Ministry of Health, Department of Public Health, Nigeria. Available at: http://www.who.int/hiv/pub/guidelines/nigeria_tb.pdf

Annex 1
TB surveillance data quality standards with examples

Many of the 13 standards from the *WHO Checklist of standards and benchmarks for TB surveillance and vital registration system* can be used to assess the data quality of NTP routine surveillance systems. In particular, the following standards should be considered on a regular basis:

- **Case definitions (Standard 1).** The case definitions used in TB surveillance and the uniformity with which they are adopted are the first things that must be considered when assessing data quality. Having standardized and universally applied case definitions is essential to provide consistent information on epidemiological trends and control programme performance, and to make accurate national, regional and global comparisons. Case definitions that are unclear, inconsistent, or not standardized are detrimental to such monitoring and make analysis of aggregated data difficult, if not impossible. As such, assessing the adherence of case definitions as used in the national surveillance system is vital to interpreting the data collected using the system.

  Example: The National Tuberculosis and Leprosy Control Programme in Nigeria has developed and distributed the *Worker's manual on the management of tuberculosis and leprosy diseases (4)*. TB case definitions were clearly defined in the manual, including differentiation between laboratory-confirmed and clinical cases, new and previously treated cases, and pulmonary and extra-pulmonary cases. Furthermore, these case definitions are a part of the routine training for TB management in the country. Thus, the TB case definitions in Nigeria are consistent with WHO guidelines, and the surveillance data in Nigeria meets this standard. As such, the NTP can be reasonably confident that throughout the country, cases are being consistently recorded according to these definitions, which is the first step in achieving quality data.

- **Minimum set of reported variables (Standard 2).** WHO has outlined a minimum set of variables that represent the fundamental attributes needed to assess data quality in a TB surveillance system.[m] As such, the following data should be collected and reported for all TB cases: age, sex, year of registration, bacteriological results, history of previous treatment, and the anatomical site of disease. Ensuring that the data for each of these variables is collected across the surveillance system will enable better assessment of data quality (e.g. external and internal consistency).

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m.   Age or age group, sex, year of registration, bacteriological results, history of previous treatment, anatomical site of disease, and for case-based systems, a patient identifier (e.g. numeric ID).

Example: In Nigeria, the TB surveillance system is paper-based at the facility level. Patient data are collected and then recorded in facility TB registers. Aggregated reports are compiled at the local government area (LGA) level and sent to the NTP through the state and zonal TB supervisors who validate the data before forwarding the reports. An aggregate electronic database was developed and installed in 2013 with the aim of collecting data and analysis of trends at the LGA and state levels. Data are routinely collected for the following variables: age, sex, year of registration, bacteriological results, history of previous treatment, and anatomical site of disease. In addition, a patient identifier is assigned by the LGA supervisor at the facility level; guidelines for generating the identifiers are provided in the national guidelines. Based on the assessment, a minimum set of variables is captured for all TB cases, so this standard is met in Nigeria. This means Nigeria is routinely collecting information on enough variables to assess the quality of the data collected.

- **All data submissions received and processed (Standard 3).** Paper-based systems that follow WHO guidelines rely on quarterly reports compiled at TB BMUs, where the TB registers for a set of health facilities are aggregated. These quarterly reports are sent up an administrative chain, with aggregation sometimes occurring at each stage in the chain. The national aggregates should be based on reports from 100% of BMUs (i.e. the lowest level at which aggregation occurs) in the country for the year being evaluated. Using less than 100% of expected quarterly reports or data files can result in many cases not being included in the national statistics.

  Example: In Uganda, it is possible to know at the national level the number of districts submitting reports each year, out of the expected total. In 2011, 468 out of 468 expected reports were received at the national level.

- **Internal consistency** (**Standard 4** for aggregate data, **Standard 5** for case-based data). Sub-totals of the number of TB cases by age group, sex and case type collected on source documents by health care facilities should equal the total number of reported TB cases reported by the subsequent BMU.

- **External consistency (Standard 6).** Comparing the NTP's TB surveillance data with the global epidemiology of TB is a method of measuring the quality of a surveillance system, and hence the data collected through it. For NTPs, external consistency can be evaluated by calculating the percentage of children diagnosed with TB within the programme and comparing it with the global average (childhood TB cases ($\leq$15 years) should account for 5–15% of all TB cases in low- and

middle-income countries, and less than 10% of all TB cases in high-income countries).

Example: Data collected by the Division of Leprosy, TB, and Lung Disease surveillance system in Kenya were externally consistent between 2008 and 2012. The percentage of childhood TB cases was between the acceptable ranges for a low-to-middle income country (5–15%) within these five years with only little variation between years (Figure A1).[n]

FIGURE A1
The proportion of childhood TB cases among all notified TB cases in Kenya, 2008–2012.
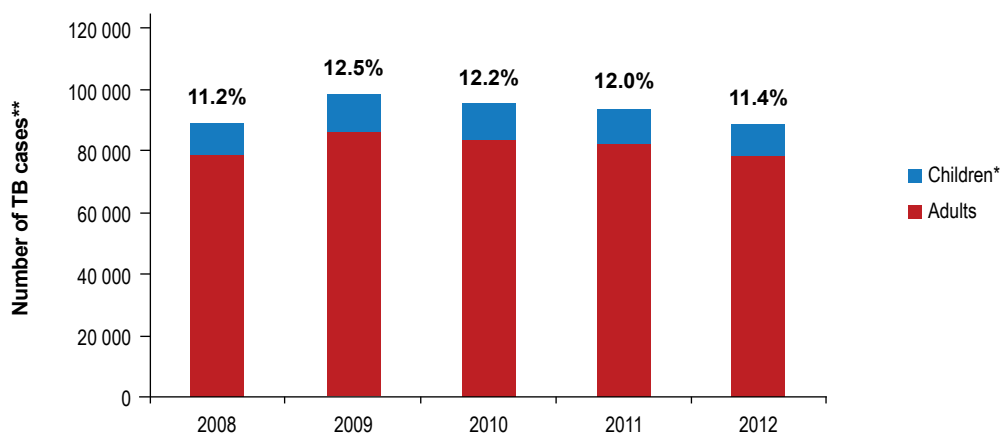
*   Cases were ≤15 years old. All paediatric cases were considered to be new cases.
**   Cases include smear positive, smear negative, extrapulmonary, and smear not done. Retreatment cases were excluded from this analysis

- **Internal consistency (Standard 7).** Finally, it is vital to assess the consistency of data from within the programme. It is known that changes over time with TB cases and deaths should be minimal because even in the best of situations, the decline in TB incidence has been no more than 10% per year, nationally. The minimum set of variables (described above) can therefore be examined over time at the national, provincial or other administrative levels, with any substantial differences suggesting inconsistencies in data reporting and recording, or otherwise requiring an explanation. Specific suggestions for analyses include changes in the ratio of notified pulmonary-to-extrapulmonary cases, ratio of male-to-female cases, proportion of childhood TB cases out of all cases, case notification rate for all forms of TB, case notification rate for new smear-positive TB, and the ratio of TB suspects

n.   Data from the UK and the Netherlands have recorded the best declines in incidence at a national level of 10% just after 1945. The current best performing, high-burden countries are Cambodia and China with recorded declines of 3–5% incidence since 2000.

to notification. Finally, if mortality data are available, changes in the national number of reported TB cases should be consistent with changes in national TB mortality.

Chapter 2
Analysis of case-based TB notification data

Audience:

General readers, in particular monitoring and evaluation officers and epidemiologists, at any administrative level, working in NTPs with case-based surveillance data.

Expected outcomes:

By the completion of this chapter, the reader should be able to understand:

- the value of case-based TB notification data for describing the epidemiology of TB and the programme implications for the NTP?
- how to assess the quality of case-based TB notification data?
- how to analyse, report and interpret case-based data?
- how analysis of case-based data can lead to changes in practice and policy.

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2.1 Case-based notification data: what they are and why they are important

Case-based surveillance data contain records for which an episode of TB and associated treatment information is the unit of analysis (*1*). Data in a case-based system can be combined to generate aggregate data, but keeping a separate record for each TB case allows for analyses that are more detailed than is possible for systems with only aggregate data. Surveillance systems utilizing case-based notification data are the ideal, although many high TB burden countries currently use systems based on aggregated data. NTPs can analyse case-based TB surveillance data to better target interventions locally and nationally by identifying population characteristics that predispose people to higher risk of disease and poor outcomes. NTPs can also use case-based data to identify disease outbreaks and guide timely public health actions to ensure appropriate management of TB cases and contacts, and inform policy by assessing progress in TB control, as compared with national and international targets (*2*). The types of analyses that NTPs conduct may differ, however, depending on the purpose or objectives of the work.

For case-based TB surveillance data, each case represents a single entry in the system to which additional information is added during treatment. A unique identifier is often captured within the system to link different pieces of information related to the TB case. In some countries, NTPs use a unique personal identifier (e.g. social security number) to facilitate linkage of different episodes, identify duplicate entries of the same episode, and link to other national databases. Occasionally, only a particular district or health care facility may use this identifier. This can make it difficult to identify previous episodes of TB, particularly if the patient had been previously treated elsewhere.[a]

Although establishing an electronic, case-based surveillance system can require more resources and coordination than maintaining a paper-based system using aggregate data, it is preferable for many reasons (*1*):

- Records can be used for clinical management of patients to ensure high quality care and to monitor treatment outcomes.
- Longitudinal profiles from records of every patient can be compiled for each TB case, enabling easy case-based analysis (e.g. analysing characteristics among sub-groups of TB patients or the effects of patient characteristics on treatment outcomes).
- Variables of interest, such as risk factors for TB (e.g. smoking status or diabetes),

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a. Patient-based records, for which an individual person rather than a TB case is the basic unit of recording, allow a patient's previous treatment history to be known as long as coverage of the system is national and the system is built to recognize relapsed TB patients automatically using records of their earlier TB episodes. However, many systems do not satisfy these criteria and instead capture case-based data.

can be added to the surveillance system and analysed to better understand the TB epidemic.

- Data quality checks can be easily implemented to help ensure the accuracy and validity of the data (e.g. identifying duplicate entries or implausible data combinations, such as a patient being pregnant and male).
- Records can be linked to other databases to retrieve additional information (e.g., drug susceptibility results from a laboratory information system). This can enhance the quality, and expand the scope of use, of data.
- Reports can be generated automatically at any time, without having to wait for quarterly aggregated reports to become available.
- A richer quantity of data is available for analysis, interpretation, and use by staff in the NTP.

Considering these benefits, in settings where the TB surveillance system continues to rely upon quarterly paper forms compiled from district registers, NTPs may want to carefully consider the benefits of an electronic case-based system.

This chapter describes the standard approaches for analysing case-based data so that readers can plan and conduct similar analyses. This includes how to develop an analytic plan, prepare data for analysis, and analyse and interpret routine surveillance data. A brief introduction to conducting more in-depth analyses is provided at the end of the chapter. To learn more about the concepts and analytic approaches described, please refer to the WHO publication *Basic epidemiology* (*3*), which provides detailed definitions and step-by-step explanations about epidemiologic concepts.

Steps in case-based data analyses

Case-based data offer expanded opportunities for data analysis. Recording and reporting of TB surveillance data in both aggregated and case-based systems is based on internationally agreed upon common principles (*4*), with most countries collecting demographic, clinical and bacteriological information on TB cases in their surveillance systems. In fact, WHO recommends the collection and analysis of a minimum set of variables as part of the *Checklist of standards and benchmarks for case-based TB surveillance data* (i.e. age/age group, sex, year of registration, bacteriological results, history of previous treatment, type of disease and unique ID) (*5*). However, many countries – especially those using case-based systems – routinely collect and analyse additional variables based on their own national context, epidemiologic profile, and TB control priorities. For example, NTPs in the United States of America and the European Union (EU) routinely analyse and report data on nativity (birth in or outside a given country). Analyses of risk factors, drug-resistant TB, and trends at the sub-national level (e.g. state, district or region) are also common.

The process of analysing case-based data involves a number of steps, many of which occur before starting data analysis (Figure 1). These initial steps are important for planning the work and determining the quality of the data, which will consequently impact how the analyses can be used to inform TB programmes or otherwise add to the body of TB research.

FIGURE 1
Steps in analysing case-based data

2.2 Developing an analytic plan

Before undertaking analyses for routine or research activities, the person designated within the NTP to conduct the work, often an epidemiologist, should develop an analytic plan. An analytic plan is beneficial for two reasons. Firstly, it can help define the key steps, skills and software needed when approaching analyses of case-based TB surveillance data (i.e. what statistical tests will be used and what additional information, tools or skills are required to complete the analyses). Secondly, an analytic plan provides a road map to ensure the epidemiologist undertakes analyses in a targeted and efficient manner. The epidemiologist can revise the analytic plan once analyses are underway, as required. An analytic plan should include:

- analytic objectives and research question(s);
- study population, along with the inclusion and exclusion criteria;
- variables to be used and key definitions;
- table shells and sample figures;
- guidance on how to deal with missing values;
- analyses to be carried out; and
- statistical tests to be applied.

An example of an analytic plan detailing these elements can be found in Annex 2.

Statistical software must be acquired before the analytic plan can be implemented. The epidemiologist can import the case-based data into various proprietary statistical packages for analysis, such as R, SAS, Epi Info, SPSS, and STATA. He/she can also use geographic information systems (GIS) for mapping and spatial analysis. While these types of analyses can be done at local and national levels, an experienced epidemiologist (or data manager or statistician) familiar with the statistical programme should be available to help support the data analysis.

2.3 Preparing the dataset

Once the epidemiologist has prepared an analytic plan, he/she should prepare a dataset. This involves multiple steps that begin with general data cleaning and that end with a clean, 'frozen' dataset that can be used for analyses.

Data cleaning

Recording and reporting of surveillance data will sometimes contain errors. As data should be clean before they can be analysed, standard procedures must be in place to minimize, identify and fix incorrect records within datasets. This ensures data analyses will produce less biased and more easily interpretable results; it also allows for continual critique of and revisions to the established data collection process. Data cleaning is much easier in case-based surveillance systems than in aggregated data systems because the former make it possible to more easily assess and fix data problems. Electronic systems are also preferred over paper-based systems because automated validation checks can be implemented in electronic systems. Electronic databases can also be easily queried to assess quality.

To ensure clean data, the epidemiologist should follow these general principles:
- Maximize data quality during collection and entry;
- Examine data systematically to note missing, inaccurate, inconsistent, misclassified and implausible values and duplicate records; and
- Address erroneous data points in a systematic fashion.

Firstly, it is essential that the epidemiologist takes steps to maximize quality as data are collected and entered. To do this, it is useful to develop standard operating procedures (SOPs) for data collection, entry and review at each administrative level of the TB control programme (e.g. local, district, provincial and national). This promotes a unified approach

to data collection and entry and raises awareness of data quality among all people involved in these processes. After the development of such SOPs, it is critical to provide trainings to provincial and local partners to introduce and review the SOPs and to build capacity for data collection and management. Provision of written manuals or posters of the SOPs to all those involved with recording and reporting of TB data can help with uptake and ensure compliance. In addition to SOPs, it is essential that the epidemiologist ensures that the database is designed to minimize data entry errors.[b] For example, free text fields for data entry should be minimized to help ensure valid values are entered; instead, predefined drop-down menus or value ranges should be used. Similarly, data validation rules that are incorporated into the database (e.g. date of diagnosis ≤ treatment start date) should be developed. Finally, the epidemiologist should ensure that the database is designed so important data values cannot be left blank. This can be done with error messages preventing data entry clerks from proceeding until the values are entered. Proactively engaging in these steps will ensure that the epidemiologist has fewer errors to address during data cleaning.

Example:
Taking steps to ensure the use of high quality data

In the United Kingdom, Public Health England (PHE) manages a web-based TB surveillance system. This system is designed to maximize data quality as data are collected and entered. Within data entry screens, there are a limited number of free text fields, with most fields using predefined drop-down menus to ensure that values entered are valid. There are also automatic data validation checks to prevent data entry errors, such as 'date of symptom onset' must precede 'date first presented to clinic', which must precede 'treatment start date'. Similarly, 'date of birth' cannot be a date in the future, and data for 'treatment outcome,' of cured or completed treatment regimes cannot be recorded until six months after the 'notification date'. In addition to these measures, many regions run quarterly data reports to identify and correct errors. Incompatibility between variables for a case are flagged and followed up at the clinic where the case originated.

After data are entered, the epidemiologist should systematically and thoroughly review missing, inaccurate, inconsistent, misclassified, implausible or duplicate values. He/she should do multiple different checks to look for such values. For example, he/she should check to see if the same individuals are represented more than once in the system (i.e. search for duplicate cases). The responses for categorical variables (e.g. smear status)

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b.   Double data entry is not typically recommended for case-based TB surveillance data.

should also be checked to ensure values are limited to the categories specified for that variable (i.e. positive, negative or smear not done for the variable 'smear status'). Similarly, the ranges for continuous variables (e.g. age and weight) should be examined (i.e. search for responses out of normal or plausible range). Finally, data points should be checked to see if they are logical and consistent (e.g. a case cannot be male and also pregnant; a patient's age should correspond correctly to the date of birth).

Example:
Data quality control

The Netherlands NTP conducts active duplicate identification at the national level. They use a combination of date of birth, year of diagnosis and health care facility code and also sex, diagnosis, or postal code as needed. Local staff are contacted about possible duplicates. If local staff confirm a duplicate entry, the municipal health centre team consolidates and removes the duplicate data.

The last step in ensuring data are clean is for the epidemiologist to address incorrect data points in a systematic fashion. There should be clear protocols in place explaining how erroneous data must be dealt with. Standard procedures should be developed to identify and, if appropriate, fix errors in records when they arise. For example, to check that erroneous data points are deleted, all inaccurate or missing data should be dealt with as soon as they are found. Note that a single rule for dealing with missing or inaccurate data should be adopted and applied to all data. The ideal procedure begins with returning to the source data (e.g. data kept at the local level), to verify and correct entries.

Example:
Fix errors when possible

In the United Kingdom, PHE follows up data discrepancies identified at the regional level (through standard quarterly reports) by contacting the clinic where the data originated. Within the United States, public health officials in each state are encouraged to cross-check missing or obviously inaccurate records in the database with the patient's medical charts.

There are many ways to review, identify and address missing or erroneous data prior to starting an analysis of case-based surveillance data. Engaging in data cleaning steps on a regular basis can catch more errors and do so more quickly than attempting to do so months (or years) after collection. Furthermore, conducting regular data audits and analy-

ses, holding special trainings on data quality assurance, incorporating data quality checks into routine supervision, and following SOPs for data collection and entry, can all help to ensure that errors in the dataset are minimized and more easily addressed.

Addressing missing data

While cleaning the dataset, it is important that the epidemiologist considers how to address missing values. Surveillance data often have missing information because patients may not know or may refuse to provide the requested details or providers may not fill in the necessary data. Nevertheless, the epidemiologist can easily find missing data by running 'frequency' procedures and looking for the number of cases with missing data. Most software programmes provide an option that allows users to determine if they want missing values to be included in statistical calculations (Figure 2). If there are many cases with missing values for a particular variable, then the results of analyses using that variable could be biased.

FIGURE 2
The 'Include Missing Values' feature of Epi-Info 7
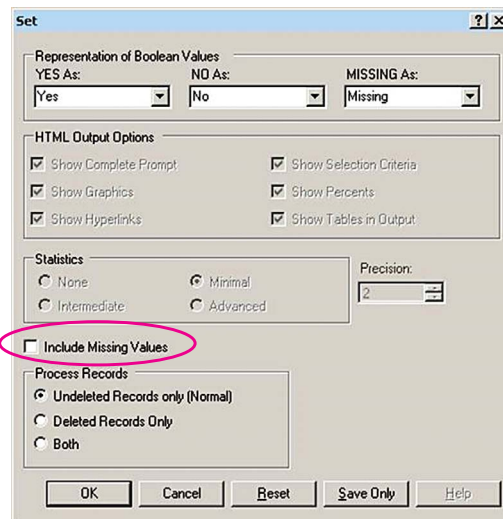
Once the epidemiologist has identified the missing data, he/she will need to address the cases with missing values. Ideally, he/she should first check the original data source to confirm missing values. If the values are found in the original data source, the epidemiologist should then correct the values in the dataset. If the values are also missing in the original data source, he/she will need to make a decision as to how missing data will be analysed and reported. Frequently, missing value codes (e.g., 9, 99, 999 or '*') are used to define a missing value (6). This can be seen in Table 1, where missing values were coded as '999' for the continuous variable 'age in years' in a small dataset of 15 cases. Even after

reviewing the original forms, the epidemiologist finds that three cases have missing data. Although the number of cases with missing data appears small, three cases with missing data means 20% of all cases have no information on age.

TABLE 1
Frequency of cases with specific age values

Age in years	Number of cases with an age value (Total=15)
5	1
17	4
32	1
45	3
58	1
66	2
999	**3**

Sometimes an epidemiologist may set a limit (i.e. cut-off) for the percentage of cases with missing data for determining if such cases will be eliminated or presented as part of the results. For example, if a variable is missing >5% of data, then it may be worthwhile to present the missing data as part of the results (e.g. in a category titled 'missing') to help ensure all of the information is presented. This ensures that problematic data are recorded when interpreting the data (see also the table in Annex 2). Alternatively, if very few cases for a given variable have missing data, then it may be worthwhile to exclude the cases with the missing data from the analysis. Keep in mind that in using this technique the total number of cases excluded from analysis could be quite large if there are many cases missing a small number of values for different variables. Techniques such as multiple imputations have been developed to impute or assign values to variables with missing data by using information from other cases in the dataset (7). These techniques will not be described here, but additional information can be found in Chapter 16 of *Tuberculosis prevalence surveys: a handbook* (8).

Identifying outliers

After addressing missing data, it is important for the epidemiologist to explore the data for extreme values, also known as outliers. Outliers are values that fall outside the upper and lower limits of what would be considered reasonable for a given variable. Outliers are by definition extreme values that can influence the results of an analysis and, therefore, need to be investigated.

Some software programmes have 'aberration detection' functions to spot individual data

errors. A simpler method to investigate outliers is to look for suspicious values that are incompatible with the rest of the data. This can be done by examining minimum and maximum values (e.g. an age of 108 should raise suspicion). Often it is easiest to find outliers by graphing the data using a histogram or similar data visualization approaches.

For example, consider an instance where an epidemiologist wanted to determine the average age of 1500 TB cases. After looking at the continuous variable 'age' in the dataset (Figure 3), he/she identified two values that appeared to be outliers: one case with an age of 95 and another with an age of 99. The next highest age recorded was 67.

FIGURE 3
Number of TB cases in a district, by age (in years)
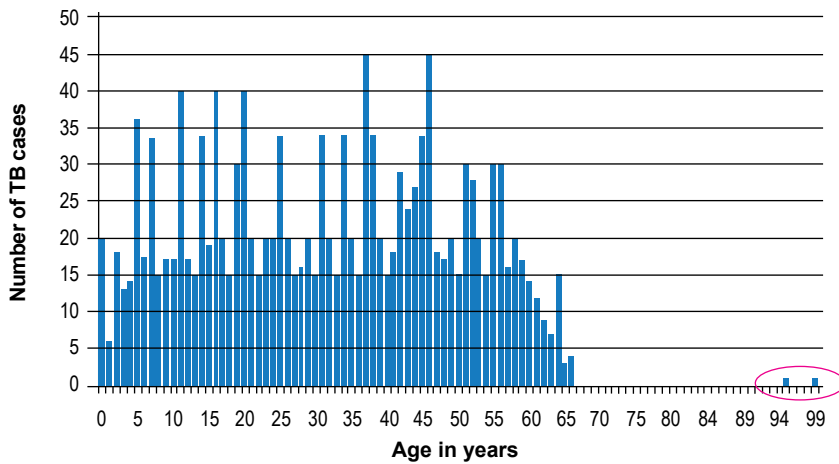
If the epidemiologist has identified outliers, he/she is recommended to first check the original data source to identify and correct any errors in data values. In the case above, the epidemiologist checked the TB treatment cards (the original data source) and found the case with the age of 99 was actually nine years old. He/she therefore changed 99 to nine in the dataset. For the second case (age 95), the treatment card could not be located, so the epidemiologist could not adjust the age. In this case, possible ways the epidemiologist could deal with the outlier in the analyses include: coding the outlier as missing, re-coding age in years (a continuous variable) to age group (a categorical variable) and thus minimizing the effect of the outlier, or excluding the case with the outlier from the analysis.

De-duplication of datasets

For case-based data, a common source of error is the presence of duplicate case records (i.e. the same information for a patient is captured more than once in the surveillance system). Duplicate records are problematic because they can artificially inflate the number

of TB cases that are recorded and reported. This makes the local and national figures on TB burden inaccurate. Duplicate cases may originate due to a variety of reasons. Errors in data entry (e.g. misspelling) are the most basic reason for duplication. Alternatively, patients may be reported to the NTP more than once if they move between facilities – Box 1 (9).

To ensure data are accurate, it is important that the epidemiologist check for and address duplicate cases in case-based surveillance systems. A simple way to detect duplicate cases is to run a frequency test on the unique identifier within the system; often the unique ID is the district ID number (e.g. district code/year/district serial number) or a national personal identifier (e.g. the United States Social Security number and the United Kingdom National Health Service number).

After identifying all duplicates, the epidemiologist should mark duplicated records as duplicates and remove the duplicate case(s) from the analysis (10). In the example shown in Table 2, the first case for district ID number 546/2009/23 (Bobby Smith) was marked as a duplicate and not used in the analysis.

TABLE 2
Identification of duplicate ID numbers in a dataset

#	District ID#	Name	Date of Birth	Sex
~~1~~	~~546/2009/23~~	~~Bobby Smith~~	~~12/12/1973~~	~~M~~
2	546/2009/23	Bob Smith	12/12/1973	M
3	145/2009/10	Sue Mary	3/12/1999	F
4	897/2009/43	Tanya Jones	10/1/1956	F
5	234/2009/88	Melinda Frank	9/8/1955	F
6	546/2008/23	Bill Smith	11/9/1979	M
7	009/2009/01	Irwin Law	5/9/1983	M
8	115/2009/67	Burt King	4/10/1975	M
9	768/2009/99	Jason Kirk	5/6/1965	M

Re-coding variables

After data are cleaned, the epidemiologist should consider recoding variables. Data collected by surveillance systems may be formatted in such a way that their structure makes it difficult for the epidemiologist to conduct his/her desired analyses (e.g. age is captured as a continuous variable, but the analysis requires age to be a categorical variable). In such instances, he/she can manipulate or re-code an existing variable into a new variable to better suit the analytical needs and required statistical calculations.

BOX 1
Case study: Preventing duplication of cases in Brazil

In the mid-2000s, the Brazil NTP sought to improve its national TB notification system. In addition to extending the coverage of the surveillance system, it developed processes to systematically validate data and link records already in the database. These processes were vital because there was duplication and misclassification of records for various reasons (e.g. cases relapsed, cases were notified by more than one health care unit, errors in data entry). In 2008, the NTP used probable record linkage to identify duplicates and correct erroneous data already in the database. This was done in a series of successive steps. First, they matched records electronically by sex and name (first name and surname), and then manually compared records using variables, such as the full name of the patient, full name of the patient's mother, date of birth, date of notification, and the patient's address. Ultimately, this process revealed that almost one-quarter of all records examined belonged to patients with multiple records (e.g. transfers, retreatments and relapses); 6.6% were duplicate records. The removal of these records significantly altered the national TB statistics. From 2001–2007, notification rates of new cases increased from 2.3% to 6.3%, and the proportion of cases cured increased from 1.5% to 4.9%. These results demonstrated the value of establishing mechanisms for preventing duplication in a case-based TB surveillance system.

Source: **Bierrenbach AL et al. Duplicates and misclassification of tuberculosis notification records in Brazil, 2001–2007. International Journal of Tuberculosis and Lung Disease. 2010;14(5):593–599.**

In recoding variables, the epidemiologist can modify the new variable in many ways (Table 3). For example, re-coding may involve re-assigning values, such as changing values from letters to numbers (e.g. changing inputs from male and female to the corresponding numbers one and two). It could also involve combining or collapsing ranges from the original variable to create a new variable. For example, an 'age group' variable could be created by assigning 0–25 year-old patients into category one and 26–50 year-old patients into category two, while those aged over 50 years of age, into category three. Creating these broad ranges is especially useful when the number of responses in the original categories is too small for statistical analysis. It is also possible to re-code more than one variable to construct another variable. For example, a variable for body mass index (BMI) – calculated as weight (kilograms)/height (metres)^2 – can be derived from two independent variables, height and weight.

TABLE 3
Examples of recoding of variables in a sub-set of case-based data

ID #	Sex	Sex	Age (years)	Age Group	Height (m)	Weight (kg)	BMI
	(Original, Text Variable)	(Recoded, Numeric Variable) Male = 1 Female = 2	(Original, Continuous Variable	(Recoded, Categorical Variable 0-25 years=1 26-50 years=2 >50 years=3	(Original, Continuous Variable)	(Original, Continuous Variable)	(Recoded: BMI= kg/(m²)
001	M	1	10	1	1.35	30	16.5
002	M	1	25	1	1.81	55	16.8
003	F	2	37	2	1.73	60	20.0
004	F	2	21	1	1.79	58	18.1
005	F	2	62	3	1.65	51	18.7
006	M	1	55	3	1.75	56	18.3
007	M	1	26	2	1.85	73	21.3

Linking datasets

After the variables are in the correct format, the epidemiologist should check the dataset to make sure all the necessary data elements are included to conduct the proposed analyses. In some cases, the variables needed for a particular analysis may not be available in routine TB surveillance data but may be available from other data sources (e.g. laboratory and/or vital registration data). The linkage of TB cases from case-based surveillance data with other data sources can considerably strengthen an analysis by providing a more complete picture of the situation (*11*). Epidemiologists can use record linkage techniques to help identify the same person in difference datasets and this is usually accomplished using a personal identification number, such as a social security number.

When consolidating several different databases into one central database, epidemiologists use record-linkage to accurately identify whether two or more records relate to the same individual. They can also perform record-linkage manually by visually comparing records. However, this is very labour intensive and inefficient with large datasets (*9*). The process of record-linkage is usually performed using special software (e.g. Link Plus) using either deterministic record linkage or probabilistic record linkage. In deterministic record linkage duplicate cases are detected by identifying all records that contain exactly the same data in one or more fields, ideally using a personal identifier. Probabilistic linkage is based on a score that reflects the probability that the records relate to the same person.

Finalizing the dataset

After taking the necessary steps to clean and prepare the case-based data, the final step the epidemiologist must take before beginning analysis is to finalize (or 'freeze') the dataset. Freezing the final analytical dataset means the epidemiologist should make no additional changes to it (e.g. updating or deleting), so all analyses should originate from the same set of data and will be consistent in terms of the number of cases and quality of data. Any manipulation of data within the frozen dataset should then happen as a part of the analytic process itself through, for instance, selection of cases, sub-setting data, re-coding, etc. Once the frozen database is in hand, the epidemiologist can move to the next step: data analysis.

2.4 Data analysis: conducting and interpreting descriptive analyses

Descriptive analysis (also commonly referred to as descriptive statistics) is the first step of statistically analysing case-based data. Conducting routine descriptive analysis allows for ongoing and timely review of case-based data. Epidemiologists use descriptive analyses to describe and present data in terms of person, place and time. Calculations such as averages, frequencies and rates are examples of descriptive analyses. Results of descriptive analyses are often presented using tables, graphs, charts and maps (Figure 4).

FIGURE 4
Using maps is a clear way to display results of a geographical descriptive analysis using case-based data

Reported a new TB case
Did not report a new TB case
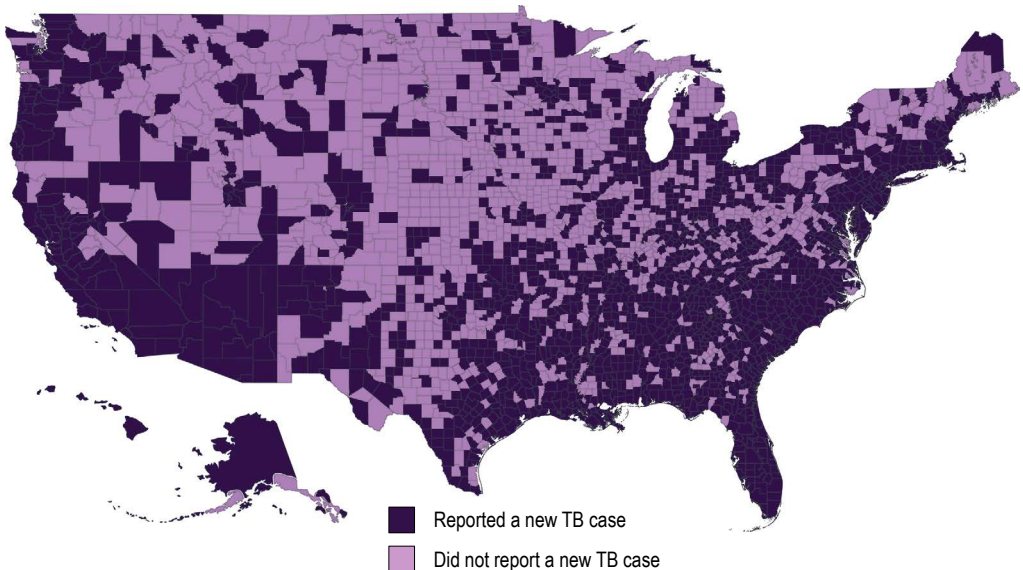
(*Source:* Originally published in http://www.cdc.gov/mmwr/pdf/wk/mm6211.pdf)

Univariate and bivariate analyses

Descriptive analysis is an important first step when conducting analyses because descriptive analyses transform the data into meaningful information. A list of raw data generated from a case-based surveillance system is difficult to interpret, particularly if there is much information (i.e. many variables) captured for each TB case. An epidemiologist uses descriptive analysis to summarize a line list of TB cases to assist in the interpretation of data.

To understand how and why descriptive analyses are useful to epidemiologists, consider a theoretical example of TB case data in District X, which had 100 TB cases reported in 2013. Table 4 shows a line list of characteristics for 10 of the 100 TB cases.

TABLE 4
Sample of TB case data from District X

Year	Country	Sex	Disease Site	HIV Status	Profession
2013	X	Male	Pulmonary	Positive	Miner
2013	X	Male	Pulmonary	Negative	Miner
2013	X	Female	Pulmonary	Negative	Nurse
2013	X	Male	Extrapulmonary	Negative	Farmer
2013	X	Female	Pulmonary	Positive	Farmer
2013	X	Male	Extrapulmonary	Negative	Miner
2013	X	Male	Pulmonary	Positive	Miner
2013	X	Female	Extrapulmonary	Negative	Shop Keeper
2013	X	Female	Pulmonary	Negative	Student
2013	X	Male	Pulmonary	Negative	Miner

If Table 4 included all 100 TB cases, it would be difficult to look through all characteristics of 100 TB cases and conclude anything meaningful about the situation. Questions such as what type of TB is most common, or whether more men or women have TB in this district, can be difficult to answer with the raw data. Descriptive analyses are useful to summarize the data to turn them into usable information. Knowing this, the district TB officer in District X took the line list of TB surveillance data and used descriptive analyses to create several charts to help answer basic questions about the local TB epidemic.

The district TB officer summarized the line list data and found that, of 100 cases, more TB cases occurred among males than females (Figure 5). This type of analysis using only a single variable is an example of univariate analysis. Univariate analysis is the simplest method of descriptive analysis, and can be used to describe frequency distributions, proportions and measures of central tendency (i.e. mean, median and mode). Univariate analysis results are easy to present and easy to interpret, and are therefore commonly

used in reports, such as annual TB case surveillance reports, that are disseminated to a wide range of audiences.

FIGURE 5
TB cases in District X, by sex, 2013
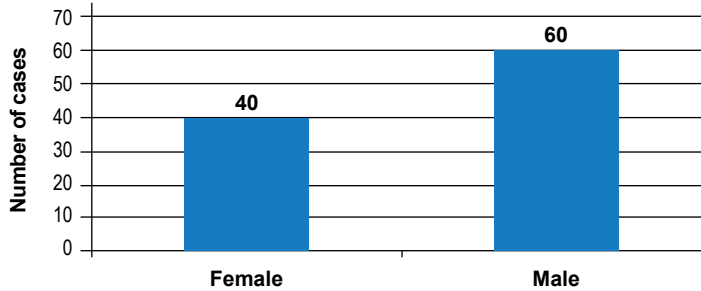
When case-based data are available, the epidemiologist can take the analysis a step further. In this case, the district TB officer had access to case-based data. The officer decided to investigate differences in the type of TB disease between male and female TB cases in the district. This is something that may not have been possible if only aggregated data were available.

FIGURE 6
TB cases by sex and disease site, District X, 2013
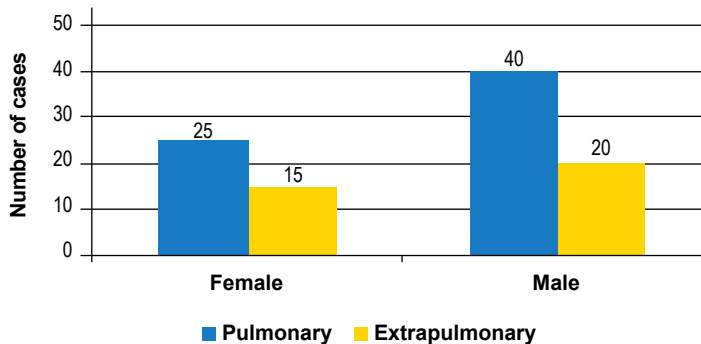
Similar to the previous example, Figure 6 shows that more TB cases occurred among males (n=60) than females (n=40). It also shows that there was more pulmonary (n=65) than extrapulmonary (n=35) disease. Most importantly, it compares pulmonary and extrapulmonary disease within and between sexes. From this, the district TB officer learned that pulmonary TB was more common than extrapulmonary TB among both males and females. A similar percentage of males (40/60=67%) and females (25/40=63%) had pulmonary TB. This is a type of bivariate analysis as it involves the analysis of two variables (e.g. sex and type of TB) and assesses the relationship between the two variables.

With case-based data, epidemiologists can also analyse more than two variables together. Knowing this, the district TB officer decided to do a slightly more complicated analysis. The officer wanted to learn more about the role of HIV status on type of TB disease, considering sex. Because the officer had case-based data, it was possible to conduct bivariate analysis of HIV status (positive or negative) by type of TB (pulmonary or extrapulmonary) and stratify (i.e. separate) the results by sex (Figure 7).

FIGURE 7
HIV status by type of TB stratified by sex, District X, 2013
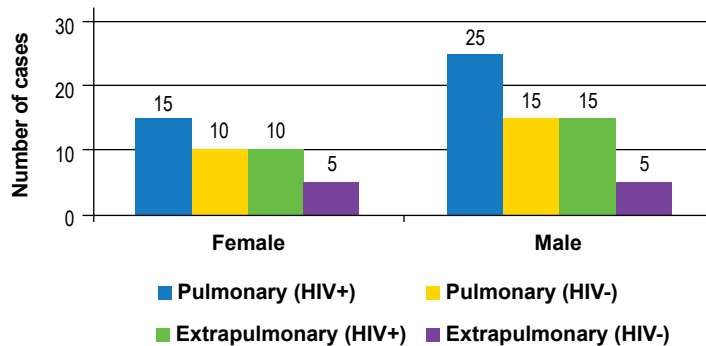
The district TB officer concluded that regardless of sex, the majority of TB patients were HIV positive (Female: 25/40=63%, Male: 40/60=67%). Specifically, it was noted that for both males and females, the greatest number of TB cases were pulmonary TB and HIV positive (females: 15/40=38% and males: 25/60=42%).

Rates and trends

Epidemiologists also use descriptive analyses to routinely monitor trends in TB incidence rates and case counts over time, as well as to identify changing rates, outlying data and other data discrepancies. Such analyses are typically done quarterly and/or yearly. Observations are evaluated to assess whether they reflect true changes in trends or are the result of data input or management errors. While these types of analyses can be done using aggregated data (see Chapter 1), they are equally important for routine analysis of case-based data.

To understand how and why case-based data are analysed for trends, consider TB surveillance in the United States, where monitoring annual TB trends is an important aspect of TB surveillance. Every year, public health officials publish a surveillance report of the nation's TB cases. This is what public health officials saw for TB cases notified nationally during 2000–2009 (Table 5).

TABLE 5
Number of TB cases notified, United States, 2000–2009

Year	Number of TB cases reported
2000	16 209
2001	15 945
2002	15 056
2003	14 836
2004	14 499
2005	14 064
2006	13 734
2007	13 280
2008	12 906
2009	11 545

Public health officials used these data to answer a variety of questions about trends in the number of TB cases notified over time. Because it is difficult to tell much about the data by looking at it in table format, the public health officials created a graph of TB cases by year. This is a simple and often easier way to visually examine trends in TB cases (Figure 8).

FIGURE 8
Number of TB cases notified by year, United States, 2000–2009
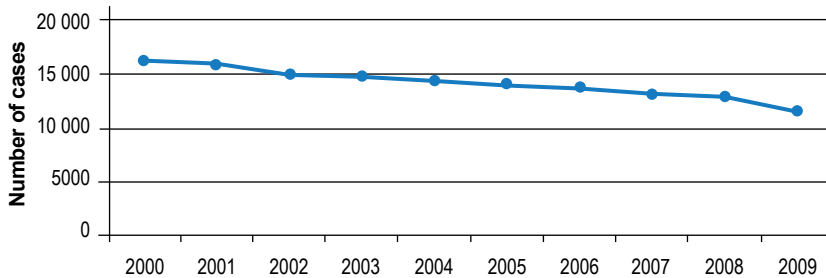
Both the table and graph (Table 5 and Figure 8) show that the number of notified TB cases in the United States has been steadily decreasing since 2000. However, after examining the TB trends graphically, public health officials suspected that there was an unusually steep decrease in notified TB cases from 2008 to 2009. They decided to do further analyses to examine this decrease; specifically, they looked at rates.

Other descriptive analyses

Epidemiologists commonly calculate and report incidence rates in descriptive analyses of case-based data. An incidence rate is the number of new cases of a disease or event among a specific population in a specified time period. The incidence rate can be more informative than the number of reported cases, because it takes into consideration differences in population size (See Box 2), a factor that can impact the total number of reported cases. Calculation of incidence rates requires availability of appropriate population or denominator data. For example, the 2012 incidence rate of childhood TB is the number of new cases of TB among all children aged 15 and under, living in a given country in 2012.

Health officials in the United States calculated annual TB incidence rates to examine the unusual drop in TB cases from 2008 to 2009 (Table 6). From this analysis of incidence rates, public health officials were able to make population-based comparisons over time and found that the drop in incidence rate from 2008 to 2009 was larger than expected based on trends in previous years.

TABLE 6
Rate of notified TB cases, 2000–2009, United States

Year	Incidence rate of TB cases* per 100 000 population
2000	5.8
2001	5.6
2002	5.2
2003	5.1
2004	4.9
2005	4.8
2006	4.6
2007	4.4
2008	4.2
2009	3.8

*Using population data for each year, incidence rates were calculated as (number of cases in a year/population in that year) per 100 000 people.

BOX 2
Using rates to compare disease burden in different populations

City A

$$\frac{105 \text{ TB } cases \text{ in } 2012 \times 100\ 000}{1\ 651\ 894 \text{ } pop \text{ in } 2012} = \frac{10\ 500\ 000}{1\ 651\ 894} = 6.4 \text{ per } 100\ 000$$

City B

$$\frac{48 \text{ TB } cases \text{ in } 2012 \times 100\ 000}{1\ 680\ 102 \text{ } pop \text{ in } 2012} = \frac{4\ 800\ 000}{1\ 680\ 102} = 2.9 \text{ per } 100\ 000$$

City C

$$\frac{81 \text{ TB } cases \text{ in } 2012 \times 100\ 000}{553\ 523 \text{ } pop \text{ in } 2012} = \frac{81\ 000\ 000}{553\ 523} = 14.6 \text{ per } 100\ 000$$

By calculating the rates to the same adjustment factor (per 100 000 population) it is possible to compare the rates of these three cities even though they have different TB case counts and different base populations. From this city comparison we can conclude that City C has a higher rate of TB than the other two cities. In other words, even though City A has more cases, the population of City C is more affected by the disease.

Other types of information used for further examination of data

For some types of data, such as demographic or behavioural risk factors, it might not be possible to obtain accurate population denominators. For example, calculating rates of TB among people who use alcohol requires evidence of how many people in the area of interest use alcohol. However, this information may not be available. In the absence of denominator data, there are other ways to analyse data trends. Graphs such as Figure 8 show the number of TB cases over time, which epidemiologists can use to visually determine if trends are changing.

With case-based data, it is also possible to stratify graphs to show trends of more than one variable. For example, public health officials in the United States examined a variety of demographic and risk factors to further understand the drop in TB burden between 2008 and 2009, including the birthplace of TB patients (i.e. US-born or born outside the US).

They created a graph to examine the trends of TB burden based on the TB patients' place of birth (Figure 9).

Examining the number of TB cases in the United States by year from 2000–2009 indicates that the number of TB cases among people born in the United States is declining faster than the number of cases among people born elsewhere (12). Furthermore, this graph reveals that from 2001 to 2009, more TB cases were reported among people born outside the United States than among those born in the country. With regard to the 2009 drop in reported TB cases, it is clear that the decreasing trend applies to both categories of people (Box 3).

In summary, descriptive analyses are important to describe the epidemiology of TB and monitor trends over time in local and national populations. In the theoretical example of District X, the TB officer was able to investigate characteristics of TB patients and adjust the district's programme accordingly. In the United States example, continual routine analysis of case-based data enabled public health officials to facilitate the early detection of changing trends and identify why trends may have altered. While the majority of analyses that are conducted by national programmes are similar to those described above, there are also other more in-depth analyses that may be conducted using case-based data which are described briefly in the next section.

FIGURE 9
Number of TB cases among people born in and outside the United States
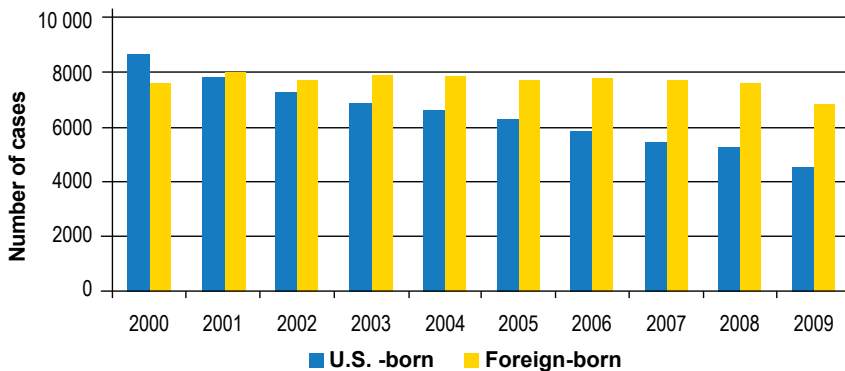
BOX 3
Case study: United States

Each year, state TB programmes send their information on confirmed TB cases to the US Centers for Disease Control and Prevention (CDC) for inclusion into the national TB surveillance system (NTSS). Early in 2010, after analysing preliminary 2009 case counts, CDC discovered an unprecedented decline in the number of cases and the calculated incidence rates. The overall rate declined 11.4% from 4.2/100 000 in 2008 to 3.8/100 000 in 2009 in the preliminary data received. It was the greatest decrease ever recorded for a single year and was the lowest recorded rate since TB surveillance began with full national coverage in 1953. An extensive analysis of the preliminary data showed that the decline of TB incidence rates occurred in nearly every sub-group of the population. Cases of foreign-born and those born in the country declined 9.0% and 15.8%, respectively. There were declines in every racial and ethnic group, ranging from 9.0% among non-Hispanic Asians, to 15.2% among non-Hispanic whites. Even culture-positive pulmonary TB cases declined 13.6% and culture-negative pulmonary TB cases declined 17.5%. The unexpected decline in incidence rates could have indicated better TB programme implementation re-sulting in fewer cases of TB being diagnosed, signalling a significant step toward TB elimination in the country; however, it could also have been the result of population shift, under-reporting, or under-diagnosis of disease.

There had been notable changes in the national surveillance system in the preced-ing year. Many states had begun the transition from reporting TB case data electron-ically through a system developed by CDC to using their own web-based reporting systems and had adapted the revised report of verified tuberculosis (RVCT) form, the standardized reporting form used across the United States. A revised RVCT had been introduced nationally in 2009. Some of the new web-based reporting systems lacked all the validation procedures that had been present in CDC's older reporting system. Due to the economic downturn in many states, there were anecdotal reports of reduction of TB staff in certain local areas. Because of these changes, the CDC (along with state TB programmes) embarked on an extensive investigation of case finding and practice at the state and local level.[a,b] The investigators ruled out soft-ware system changes as the cause for the decrease in TB incidence rates. States that were using different types of web-based reporting systems experienced declines. CDC-funded clinical mycobacteria laboratories around the nation reported receiv-ing 5.9% fewer clinical specimens for TB testing from 2008 to 2009.

a. Centers for Disease Control and Prevention. Decrease in Reported Tuberculosis Cases — United States, 2009. Morbidity and Mortality Weekly Report. 2010;59:289–294.

b. Reported Tuberculosis in the United States, 2009. Atlanta: United States Department of Health and Human Services; 2010.

Box 3 - continued

The United States National Tuberculosis Controllers Association surveyed all 59 reporting areas (states and territories) for changes in surveillance, diagnostic laboratory procedures and staffing. Among the 93% of TB programme managers who responded to the survey, there was no indication that any of these changes led to the unexpected decline in cases. In fact, states that experienced staff reductions and reported at least 100 cases of TB showed a smaller decrease in case counts than similar states that experienced no reductions in staff. In ten high-burden counties across the nation no unreported cases were discovered. CDC investigators conducted a detailed case finding study in the states of Pennsylvania and Georgia.

The study did not reveal substantial under-reporting or under diagnosis of TB cases.[c] A statistical analysis of monthly case counts for the past ten years showed that there was a significant difference between observed and expected TB cases by treatment start date among those born in the country and non-US-born cases. Non-US-born cases experienced a significant decline in case counts starting in October 2007, and these decreases were consistent with trends seen in the non-US-born population as reported by the U.S. Census Bureau and those seen by the United States of America Department of Homeland Security among unauthorized immigrants.[d] The authors concluded that the observed decline in the 2009 TB incidence rate reflected a true decline in the number of TB cases diagnosed in the country.

c.   Centers for Disease Control and Prevention. Assessment of declines in reported tuberculosis cases — Georgia and Pennsylvania, 2009. Morbidity and Mortality Weekly Report. 2011;60:338–342.
d.   Winston CA et al. Unexpected decline in tuberculosis cases coincident with economic recession — United States, 2009. BMC Public Health. 2011;11:846–857.

2.5 Data analysis: conducting and interpreting more complex analyses

Although case-based data allow for more in-depth descriptive analyses than is possible with aggregated data, the greatest advantage of case-based data is the ability to conduct more complex analyses, such as stratified and multivariable analyses (e.g. regressions). Epidemiologists use these more in-depth analyses to allow for statistical examination of the relationship between two or more variables. Specifically, such analyses allow associations between variables (e.g. risk factors and a disease outcome) to be established, which can provide the stronger evidence needed to lead to successful TB programming and policy-making.

Stratified analysis allows for a third variable in the analysis. Epidemiologists use stratified analysis with case-based data to help determine whether a third variable influences (i.e. confounds) the relationship between two other variables under study. A confounding

variable is related to and can mask the real association between the two other variables. For example, in an investigation of the relationship between lung cancer and alcohol consumption, smoking may be a confounding variable if it is associated with alcohol use and is also an independent risk factor for lung cancer. Stratified analysis can help tease out the real relationship. An example of a stratified analysis is provided in Annex 3. In the case of taking into account the effects of multiple variables that may potentially influence the relationship between the two main variables being investigated, multivariable analysis is needed. Epidemiologists can do stratified analysis manually while multivariable analysis requires a statistical software programme.

The most commonly used statistical methods used by epidemiologists in multivariable analyses are logistic regression, linear regression and survival analysis. Brief explanations and examples of these analyses are provided below.

Epidemiologists use logistic regression to identify independent variables that are associated with a categorical outcome, usually a binary outcome (i.e. two categories) or a multinomial outcome (i.e. more than two categories). An example of a binary outcome might be treatment success (one=Yes or two=No) and an example of a multinomial outcome might be treatment outcome (one = treatment cured or completed, two = died, default or failure, and three = transfer out). The independent variables may either be categorical (e.g. pulmonary, extrapulmonary or both), ordinal (e.g. poor, moderate or good) or continuous (e.g. age in years).

Examples of independent variables may be age, gender, heavy alcohol use, or type of directly observed therapy. In logistic regression odds ratios are measures of association used to quantify the effect between the independent variables and the outcome. Results of multivariable logistic regression analyses can, for example, help to identify the characteristics of patients most at risk for unfavourable outcomes, as well as characteristics of patients that should be prioritized to improve treatment outcomes. An example of a multivariable analysis using logistic regression is provided in Annex 3.

Linear regression is a type of multivariable analysis that is used by epidemiologists to define associations between independent variables and outcomes that are continuous and normally distributed (i.e. when all of the values are plotted they are distributed in a symmetrical fashion, like a bell curve, with most of the values situated around the median/mean). For example, the outcome in a linear regression analysis may be height in centimetres and independent variables in the model may be age, gender, nationality or nutrition status. In TB epidemiology, linear regression has often been used to investigate associations among countries rather than among patients, for example, between national-level indicators (e.g. HIV prevalence or gross domestic product) and trends in TB incidence (*13*).

Epidemiologists use survival analysis to assess not only who has a greater risk of an outcome such as death, but also to assess the timing of those outcomes, and to take this into account when analysing risk factors for given outcomes. For survival analysis, Kaplan-Meier curves are used to assess time to an event or outcome, and Cox proportional hazards models identify risk factors for the outcome. An important assumption is that the risk (hazard ratio) for the outcome does not change over the study time period.

In conclusion, case-based data offer a wide range of opportunities for in-depth analysis of surveillance data. People interested in doing such analyses can consult with more experienced epidemiologists or statisticians and refer to additional texts, such as *Basic epidemiology* (*3*).

2.6 Communicating findings

Sharing results from analysis of TB surveillance data keeps programme staff, policy-makers, the public, and researchers informed about the local TB epidemic, changing trends and programme performance. Effectively communicating the results of an analysis helps NTPs increase awareness of the burden of TB locally and nationally, share information about progress in reaching targets, enhance demand for TB services, create support for changes in TB policy, and remind audiences of behaviours that impact TB prevention and treatment (*15*). Examples are provided below of different strategies that NTPs use when communicating results of TB analyses to different audiences.

Programme staff: When communicating with TB programme staff an annual report that summarizes case-based TB data is a good way to disseminate results from routine analysis. Annual reports, which are usually compiled the year after data were collected, can provide comprehensive and up-to-date assessments of the TB epidemic nationally. NTPs usually identify key indicators to include in the report based on their national priorities and the analyses often remain the same from year to year so NTPs can monitor progress and challenges in implementing TB control over time. Examples of routine analyses using surveillance data conducted and reported annually are available on-line from the United States of America[c] and from the United Kingdom.[d]

To monitor TB control efforts more frequently, brief reports can be an effective tool to efficiently communicate with local TB programme staff on a routine basis. For example, in the United States the National Tuberculosis Indicators Project (NTIP) provides reports to

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c.   See: http://www.cdc.gov/tb/statistics/reports/2012/default.htm
d.   See: http://www.hpa.org.uk/webc/HPAwebFile/HPAweb_C/1317139689583

local jurisdictions that allow them to track their progress toward national objectives using standardized indicators developed based on national priorities for TB control in the country. The reports are generated from case-based surveillance data that are reported by the local jurisdictions. Data are updated weekly in order to provide local jurisdictions with the most recent data for programme monitoring and evaluation purposes. For example, one of the NTP objectives is to increase the proportion of newly diagnosed TB patients who complete treatment within 12 months to 93.0% by 2015 (Figure 10). Each jurisdiction can use the NTIP system to monitor their progress and to help identify barriers if they are not meeting the objective.

Policy-makers and the public: When communicating the results of surveillance analyses with the public, including policy-makers and media representatives, fact sheets are an effective way to describe the background and context for TB in a country. A fact sheet is a brief report, usually no more than two pages, that is intended for general audiences. A fact sheet may, for example, describe the causes of TB, the burden and distribution of TB (e.g. based on the analysis of surveillance data), and provide recommendations for actions to be taken. Fact sheets are also easily updated and replaced with more current information as additional data become available. Examples of TB fact sheets are available online at the WHO website.[e]

Researchers: A commonly used method to communicate findings to an academic audience is a published article in a scientific journal. Most scientific papers follow a similar format, including the following sections: abstract, introduction or background, materials and methods, results, discussion, and conclusions. When presenting the results of an analysis of surveillance data, it is useful to start with the general and move to the specific (e.g. first present the national TB rate and then present rates for sub-groups). It is also important to use a simple writing style with short sentences and transitions to help provide the audience a 'road map' as they read. Readers can find additional information about writing and presenting scientific papers in the book *Field Epidemiology* (*16*).

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e.   http://www.who.int/tb/publications/factsheets/en/

FIGURE 10
Completion of therapy sample report from the United States National Tuberculosis Indicators Project

Completion of Therapy

National Tuberculosis Indicators Project

Data Updated: 03/18/2013

National Objective:

For patients with newly diagnosed TB for whom 12 months or less of treatment is indicated, increase the propotion of patients who complete treatment within 12 months to 93.0% by 2015.

Treatment Completion Within 12 Months for Eligible Patients

Sample Juristiction 2009 to 2013

Cogort Period	2009	2010	2011	2012	2013	–	2015
Completed Treatment Within 12 Months (%)*	100.0	80.0	100.0	60.0	–	–	
Program Targets (%)	N/A	95.0	95.5	96.0	96.5	–	N/A
State Average (%)	94.2	93.2	94.9	38.0	0.0	–	
National Average (%)	87.8	84.7	79.6	34.6	2.4	–	
National Target (%)						–	93.0
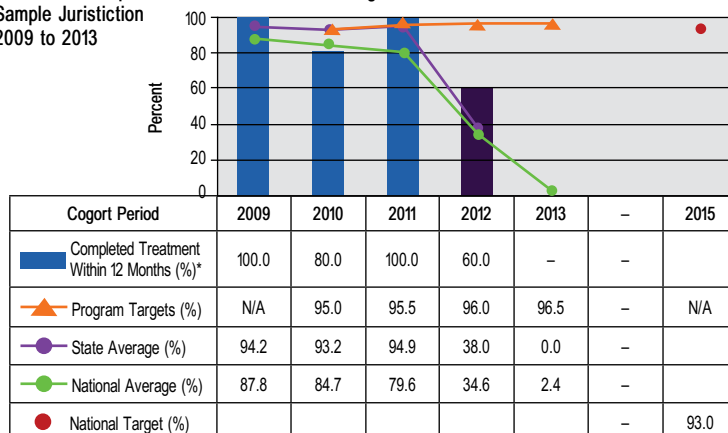
* Alternative colours on the chart indicate that the data are incomplete.

Cohort Period	2009	2010	2011	2012	2013
Total Eligible Patients (N)	4	5	12	5	0
Patients Completed Treatment (Ever) (n)	4	5	12	3	0
Patients Completed Treatment Within 12 Months (n)	4	4	12	3	0
Patients Did Not Completed Treatment	0	0	0	2	0

Objective: For patients with newly diagnosed TB for whom 12 months or less of treatment is indicated, increase the propotion of patients who complete treatment within 12 months.

Indicator: Percent of patients with newly diagnosed TB, for whom therapy for 12 months or less is indicated, who completed treatment within 12 months (366 days).

Cohort: All TB patients, for whom 12 months of treatment or less is recommended, alive at diagnosis, initiated treatment with one or more drugs, and counted in the cohort period of interest. Patients with any rifmpin-resistant TB or meningeal TB, and children aged 14 or younger with disseminated TB are excluded. Disseminated TB is defined as miliary site of disease, evidence of miliary TB on chest radiograph, or a poritive blood culture. Patients who died are excluded. For cohort 2009 and later, patients who moved out of the U.S. during treatment are also excluded.

Data Sources: RVCT fields: Date Reported, Date Counted, Date of Birth, Status at TB Diagnosis, Site of TB Disease, Culture of Tissue and Other Body Fluids, Initial Chest Radiograph and Other Chest Imaging Study, Date Therapy Started, Initial Drug Regimen, Initial Drug Susceptibility Results, Moved, Date Therapy Stopped, Reason Therapy Stopped.

Calculation: [Number of patients who complete treatment in less than or equal to 366 days who were eligible to complete treatment within 12 months / Cohort] x 100

2.7 Conclusion

In summary, the analysis of high quality case-based surveillance data is important for national and local TB programmes to understand the epidemiology of TB and its programmatic implications. The examples throughout this chapter demonstrate how case-based surveillance data can be used to monitor trends in TB, determine the possible causes for changing trends, identify and prioritize specific sub-populations, and better inform TB programmes to direct their efforts and resources towards TB reduction or elimination.

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Annex 2
Analytic plan example

Objective: To describe trends and characteristics of TB among children and to compare against trends of TB among adults in the Netherlands.

Specific objectives: Describe and compare characteristics of TB cases among children and adults. Describe and compare trends in TB notification among children and adults.

Hypothesis: The rate of TB incidence in children is changing at the same rate as in adults.

Study population: TB patients, notified in the Netherlands in the period 2000–2012.

Definitions:

- Childhood TB: from birth to 14 years of age at the date of notification.
- Adult TB: a person at least 15 years of age at the date of notification.

Variables to be used in analysis: date of notification, date of birth, sex, country of birth, time since entry into the Netherlands in case of a foreign-born TB patient, Bacillus Calmette–Guérin (BCG) vaccination status (scar and/or vaccination booklet), site of TB disease (extrapulmonary and/or pulmonary), history of contact with TB patient, diagnostic laboratory results (smear, culture), HIV status, case finding method (passive, contact investigation, immigrant screening), treatment outcome.

Data preparation:

- Age calculated using the time interval between date of birth and date of notification.
- Population sizes of children and adults to be included in the dataset through a link to the population data from the Netherlands Bureau of Statistics.
- Missing values to be included in the analysis and presented when the percentage of cases with missing values for a given variable is greater than 5%.
- Analysis software: STATA, SAS, SPSS

Procedures to protect data confidentiality:

Permission to obtain and analyse the data from the national electronic TB register (NTR) for the objectives stated, to be obtained from the NTR registration committee. The NTR does not contain personal identifiers such as names and addresses, so data are anonymous, meaning that the need for informed consent is not necessary.

Statistical approach:

- Description of study population (see Table A1 below). Differences in proportions between childhood and adult TB cases to be tested using a chi-square test.
- Calculation of notification rate per year for childhood and adult TB cases.
- Linear regression to describe the trends in notification rates for childhood and

adult TB cases over the period 2000–2012. To determine if the trend is different between children and adults, an interaction will be tested between a person's age (child versus adult) and notification rate. If there is a significant interaction, the slopes of the trend lines for childhood and adult TB cases are significantly different.

- The level of significance employed for all tests is 0.05.

TABLE A1
Description of study population

	Childhood TB cases		Adult TB cases		p-value
	n	%		%	
Sex					
Male					
Female					
Missing					
Country of birth					
Netherlands					
Foreign country					
Missing					
Evidence of BCG vaccination					
Yes					
No					
Missing					
Site of TB disease					
Pulmonary					
Extrapulmonary only					
Missing					
History of contact with TB patient					
Yes					
No					
Missing					
HIV status					
Positive					
Negative					
Missing/Unknown					
Smear result					
Positive					
Negative					
Missing/Not done					

Culture result					
Positive					
Negative					
Missing/Not done					
Case finding method					
Complaints					
Contact investigation					
Immigrant screening					
Missing					
Treatment outcome					
Cure					
Completed					
Death					
Failure					
Loss to follow-up					
Missing					
Total					

FIGURE A1
Number of childhood and adult TB cases notified per year
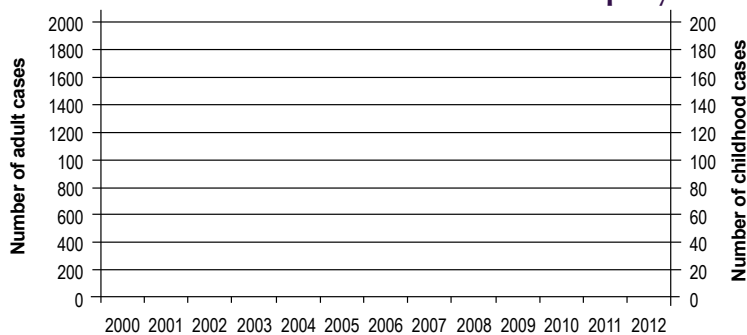
FIGURE A2
TB notification rate per year, for childhood and adult TB, with trend line as predicted by linear regression
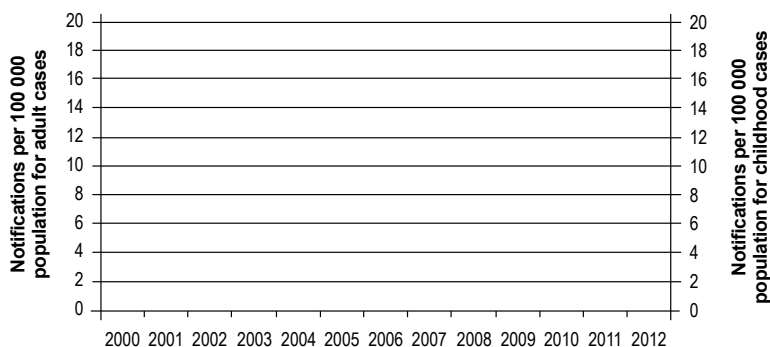
Annex 3
Example of stratified and multivariable analyses to assess risk factors for loss to follow-up

Overall, the treatment results for new smear-positive pulmonary TB patients in country A in 2010 showed 7% loss to follow-up. Let us look at some patient characteristics associated with treatment default. Included in the analysis are 20 374 new smear-positive pulmonary tuberculosis patients who started on treatment in country A in 2010, with treatment success and loss to follow-up as treatment outcomes.

From Table A2 it is evident that the majority of patients with a successful treatment outcome are male (61.9%) but that the largest proportion of patients who were lost to follow-up during treatment was also male (74.3%). The unadjusted odds of being a male among those with successful treatment are 11 832/7276=1.6, and for those lost to follow-up the odds are 948/328=2.9. This means that for a male the odds of being lost to follow-up are 1.8 (2.9/1.6=1.8) times larger than the odds for a female to be lost to follow-up. Other patient characteristics significantly associated with loss to follow-up at the bivariate level (i.e. not taking into account any other variables in their association with the outcome, loss to follow-up) were homelessness, alcohol use, and living in an urban area. This means these factors are statistically significantly associated with loss to follow-up because the 95% confidence intervals do not cross one.

TABLE A2
Patient characteristics of new smear-positive pulmonary tuberculosis patients started on treatment in country A in 2010, by treatment outcome (N=20 374)

Variables		Treatment success (n =19 108)		Loss to follow-up (n =1266)		Bivariate analysis	
		n	%	n	%	Unadjusted odds ratio (OR)	95% confidence interval (CI)
Gender	male	11 832	61.9	948	74.3	1.8	(1.6-2.0)
	female	7276	38.1	328	25.7		
Homeless	yes	309	1.7	107	2.1	5.6	(4.6-6.8)
	no	18 799	98.3	1168	97.2		
Heavy alcohol use	yes	825	4.4	168	13.2	3.4	(2.9-3.9)
	no	18 283	95.6	1107	86.8		
Residency	urban	10 324	54.2	896	70.5	2.0	(1.8-2.5)
	rural	8716	45.8	375	29.5		

In stratified analysis, the odds ratio for one patient characteristic can be calculated while taking into account (or 'controlling for') a third variable. For example, social circumstances among patients who are homeless sometimes mean that they experience other co-morbidities or risk factors for TB, besides being homeless. For example, heavy alcohol use may occur more frequently in homeless patients than non-homeless patients. And in country A the surveillance data suggest this is the case, with a greater proportion of homeless patients being registered as heavy alcohol users. However, the odds ratio for loss to follow-up in heavy alcohol users is similar for homeless patients (OR=1.8) and non-homeless patients (OR=1.9). This means that when the results are stratified by homelessness, the odds ratio for heavy alcohol use (1.8–1.9) is lower than the odds ratio for heavy alcohol use in the overall data (OR=3.4, Table A2). The odds ratio for heavy alcohol use, adjusted for the living situation (homeless or not), was lower than the crude, or unadjusted, odds ratio.

TABLE A3
Treatment outcomes stratified by living condition of the patient and amount of alcohol used by the patient

		Homeless				Not homeless			
		Treatment success		Loss to follow-up		Treatment success		Loss to follow-up	
		n	%	n	%	n	%	n	%
Heavy alcohol use	yes	144	46.7	65	60.8	2395	12.7	249	21.3
	no	165	53.3	42	39.2	16 405	87.3	919	78.7
		OR=1.8 ((144/165) / (65/42))				OR=1.9 ((2395/16405) / (240/919))			

The same procedure can be used to take account of (control for) several variables at the same time, in multivariable analysis. This should be done using statistical software. Table A4 shows the results of a multivariable logistic regression model that contains all four variables described above. Instead of the odds ratio for heavy alcohol use being adjusted only for homelessness (Table A3), Table A4 shows that the odds ratio for heavy alcohol use has been adjusted (controlled for) for homelessness, gender and residency. The results show that even after additional adjustment for gender and urban or rural residency, the odds ratio for heavy alcohol use is 1.8, which is similar to what it was when only adjusting for homelessness.

All odds ratios shown in Table A4 are above one (unity) and have 95% confidence intervals that do not include one, indicating that even after adjustment, all odds ratios remain significantly associated with loss to follow-up. This shows that male sex, homelessness,

heavy alcohol use and urban residency are independent risk factors for loss to follow-up during treatment. This means that the odds of male patients who are not homeless or heavy alcohol users and are living in rural settings being lost to follow-up during treatment is 1.5 times higher than the odds for female patients with similar other characteristics.

The magnitude of the associations decreased after adjusting for 'confounding'. The values of the adjusted odds ratios (Table A4) are lower than the unadjusted odds ratios (Table A2). This means that there is overlap in the different patient characteristics associated with loss to follow-up. So heavy alcohol users are more often male, homeless and living in urban settings, than those not using alcohol heavily. The NTP may use these results to train DOT providers to provide extra (e.g. psychosocial), support to patients with these characteristics who are likely to experience loss to follow-up, in order to enable them to finish their anti-TB treatment.

TABLE A4
Multivariable analysis results (loss to follow-up during treatment)

Variables		Multivariable analysis	
		Adjusted odds ratio (OR)	95% confidence interval (CI)
Gender	male female	1.5	(1.4-1.7)
Homeless	yes no	3.5	(2.8-4.3)
Heavy alcohol use	yes no	1.8	(1.5-2.1)
Residency	urban rural	1.5	(1.3-1.7)

Chapter 3
Using genotyping data for outbreak investigations

Audience:

(1) Epidemiologists and monitoring and evaluation officers who have access to TB genotyping data and want to use them for TB surveillance and outbreak investigation.

(2) Staff in NTPs that lack access to genotyping data but who are interested in learning about TB genotyping and how it could be useful to their programmes.

Expected outcomes:

By the completion of this chapter, the reader should be able to understand:

- How genotyping data can be used to describe the epidemiology of TB and investigate an outbreak.
- How to analyse, report and interpret genotyping data.
- How analysis of genotyping data can lead to changes in practice and policy.

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3.1 Genotyping data: an overview

Introduction

With modern technology, scientists are able to understand TB on a molecular level. Genotyping is a special laboratory method used by scientists[a] to analyse the genetic material (e.g. DNA) of *Mycobacterium tuberculosis*, the bacteria that causes the majority of TB disease in humans. By genotyping *M. tuberculosis*, scientists have learned that there are many different varieties of TB, which are called 'strains'. Each strain has a unique 'genome', which refers to the complete set of genetic material in the organism. Most genotyping methods, other than whole genome sequencing, look at selected sections of the TB genome, which are known to have variability that can distinguish between different strains of *M. tuberculosis*.

The understanding of the TB genome has opened many new doors for TB research and programmes. As a result, the availability of genotyping technology has expanded rapidly around the world. As these data become increasingly available, public health programmes also have the opportunity to use genotyping to improve their TB surveillance and control programmes.

Purpose and uses of genotyping

Genotyping allows scientists to compare TB bacteria among cases to determine if and how TB transmission is occurring. Scientists do this by seeing whether the bacterial isolates[b] are genetically variable. If TB isolates have matching (non-distinguishable) genotypes, they are considered to be the same strain; if they have non-matching (distinguishable) genotypes, the TB isolates are considered to be different strains.[c]

Epidemiologists can use the data on matching genotypes to track if and how TB has spread between people and communities. Matching TB isolates are more likely to have come from a common source, for example, and are considered to be in the same chain of transmission. If there are two or more TB cases with matching TB genotypes, known as a 'cluster', epidemiologists can do further investigations to determine if the cases could be linked, which would indicate transmission. Specifically, epidemiologists investigate links

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a.   Basic information on genotyping can be found on the US CDC website at:
      http://www.cdc.gov/tb/publications/factsheets/statistics/genotyping.htm

b.   'Isolate' refers to the tuberculosis bacteria that have been grown in culture media, not directly isolated from a sputum sample.

c.   Scientists have different criteria on when genotypes can be said to be indistinguishable. This is because there is always potential for laboratory contamination or for typing methods to fail. It is outside the scope of the current publication to explore this issue.

between cases, which include associations between time, geography, and drug resistance, among other factors. In other words, epidemiologists ask if there is a commonality, such as a shared space and time, which could explain transmission. If scientists find an epidemiological link between TB cases with indistinguishable genotypes, it suggests that transmission may have occurred. On the other hand, TB isolates that do not match are more likely to have come from different sources. For example, a TB case with a unique genotype could have arisen from activation of a latent TB infection.

Genotyping data are most powerful in case-based reporting systems that have laboratory data linked to routine surveillance data. When laboratory and case data are linked in this way, a TB programme can use genotyping results in combination with epidemiological information to:

- Identify outbreaks that require public health action.
- Determine whether recent transmission is likely to have occurred between TB cases.
- Assess whether episodes of TB disease are due to reactivation or re-infection.
- Detect false-positive cases of TB.
- Identify and monitor the TB strains circulating in different population groups over time.

The way genotyping data is used varies according to specific goals. In public health, TB genotyping data is generally used to investigate transmission and outbreaks. Hence, this chapter first introduces what genotyping is and how it is undertaken. How TB programmes use these data to investigate transmission and outbreaks, and learn more about local TB epidemiology, is then explained. Fictitious genotyping data from the United Kingdom (UK) are used for illustrative purposes, and epidemiologists can use many of the same processes and techniques to look at data in high-burden settings, if resources are available. By the end of the chapter, readers will know when and how genotyping analyses can be used and what the results of these analyses can demonstrate about transmission.

Intended audience

Currently, TB programmes in low TB burden countries use genotyping far more than programmes elsewhere because they have easier access to genotyping technology and fewer TB cases; this makes it possible to implement genotyping as part of routine programming. However, research in high TB burden countries has demonstrated that TB genotyping is both possible and worthwhile, although it might be used in slightly different ways. For example, TB genotyping in a high TB burden municipality in Brazil improved understanding of local transmission, which generated information on how and where TB control and

prevention programmes could improve (*1*). Similarly, genotyping in Ethiopia shed light on local transmission (*2,3*), including among vulnerable sub-populations, such as children (*4*), facilitating improved TB monitoring and control.

Considering the utility of TB genotyping but the lack of capacity in many high TB burden countries to undertake it, this chapter is written for two audiences: staff such as epidemiologists and monitoring and evaluation officers, who have access to TB genotyping data and want to use them to improve the TB programme; and staff interested in learning what genotyping is and what it could do for their TB programme. Consequently, this chapter describes some ways in which genotyping can be used in TB programmes, both now and in the future. By providing readers with a basic understanding, it can also encourage them to consider how genotyping can be applied more specifically in their high-burden settings.

3.2 Preparation of data

Although the focus of this chapter is not intended to centre on laboratory techniques or practices, a simple understanding of how scientists generate genotyping data will help us better understand how we can use these data to answer public health questions.

Differentiating TB strains

Scientists use four main molecular methods to differentiate between strains of TB bacteria: restriction fragment length polymorphism (RFLP); spoligotyping; mycobacterium interspersed repetitive unit-variable number tandem repeat (MIRU-VNTR); and whole genome sequencing. Scientists can use these methods separately or in combination. The methods differ in their ability to tell one genotype from another because they examine different parts of the bacterial genome. The differences in how the methods work can determine the number of TB cases considered to be in the same cluster (i.e. the number of TB cases with indistinguishable genotypes). As a result, it is sometimes better if scientists use more than one method to analyse TB isolates, depending on the specific methods chosen (Table 1).

For example, if scientists only used the spoligotyping method, unrelated TB strains may appear to be related (i.e. the TB isolates appear to have the same genetic pattern) because spoligotyping is less specific at distinguishing between TB isolates than other methods. This would make it appear that there were a few large clusters of TB cases. This could mistakenly lead public health officials to believe that there had been a high level of TB transmission recently and cause them to erroneously conclude there was a large TB outbreak. However, if scientists used this method along with MIRU-VNTR typing, they may

find that these large clusters of TB cases were actually made of many smaller TB clusters. As a result, public health officials would realise cases were not linked through a common source, so there was no reason to believe transmission was occurring. The programme could then avoid spending time and valuable resources on cluster investigation.

Each of these methods has unique limitations and the method(s) selected by countries depends on many factors, such as the TB programme's available technology, expertise and budget (Table 1).

TABLE 1
Advantages and disadvantages of various genotyping methods

Method	Advantages	Disadvantages
Restriction fragment length polymorphism (RFLP)	High discriminatory power for distinguishing between stains Highly stable with a half life of 3.2 years (rate at which the biomarker changes)	Requires a viable culture and large amounts of DNA Labour intensive and time consuming Requires technical expertise and specialist software for analysis Comparative analysis of RFLP patterns is difficult between different laboratories Discriminatory power is poor for strains with low copy numbers of IS6110
Spoligotyping	Requires small amounts of DNA and does not require viable organisms Rapid and reproducible results Easy to compare results between laboratories Accurate discrimination between strains with a low copy number of IS6110	Low discriminatory power when used alone
MIRU-VNTR	Higher discriminatory power than spoligotyping Rapid and reproducible results Easy to compare results between laboratories Cheaper than other genotyping methods	Lower discriminatory power than RFLP Not always able to obtain a complete MIRU-VNTR profile Stability/mutation rate of biomarker is unclear
Whole genome sequencing	Highest discriminatory power Stable biomarker Can determine the direction of transmission	Expensive Requires technical expertise and specialist software for analysis Interpretation of results is complicated

Identifying and naming clusters

Once scientists have differentiated between TB isolates based on genotype, they use specific computer software, such as BioNumerics,[d] to group them into clusters, should they exist. NTPs may choose to incorporate such software into its routine surveillance system. The advantage of this is that the system can be designed in a way that is most convenient and useful for both the programme's field and analytical work.

After identifying clusters, scientists assign each cluster a unique number or name. It is important that this number or name remains consistent in order to allow easy information sharing. A consistent name also ensures that epidemiologists count and investigate all cases in the cluster. For example, if different areas of a country use different cluster numbers or names then epidemiologists may investigate a single cluster as two separate incidents rather than one. Similarly, if cluster names or numbers change over time then public health officials may fail to link the recent cases to older ones. Many countries have developed specific nomenclatures based on the lineage of a strain or country-specific geography. For example, in the United Kingdom the cluster number incorporates the lineage followed by a unique number (e.g. B0001 = Beijing strain number one). In addition, for some methods of genotyping, such as MIRU-VNTR, standardized international nomenclatures exist that allow cluster comparisons between countries (*5*).

3.3 Analysing outbreaks

Genotyping data can be used to answer specific questions about TB transmission and for analysis of potential outbreaks. Specifically, we can ask:

- Are any cases false positives?
- Should we consider this situation to be an outbreak?
- Has transmission occurred recently?
- Are the cases we see due to reactivation or re-infection?
- How does TB transmission compare between different population groups over time?

The purpose of conducting an outbreak investigation is to prevent further TB transmission by quickly diagnosing and treating individuals found to have active disease or latent infection. By using genotyping data to answer the above questions, NTPs can maximize their resources to find, treat and prevent TB. Eventually, this can enable a TB programme to promote more effective policies to stop TB transmission and improve case-finding.

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d.   See: http://www.applied-maths.com/bionumerics

Genotyping can greatly improve the success of an outbreak investigation. In countries with a low TB burden, scientists can genotype all TB isolates prospectively, which can allow them to rapidly detect and investigate clusters as potential outbreaks. In countries with a high TB burden, NTPs can chose different approaches, such as genotyping isolates from selected populations in which they suspect an outbreak, and/or genotyping isolates in areas where they would like to know more about the TB epidemic, including transmission. For example, genotyping could be carried out for cases in a specific locality, a hospital, or a sub-population, such as children (1–4).

Identifying outbreaks involves a few components: Excluding false positive cases; investigating epidemiological links (e.g. did cases share a common time or place that could account for transmission?); examining drug resistance; and considering each case's history of TB. Each of these components will be considered and examples used to highlight how epidemiologists should consider them in an outbreak investigation. The examples provided are based on a fictitious outbreak investigation in the United Kingdom (a low TB burden country), although the general theory and processes can be applied in settings with a high TB burden.

Excluding false-positive cases

Once cluster data are available, the first step epidemiologists should take in investigating potential outbreaks is to determine whether the increase in the number of TB cases observed is real. We must consider the possibility that some of the cases are false-positives when consecutively processed samples from a single laboratory have indistinguishable genotypes. In such cases, results should be queried with the laboratory to establish whether samples were batch processed or shared a safety cabinet, which may indicate contamination. Information about sputum smear status, whether the culture growth was unusually slow, and whether only one of the specimens taken were culture positive are also helpful. If the answer to any of these questions is positive, it may be more likely that a contamination has taken place. Finally, cases should be discussed with the treating clinician to find out whether patients had symptoms consistent with TB. If the clinical picture does not look like TB, in addition to the laboratory information, then it is likely that the cases are false positives.

Epidemiological links

Once we have confirmed that the increase in the number of cases is real, we should review demographic, clinical and risk factor information to determine if epidemiological links exist between the cases in the cluster. A confirmed epidemiological link requires evidence that cases were in the same place at the same time when one of the cases had active

and contagious TB (i.e. sputum smear-positive pulmonary TB). A possible epidemiological link may involve cases being in the same place but at an unknown time. Epidemiologists investigate epidemiological links by examining the characteristics of the TB cases within a cluster. For example, they can compare the social risk factors or place of residence among the cases. If there are similarities and it is plausible the cases could be related.

There are several ways to organize cluster data to see epidemiological links. Initially, it is easiest to view the cluster as a line list of cases that displays all the relevant demographic, clinical, laboratory and social risk factors, such as history of drug use, heavy alcohol use, time in prison and homelessness. The purpose of this is to look for similarities and differences between TB cases. It is most useful to view the cases in chronological order of clinical presentation or reporting to determine the chain of possible transmission and the person likely to be the source case. For instance, the source case (i.e. the original person with pulmonary disease who infected others) could be the first case to be diagnosed or reported in the cluster, or he/she may be the person with the earliest onset of symptoms.

TABLE 2
Cluster review report (UK)

Cluster number: B1006[*]
MIRU-VNTR: 424352332517333456443372[**]

Unique patient identi-fier	Case report date	Age	Sex	Geog-raphy	Postal code	Place of birth	Years since entry to UK	Site of disease	Sputum status	Pre-vious TB	Onset of symptoms	Risk fac-tors	Drug resist-ant
1	01/05/2013	26	F	London	NW11 5BT	UK	NA	Pulmo-nary	Positive	No	14/02/2013	Drug use	No
2	20/06/2013	33	F	London	NW11 8EL	UK	NA	Pulmo-nary	Positive	No	12/05/2013	Drug use	No
3	28/08/2013	26	M	London	NW11 8EE	Jamai-ca	13	Pulmo-nary	Nega-tive	No	25/07/2013	Prison	No
4	01/09/2013	31	F	London	NW11 3AZ	India	10	Extra-pulmo-nary	NA	No	06/05/2013	Drug use	Isoni-azid resist-ance
5	12/12/2013	52	F	London	NW11 9EQ	UK	NA	Extra-pulmo-nary	NA	Yes	04/11/2013	None	MDR-TB

* Data are fictitious.
** A cluster is defined as two or more cases with indistinguishable TB genotypes. Unique strains are generally considered to arise as a result of reactivation and are not part of a recent chain of transmission. An isolate with a strain with one differing loci would not be considered to be part of the cluster.
NA - Not available

BOX 1
United Kingdom – Example 1

Let us consider the data presented in Table 2 to learn how we can use geno-typing data to assess a potential outbreak. This table lists cases in the United Kingdom that scientists classified into cluster B1006. These cases are in a cluster because each had indistinguishable genotypes based on the MIRU-VNTR (42435233251733456443372). This means transmission between the cases was a possibility, so we now need to determine if there are epidemiological links that could have made transmission likely (e.g. shared time and space). Note that if the genotypes had all been dissimilar, they would not be in a cluster, so there would be no evidence for linkage and no need to investigate an outbreak.

When we look at a cluster, the first thing we examine is when cases became ill. In cluster B1006, we see that five TB cases were reported in a seven-month period. We use the case report date to determine a time period because it is a verifiable date; it is the date when the case became a laboratory or clinically-confirmed case of TB. In addition, the case report date is a mandatory variable, so data are complete. We generally do not use date of symptom onset because this is self-reported by the patient and is thus more likely to be inaccurate or missing. However, if we know the date of symptom onset it is important to use it to assess the duration of symptoms prior to receiving a TB diagnosis or starting on treatment. From this, we can determine how long the case has been infectious in the community and the extent to which the case could have transmitted TB to other individuals. Based on this knowledge, we can re-assess the order in which the cases arose in the cluster. Due to late notifications it is possible the case became ill several months prior to the case report date.

After looking at time period (e.g. case report date and date of symptom onset), we can examine other variables. In this situation, we can see from the postal codes that all of the cases appeared to have been residents in the same neighbourhood in London. The majority of cases also shared other key characteristics: they were female, between 25–35 years of age, primarily born in the UK, had pulmonary disease with two cases also being sputum smear-positive, and had a history of drug use. The two cases born in other nations had been living in the UK for more than ten years. Based on this information, it seems very possible that there were epidemiological links between the cases (i.e. the cases may have been in the same location and at the same time). We can hypothesize that shared drug use was the most probable epidemiological link, but more investigation is necessary to confirm these hypotheses.

After viewing the data as a line list, it is useful for us to view them in a graphical, or an otherwise visual format. Displaying the data from Table 2 in a diagram makes it easier to see the key variables of interest and easier to identify epidemiological links (Figure 1). In this diagram, the epidemiologist has placed each TB case on the timeline based on the case report date. The shapes and colours of the individuals indicate the site of disease. The tails behind each individual case display the length of time from onset of symptoms to the case report date. Risk factors, specifically drug use and prison history, are also indicated on the diagram. Finally, additional information on age and sex are shown in a table to the left of the diagram.

FIGURE 1
Example of a cluster diagram, United Kingdom (Cluster B1006)

Patient	Age	Sex	Drug resistant
1	26	F	No
2	33	F	No
3	26	M	No
4	31	F	Isoniazid resistance
5	52	F	MDR-TB

Feb-13   Mar-13   Apr-13   May-13   Jun-13   Jul-13   Aug-13   Sep-13   Oct-13   Nov-13   Dec-13

Key

Site of Disease		Country of Birth		Risk Factors	
♟	Pulmonary sputum smear positive		UK	D	Drug use
▲	Pulmonary sputum smear negative		Jamaica	P	Prison
●	Extra-pulmonary		India		
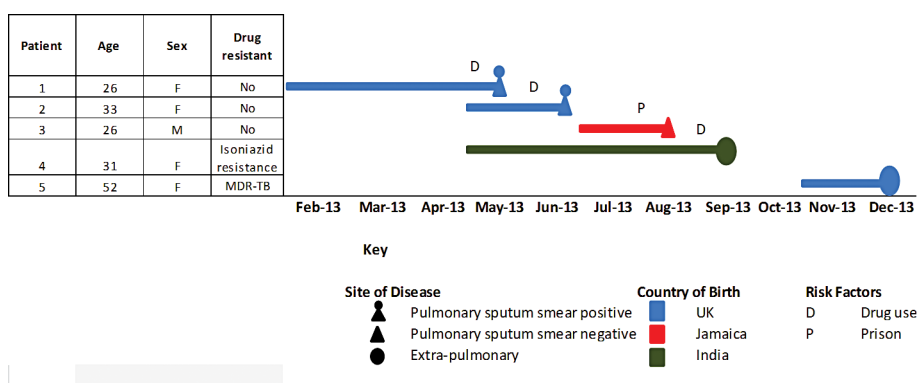
BOX 2
United Kingdom – Example 2

As discussed earlier, when assessing whether transmission between cases in a cluster was likely, we must consider the date the case was reported, the onset of symptoms if available, the site of disease, whether the cases were infectious (i.e. pulmonary) and the level of infectivity (i.e. sputum smear-positive cases are considered to be more infectious than smear-negative cases). Although all of this information was available in Table 2, it is easier to interpret using Figure 1. By placing the cases on a timeline by site of disease and sputum status we can observe which cases could have transmitted TB.

In cluster B1006, Patient Four (from India), was an extrapulmonary case who began displaying symptoms before Patient Three (from Jamaica), even though Patient Four was reported later. Patient Four could therefore not have acquired TB from Patient Three because Patient Four had an earlier date of symptom onset

Box 2 - continued

than Patient Three. Moreover, Patient Three likely did not acquire TB from Patient Four as Patient Four had extrapulmonary TB, and thus was not infectious.

Furthermore, Patients One, Two and Four were all drug users, which is a known risk factor for TB infection and disease (6). Combining the risk factor information with the date of onset of symptoms, we can hypothesize that transmission may have occurred between these cases in a social setting associated with drug use.

Drug resistance patterns

When assessing the likelihood of transmission, we must also consider drug resistance patterns among the TB cases in the cluster. It is unlikely that cases with TB isolates with very different resistance patterns were in the same chain of transmission. This is especially true if a cluster has a combination of cases with either fully sensitive or drug-resistant disease. While it is possible that a fully sensitive TB case could have transmitted TB to an individual who then developed secondary resistance, it is not possible that a case with drug-resistant TB could have transmitted drug-sensitive TB to another person. Furthermore, a TB case whose isolate is resistant to several drugs cannot have transmitted TB to a case whose isolate is resistant to fewer drugs. In countries with facilities to carry out genotyping, TB programmes typically carry out drug sensitivity testing routinely, meaning drug sensitivity patterns should be available for each isolate in the cluster.

BOX 3
United Kingdom – Example 3

We can look at drug resistance patterns to better understand the possible transmission chain in cluster B1006. From Table 2 and Figure 1, we can see that Patient Four has TB resistance to isoniazid, whereas Patients One, Two and Three have fully drug-sensitive TB. Based on the date of onset of symptoms, we have already established that Patient Three could not have infected Patient Four. The drug resistance results support this hypothesis as Patient Four was infected with isoniazid-resistant TB before Patient Three became infected with fully drug-sensitive TB. Patient One could have infected Patient Four, who then acquired resistance to isoniazid. Patient Five has multidrug-resistant TB (MDR-TB). Thus, it is also possible that Patients One, Two or Three may have transmitted TB to Patient Five, who then developed additional resistance.

Previous episodes of TB

There is one additional piece of information that epidemiologists must consider when investigating transmission chains: history of TB. A case of TB could be the result of a person being newly infected with TB, a person with latent TB that is activated, or a person who has relapsed after previously being treated for TB. Genotyping data can help distinguish between a new infection and a relapse of a previous disease, and therefore offers important information about transmission.

In low TB burden countries, historical TB isolates may be available for cases with a history of TB. If such isolates are available, scientists should retrieve them (and the genotype) and compare them with the current isolate. If genotypes between episodes differ, this provides evidence that the person has experienced a new infection (i.e. re-infection) and not relapse (i.e. reactivation). As such, the person may be part of a recent chain of transmission. On the other hand, if the genotypes are indistinguishable, this suggests that reactivation of TB is more likely.

In high TB burden countries, historical TB isolates are less likely to be available, but history of TB can still provide important context for assessing whether a patient is involved in transmission and part of an outbreak. For example, the treatment outcome for the previous episode should be reviewed. If the person did not complete treatment then this suggests that the current episode is due to relapse or ongoing disease rather than recent transmission, which would place the individual earlier in the timeline. This person is likely to have been infectious for an extended period of time, likely giving rise to recent cases in the cluster. If the person previously completed treatment then he/she may be more likely to be in a recent chain of transmission. Even if historical isolates are available, in high-burden settings common strains circulate frequently, so re-infection with the same strain is also possible. The contact tracing information from the previous episode should be reviewed as it is also possible that a source case was not previously identified and the individual has become re-infected from an undiagnosed individual.

Presenting epidemiological links between cases

Once epidemiologists have viewed the cluster by variables related to time, person, and place, they can better investigate epidemiological links. As discussed earlier in this chapter, genotyping data and patient information collected during an outbreak investigation may provide evidence of transmission in a specific setting, such as a prison, school, workplace or neighbourhood, and help identify epidemiological links between cases. It is important that the epidemiologist collates and presents these data in a way that clearly shows such potential links. This helps to identify individuals or settings around which the TB programme should carry out further screening or other public health interventions. Figures 2 and 3 show

BOX 4
United Kingdom – Example 4

In cluster B1006, Patient Five is the only case who had a previous episode of TB. IT is important to understand if Patient 5's current episode of TB was part of the same transmission chain as Patients One, Two, Three, and Four, so we investigate the details about her previous TB episode. Follow up with the clinician who treated Patient Five reveals that her previous TB episode was in June 2012. She had been diagnosed with pulmonary sputum smear-positive TB, but she did not adhere to the prescribed treatment. Although risk factor information had not been recorded at that time, the patient was, in fact, a drug user.

Based on this new information about Patient Five, we need to consider the following scenarios. It is possible that Patient Five relapsed due to treatment failure and has now developed MDR-TB as a result of treatment non-adherence (reactivation). This would mean the patient was not part of the recent transmission chain. If this is the case then this person may not be part of the outbreak and further investigation into epidemiological links between this individual and the others may not be necessary. However, the genotyping data could show that Patient 5 was sick as a result of being re-infected with TB, if her previous episode of TB was caused by a different strain. She could therefore be part of the recent chain of transmission, so we should investigate the person as part of the current outbreak.

In either scenario, we should engage in contact tracing for Patient Five to investigate if she was the source of the outbreak, as she was the first to be diagnosed, was infectious, and had a social risk factor (i.e. drug use) in common with the other cases. If we identify her to be the source case, this may suggest that contact tracing failed to identify contacts. We should thus review contacts to ensure we have diagnosed all active cases.

Because we have identified possible epidemiological links, we should further investigate this cluster to confirm these links and identify a transmission setting around which to carry out extended contact tracing. This is done to prevent onward transmission of TB by identifying and treating any additional active cases of TB in the community that have not yet been detected by the NTP. In this case, our further investigations could entail gathering more information on the cases, such as the setting where drug use took place, detailed prison history such as facilities and timing, occupation, regular places of socializing, any significant travel, frequent visitors and previous place of residence.

FIGURE 2
Epidemiological links between cases and transmission settings within a cluster
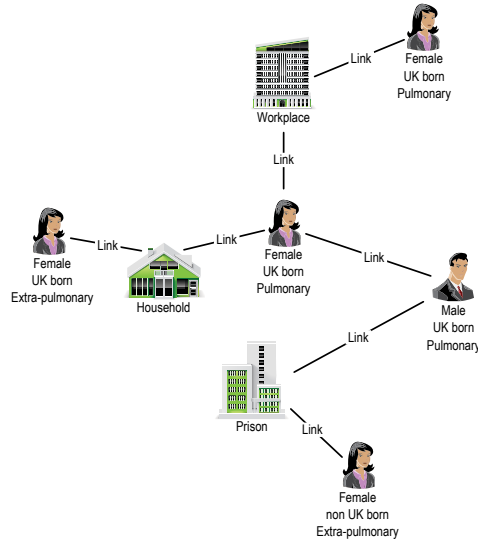
This diagram was created in IBM® i2® Analyst's Notebook®, accessible at http://www-03.ibm.com/software/products/us/en/analysts-notebook/. Relevant demographic or clinical information is displayed underneath each case. Drug use is indicated by a symbol above each case. The epidemiological links between cases and settings are shown by lines.

FIGURE 3
Diagram illustrating epidemiological links between cases and to transmission settings in a cluster
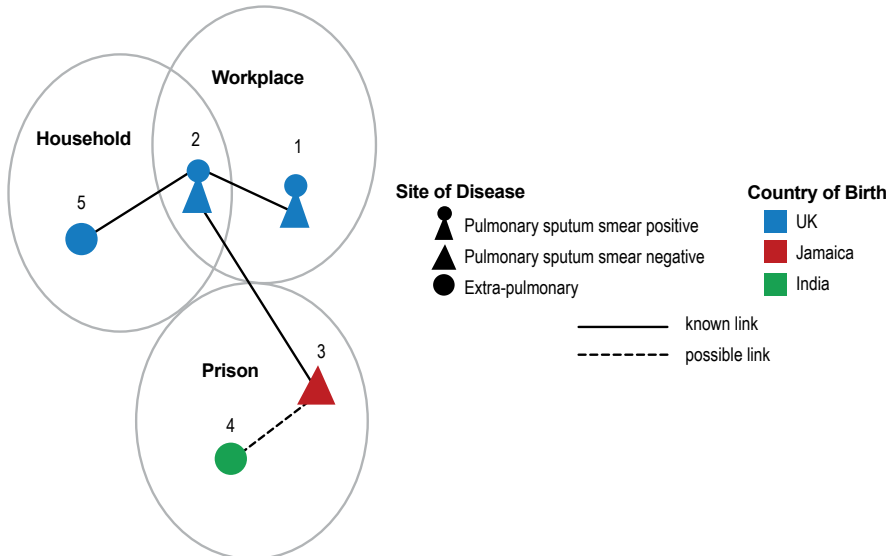
This diagram was created in PowerPoint. Each case is shown by a symbol and patient characteristics are indicated by the shape or colour of the symbol. Links are drawn between cases. The order of when the cases were reported is indicated by a number above each case. Transmission settings are shown as circles in the style of a Venn diagram and cases are placed within each associated setting.

how an epidemiologist can display epidemiological links and transmission settings pictorially. Such figures can be created using specialized software (Figure 2) or basic software such as PowerPoint (Figure 3). Epidemiologists can adapt the figures by adjusting symbols to display the information that is most relevant to their outbreak investigation.

BOX 5
United Kingdom – Example 5

We can use Figures 2 and 3 to visualize epidemiological links between cases in this cluster. In Figure 2, we can see which cases might have the greatest number of epidemiologic links or be at the centre of the outbreak. In this figure, we see that the person at the centre of the outbreak is linked to three other cases directly; she is linked to two cases through the household (one household member and one partner who would have spent time in the house) and to one case through work (one work colleague). In addition, we see that two other cases are linked through a prison. In Figure 3, we see the same information presented in a different format. This figure helps assess what settings individuals have in common by placing the cases within the setting. It also uses symbols to show the country of birth and the site of disease more clearly.

Once epidemiologists have gathered all relevant information and completed the necessary diagrams, the TB programme should consider the following questions:

- Were all the contacts of patients in each setting identified? Were they all screened?
- Is it possible that there were additional active TB cases that were not diagnosed or may not have been confirmed by culture?
- How extensive was the contact tracing that was carried out for cases with previous episodes of TB? Could some of their contacts have been missed?

Once the programme answers these questions, epidemiologists should complete the outbreak investigation with public health officials and clinical staff. This entails that they first identify the contacts of cases associated with the transmission setting(s). Next, they invite contacts for TB screening. Finally, they ensure that people found to have TB disease or infection are quickly started on TB treatment as per national guidelines.

3.4 Analysing large clusters

It is easy to review genotype clusters in a line list or cluster diagram when there are few cases, as was the case in the preceding section. If there are many cases in a cluster (i.e. >10), however, epidemiologists must use different data analysis and display approaches. With large amounts of cluster data, epidemiologists generally display the information for time, person and place separately and then combine them to view a complete picture of the cluster, after which they can pictorially identify epidemiological links.

Displaying time, person and place

To begin, the epidemiologist examines the distribution of cases over time. This chapter has already shown how epidemiologists use timelines to examine the plausibility of transmission. However, epidemiologists can also use timelines to examine the growth of a cluster (i.e. the number of new TB cases detected over time). This can be presented as a standard epidemic curve, as seen in Figure 4.

A sudden increase in the number of cases may be indicative of recent transmission, as a person is most likely to develop TB soon after being infected with M. tuberculosis. The chance of developing active disease decreases over time, with many people never developing active disease. It is therefore extremely unlikely that several cases would spontaneously reactivate at the same time with the same strain of TB unless the number of genotypes commonly circulating in the population is limited. However, epidemiologists should investigate any increase in the number of TB cases with indistinguishable TB genotypes to determine if there is a real outbreak because observed increases may not always be real, as previously discussed (e.g. errors in laboratory diagnostics or batch reporting of cases).

FIGURE 4
Epidemic curve of TB cases in a cluster
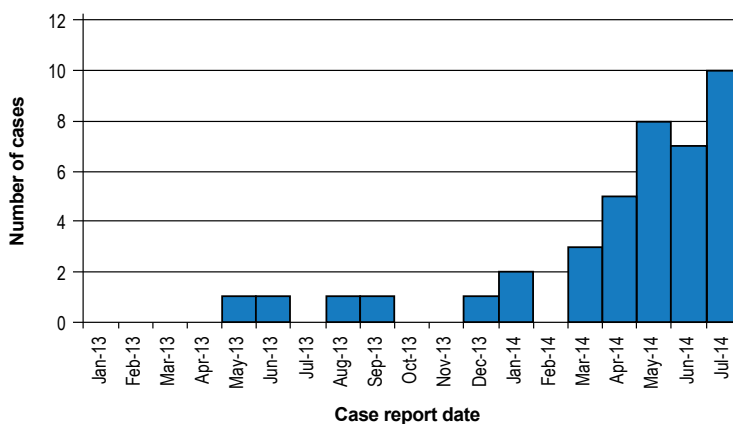
BOX 6
United Kingdom – Example 6

Figure 4 shows an increase in the number of cases in a single cluster that occurred in a particular setting between December 2013 and July 2014. In this cluster, the average number of TB cases increased from 1 to >3 cases per month between December and June 2014, and up to 10 cases in July 2014. Clearly, this pattern is different to the norm and could be indicative of an outbreak. However, before we conclude that there has been an outbreak of TB, observed increases must be confirmed as real. This requires exclusion of laboratory contamination or changes in reporting, in order to determine if these are possible reasons for the observed increase in cases. In particular, the possibility of false-positives must be considered when consecutively processed samples from a single laboratory have indistinguishable genotypes. In such a case, we should query the results with the laboratory to investigate whether samples were batch processed or shared a safety cabinet, which may indicate contamination. Finally, we should discuss with the treating clinician to ascertain whether patients had symptoms consistent with TB, whether the sputum smear status was negative and whether only one of the specimens taken were culture positive. Once we have verified the increase in the number of cases, we should review demographic, clinical, and risk factor information to assess possible epidemiological links, as previously discussed.

After epidemiologists confirm the observed increase in cases, they plot information about the patients, including demographic, clinical and risk factor characteristics, on the epidemic curve (Figure 5). This provides more information about how transmission may be occurring in the community. For example, it can highlight the populations in which transmission is happening and show how this has changed over time.

FIGURE 5
Epidemic curve of TB cases in a cluster by place of birth

UK born ■ **non UK born** ■
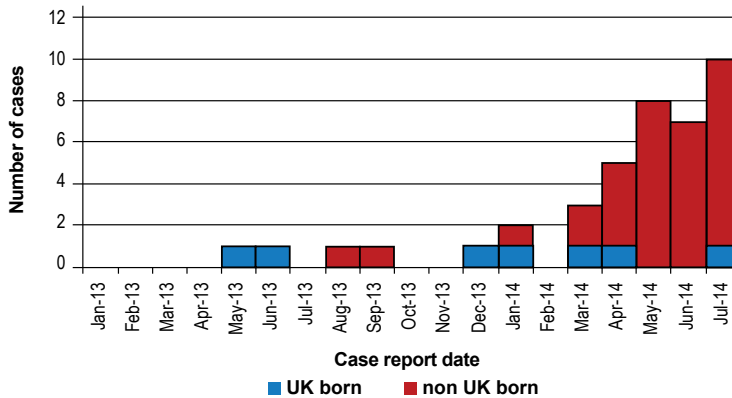
TABLE 3
Summary of numbers and proportions of cases in the cluster

Characteristic	n	%
Age (25-35 yrs)	35	88
Sex (Female)	35	88
UK born	15	38
Site of Disease	30	75
Sputum Positive*	24	80
Previous TB	2	5
Social Risk Factors**	22	55
Total	40	100

* Pulmonary cases only.

** Social risk factors include drugs, alcohol, prison and homelessness.

BOX 7
United Kingdom – Example 7

Figure 5 shows that cases diagnosed earliest in the cluster are among UK-born patients, with the number of non-UK born cases increasing over time. This suggests that transmission may have occurred initially from the UK-born to the non-UK born population. After a certain period, transmission continued to occur most readily among the non-UK born.

Table 3 shows that the majority of cases in this cluster are 25–35 years old (88%), female (88%), non-UK born (62%) and pulmonary sputum smear-positive (80%). We also find that over half of the cases (55%) have social risk factors for TB (i.e. history of drug use, heavy alcohol use, time in prison and homelessness).

After assessing genotyping data with an epidemic curve, epidemiologists assess the characteristics of TB cases within a particular cluster. They do this by summarizing the demographic, clinical and social risk factor data for cases in the cluster. They calculate numbers and proportions for each characteristic and compare them to the total number of cases in the cluster (Table 3).

If the TB programme examines the cluster, it can be useful for staff to compare the characteristics of the local cluster to all the cases with the same TB genotype in the country, if this data is available (e.g. the national cluster, which includes cases from the local cluster and other cases with the same genotype in the country). This allows the programme to assess whether the cases in the local cluster differ from other cases with this genotype in the rest of the country. If the local cases look different from those on the national level, this could suggest that transmission is occurring locally (Table 4).

TABLE 4
Comparison of numbers and proportions of cases (local and national clusters)

Characteristic	Local		National	
	n	%	n	%
Age (25-35 yrs)	35	88	48	40
Sex (Female)	35	88	42	35
UK born	15	38	75	63
Site of disease	30	75	90	75
Sputum positive*	24	80	72	80
Previous TB	2	5	7	6
Risk factors**	22	55	40	33
Total	40	100	120	100

* Pulmonary cases only.
** Social risk factors include drugs, alcohol, prison and homelessness.

In addition to viewing similarities in the demographics and social risk factors among TB cases, it is also important for epidemiologists to view cases in the cluster in terms of geographical proximity either to each other or to places where they suspect transmission may have occurred. The epidemiologist can do this by using the postal code/zip code or address to derive coordinates for latitude and longitude. They can then export the data into GIS software packages[e] to produce maps. They can add case characteristics and landmarks or settings to

e.   E.g. ArcGIS (http://www.esri.com/software/arcgis/)

the map and calculate the distances between cases. Where GIS or other mapping software is not available, epidemiologists can use simple paper-based maps. This works especially well if the epidemiologist has approximate or full addresses for cases and/or suspected sites of transmission. Either way, it assists in displaying where TB transmission may have occurred by identifying the residence and/or neighborhood of the TB cases within a potential cluster.

BOX 8
United Kingdom – Example 8

Table 4 highlights clear differences between the local and national clusters. The local cluster is predominantly non-UK born (62%), female (88%), and aged between 25 and 35 years old (88%). The cases in the national cluster are mainly UK-born (63%), male (65%), and only 40% are between the ages of 25 to 35. In addition, the local cluster has a higher proportion of cases with social risk factors than the national cluster (55% versus 33%, respectively). This may indicate that local transmission is taking place among a non-UK born female population in high-risk groups. Increased investigation and surveillance should occur at the local level to determine if this is indeed the case.

BOX 9
United Kingdom – Example 9

In Figure 6 we see this cluster's TB cases mapped by place of residence (using ArcGIS 10). The cases are coded by different symbols based on place of birth (UK born or non-UK born). This map reveals how close the TB cases live to one another. In addition, it shows clustering of non-UK born cases in the centre of the map, and clustering of UK-born cases in pockets along the outskirts of the map. This can help to identify geographical areas where transmission may be occurring.

FIGURE 6
GIS mapping of clustered TB cases by place of birth
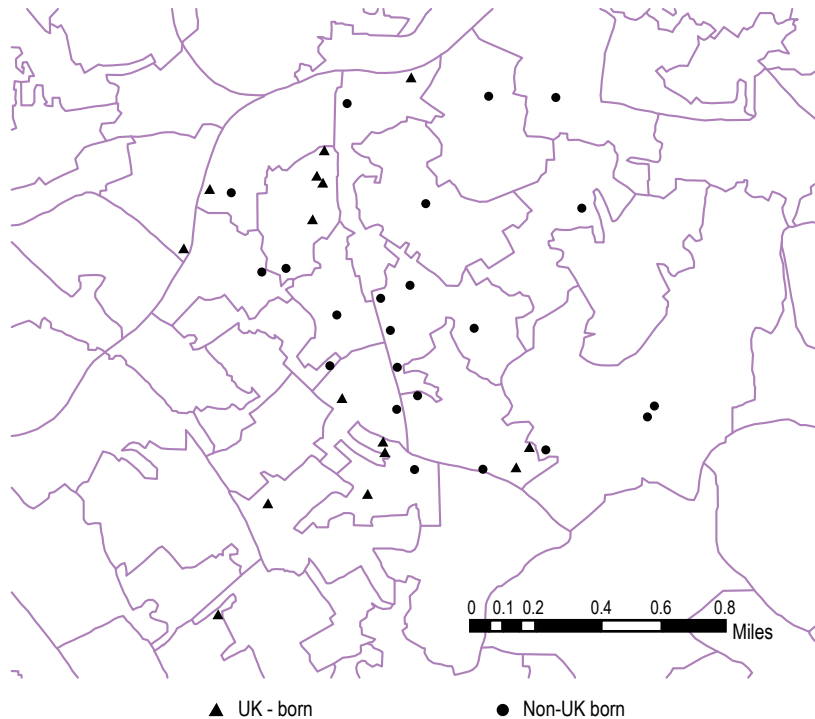
3.5 Limitations of genotyping data

Despite the power of genotyping data, there are limitations that TB programmes must understand before using it to detect TB outbreaks.

Firstly, epidemiologists must remember that different genotyping methods (i.e., RFLP, MI-RU-VNTR, spoligotyping and whole genome sequencing) have varying levels of discrimination. That is, each method has a different ability to distinguish between genotypes. If a method is not discriminatory enough, cases will be wrongly clustered and will not represent true transmission.

Secondly, epidemiologists must remember that even when using highly discriminatory methods to distinguish between genotypes, clustering based on genotypes does not always represent transmission. Common strains circulating in a population or simultaneous reactivations of latent TB are both examples of how cases could be in a single cluster but not be the result of recent transmission. This can be a particular problem in high TB

incidence settings. For example, in South Africa, the Beijing strains of TB are endemic and circulate widely. This means that most genotyping methods will not be discriminatory enough alone to detect true transmission of TB (9). In addition, in low incidence countries where the majority of TB cases arise from imported strains from high TB burden countries, very large molecular clusters may represent transmission of common strains abroad. Therefore, in both high- and low-burden settings, it is always crucial for epidemiologists to obtain epidemiological information, such as time of illness, places visited, and demographic and social risk factors that can establish probable cause for transmission. As such, the quality of epidemiological data is very important in any analysis using genotyping data. Missing or inaccurate data can lead to missing or erroneous links between cases and settings, which can result in additional linked TB cases remaining undiagnosed or experiencing delays in diagnosis. The TB programme should therefore make every effort to minimize the amount of data missing for key variables and ensure data quality assurance procedures are in place.[f]

Finally, sampling bias is often unavoidable. Sampling bias occurs when the sample population does not represent the true population. Genotyping relies on obtaining a culture, so non-culture confirmed cases are excluded from genotype clusters (8). Consequently, some TB cases will be misclassified as having unique TB genotypes, and TB cases that are part of an outbreak will be missed. This results in an under-estimation of transmission. Sampling bias can be a particular limitation in countries that do not carry out universal typing on all isolates, or where a high proportion of cases are migrants who may leave the country prior to diagnosis. In such cases, many strains may be misclassified as unique, which prevents clusters and transmission events from being detected. It is also important to acknowledge this limitation in studies where time periods are fixed, and genotyping may not have been carried out on isolates from cases diagnosed before or after the study time period. This can also lead scientists to misclassify clusters as small or slow growing if they detect the last few cases in a controlled cluster at the beginning of the study period or the first few cases in a cluster arise at the end of the study period.

3.6 Special considerations for genotyping in high TB burden settings

To date, TB genotyping is generally conducted routinely in low TB burden settings, so the best ways for using genotyping data in high TB burden settings are still being determined. Although the principles of genotyping are the same between settings, there are some differences in how epidemiologists should apply genotyping for public health purposes in high TB burden settings. In particular, there are specific limitations associated with using

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f. For more information on minimizing and dealing with missing case-based data, see Chapter 2.

genotyping data in areas with high levels of TB transmission.

It may not always be possible or worthwhile for the NTP to use genotyping for in-depth cluster investigation in high TB incidence settings in the same way it is used in low-incidence settings. This is often because outbreak investigation is resource intensive and the resources and staff may not be available. Specifically, in countries with high levels of TB transmission, the risk of acquiring TB in the general community is high, which means it is extremely difficult to identify specific transmission settings for targeting screening and public health interventions. This becomes more difficult if there are limited numbers of strains circulating in the population (9).

NTPs in high TB burden countries can use genotyping in an outbreak investigation that is already ongoing to confirm or refute transmission, rather than using it prospectively to detect and investigate all clusters. For example, if TB cases are identified in a school and screening then identifies further active cases, genotyping may help to confirm if the children have been in a transmission chain, which would lead to extended contact tracing around this setting. If the children do not have the same strain then transmission has not occurred and less resources can be spent on the investigation. Genotyping can also be used in specific sub-groups or sub-settings to understand the local TB epidemiology and this can contribute to improvements in TB control. For example, studies in Brazil and Ethiopia found genotyping in sub-groups (e.g. children) or sub-settings (e.g. a single geographic area) useful in better understanding the local TB epidemic and control programme (2–5).

If the NTP decides to use genotyping prospectively, it should focus on detecting priority outbreaks where strains are associated with poor treatment outcomes, such as strains of MDR-TB or XDR-TB, strains that result in high levels of mortality, or strains with increased virulence. In order to detect these outbreaks, a repository of baseline data linking circulating strains to geography is most useful. The NTP can then monitor changes in the number of cases with particular strains as part of routine surveillance. They can use the tools previously described in this chapter to visualize trends by space and time and highlight unexpected increases in the background number of cases. A wider community screening approach based on geographical data or 'hotspots' of TB may be more effective in detecting further active cases and reducing onward transmission, rather than putting efforts into gathering information for cluster review, which is resource intensive and unlikely to result in a higher yield of secondary active cases.

3.7 Conclusion: using genotyping data for public health

Despite the limitations of genotyping data, they offer revolutionary opportunities to bet-ter understand local epidemics in both low- and high-burden TB settings. By examining the TB genotypes circulating in a population over time, the most common, or endemic, genotypes can be determined. This information can be used to derive baseline levels of transmission for each genotype by calculating an average number of cases per month or quarter. By detecting an excess in the number of TB cases with a specific genotype com-pared with baseline data, an increase in transmission can be detected. Furthermore, by combining genotyping data with epidemiological data, a TB programme can develop a more detailed picture of TB transmission in its communities, allowing public health offi-cials to target high risk populations with interventions.

Characteristics of TB cases can also be summarized for each TB genotype and used to create targeted TB control strategies. The success of these strategies can then be assessed by monitoring the reduction in the number of cases within a genotype cluster. Finally, creating a repository of genotypes can also be useful for detecting new genotypes arising in the population as a result of recent transmission from imported cases or reactivations. Considering the information that can be gained from using genotyping data in analysis, if used properly, these data promise to be a tremendous asset to public health, offering means to greatly improve TB control and prevention.

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Chapter 4
Analysis of factors driving the TB epidemic

Audience:

(1) Epidemiologists, statisticians and monitoring and evaluation officers.

(2) Staff in NTPs who are interested in learning about factors that drive the TB epidemic and how it could be useful to their programmes.

Expected outcomes:

By the completion of this chapter, the reader should be able to:

- Be aware of the purpose and process of ecological analyses.
- Appreciate the rationale for using trends in TB notifications as an imperfect proxy for TB incidence.
- Critically review plots of time-series of programmatic, health, macro-economic data over time in relation to series of TB case notifications.
- Plausibly infer the extent to which trends in case notifications reflect real changes in underlying TB incidence, by interpolating diverse data.

Authors:

Charalambos Sismanidis, Ellen M.H. Mitchell, Emily Bloss, Philippe Glaziou

4.1 Ecological analysis

Ecological analysis refers to studying variation among populations or catchment areas. It is a useful tool for making broad statements and building hypotheses about how social, economic, political, cultural, epidemiological and health system factors act positively or negatively to influence the course of TB epidemics. Ecological analysis is primarily an exploratory, rather than a confirmatory, tool. Ecological analysis uses averages or other aggregate metrics to explore relationships among macro-level contributors to TB dynamics that cannot be studied in other ways.

What can be explained with ecological analysis?

Ecological analysis is most frequently used to try to plausibly interpret trends in TB burden over time and among geographical areas (within or across countries). However, it has also been helpful to explore variation in the proportions of cases with bacteriological confirmation and to query reasons for variation in proportions of pulmonary versus extra-pulmonary TB.

Simple exploratory ecological analysis can be performed by TB programme staff and has been helpful in high-burden settings to show how seemingly distal social and economic development can have an influence on TB case notification (*1*). The analytic principles and tasks described in this chapter are in reference to TB case notification (as a proxy for TB incidence), but are also valid for deciphering other puzzling issues of attribution in TB control as well.

4.2 TB incidence

Incidence is the number of new TB episodes arising over a certain period of time, for TB this is typically defined as one calendar year. Due to the limitations of current TB diagnostic tools, the long latency period from infection to disease, and the diverse ways that TB manifests, the direct measurement of TB incidence in the general population is both impractical and resource intensive. To date, no country has conducted a nationally representative incidence survey. Incidence surveys would need to include a very large cohort of individuals (e.g. in excess of 50 000) and this cohort would need to be frequently screened over a period of at least one year, with minimal loss to follow-up to ensure validity of results.[a]

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a.   The incidence of sputum smear-positive pulmonary TB cannot be derived from results of tuberculin surveys in school children. Although this was a method used in the past, it has recently come under scrutiny and the underlying assumptions are no longer considered satisfactory [van Leth F, van der Werf MJ, Borgdorff MW. Prevalence of tuberculous infection and incidence of tuberculosis: a re-assessment of the Styblo rule. Bull World Health Organ 2008; 86: 20-6.]

Incidence is therefore typically derived from routine TB cases notified to NTPs, even though there is uncertainty about the number of cases diagnosed but not reported (i.e. notified to NTPs) and the number of cases not diagnosed at all (Figure 1).

FIGURE 1
Relationship between incident (new) TB cases and TB case notification in a calendar year
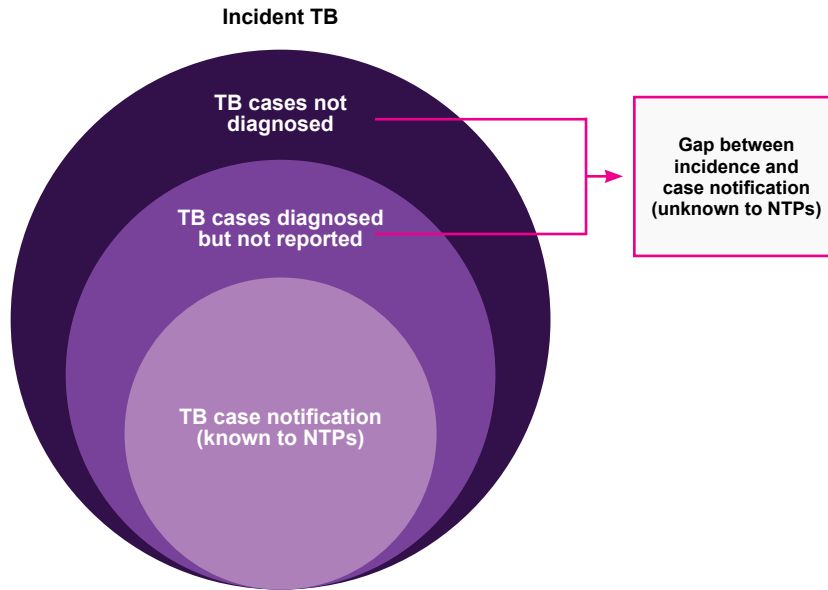
In high-income countries with high-performance TB surveillance and health systems (e.g. in the United Kingdom or the United States), case notification systems capture all, or almost all, incident cases.

In other countries, however, routine case notifications provide biased data.
- Firstly, the private sector is more prone to not report newly diagnosed cases, as commonly observed in Asia and other parts of the world.
- Secondly, not all cases may be diagnosed, particularly in countries lacking health insurance and social protection or equivalent mechanisms, or where the coverage and performance of health services and laboratories remains weak. Common reasons for low levels of diagnosis include: lack of symptoms in a significant proportion of existing TB cases; symptoms not judged severe enough by patients for them to seek medical care; or that people sought health care but were judged to not have TB by care providers.
- Thirdly, only about half of reported TB cases in low- and middle-income countries are definite TB cases – that is, cases that are bacteriologically confirmed. In many

countries, diagnostic procedures are mostly limited to sputum smear microscopy, which has only limited sensitivity.

Measuring both the level of and trends in TB incidence in low- and middle-income countries is therefore a challenge. The interim solution is to conduct ecological analyses using the data that are available (i.e. case notification) to promote the understanding of determinants of the TB epidemic and how they impact changes in trends. Meanwhile, we should also strive to strengthen the performance of TB surveillance systems so that they cover all providers of health care and minimize the level of under-reporting. While we know that case notification do not approximate actual incidence in the past or the present, we expect the confluence of improvements in TB control should eventually lead to a convergence in the future. Below is an example of time trends in estimated TB incidence and case notifications for Indonesia (Figure 2), where an expansion of the surveillance system in recent years to also include case notifications from large public and private hospitals in recent years has decreased the gap with estimated incidence.

FIGURE 2
Time trends in estimated TB incidence (blue line) and TB case notification (red line) in Indonesia, 1990–2011. Dotted blue lines show the uncertainty interval for estimates of TB incidence.
Source: **WHO TB database**
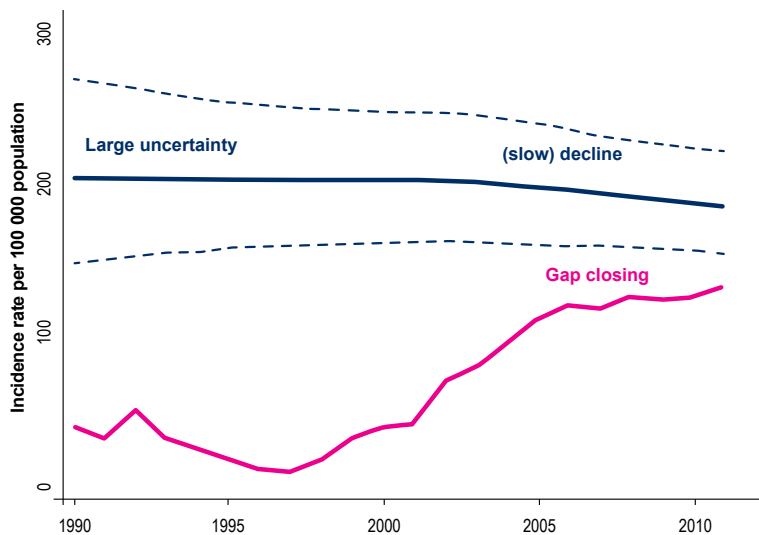
4.3 Using ecological analysis to understand TB epidemics

The compilation and review of data on factors known to drive changes in the TB epidemic should be done systematically and can provide invaluable insights into understanding the

level of and trends in TB burden, especially in countries with weak surveillance systems that produce data of questionable quality. For example, to assess how good a proxy TB case notification is for true TB incidence, we need to determine if the observed trends in case notification are plausible in light of what we know about factors that drive changes in TB epidemics. We look for a logical coherence between the observed trend in case notification and all the various influences of the TB epidemic. In this chapter we refer to these influences interchangeably as drivers, factors or parameters. The types of tasks that we perform under the rubric of ecological analysis and their intended purpose are summarized in Table 1.

TABLE 1
Recommended list of ecological analytical tasks and the purpose they serve

Analytical tasks	Purpose of the task
Review published meta-analyses, and in their absence, available literature (evidence) on the role of specific factors in shaping TB epidemics	To assess the social, economic, political and biological **plausibility** of potential relationships To comprehend the **expected strength of association**
Observe time-series graphs of case notification (both in terms of absolute numbers and rates per capita) and factors known to be associated with TB	To identify and explain changes in observed trends To assess the **temporal relationship** between factors and case notification To hypothesize on the direction in which each factor is driving TB disease burden
Observe variations of case notification across age, sex, regional and TB case types	To assess the **consistency** of observed trends
Observe the magnitude of changes in drivers and compare with magnitude of changes in case notification	To detect any potential **dose-response relationships**
Compare with other countries in the region with similar characteristics	To assess the coherence of the hypothesized explanation of trends

For a detailed list of the types of factors that could be investigated for the purposes of TB ecological analyses, along with associated examples and suggested interpretation, see Annex 4.

4.4 Conceptual framework for ecological analysis

To help your intended audience understand the ecological analysis, we recommend that you provide a conceptual framework that specifies the underlying hypothesis you have about the relationships among the main variables. These can be very simple summarized depictions of experts' initial beliefs about the role of different factors, such as the one shown in Figure 3.

FIGURE 3
Conceptual framework on which direction factors associated with TB are expected to drive disease burden

HIV prevalence
Diabetes prevalence
Aging of the population

ART coverage
IPT coverage
GDP increase
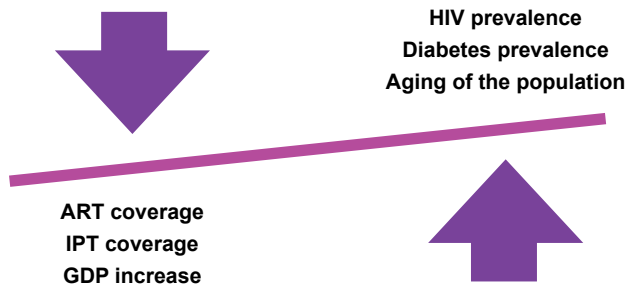
Conceptual frameworks could also be a lot more nuanced, multi-layered hypotheses, such as the one in Annex 5.

The simpler the design of the conceptual framework the easier you will convey the negative and positive relationships you are exploring and implicitly help to justify your choice of a particular constellation of factors. The intended audience should be able to readily grasp the rationale for the ecological analysis. While some audiences will immediately perceive the underlying epidemiologic logic without a visual, others will need the benefit of a clear conceptual framework to perceive the negative and positive influences.

What if certain key information is unavailable for all domains?

Given that not all the data on all topics will be available (or in the appropriate units or years), it is necessary to be opportunistic – making use of the data that are available for the time periods and unit of analysis you require, while acknowledging their limitations.

How should we prioritize the domains and indicators to include?

It can be challenging to determine what elements to include in an ecological analysis. An epidemiologist can advise you on the relative strength of association found in the

literature (e.g. meta-analyses). However in-depth discussion of the domains (explained in Annex 4) and of indicators among local experts should guide the prioritization since TB epidemics can be profoundly contextual. One approach is to brainstorm among TB experts a full list of all potential factors that may play a role, and then reach consensus on a prioritized list of probable drivers that can be feasibly and efficiently explored. Here is an example from a South Asian country (Table 2).

TABLE 2
Prioritized list of domains and factors influencing TB incidence

Domains	Factors driving incidence downwards	Factors driving incidence upwards
Health sector-level protection and prevention interventions	Improved health system performance	Limited health insurance coverage
Transmission	Transition to ambulatory care	Rapid urbanization Increased migration
Vulnerability	Decline in economic inequalities Decrease in smoking	Aging of the population Increasing HIV Increasing diabetes
Screening & diagnosis	The scale-up of DOTS (long term) PPM approaches (long term)	The scale-up of DOTS (CNR) PPM approaches (CNR)
TB treatment	Expanded treatment centres	
Recording & reporting		

CNR - Case notification rate

Note that while some factors have a demonstrably beneficial effect on TB incidence, paradoxically, by increasing the case notification rate over the short term, they give the false impression of a resurgent TB burden. For example, the scale up of DOTs, PPM, active case finding (ACF) and improvements in recording and reporting will increase the number of TB patients under care within the surveillance system, by closing the gap between real incidence and case notification.

Once the main domains and drivers have been defined, you should compile as much supporting data as you can find that are relevant, timely, valid and in the appropriate units.

If the ecological analysis is being conducted as part of a formal programme and policy evaluation, we recommend prioritization of the arenas that the NTP and health stakeholders can positively influence through changes to policy and practice. Identifying drivers of the epidemic that are beyond the control of your intended audience often serves a limited purpose.

What if there are no data on something that experts deem as important?

When can a proxy be used? How does one determine whether a proxy is an appropriate one? Often what we want to measure is not available at the level of aggregation we require or for the time period we need it. So we frequently rely on proxy variables to help us. A suitable proxy variable will be one with an established close correlation with the metric we wish to include. Consult the literature on the strength of proxies used in other settings. The more distal the proxy is to the driver you wish to measure, the less likely it will actually mirror the unattainable quantity.

4.5 Preparing your data for analysis

It is critical to do a sober assessment of the quality of any data you choose to include before you begin. Avoid data that are too old (to be defined in advance according to the objectives of the analysis), as well as data that do not remotely correspond to your chosen unit of analysis (e.g. your desired unit of analysis is district, but you only have aggregate regional data available). Most importantly, you need to have information on factors at multiple time points if you want to relate trends in factors to trends in case notification rates (CNR).

Aligning data across incompatible geographical units (Figure 4) is time consuming, but a necessary step in ecological analysis. If the data you wish to use are provided in a unit of analysis lower than the one you have chosen, then you must aggregate your data. Most statistical software packages offer an aggregation command.

FIGURE 4
Different level analysis units, starting from the lowest (individual patient) moving on to higher aggregated geographical levels

Aggregate level 2 (e.g. region)

Aggregate level 1 (e.g. district)

TB basic management unit

Health facility

Patient
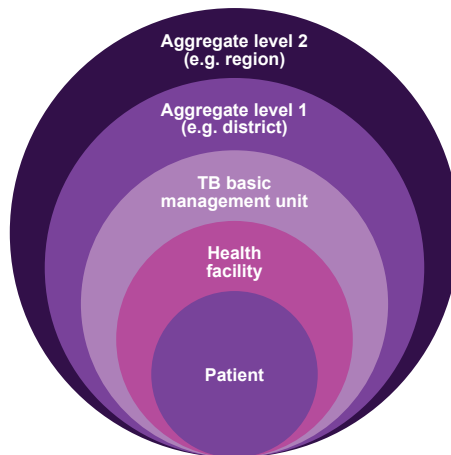
4.6 Case studies

Ecological analysis lends itself well to visualization and communicates powerfully to a wide variety of stakeholders. Once your data are assembled, start the analysis by visualizing the relationships with time series graphs and scatter plots. Clearly the types of analyses possible depend on the data available and the particular circumstances of each country.

In this section we offer a series of illustrative examples to show how different countries have graphed their data in a stepwise fashion to build a plausible interpretation of trends in case notification. The first step could be to look in detail at case notification over time to note the direction, timing and slope of changes.

Figure 5 shows two illustrative country examples that highlight the need for triangulation and contextual information to derive meaningful conclusions. CNR has increased steadily in Indonesia over the decade and an arrow indicates that the onset of this increase coincided with the adoption of the DOTS strategy. The issue of timing (also called the temporal relationship) between drivers and trends is a clue that helps assess a potential causal link. We expect to see changes in drivers precede changes in case notification.

FIGURE 5
Trends in case notification rates per 100 000 population, Indonesia (1990–2011). *Source:* **WHO TB database**
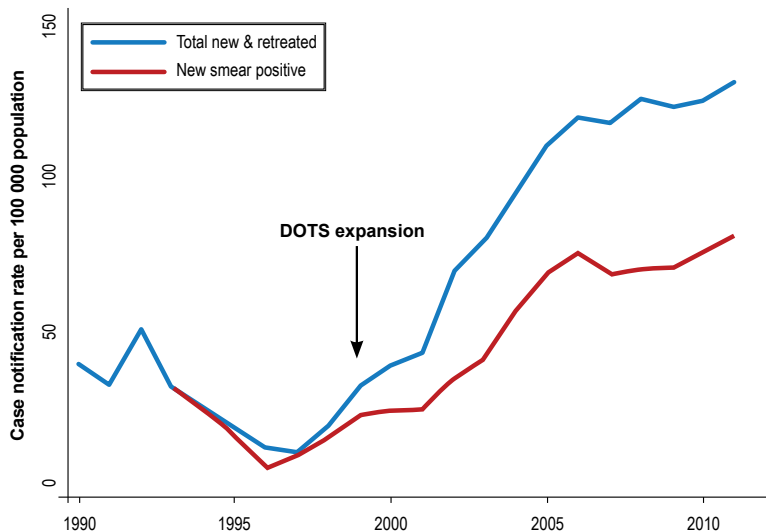
In contrast, the example from Viet Nam (Figure 6) reveals the presence of two distinct trajectories in reported TB case notification rates. A stable rate of TB notification and a declining proportion of smear positive TB presents an interpretive challenge.

FIGURE 6
Trends in case notification rates per 100 000 population in Viet Nam, 1990–2011 (black: all forms, red: smear positive).
Source: **WHO TB database**
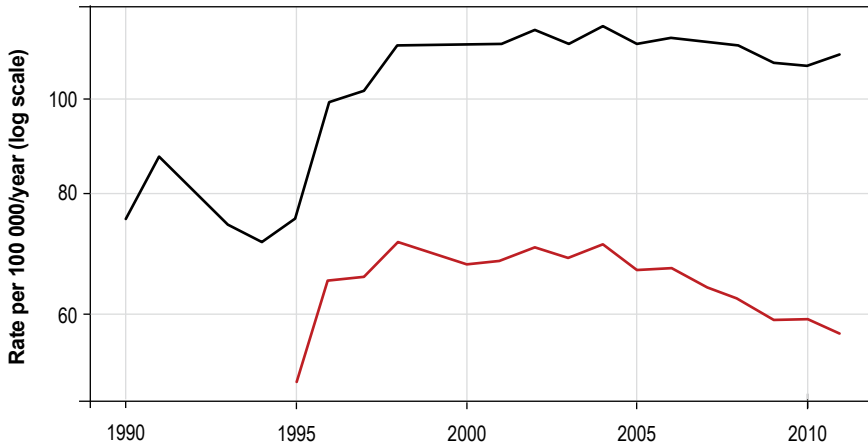
After reviewing the aggregate trend in case notification over the desired period, the next step is to explore age, sex and regional differences as described in Chapter 1. This is done both as a data quality assurance step as well as to discern if the national data are obscuring distinct drivers that may signal the presence of regional dynamics or micro-epidemics in a country.

To explore sub-national differences in time-series data, the Indonesia team plotted case notification for all 34 provinces (Figure 7). Comparison of these time-series data suggests that while there is a generalized increase in case notification in most provinces, there may be some areas with unique epidemic dynamics and disease drivers. As Indonesia is an archipelago of islands this is to be expected. It remains to be investigated whether the variability in CNRs at the provincial level reflects differences in disease burden, differences in TB detection and reporting coverage, or both. Errors in reporting (including geographical differentials in error) also cannot be ruled out.

In countries that have completed a national TB prevalence survey, one way to hypothesize about the relationship between sub-national levels of disease burden expressed in adult pulmonary TB prevalence levels and TB case notification is to plot these (Figure 8).

It should be noted that the prevalence survey was not powered to estimate state-level prevalence rates but this is still a useful exercise in hypothesis generation and further complements field investigations at the state level.

FIGURE 7
**Provincial and national (100_Indonesia) level time-series of notifi-
cation rates for all forms of TB (red) and smear-positive (blue) TB in
Indonesia (1998–2011).** *Source:* NTP Indonesia

How many influences can one explore? How many drivers can be included in a single graph or explanatory model?

You can produce as many exploratory graphs and comparisons as you have good data for. However, to explore the influence of a large number of factors upon case notification within a single explanatory model, you may find that you need to consult a statistician to help with statistical approaches to overcome what is known as the "large p small n problem". This problem refers to situations when you have many influencing factors but not many observations (e.g. years or BMUs). For example, when a small country has 34 health districts, 13 provinces, and 4 regions then the largest sample size would be 34, which might be too few if the NTP wanted to understand dozens of potential influences upon district case notification rates.

Challenges and limitations of ecological analysis

Ecological analysis is a macro-level exercise that attempts to explain the shape of complex systems, and confounding and covariance are often a risk. Ecological analysis has earned a

bad reputation in some circles because it relies heavily on the use of averages and proportions, which are acknowledged to be imperfect reflections of the variability in a particular place or time. This over-simplification is what makes ecological analysis both appealing and accessible, but simultaneously prone to error. While it is unlikely that major drivers of TB are unrecognized, it is often the case that key elements are unmeasurable or unavailable. Finding enough data with all the same units of analysis and time periods is almost always a challenge. Lack of detailed monitoring data on policy implementation and pace of programmatic scale up can make it challenging to properly attribute efforts to outcomes.

FIGURE 8
Scatter-plot of state-level adult, pulmonary TB prevalence and case notification rates in Nigeria (2012) *Source:* **NTP database and 1st National TB Prevalence Survey, Nigeria**
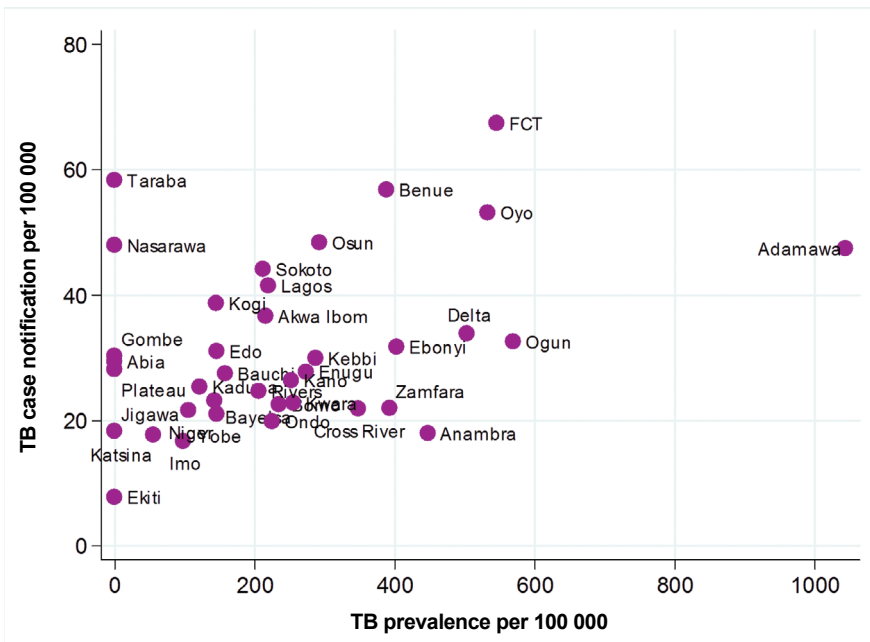
4.7 Conclusion

Solid ecological analysis can help to tell a powerful story of the myriad of influences on TB epidemics over time and among geographic areas. Sometimes the process does not result in a single simple narrative, but rather several plausible and coherent explanations. Systematic scrutiny of the major elements of the groups of factors that shape TB epidemics and careful application of plausibility criteria can help NTPs to discern whether their attempts to control TB disease are having an impact, as well as how to enhance that impact on the epidemic.

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Annex 4
Which types of data should be investigated as part of TB ecological analyses?

A good ecological analysis does not have to include every factor that affects TB epidemics, but it should at least consider the use of metrics from these six domains (Figure A1).

Schematic of domains of influence on TB epidemics
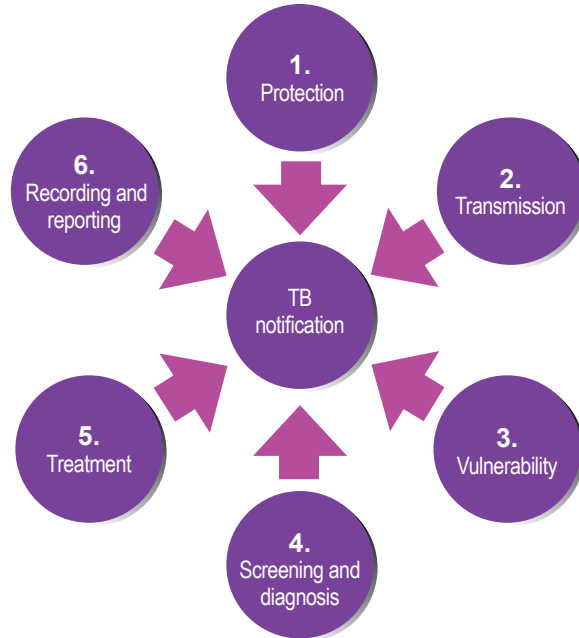
1. Health sector-level protection and prevention interventions

These are public health interventions designed to prevent TB infection and protect those infected from developing active disease. These factors are strategic to include in an ecological analyses because they are forces within the control of the health sector. Therefore insights about these factors can be translated directly into improved policy and practice. An illustrative list of factors that could be included in an ecological analysis includes:
- Administrative, environmental and personal infection controls in congregate settings.
- Antiretroviral coverage among people living with HIV.
- Coverage of latent TB infection treatment.
- BCG vaccination coverage.
- Under-five mortality rate per live birth (Figures A2 and A3).

FIGURE A2
Time trends in under-five mortality rate per 1000 live births in Viet Nam, 1990–2010 (log scale). The under-five mortality rate is used here as an overall indicator of health system performance. It has declined spectacularly over the past two decades, reaching a level in 2011 that is comparable to the level observed in Western Europe in the mid-1960s. This factor is expected to drive TB burden downward. *Source:* World Bank
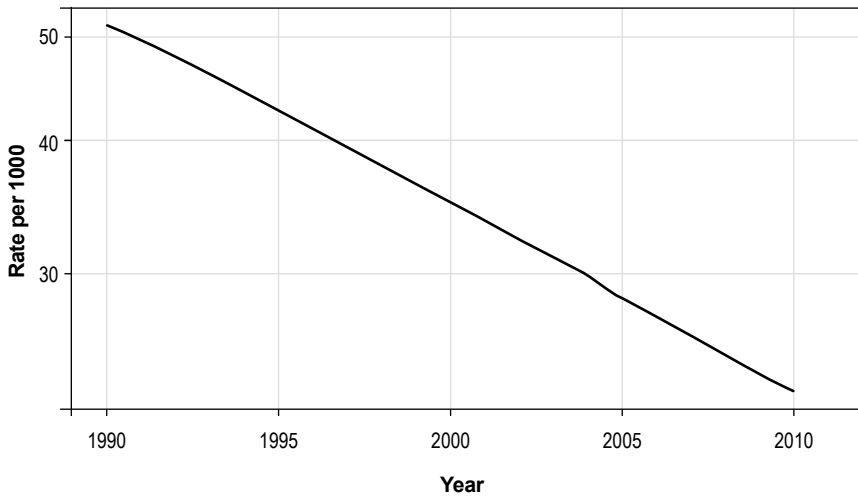
FIGURE A3
Scatterplot of under-five mortality rate per 1000 live births against GDP per capita (2010). Each blue dot represents a country pair of data points. Nigeria is shown in red. The rectangle encloses countries with GDP between 1000 and 1500 USD per capita. This suggests a lower level of performance of the health system (as measured through the under-five mortality rate indicator) in Nigeria than could be expected relative to the size of the economy. *Source:* World Bank
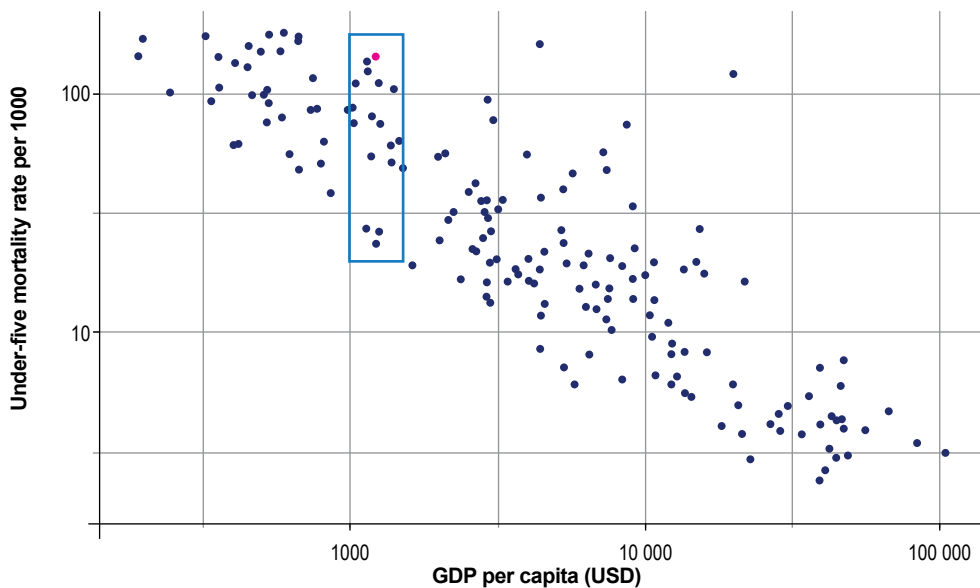
2.Transmission

These factors are often related to urban and industrial design, housing policies, correctional and detention practices. These are often issues outside the immediate scope of influence of NTPs. Nevertheless, they can be found to play a potent role in TB epidemics (*2,3*).

Examples of factors that play a critical role in transmission of TB include:
- Incarceration rates.
- Mean duration of incarceration (sentencing norms).
- Coverage of deep-pit hard rock mining operations.
- Mean number of people per bedroom or per cell.
- Population density (people per square metre).
- Proportion living in sub-standard conditions (crowding).
- Size of the economy, as measured for example through GDP per capita (Figure A4).

FIGURE A4
Time trends in GDP per capita (log scale) in Viet Nam, 1990–2010.
The economy has expanded over the past two decades at an almost constant rate of growth per year. The Asian financial crisis of the late 1990s had a limited impact. This factor is expected to drive TB burden downward.
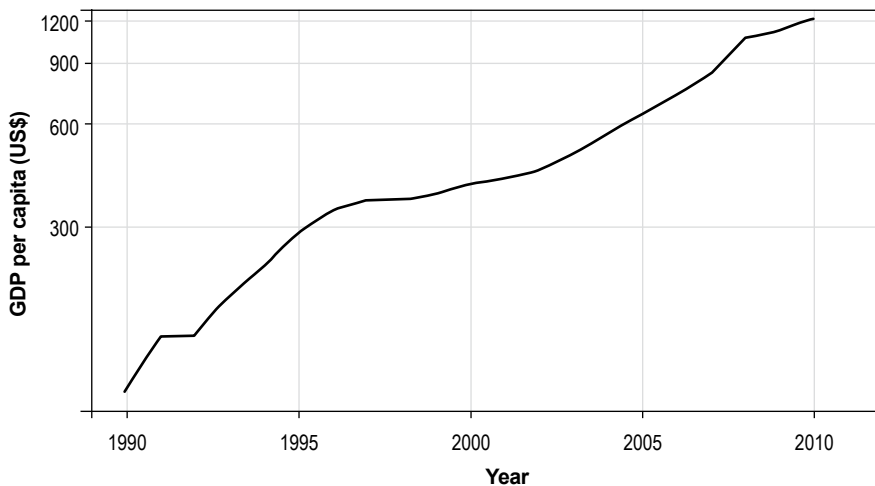
3. Vulnerability

A population's vulnerability to TB infection and break down to TB disease is a wide ranging topic and much of what we know about vulnerability has come from ecological analyses (*4*). These indicators can either be very directly linked to TB vulnerability via damage to the immune system (such as HIV and diabetes), or they can be more upstream indicators of physical vulnerability that stem from different forms of social exclusion such

as illiteracy, marginalization as well as inequalities based upon income, gender, religion, race and nationality. Examples of factors that reflect increased TB vulnerability among a population include:

- Coverage of health insurance and social protection programmes and the percentage of health care expenditure accounted for by out-of-pocket payments.
- Prevalence of HIV infection (Figure A5).
- Prevalence of diabetes.
- Prevalence of smoking, alcohol dependency, injecting drug use, indoor air pollution.
- Prevalence of wasting and stunting, malnutrition.
- Gini coefficient.
- Literacy rate.
- Gender inequality Index.
- Unemployment rate.
- Prevalence of internal displacement or homelessness.
- Prevalence of silica dust exposure.
- Prevalence of previous TB and fibrotic lesions.
- Demographic changes, for example aging of the population (Figure A6).

FIGURE A5
Time trends in HIV prevalence in 15–49 year old population in Nigeria, 1990–2011. Expected to have driven TB burden upwards between 1990–2000, stable ever since. *Source:* AIDSinfo database
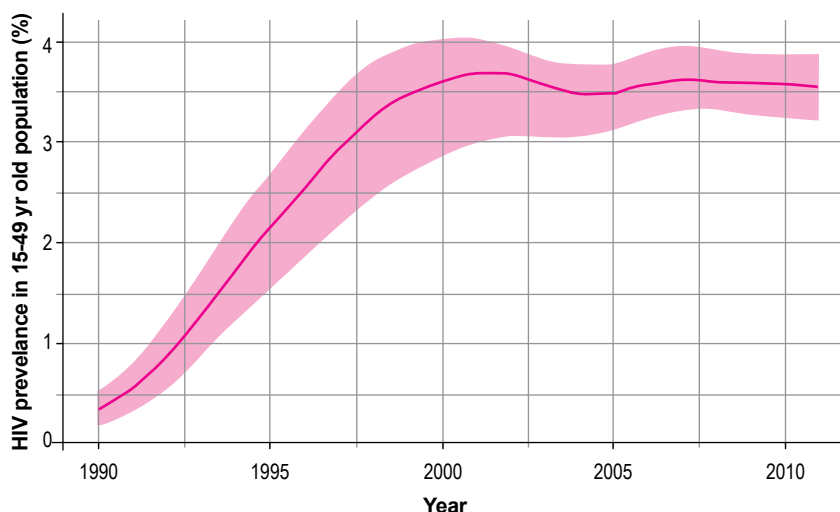
FIGURE A6
1990 and 2010 population pyramids of the general population in Nigeria representing the distribution of the population by age and sex.
Population demographics have remained stable over the past 20 years in Nigeria. Depending on age-specific distribution of TB burden in the country demographics could drive TB upwards or downwards. *Source:* **UNPD database**
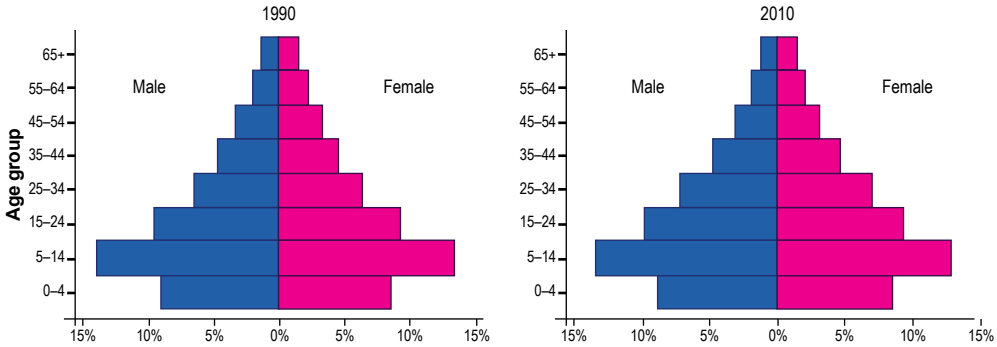
4. Screening and diagnosis

Screening and diagnosis measures refer to all the forces that influence health care seeking and the probability that TB symptoms are recognized and disease is diagnosed within the health system. These measures are relatively straightforward and well within the purview of the NTP to improve, so these are very worthwhile to include in ecological analyses that look at variation in TB case notification and distributions of notified TB cases (pulmonary vs extra pulmonary). Some commonly used measures include:

- Proportion uninsured – without health care coverage – access to free TB diagnosis.
- Mean number of people screened for TB per 100 000 population.
- TB screening rates for high risk groups.
- Awareness of TB symptoms as reported in surveys (e.g. Demographic Health Survey TB module).
- Health seeking behaviour for prolonged cough, fever and other TB symptoms, as reported in surveys.
- TB investigation rates per 100 000 population (No of samples submitted/100 000).
- Mean number of chest X-rays per 100 000 population.
- Mean number of GeneXpert modules per 100 000 population.
- Mean number of diagnostic centres per 100 000 population.
- Mean number of culture laboratories and/or drug sensitivity testing (DST) laboratories.
- Mean number of nurses, doctors and/or radiologists per 100 000 population.
- People living with HIV stigma index, impact on health seeking behaviour.

• Coverage and performance of PPM/community/active case-finding initiatives.

Here is an example of the kind of time-series data that are compiled to document expanding diagnostic capacity and coverage (Figure A7).

Contribution of PPM and active case finding on TB case notifications, expressed as a percentage of the total number of TB cases notified in Viet Nam. *Source:* **Viet Nam NTP**
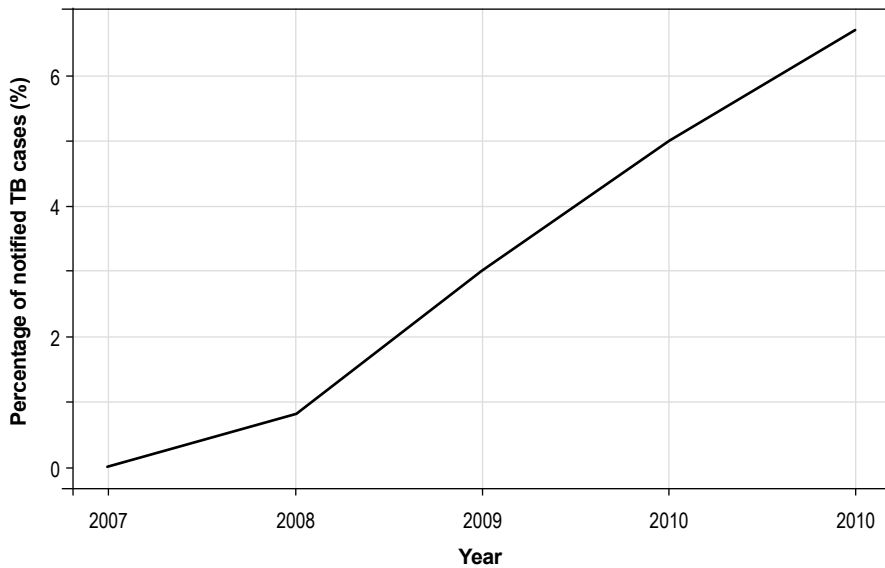
5. TB Treatment

Treatment measures also deserve strong consideration in ecological analyses because of the well established effect of TB treatment on disease dynamics. Some of the measures of TB treatment that are used in ecological analyses include:

• Treatment success rates (Figure A8).
• Mean sputum conversion time.
• Rates of TB treatment support.
• TB patient mortality rates.
• Coverage of directly-observed treatment.
• Drug commodity management indicators.

An example of the overall treatment success percentage over time is shown in Figure A8. The dashed line represents the global 85% treatment success target, met for the first time in 2011.

FIGURE A8
Treatment success (either cure or treatment completion) percentage among the national new smear-positive case notification cohorts in Nigeria, 1996–2011. *Source:* **WHO TB database**
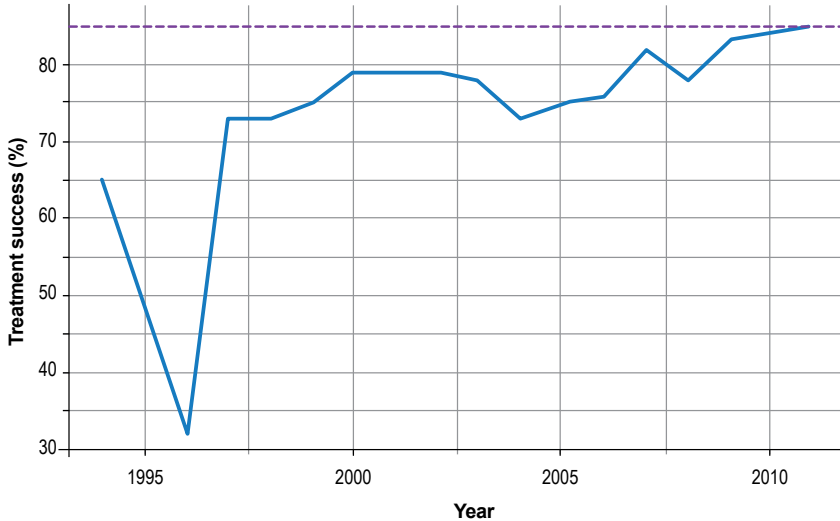
Figure A9 shows an example of the scale up of ancillary HIV care for co-infected TB patients over time in one province in Mozambique. These data can be overlain to help explore treatment outcomes in the cohort.

FIGURE A9
Time series of scale up of cotrimoxazole prophylaxis and antiret-roviral therapy coverage among HIV positive TB patients in Gaza province, Mozambique 2006–2012. *Source:* **Mozambique NTP**
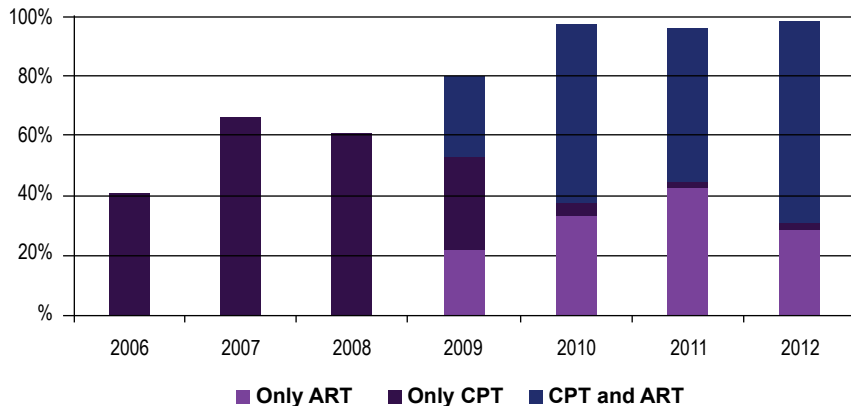
Occasionally it is also worthwhile to look at the time lag of treatment following diagnosis as a means of understanding the possible role of delays in provision of care. Taken together, these figures show both an increase in coverage as well as an initial increase in time-liness of antiretroviral therapy provision. These trends seem to coincide with increases in TB treatment success among HIV positive TB patients (Figure A10).

FIGURE A10
Timeliness of antiretroviral therapy provision in relation to TB treatment success, Mozambique 2006-2012. Source: Mozambique NTP [ART: antiretroviral therapy; HIVTX: HIV treatment success among HIV positive TB patients]
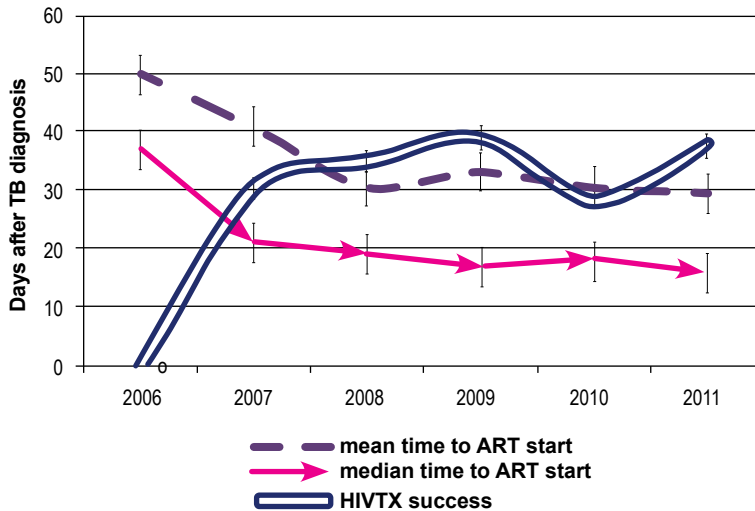
6. Recording and reporting

Changes in the way TB is recorded and reported often have profound effects on the volume and quality of data that are notified. This can complicate the interpretation of ecological analyses. Therefore it is always worthwhile to look closely to ensure that re-classification, transitions from paper to electronic systems and other reforms in record keeping do not obscure understanding of the underlying TB epidemic. Some potential factors to consider include:

- Changes in the level of under-reporting (e.g. results of inventory studies).
- Changes in the number and/or catchment area of BMUs.
- Dates when new recording and reporting forms were introduced or changes in case definitions took effect.
- Changes in policies regarding mandatory reporting.
- Participation rates of private providers in the reporting system.
- Results from a systematic assessment of TB surveillance data using the WHO checklist of standards and benchmark WHO checklist of standards and benchmarks for tuberculosis surveillance and vital registration systems (Chapter 1).
- Dates when electronic systems were rolled out.

Some experts include a seventh domain of **Government and international donor funding for TB control.** This is an important area and certainly a potent driver of TB control efforts, however it is considered by some to be an 'upstream' influence with impacts felt proximally within many of the other domains.

Annex 5
Example detailed conceptual framework on how factors influence TB burden

(red represents contribution to an increase, while green to a decrease, in TB burden)

Upstream factors
- Migratory flows
- Income inequality
- Educational and informational inequality
- Economic, gender, cultural, political and religious constraints to health seeking
- Stigma

Proximal determinants of TB vulnerability
- Age
- Malnutrition
- HIV prevalence
- Diabetes prevalence
- Smoking, alcoholism, drug dependency

Proximal determinants of TB transmission
- Urbanization and housing
- Crowding
- Incarceration rates and sentencing norms
- Hospitalization rates and norms
- Poor infection control

Proximal determinants of TB protection and prevention
- Antiretroviral coverage for PLHIV
- Effective screening and triage of vulnerable populations
- Latent TB treatment coverage for vulnerable populations
- BCG vaccination coverage

Diagnostic factors
- Access to diagnosis
- Health-seeking behaviour
- Diagnostic infrastructure
- Diagnostic quality
- Turn-around time of results

Treatment factors
- Access to treatment
- Efficacy of medicines
- Availability
- Quality of care
- Treatment support

Recording & reporting factors
- Under-reporting
- Misclassification
- Non-participation in reporting systems

Chapter 5
Drug-resistant TB: analysis of burden and response

Audience:

This chapter aims to guide staff responsible for monitoring and evaluation at the national and sub-national levels of control programmes, as well as technical partners, to improve the surveillance of drug-resistant TB (DR-TB). The contents also aim to assist staff designing operational research.

Expected outcomes:

By the completion of this chapter, the reader should be able to understand:

- The principles behind the analysis of data from DR-TB surveillance and surveys, as well as the disease epidemiology and associated burden of disease, including the distribution of disease geographically (i.e. by age and sex, and among specific population groups).
- The main indicators of DR-TB programme performance, using and interpreting routinely collected data in terms of case detection, start of treatment and treatment outcomes.

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5.1 Methodology

Definitions

Drug resistance surveillance data are collected for new (previously untreated) and previously treated TB cases separately, through special surveys or continuous surveillance. Special surveys are studies, ideally repeated every three to five years, measuring drug resistance among a representative sample of notified, bacteriologically-confirmed patients with pulmonary TB. Continuous surveillance is a surveillance system based on routine diagnostic drug susceptibility testing (DST) of all bacteriologically-confirmed TB patients (*1*).[a]

The main definitions and indicators used to assess programme performance have been defined elsewhere (*2–4*). When monitoring DR-TB cases in TB programmes, the focus is on those infected with strains showing in vitro resistance to rifampicin (RR-TB). These could be mono-, poly-, multidrug- resistant (MDR-TB) or extensively drug-resistant (XDR-TB).[b]

Data sources

In a drug resistance survey, the main data source is the survey database that is designed to capture both clinical and laboratory data.

For continuous surveillance of drug resistance and for the purposes of assessing the performance of programmatic management of drug-resistant TB (PMDT), the main data sources comprise the following:

- Basic management unit (BMU) TB register (or district TB register).
- Second-line TB treatment register (previously category IV register).
- Laboratory register for culture, Xpert MTB/RIF and DST.
- TB treatment card (first- or second-line).

These data sources may only be available in paper format, although they are increasingly being replaced by electronic systems (*5*). This development greatly enhances efficiency in managing data, deriving the necessary indicators and performing more frequent analysis. With the increasing interest in mapping the exact location of patients in order to identify

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a.   The document *Guidelines for surveillance of drug resistance in tuberculosis. 4th ed.* (WHO/TB/2009.422). describes in detail most of the concepts mentioned in this chapter related to the design, implementation and data analysis of special surveys (*1*).

b.   In contrast to other TB patients, those with RR-TB require much longer treatment and, as a result, monitoring is more protracted with a specific set of diagnostic and outcome indicators.

hotspots of DR-TB and to improve services (6), coupled with the widespread availability of cellular phones equipped to capture global positioning system coordinates, it is likely that geographic information system (GIS) data will become more important for routine TB care and prevention. The release of new anti-TB drugs for use in MDR-TB patients ahead of the completion of Phase 3 trials means that pharmacovigilance is destined to become a vital component of any routine surveillance system. Special data collection questionnaires and software have been developed for this purpose (7).

Methods used to describe and analyse data

The methods commonly employed to describe and analyse TB drug resistance data include:

- Simple descriptive statistics in the form of standard indicators such as frequency tables, as well as graphics based on these statistics (most commonly line graphs and bar charts to depict time trends and proportionality and maps to depict variations within a country). A country example is shown in Box 1.
- Testing of hypotheses related to the determinants of drug resistance and the risk factors associated with treatment outcomes. The most commonly used techniques employed in such cases are illustrated through a number of country examples in this chapter. These examples have mostly been drawn from country surveillance data reported to WHO and are intended to show how and to what extent such data can be used, mindful of the limitations in accuracy of some of these datasets. The same patterns and associated interpretations could apply to several other countries that have not been included.

Special surveys

When analysing data from special surveys, the following four basic descriptive analyses should be considered.

Patient intake. The number of patients included from each diagnostic centre or cluster in the survey should be compared with the expected number of notified cases based on the sampling method, disaggregated by treatment history. For example, if the target cluster size for new cases is 40, the actual number of new patients enrolled in each cluster should be compared with the target size of 40. Should a lower number of new patients be enrolled, actions should be taken to improve patient participation and ultimately reach the cluster target size.

Missing data. Calculate the percentage of individuals for whom data on drug resistance to isoniazid and/or rifampicin are missing, summarized by age group, sex, treatment history, cluster and any other important variables available in the survey results.

BOX 1
Country "dashboard" of summary indicators for MDR-TB data

Visualizing key indicators by means of simple graphics and tables is extremely helpful. Among the advantages of electronic recording and reporting is the flexibility and ease with which such visualization can be achieved. In recent years, the WHO Global TB Programme has developed a dashboard that groups together country or regional indicators drawn directly from the WHO global TB data collection system (see Figure 1). Individual TB programmes can custom design such tools according to their preference and add other specific information as required.

FIGURE 1
Summary profile with key indicators on MDR-TB.
***Source*: WHO Global TB Database www.who.int/tb/data**

Indicators of diagnosis, notification and treatment of multidrug-resistant TB, by region or country and year

Uzbekistan

Time trend, cases

Treatment outcomes of MDR-TB cases, %

● Notified TB   ● Notified MDR-TB

■ Successful ■ Died ■ Treatment failed ■ Lost to follow-up ■ Not evaluated
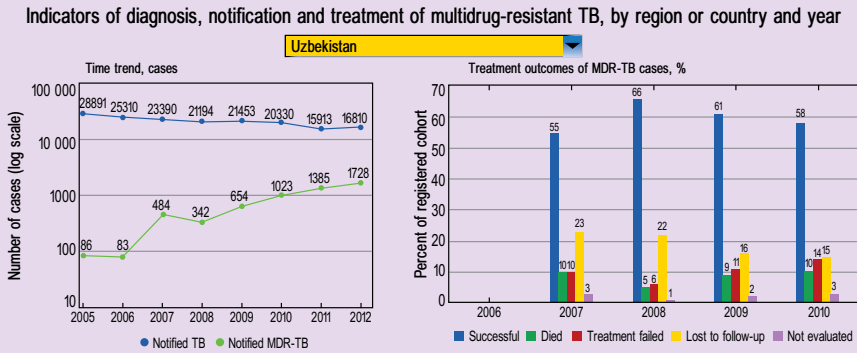
		New cases		Previously treated cases			
Estimated number of MDR-TB cases among notified pulmonary TB cases in 2012		2400 (1800–3000)		1600 (1400–1900)			
	2005	2006	2007	2008	2009	2010	2011	2012
Notified TB cases	28 891	25 310	23 390	21 194	21 453	20 330	15 913	16 810
Notified MDR-TB cases (absolute number)	86	83	484	342	654	1023	1385	1728
Notified MDR-TB cases (rate per 100 000 population)	0	0	2	1	2	4	5	6
Patients started on MDR-TB treatment					464	628	855	1491
MDR-TB cases with recorded treatment outcomes			330	294	464	628		
% of new TB cases with drug susceptibility testing (DST) results	0	3	6	5	12	60	10	52
% of previously treated TB cases with drug susceptibility testing (DST) results	5	4	10	9	30	26	11	39

* % TB cases with 1st line DST exceeding 100% shown as 100%: this may happen if TB notification is incomplete especially in systems where reporting of TB and DST are not linked.
* Outcomes for MDR-TB reported two years after the end of the year of enrolment. Patients may have not been necessarily treated using internationally-recommended regimens or norms

The indicators on this page are intended to monitor the progress of countries to key drug-resistance targets in the Global Plan to stop TB 2011-2015	
Indicators	**Target for 2015**
% of new bacteriologically positive TB cases reported with drug-susceptibility testing (DST) results	≥ 20%
% of previously treated TB cases reported with drug-susceptibility testing (DST) results	100%
% of patients with confirmed MDR-TB completing treatment successfully	≥ 75%
% of confirmed MDR-TB cases for whom outcomes are reported	100%

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Drug resistance patterns. A table should be created describing the proportion of patients with resistance to individual/combinations of drugs. This information should be disaggre-

gated according to new and previously treated patients. This analysis should be conducted including/excluding multiple imputation for missing data (Table 1). Variations in the proportion of TB cases with MDR-TB between different regions in a country may then be observed (Box 2).

Determinants of resistance. Cases found with DR-TB are commonly stratified by age group, sex, HIV status and other patient demographic and clinical data collected during the survey. Table 2 shows the findings from a recent survey in Belarus, where 32% of new and 76% of previously treated patients have MDR-TB (8). In this analysis, MDR-TB was found to be independently associated with previous treatment, imprisonment, unemployment due to disability, smoking, heavy alcohol consumption and HIV infection. Some of the associations may lie on the causal pathway of MDR-TB (e.g. previous treatment or imprisonment) while others may represent an effect of chronic illness on social status (e.g. disability).

TABLE 1
Example of patterns of resistance to first-line anti-TB drugs

	No (% [95% CI])		
Drug resistance pattern	**New (n=1 050)**	**Previously treated (n=291)**	**Total (n=1 344)**
Susceptible to all drugs	**87.7 (84.0-90.6)**	**56.8 (50.5-62.9)**	**81.3 (77.3-84.7)**
Any drug resistance			
- Any resistance to H	5.3 (4.0-7.0)	35.8 (29.9-42.0)	11.7 (9.1-14.8)
- Any resistance to R	1.6 (0.9-2.9)	28.9 (23.9-34.4)	7.3 (5.2-10.0)
- Any resistance to E	0.9 (0.4-2.1)	17.8 (13.5-23.3)	4.4 (3.2-6.0)
- Any resistance to S	9.9 (7.4-13.0)	33.1 (27.1-40.0)	14.7 (11.8-18.0)
Total any drug resistance	12.4 (9.4-16.1)	43.2 (37.1-49.5)	18.8 (15.3-22.8)
Monoresistance			
- Mono resistance to H	1.5 (0.8-2.7)	2.5 (1.2-5.2)	1.7 (1.1-2.7)
- Mono resistance to R	0.2 (0.0-1.0)	0.4 (0.0-2.7)	0.3 (0.0-1.1)
- Mono resistance to E	0.2 (0.0-0.8)	0.0 (-)	0.2 (0.0-0.6)
- Mono resistance to S	6.6 (4.4-9.8)	7.1 (4.8-10.3)	6.7 (4.8-9.3)
Total monoresistance	8.5 (6.0-12.0)	10.0 (7.3-13.5)	8.8 (6.6-11.6)
Multidrug resistance			
- HR	0.4 (0.1-1.2)	4.3 (2.2-8.2)	1.2 (0.6-2.4)
- HRE	0.0 (0.0-0.7)	3.0 (1.8-5.0)	0.7 (0.4-1.3)
- HRS	0.4 (0.2-1.1)	7.0 (5.1-10.0)	1.8 (1.1-2.8)
- HRES	0.5 (0.2-1.3)	14.1 (9.9-19.7)	3.3 (2.2-4.9)
Total multidrug resistance	1.4 (0.7-2.5)	28.5 (23.5-34.1)	7.0 (5.0-9.6)
Polydrug resistance			
- HE	0.1 (0.0-0.8)	0.0 (-)	0.0 (0.0-0.6)
- HS	2.4 (1.5-3.7)	4.0 (2.2-7.2)	2.7 (1.9-3.9)
- ES	0.0 (-)	0.0 (-)	0.0 (-)
- HES	0.0 (-)	0.7 (0.2-2.9)	0.2 (0.0-0.6)
- RE	0.0 (-)	0.0 (-)	0.0 (-)
- RS	0.0 (-)	0.0 (-)	0.0 (-)
- RES	0.0 (-)	0.0 (-)	0.0 (-)
Total polydrug resistance	2.5 (1.6-3.9)	4.7 (2.6-8.5)	2.9 (2.1-4.2)

H=isoniazid; R=rifampicin; E=ethambutol; S=streptomycin; CI=confidence interval

TABLE 2
Risk factors for MDR-TB among TB cases in Belarus, 2010–2011

Characteristic	Cases		Univariable analysis[1]		Multivariable analysis[1]	
	No.	% with MDR-TB	OR (95%CI)	p	OR (95%CI)	p
Sex						
Male	1075	47.6	Ref.	-	Ref.	
Female	269	37.2	0.7 (0.5-0.8)	0.000	1.1 (0.8-1.5)	0.657
Age (years)						
15-34	328	49.7	Ref.	-	Ref.	
> 34	1016	44.2	0.8 (0.6-1.0)[2]	0.046	0.7 (0.6-1.0)	0.021
Country of birth						
Belarus	1293	45.3	Ref.	-	-	
Other	51	51.0	1.3 (0.8-2.0)	0.360	-	
Treatment history						
New case	934	32.3	Ref.	-	Ref.	
Previously treated case	410	75.6	6.5 (5.2-8.2)	0.000	6.1 (4.8-7.7)	0.000
Level of education						
University	43	34.9	Ref.	-	-	
College	345	47.3	1.7 (0.9-3.0)	0.080	-	
Secondary school	887	46.6	1.6 (0.9-2.8)	0.087	-	
Primary school or lower	69	30.4	0.8 (0.4-1.7)	0.573	-	
Living conditions						
In own house	1104	45.7	Ref.	-	-	
In rented house	185	43.8	0.9 (0.7-1.2)	0.587	-	
In dormitory	29	37.9	0.7 (0.4-1.4)	0.345	-	
Homeless	26	61.5	1.9 (1.0-3.8)	0.069	-	
Household size (no. of members)						
1	329	49.9	Ref.	-	Ref.	
2	543	46.0	0.9 (0.7-1.1)	0.209	1.0 (0.7-1.3)	0.758
3	287	42.9	0.8 (0.6-1.0)[2]	0.046	0.8 (0.6-1.1)	0.184
>3	185	40.5	0.7 (0.5-0.9)	0.020	0.8 (0.6-1.2)	0.266
Employment status						
Employed	401	42.4	Ref.	-	Ref.	
Unemployed but able-bodied	659	50.5	1.4 (1.1-1.7)	0.003	1.1 (0.8-1.4)	0.578
Retired	175	27.4	0.5 (0.4-0.7)	0.000	0.7 (0.5-1.0)	0.052
Unemployed due to disability	87	59.8	2.0 (1.3-3.0)	0.001	1.9 (1.2-3.0)	0.010
Student	22	40.9	0.9 (0.4-2.0)	0.874	1.4 (0.6-3.2)	0.417
History of imprisonment						
No	1145	42.2	Ref.	-	Ref.	
Yes	199	64.8	2.5 (1.9-3.3)	0.000	1.5 (1.1-2.0)	0.009

CI=confidence interval; MDR-TB=multidrug-resistant tuberculosis; OR=odds ratio; Ref.=reference group.

[1] All determinants were studied by logistic regression. Those whose **p**-value showed statistical significance (**p**<0.05) in the univariate analysis were included in the multivariate analysis.
[2] The CI contains the number 1.0 because of rounding.

Table 2 - continued

Alcohol consumption (days of binge drinking)[3]						
0	573	40.0	Ref.	-	Ref.	
1	61	39.3	1.0 (0.6-1.6)	0.914	1.0 (0.6-1.7)[4]	0.977
2-4	264	45.1	1.2 (1.0-1.6)	0.109	1.0 (0.8-1.4)	0.770
>4	446	53.8	1.8 (1.4-2.2)	0.000	1.3 (1.0-1.8)	0.038
History of smoking[d]						
No	288	31.6	Ref.	-	Ref.	
Yes	1056	49.3	2.1 (1.7-2.7)	0.000	1.5 (1.1-2.0)	0.021
HIV status						
Negative	1249	44.6	Ref.	-	Ref.	
Positive	72	68.1	2.6 (1.7-4.1)	0.000	2.2 (1.4-3.5)	0.001
Unknown	23	26.1	0.4 (0.2-1.0)[4]	0.047	0.5 (0.2-1.3)	0.173

[3] Reported as the number of days in the previous month when the patient drank at least 5 units of alcohol.

[4] "Smoking" is here defined as the regular use of any tobacco product in the previous 5 years

Two main issues need to be taken into account when analysing data from a special survey:

- To address potential bias created by missing data, missing values should be imputed.
- In a cluster sample survey, the correlation between individuals from the same cluster should be addressed.

Details of how to perform imputation of missing values, and account for clustering, are provided in detail in the WHO guidance on drug resistance surveys (*1*).

Continuous surveillance

Analysis of data gathered from continuous surveillance systems is similar to that performed on data from special surveys. The main difference is that imputation of missing values and adjustment for clustering are not performed.

In order to ensure that continuous surveillance data are nationally representative, a high proportion of notified new pulmonary TB cases (i.e. greater than 75%) should ideally have DST results documented for at least rifampicin, as described in Standard B2.1 of the WHO TB surveillance checklist.[c]

Currently, however, WHO requires that at least 60% of new pulmonary TB cases notified in a national continuous surveillance system have documented DST results for at least rifampicin in order to be considered representative.

c.   The checklist and user guide are available on the website of the WHO Global Task Force on TB Impact Measurement: http://www.who.int/tb/advisory_bodies/impact_measurement_taskforce/en/

Sometimes, data from only part of the country are available (Box 2). In some instances sentinel surveillance systems operate as an interim measure before moving to full continuous surveillance (*1*).

BOX 2
Sub-national statistics and drug resistance surveillance

Drug resistance surveys are usually powered to give national-level estimates of drug resistance among TB patients. For the survey to also be considered representative at a sub-national level, the sample size would need to be substantially increased, raising the costs beyond what most countries can afford. As a result, the differences between provinces in the prevalence of MDR-TB are often only statistically significant between sites that have extreme values (compare the regional values in Figure 2).

FIGURE 2
The percentage of MDR-TB in new and previously treated cases with 95% confidence intervals, by region/city, Uzbekistan (2010–2011) nationwide DRS
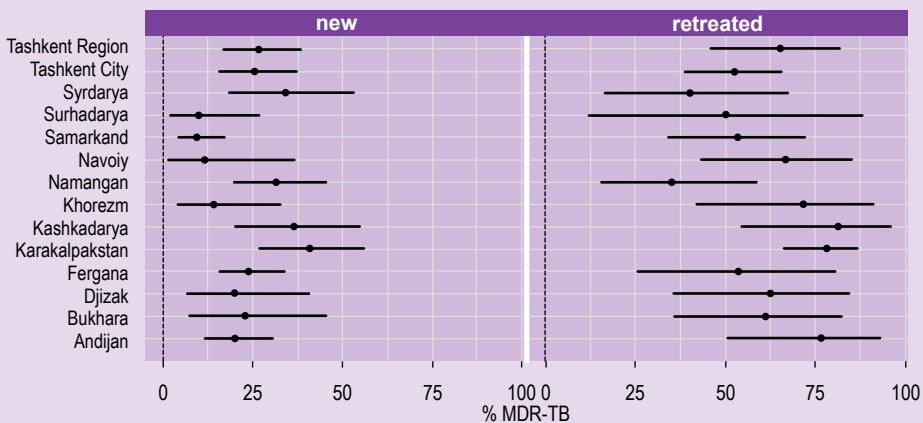
Conversely, in countries with comprehensive, continuous surveillance systems limited to only certain administrative divisions, regional data can be used to derive the best possible estimation of drug resistance. For example, in the Russian Federation, the Ministry of Health publishes annual information on the percentage of MDR-TB among new and previously treated TB cases for all of the regions and cities in the country (Federal Subjects) (*10*). These data are reviewed by WHO to assess their representativeness according to the criteria described above.

## 5.2. Estimation of the burden of drug-resistant TB and time trend analysis

National estimates of MDR-TB burden have been included in WHO reports since 2008 (*11*). These estimates are based on the latest and best available evidence on the proportion of MDR-TB among TB patients presenting for treatment in a given country. They are useful to quantify the effectiveness of efforts to detect and start MDR-TB patients on treatment. The estimated number of MDR-TB cases among notified pulmonary TB cases is calculated by multiplying the number of notified pulmonary TB cases by the proportion of MDR-TB among TB cases found in the most recent special survey or continuous surveillance. The calculation is performed separately for new and previously treated TB cases.

The most appropriate indicator to monitor time trends in MDR-TB is the proportion of MDR-TB cases identified in new instances of TB only (i.e. not all TB cases), which can be calculated from results of continuous surveillance or repeated drug resistance surveys. Surveys are typically repeated every three to five years to assess changes in levels of resistance. New TB cases constitute a homogeneous group of patients who can be monitored in relation to specific time-related data. This contrasts with the situation among patients with a previous history of treatment for TB, who are usually a more heterogeneous group of patients that includes relapse cases, treatment after failure and treatment after loss to follow-up.

There are at least two approaches to analyse time trends in MDR-TB among new TB cases:

- Describe the variation over time in the proportion of MDR-TB among new TB cases after plotting the proportion of MDR-TB among new TB cases by year.
- Describe the variation over time of the estimated number of MDR-TB cases among notified new TB cases (Figure 3).

FIGURE 3
Proportions of MDR-TB in new TB cases over time in Botswana and Estonia (1996–2012)
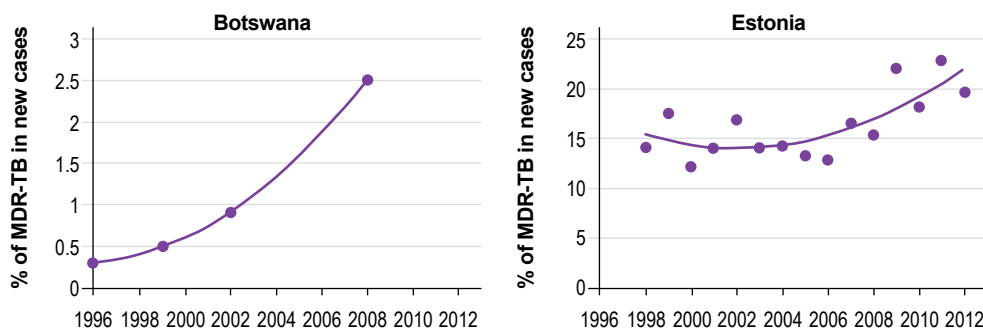
(Note different scales for Y axes)

To perform the latter (estMDRT), multiply the proportion of MDR-TB among new TB cases by the number of notified new pulmonary TB cases per 100 000 population for each year, and plot the results by year, where:

pMDR = proportion of MDR-TB among new TB cases in a given year;

newTB = number of notified new TB cases in the same year;

pop = country population in the same year.

$$estMDRT = pMDR \; x \; \frac{newTB}{pop} \; x \; 100\,000$$

Use a log scale for the y-axis. A straight line can be fitted to the data if the trend appears to be visually linear. It is then possible to calculate the average annual percentage change in the rate of MDR-TB cases expected to be found among notified new pulmonary TB patients.

Trends in the estimated number of MDR-TB cases can be compared with trends in the notification of new TB cases in the same graph.

The mean percentage change per year is given. In Botswana, for example, the TB notification rate is stable, while the estimated per capita rate of MDR-TB is increasing at an average of 19% per year (Figure 4). In Estonia, the TB notification rate and the estimated per capita rate of MDR-TB are both decreasing, although MDR-TB is decreasing more slowly than TB.

FIGURE 4
Rates per 100 000 population of notified new TB cases (purple circles) and estimated MDR-TB cases among notified new TB patients (red circles) over time in Botswana (1996–2008) and Estonia (1998–2012)
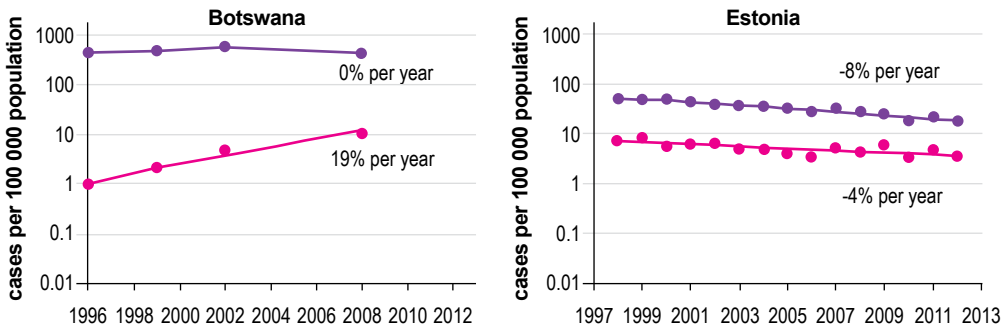
5.3 Monitoring programme effectiveness

This section is divided according to four sets of indicators: detection, enrolment, interim results and final outcomes. These indicators are recommended by WHO for assessing the effectiveness of a programme to detect RR-/MDR-TB cases, to place them on appropriate treatment and monitor their outcomes (*2*). The following sections outline the sources of data, how to calculate the indicators (defining numerators, denominators and patient sub-groups) and the timing and periodicity for the generation of indicators. In contrast to the approach of quarterly and annual reports, indicators help to better focus the attention of monitoring activities and allow the analysis of time trends. These indicators are also summarised in a table available online (*4*).

A timeline for the reporting of the four sets of indicators is shown below (Figure 5).

FIGURE 5
Timeline for reporting of indicators of RR-/MDR-TB

Detection, Enrolment: 2 yearly
Interim results: 4 yearly
Final outcomes: 1 yearly
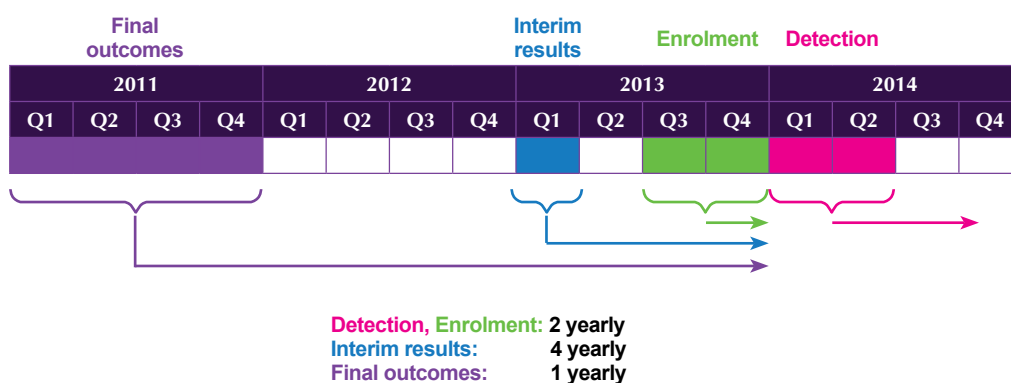
Detection

Early detection of resistance to rifampicin and isoniazid ensures that an appropriate drug regimen can be prescribed from the outset, in order to increase the likelihood of treatment success, and to reduce the chance of acquiring additional resistance. Groups to be targeted for DST vary according to national policy although WHO generally recommends DST for all previously treated patients and contacts of MDR-TB cases (*12*). DST for fluoroquinolones and second-line injectable anti-TB drugs is recommended for all MDR-TB patients.

There are five indicators to measure the progress towards universal access of TB patients to DR-TB diagnosis. The first two indicators are calculated for all cases tested as well as separately for all the risk categories listed in the national policy. The delay in testing and the frequency of MDR-TB among individuals in different risk categories are also evaluat-

ed. These parameters are important for programme managers because they are needed to evaluate how the targeting and timeliness of DST, as well as the yield of MDR cases, vary by risk category of targeted patients. In sites testing with Xpert MTB/RIF alone, Detection Indicators 1, 2 and 5 can be modified to include all cases with a rifampicin test result and the main objective changed to detection of cases with RR-TB rather than MDR-TB.

The detection indicators should be calculated every six months, usually for January to June and for July to December, calculated three months after the end of each six-month period using data from the basic management unit TB register, the second-line TB treatment card and also the laboratory registers (or their electronic equivalents). Country examples of the use of the detection indicators are shown in Box 3. The five indicators are described below.

Detection Indicator 1[d]: TB patients with result for isoniazid and rifampicin DST

Numerator: Number of TB cases with a DST result for both isoniazid and rifampicin by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases identified in each respective risk category during the period of assessment.

Data source: Numerator data are available from the laboratory register; denominator data from the basic TB register and treatment card. For some risk categories (e.g. contacts of MDR-TB), the information may not be in the treatment card and has to be traced from elsewhere in their medical records. Risk categories include all TB patients previously treated for TB, contacts of confirmed MDR-TB cases or other individuals considered to be at risk of DR-TB.

Detection Indicator 2: Confirmed MDR-TB cases detected among TB patients tested for susceptibility to isoniazid and rifampicin

Numerator: Number of confirmed MDR-TB cases by each risk category specified in the national policy during the period of assessment.

Denominator: Number of TB cases in each risk category with a DST result for both isoniazid and rifampicin during the period of assessment.

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d. In sites testing with Xpert MTB/RIF alone, the numerator in Detection Indicator 1 and denominator in Detection Indicator 2 can be modified to include all cases with a rifampicin test result, while the numerator in Detection Indicator 2 would also include all rifampicin-resistant (RR-TB) cases. Likewise Detection Indicator 5 can be adapted for use when testing for RR-TB.

Data source: Numerator data are available from the laboratory register; the denominator is identical to the numerator of Detection Indicator 1. Risk categories include all TB patients previously treated for TB, contacts of a confirmed MDR-TB case, or other individuals considered to be at risk of DR-TB.

Detection Indicator 3: Confirmed MDR-TB cases tested for susceptibility to any fluoroquinolone and any second-line injectable drug

Numerator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB drug during the period of assessment.

Denominator: Number of confirmed MDR-TB cases during the period of assessment.

Data source: Numerator data are available from the laboratory register; the denominator is identical to the (non-disaggregated) numerator of Detection Indicator 2.

Detection Indicator 4: Confirmed XDR-TB cases detected among MDR-TB patients tested for susceptibility to any fluoroquinolone and any second-line injectable drug

Numerator: Number of confirmed XDR-TB cases detected during the period of assessment.

Denominator: Number of confirmed MDR-TB cases tested for susceptibility to a fluoroquinolone and a second-line injectable anti-TB drug during the period of assessment.

Data source: Numerator data are available from the laboratory register; the denominator is identical to the numerator of Detection Indicator 3.

Detection Indicator 5: Interval between presumption of RR-/MDR-TB and DST results

Definition: The duration in days between the date when the TB patient was identified as being in a risk category as per the national policy and the date of the DST results for isoniazid and rifampicin as recorded in the laboratory register. The first date is determined by type of risk category. This date may correspond to when TB is diagnosed if universal DST is practiced, or when a laboratory result indicates treatment failure or persistent sputum smear-positivity during the course of TB treatment, or when HIV-associated TB is detected. For a possible case known to be in contact with a TB case, this date would be when the laboratory confirms MDR in the source case. This may occur before or after the diagnosis of TB in the contact (information as in the laboratory register). In sites testing with Xpert MTB/RIF alone, the indicator can be modified to include all cases with a rifampicin test result and the date of the first result showing rifampicin resistance is used, regardless

of whether the same patient was subsequently confirmed to have MDR-TB or not.

The calculation is based on all cases with DST results for isoniazid and rifampicin (susceptible or resistant) entered in the laboratory register during the six-month period of assessment. The difference in days between the two dates is calculated for all patients and divided by the number of cases with test results. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for the episodes included in the calculation. The number of episodes included in the calculation should be indicated.

Detection Indicator 1 does not relate the number of RR-/MDR-TB cases detected in a country to the number of MDR-TB cases estimated to occur based on surveillance measurements (13,14). In order to assess the impact of case detection on the actual MDR-TB burden in a country, it is useful to compare the number of RR-/MDR-TB cases detected with the expected prevalence of MDR-TB. Ratios have been used to compare detection and enrolment with the estimated MDR-TB cases that would be detected, had DST been universally provided to all pulmonary patients notified in the country (15) (calculated as indicated above).

BOX 3
Country examples

Detection of RR-TB: matching clinical and laboratory data sources

The enumeration of RR-TB and MDR-TB cases detected often requires cross-checking between different data sources. This is needed for three main reasons:

- To ensure that all laboratory-confirmed cases are accounted for.
- To link laboratory and personal data on the clinical record and thus limit repeated counting of the same individual.
- To enable a stratification of cases detected according to different risk categories envisaged in the national policy.

The table below presents an example of DST results during the period July to December 2010 in Niger. There were 24/33 (73%) cases identified as at risk for MDR-TB with DST results for isoniazid and rifampicin. Of the 24 cases identified,

Box 3 - continued

20 (83%) had MDR-TB and all of these were tested for second-line drugs. This may imply a high coverage of DST and thus representative data. However, in 2010 in Niger, there were 452 notified TB relapse cases and 215 other TB re-treatment cases (14). The statistics shown in Table 3 therefore provide information about only a selected population of patients with high levels of MDR-TB, possibly from a unit specializing in complicated TB case management.

The relatively long duration between suspicion of MDR-TB and availability of test results (between three and seven months) suggests that patients are referred after some delay and that the laboratory testing is performed at some distance from the point of care. The use of the median as a measure of the average delay, with its corresponding 25th and 75th centiles (i.e. the limits of the interquartile range), would be more meaningful, given that it is less likely to be influenced by extreme outlier values, although the arithmetic mean and the ranges are more widely understood and provide another perspective of central tendency and spread.

TABLE 3
Results for DST by risk category of patient, Niger (July to December 2010)

Risk category	Number of TB cases			
	Total	With results for isoniazid & rifampicin	Resistant to both isoniazid & rifampicin (MDR)	With MDR and tested for a fluoro-quinolone & a 2nd line injectable
Contact of MDR-TB	1	1	0	0
Failure of retreatment TB regimen	20	15	15	15
Failure of initial TB regimen	2	2	2	2
Relapses	10	6	3	3
Retreatment after loss to follow-up	0	0	0	0
TOTAL	**33**	**24**	**20**	**20**

Box 3 - continued

TABLE 4
Delay between MDR-TB presumption and DST results, Niger (July to December 2010)

Number of MDR-TB cases with information on interval	Interval between MDR suspicion and DST results (in days)		
	Mean	Minimum	Maximum
24	139	89	215

Source: Information courtesy of S Mamadou (National TB Lab, Niger), A Piubello (Fondation Damien) and A van Deun (IMT Antwerp).

The number of MDR-TB cases detected over time is often depicted as simple frequency charts.

FIGURE 6
MDR-TB cases notified in China, India and the Russian Federation (2009–2012)
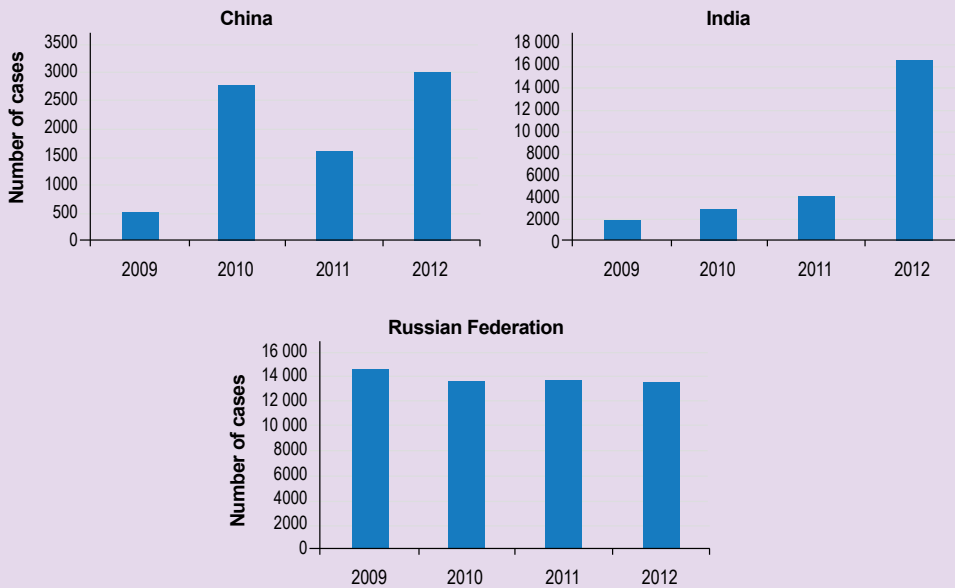
Spatial distribution of MDR-TB cases

Programme data may be used to identify patients at increased risk of MDR-TB and among whom DST should be prioritized. Spatial information on the health centre of diagnosis or the patient's residence location may improve the predictive power

Box 3 - continued

of risk analysis. The increasing availability of GPS-enabled cellular phones and other mobile devices, which can record the location of a patient's house or the site of a health encounter, now makes it possible to conduct such studies even in low-resource settings. Data on 1116 TB patients with DST results (346 with confirmed MDR-TB) 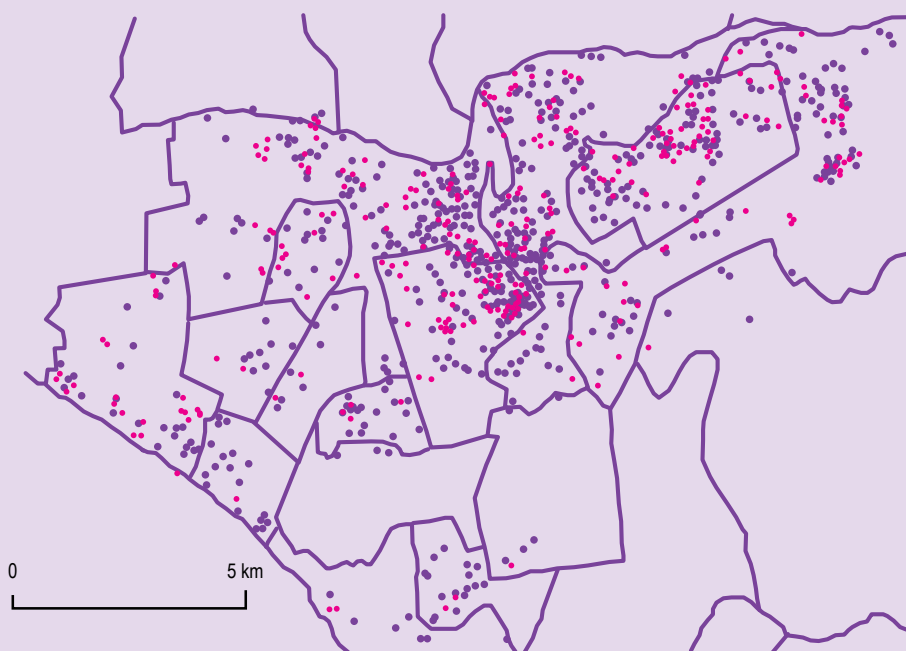in two health districts of Lima, the capital of Peru (2005–2007), were analysed for predictors of MDR-TB at the time of diagnosis (Figure 7).

FIGURE 7
Spatial distribution of drug-sensitive (purple circles) and drug-resistant (red circles) TB among patients who received drug susceptibility testing (Lima Ciudad and Lima Este, 2005–2007) (*16*)

(Note: A small random error was added to the spatial coordinates for each patient to protect confidentiality)

These results suggest that it may be useful to broaden the eligibility for DST in health centres where TB patients were more likely to have MDR-TB after adjustment for other risk factors. This has a practical application in sites where most MDR-TB cases are expected to occur among new TB cases – many of whom have no known risk factor for MDR-TB – and where resources are limited to perform DST on all new TB cases in a country or a large administrative area. The mapping of data has also been useful to generate hypotheses on the location of disease foci and allocation of resources in different settings (*6,16*).

Enrolment

Programme managers are responsible for ensuring that all patients diagnosed with RR-TB or MDR-TB are placed on appropriate treatment in the shortest time possible. This may also apply to patients at risk of RR-TB but for whom the diagnosis is not confirmed (presumptive). Detecting drug-resistance early is only beneficial if a patient is subsequently started on an adequate drug regimen.

There are four indicators recommended to assess the coverage of enrolment of TB patients on second-line TB treatment, particularly among children and females, who may not have equal access to care in certain settings. An additional stratification for HIV-positive RR-/MDR-TB patients assesses the proportion of them placed on ART. A comparison of newly enrolled-to-identified RR-/MDR-TB cases gives an indication of access to care, although patients started on treatment may have been detected prior to the period of assessment. The first three enrolment indicators can therefore be usefully expressed as a ratio of the cases eligible for treatment to those having started treatment in a given period.

These indicators should be calculated every six months, (usually for January–June and July–December), calculated three months after the end of each six-month period using data from the BMU TB register, the second-line TB treatment card and the laboratory register for culture, Xpert MTB/RIF and DST (or their electronic equivalents). Some programmes keep a separate listing of patients with MDR-TB (presumptive or confirmed) who are not on second-line TB treatment: such a list, if well maintained, can be a valuable resource for programmes to calculate needs in terms of drugs and laboratory resources and to contact patients when the required utilities are in place to guarantee that treatment can be given to them under acceptable conditions (Box 4).

Calculation

Enrolment Indicator 1[e]: RR-/MDR-TB cases (presumptive or confirmed) enrolled on MDR-TB treatment.

Definition: Number of RR-/MDR-TB cases (presumptive or confirmed) registered and started on a prescribed MDR-TB treatment regimen during the period of assessment.

Comparator: Number of RR-/MDR-TB cases (presumptive or confirmed) eligible for treatment with second-line drugs during the period of assessment.

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e.   In sites testing with Xpert MTB/RIF alone, the indicators can be modified to enumerate also RR-TB cases started on a second-line TB treatment and compare them to RR-TB cases, presumptive or confirmed.

Data source: The number of MDR-TB cases (presumptive or confirmed) is obtained from the second-line TB treatment register; the comparator data are sourced from the basic TB register and laboratory register for culture, Xpert MTB/RIF and DST. For confirmed cases the date of the DST result is used other cases are defined by the date when they are presumed to have RR-/MDR-TB (e.g. patients whose treatment has failed are classified as such when the sputum smear remains positive).

This indicator is computed for: (i) all cases; (ii) cases aged greater than 15 years of age; and (iii) females.

Enrolment Indicator 2: Confirmed RR-/MDR-TB cases enrolled on MDR-TB treatment regimen

Definition: number of confirmed MDR-TB cases registered and started on a prescribed MDR-TB treatment regimen during the period of assessment.

Comparator: number of confirmed MDR-TB cases detected during the period of assessment.

Data source: The number of confirmed MDR-TB cases on treatment is obtained from the second-line TB treatment register; the comparator data are sourced from the laboratory register for culture, Xpert MTB/RIF and DST (using the date of DST result).

This indicator is computed for: (i) all cases; (ii) cases with HIV on ART; and (iii) cases with HIV but not known to be on ART.

Enrolment Indicator 3: Confirmed XDR-TB cases enrolled on XDR-TB treatment regimen

Definition: Number of confirmed XDR-TB cases registered and started on a prescribed XDR-TB treatment regimen during the period of assessment.

Comparator: Number of confirmed XDR-TB cases detected during the period of assessment.

Data source: The number of confirmed XDR-TB cases on treatment is obtained from the second-line TB treatment register; the comparator data are sourced from the laboratory register for culture, Xpert MTB/RIF and DST (using the date of DST result).

Enrolment Indicator 4: Interval between RR-/MDR-TB diagnosis and start of MDR-TB treatment

Definition: The duration in days between the date of RR-/MDR-TB confirmation (DST results showing resistance to both isoniazid and rifampicin in the laboratory register) and the date when the patient started a prescribed second-line drug regimen, as per the second-line TB treatment register. In sites testing with Xpert MTB/RIF alone, the indicator is modified to include all confirmed RR-TB cases and the date of the first result showing rifampicin resistance is used regardless of whether the same patient was subsequently confirmed to be MDR-TB or not (i.e. the date when the patient was first found to be eligible for a MDR-TB regimen).

The calculation is based on all confirmed RR-/MDR-TB cases recorded on the second-line TB treatment register during the six-month period of assessment. The difference in days between the date of confirmation and start of treatment is summed for all patients and divided by the number of treatment episodes. The indicator is expressed as the arithmetic mean number of days with the minimum and maximum ranges for all episodes included in the calculation. If treatment was started before the confirmatory DST was reported, then the interval is marked as zero days. The number of episodes included in the calculation should be indicated.

BOX 4
Country examples

i) Comparing enrolment with detection over time

Plot the number of cases enrolled on MDR-TB treatment over time, along with the cases diagnosed with MDR-TB and other RR-TB cases during the same time period (Figure 8). This allows for a comparison of the programme's capacity to diagnose patients with its ability to treat them. For example:

FIGURE 8A
MDR-TB cases (red line) and additional rifampicin-resistant TB cases (blue line) detected compared with TB cases enrolled on MDR-TB treatment (green line), four selected countries (2009–2012)
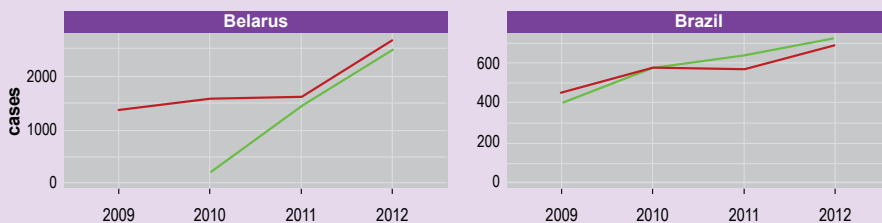
Box 4 - continued
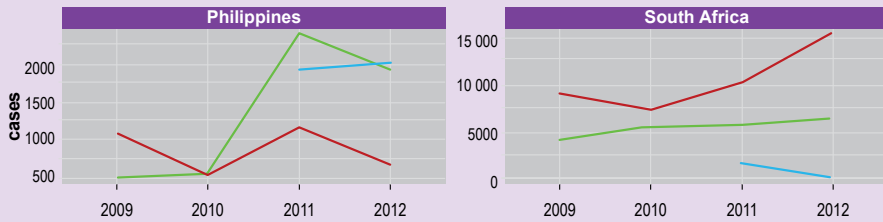
On a more practical level, if there is a large range in the numbers to be displayed on the same plot (see below), a logarithmic scale can be used, usually on the vertical axis to base ten. Moreover, a logarithmic scale also allows a visual comparison of the rates of change over time, with the gradient of the trend line representing, in this case, the mean annual percentage change in cases. If data follow a straight line using a log-scale in the vertical axis, it means that the indicator is changing exponentially (i.e. by a fixed percentage from one time period to the next).

FIGURE 8B
MDR-TB cases (red line) and additional rifampicin-resistant TB cases (blue line) detected compared with TB cases enrolled on MDR-TB treatment (green line), four selected countries (2009–2012). Vertical axis on logarithmic scale.
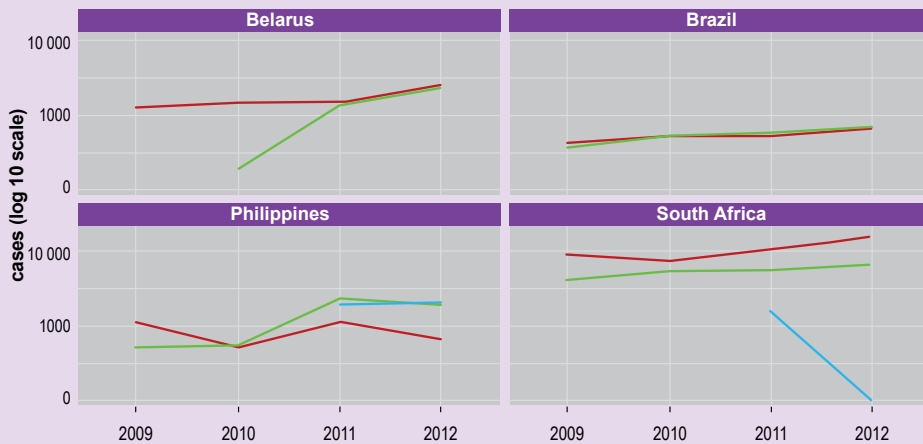
ii) Relating detection and enrolment to country estimates of MDR-TB cases

In order to assess the impact of the programme activities on caseload, the detection and enrolment indicators must also be compared with the number of MDR-TB cases that are estimated to occur in the country. For this reason, plotting the

Box 4 - continued

proportions of cases detected out of the estimated number of cases (detection ratio) against the proportion of the estimated cases that were detected (enrolment ratio) allows interpretation in terms of the share of the burden of disease (*15*). The two sets of graphs below (Figure 9) compare these two approaches by assessing these indicators for the same three countries: the first set shows the detection and enrolment as two line graphs over time, with the absolute number of cases on the vertical axis; the second compares the percentage of detected/estimated MDR-TB cases (vertical axis) to the enrolled/estimated MDR-TB cases (horizontal axis). The three coordinates are labelled with the year and a diagonal is added to depict the position that represents a 1:1 relationship in detection and enrolment. While there is improvement over time in the three countries, they differ markedly in the proportion of estimated cases that are under care.

FIGURE 9A
MDR-TB cases detected (red line) compared with TB cases enrolled on MDR-TB treatment (green line), three selected countries (2010–2012)

Box 4 - continued
FIGURE 9B
Comparison of ratios of detected cases to estimated MDR-TB (y-axis) with enrolled to estimated MDR-TB (x-axis), three selected countries (2010–2012) Diagonal represents unity in the two ratios.
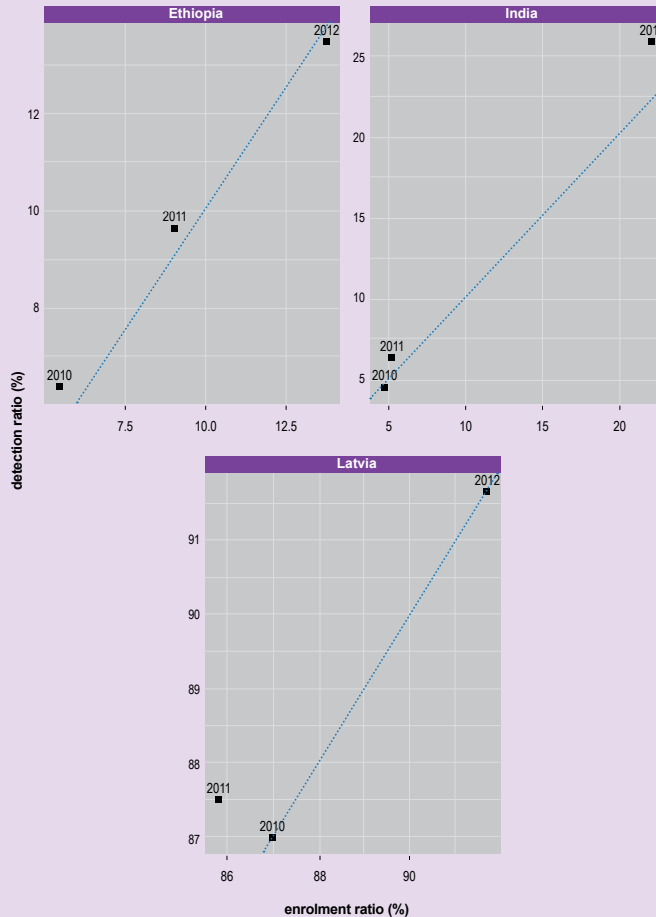
Interim treatment outcomes

Treatment for MDR-TB typically takes 20 months or more and final outcomes can therefore only be assessed two to three years after enrolment. However, an indication of how patients are responding may be needed much earlier, particularly when a drug-resistant TB treatment programme has recently started. Culture conversion to negative (for confirmed pulmonary cases) in month six and death by six months are commonly used indicators of treatment response. Information on loss to follow-up by six months is helpful. It is also useful to know how many patients started on second-line drugs for MDR-TB were

later determined not to have MDR-TB (and likewise for XDR-TB). This reflects the effectiveness of the treatment algorithm in treating patients who require second-line regimens and avoids a potentially toxic regimen in other patients who do not need them.

The period of assessment is for three calendar months (one quarter), usually counted from: (i) January–March; (ii) April–June; (iii) July–September; and (iv) October–December. All patients registered and starting treatment during the period of assessment are included in the calculation. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases that have started treatment are counted in the reporting of interim outcomes. When calculating the proportion of cases with negative culture by six months, all patients started on treatment remain in the denominator, including patients who died or were lost to follow-up before six months. An outcome is assigned according to one which is first met: for instance if a patient is lost to follow-up and dies by six months, the case is classified as 'lost to follow-up'.

Indicators are measured nine months after the end of the quarter of assessment. This gives sufficient time for culture results at month six to be issued and retrieved. All data can be extracted from the second-line TB treatment register.

Calculation

Interim Results Indicator 1[f]: RR-/MDR-TB cases on MDR-TB treatment regimen with negative culture by six months

Numerator: Number of confirmed pulmonary RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment with negative results for culture in month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim Results Indicator 2: RR-/MDR-TB cases on MDR-TB treatment regimen who died by six months

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who died of any cause by the end of month six of their treatment.

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f.   In sites testing with Xpert MTB/RIF alone, the indicators enumerate also RR-TB cases started on a second-line MDR-TB treatment who are assigned an interim result, or, in the case of Interim Results Indicator 4, were prescribed a second-line MDR-TB treatment regimen that was not warranted.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

Interim Results Indicator 3: RR-/MDR-TB cases on MDR-TB treatment regimen who were lost to follow-up by six months

Numerator: Number of confirmed RR-/MDR-TB cases registered and started on a prescribed MDR-TB treatment who were lost to follow-up by the end of month six of their treatment.

Denominator: Number of confirmed RR-/MDR-TB cases registered and started on treatment for MDR-TB during the period of assessment.

The first indicator applies only to pulmonary cases. The denominator for all indicators is all cases started on treatment, including XDR-TB cases started on prescribed treatment with second-line drugs.

Interim Results Indicator 4: Patients on MDR-TB treatment regimen found not to have RR-/MDR-TB

Definition: Number of patients started on a prescribed MDR-TB treatment regimen during the period of assessment and later found not to be RR-/MDR-TB.

Interim Results Indicator 5: Patients on XDR-TB treatment regimen found not to have XDR-TB

Definition: Number of patients started on a prescribed XDR-TB treatment regimen during the period of assessment and later found not to be XDR-TB.

In addition to these standard indicators, time-to-event statistics can be employed in TB studies to compare time needed from start of treatment until the advent of a particular endpoint, such as death or bacteriological conversion. Kaplan-Meier survival curves depicting the trend among different sub-groups of TB patients are useful to summarize these patterns in both trials but also among patients treated under programme conditions (*17, 18*).

Final treatment outcomes

The final outcome of treatment is the most important direct measurement of the effectiveness of an MDR-TB control programme. All confirmed MDR-TB patients entered on the

treatment register should be assigned one of six mutually exclusive outcomes at the end of their therapy (see below). Cases not evaluated due to transferring out, treatment not completed at the time of final assessment or missing information, are grouped together. A patient who 'transfers in' is not enumerated in the cohort of the receiving treatment centre but only in the outcome cohort of the centre where treatment was started. All patients should be assigned the first outcome they experience for the treatment being evaluated. If a case is assigned an outcome of 'treatment failed' and the patient is restarted on a revised regimen within the same year of the cohort, for the purposes of cohort monitoring the case is not re-registered for another outcome.

The same applies to patients lost to follow-up, who re-start treatment in the same year after an interruption of two months or more.[g] The outcome 'cured' is restricted to pulmonary cases. The period of assessment is in 12 calendar months, usually counted from January to December, and referred to as an annual cohort. All patients registered and starting treatment during this period are included in the calculation. In sites testing with Xpert MTB/RIF alone, the indicators need to be modified to include also RR-TB cases started on a full MDR-TB treatment regimen. Only laboratory confirmed RR-TB, MDR-TB and XDR-TB cases are counted for cohort reporting of final outcomes.

Indicators are measured 24 months after the end of the year of assessment. This gives sufficient time for most patients to complete their treatment and for the final culture results to be issued and recorded. All data can be extracted from the second-line TB treatment register. Box 5 depicts a series of country examples of how these indicators can be used to monitor treatment programme performance and to usefully interpret associations.

Calculation

Outcome Indicators 1–6: RR-/MDR-TB cases on MDR-TB treatment regimen with an outcome

1. Cured
2. Treatment completed
3. Treatment failed
4. Died
5. Lost to follow-up
6. Not evaluated for outcome

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g. As a result, the outcomes as assessed in this manner may be conservative given that a proportion of patients who re-start a new regimen after a treatment failure or loss to follow-up would ultimately be cured. A more factual assessment of long-term outcomes would be possible if a patient-based register, preferably in electronic format, is maintained to record events following the first outcome met, including relapses.

Numerator: Number of confirmed RR-/MDR-TB cases registered for MDR-TB treatment during the period of assessment assigned one of the six outcomes.

Denominator: Number of confirmed RR-/MDR-TB cases registered for treatment and starting a prescribed MDR-TB treatment regimen during the period of assessment.

This indicator is expressed as the percentage of people in each of the mutually exclusive outcomes. Programmes that have the capacity to differentiate XDR-TB from other MDR-TB cases, particularly those where XDR-TB cases represent >5% of MDR-TB, should report outcomes for non-XDR MDR-TB (including other RR-TB) and XDR-TB cases separately. MDR-TB patients found to have XDR-TB – at any time in the course of their second-line TB treatment – would be removed from the non-XDR MDR-TB cohort and enumerated in the XDR-TB treatment cohort.

Outcome indicators in HIV-infected patients should be computed separately for cases with positive HIV status in countries where HIV prevalence is ≥1% in pregnant women or ≥5% in TB patients (*2*,*19*).

BOX 5
Country examples

i) Comparing treatment outcomes between different units
Given that the outcome indicators are predicated on six standard, mutually exclusive categories, they can be represented as proportional charts for the patient cohort. Stacked bars with 100% y-axis are a frequent way of depicting them and easier to compare between units and over time than with pie-charts. The example below (Figure 10) contrasts the outcomes in two separate groups of patients in Romania. Often, as in this example, the cured and completed categories are collapsed into one (treatment success).

ii) Improving treatment success over time
It is expected that the success of DR-TB projects improves over time as staff become more experienced in running programmes. The completeness of information on patient outcomes within a cohort is important in order to draw meaningful conclusions about the likelihood of success or the risk of death among patients. At times, the improved recovery of data itself increases the proportion of success, as shown in this example from routine reporting to WHO of outcome data from Peru (Figure 11).

Box 5 - continued

FIGURE 10

Treatment outcomes for 840 MDR-TB patients registered for treatment in 2007 in Green Light Committee (GLC; left bar) and non-GLC (right bar) settings, Romania
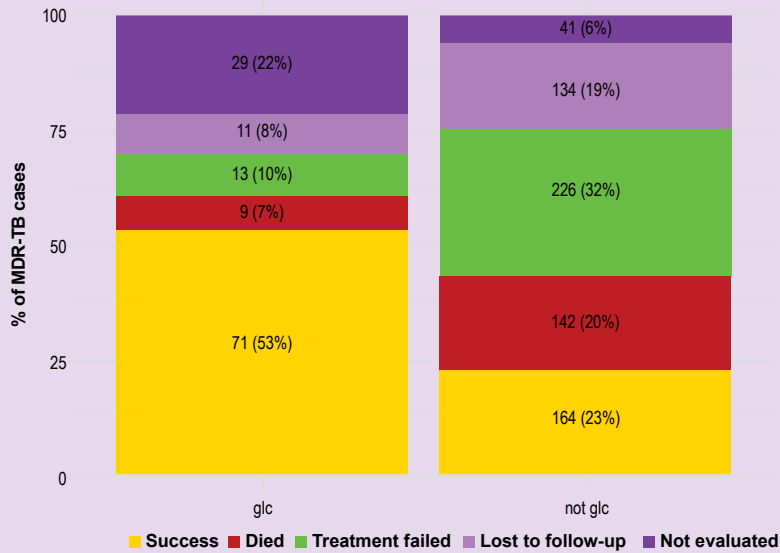
FIGURE 11

Treatment outcomes for MDR-TB cohorts starting treatment between 2007 and 2010, Peru (as reported to WHO).
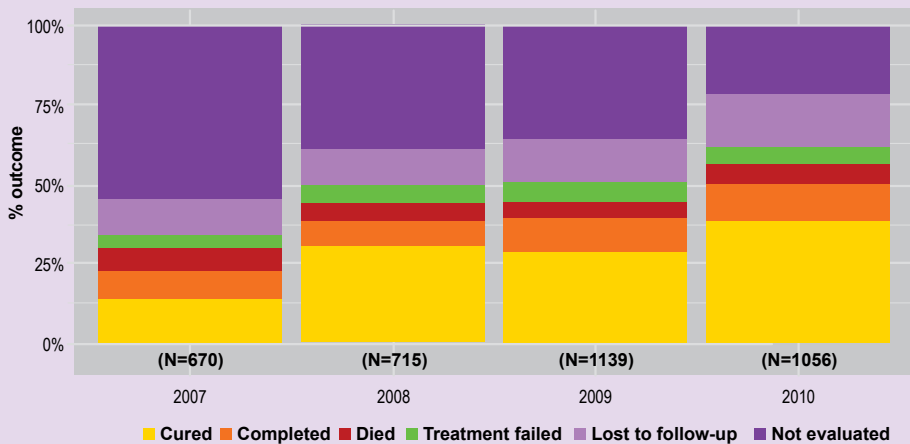
In addition to improvements in the completeness of data, other time trends in the treatment outcomes are important for managers to assess, such as:

- The proportion of treatment success that is bacteriologically ascertained (i.e. cured). If this is low, it may indicate that monitoring with culture is rare or that the data on results are not recovered from the laboratories. This proportion should not decrease over time.

Box 5 - continued

- Very high levels of success may at times point to certain problems in monitoring. For instance, patients whose treatment fails may be misclassified as 'completed' because of insufficient information on bacteriological status.

- The proportion of deaths may be high where HIV and other comorbidities are frequent. This can also reflect delays in the start of treatment and the presence of advanced disease. One of the project objectives is to try to minimize this.

- The proportion of cases lost to follow-up is a key managerial indicator and all efforts should be made to improve patient adherence and reduce losses.

- The proportion of cases with treatment failure is another key managerial indicator. In regions or patient groups with advanced patterns of resistance it is expected that treatment failures will be more common, indicating that the treatment regimens may need to be revised or that other patient-related factors predisposing to failure should be addressed.
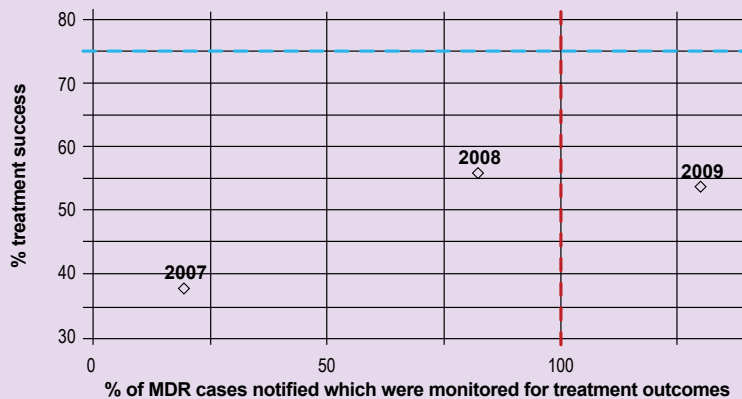
iii) Impact of MDR-TB treatment success on the MDR-TB caseload

FIGURE 12
Relationship between the percentage of MDR cases notified that were monitored for outcome (excluding unevaluated cases) and percentage success in MDR–TB cohorts, Georgia (2007 to 2009)

blue line (horizontal dotted) = threshold 75% success for MDR–TB cohorts by 2015 (Global Plan to Stop TB 2011–2015); red line (vertical dotted) = 100% treatment outcome reporting (excluding unevaluated cases in the cohort). Incomplete or delayed reporting of MDR–TB may cause the percentage of cases monitored for outcome to exceed 100% (data as reported to WHO).

If an MDR-TB treatment programme is to have an impact on the MDR-TB burden in a country, it must combine high treatment success with high coverage of patients. If either of these is low, the public health effect may be diminished.

Box 5 - continued

In the example from Georgia above (Figure 12), both success ratio and coverage increased between 2007 and 2008. In 2009, the success ratio was maintained while the coverage appears to have exceeded 100%. This can occur if patients enrolled on treatment were notified in a previous year or if cases are under-reported by the laboratory sector, with no linkage between the systems enumerating notifications and patient outcomes. The number of MDR-TB cases estimated to exist in the country should be viewed in this context. For instance, in Georgia, the cases included in the treatment cohort in 2009 represented about two thirds of the MDR-TB cases estimated to occur among pulmonary TB cases notified by the country that year.[h]

iv) Comparing the likelihood of death between different sub-groups of TB patients: discrete and continuous data

The magnitude of a relationship between a risk factor and an event (e.g. death) may be quantified using simple statistical tests. 'Two by two' tables may be used to perform Chi squared tests and generate crude relative risk estimates. For instance, the example from Brazil (Table 5) reflects the fact that treatment options are more compromised when resistance patterns are broader, and thus patients with XDR-TB generally have poorer outcomes than other MDR-TB cases (*20*).

TABLE 5
Odds ratio for death among the XDR-TB compared to MDR-TB cohort, Brazil (2010 cohorts)

	Death		Total
	Yes	No	
XDR-TB	7	18	25
MDR-TB	50	473	523
Total	57	491	548

Odds ratio: 3.68 (95% confidence limits, 1.47-9.24), P<0.05

If, in contrast to the example above, the data for the risk factor are of a continuous type (e.g. age, body-weight, interval between detection and start of treatment), other statistics can be used. In the example below of 436 MDR-TB patients started on treatment in one region of Belarus (2009–2010) (Table 6), the small difference in age at the start of treatment did not appear to be independently associated with death in a statistically significant manner.

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h.   Note: when such coverage is calculated, any unevaluated cases in the cohort need to be subtracted from the numerator.

Box 5 - continued
TABLE 6
Association between age and death among MDR-TB patients started on treatment between 2009 and 2010, Belarus.

Died	N	Mean age (y)	SD (y)	Median age (y)	25% centile	75% centile
No	284	44.1	12.7	43.8	34.9	52.6
Yes	152	45.0	10.7	46.0	37.3	52.0

(Welch two-sample t-test ; t = -0.7869, df = 357.584, p-value = 0.4319)

These analyses may be improved by considering more than one risk factor simultaneously in a regression equation (see section vii below).

v) Reducing MDR-TB burden by strengthening the performance of first-line treatment programmes

In addition to MDR-TB treatment programmes (iii above), basic programmes for drug-susceptible TB need to perform well so that less drug resistance is generated. The example from the United States below (Figure 13) illustrates the inverse relationship between increasing success rates and the number of MDR-TB cases that diminished sharply after the mid-1990s.

A linear regression of the number of MDR-TB cases by the total success ratio (Figure 14) shows a strong, inverse relationship, and this can also be visualized by plotting the number of MDR-TB cases against the treatment success ratio. This shows that a linear relationship exists and that the variation in the number of MDR cases strongly correlates with the treatment success ratio.

FIGURE 13
MDR-TB case reports (red circles, left) and % total TB treatment success (blue triangles, right), United States, (1994 to 2008)
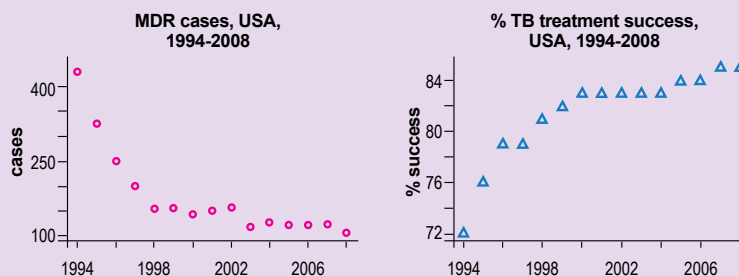
FIGURE 14
Relationship between treatment success ratio for all TB cases (%) and number of MDR–TB cases, United States, (1994 to 2008)
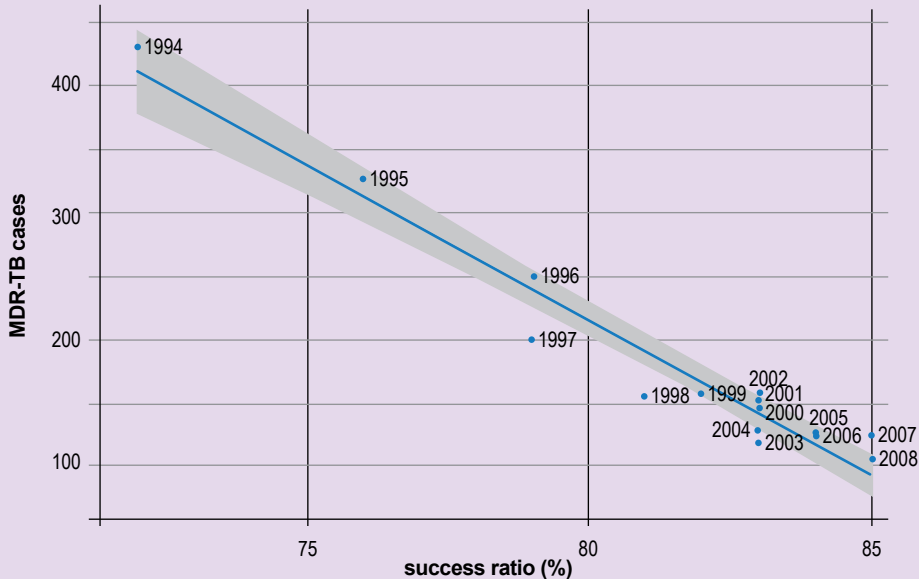
vi) Adverse events in MDR-TB: applying cohort analysis to pharmacovigilance

In contrast to the standard six-month therapy for drug-susceptible TB, MDR-TB regimens usually require 20 months or more of treatment with four second-line drugs. These regimens often lead to interactions and adverse drug reactions, ranging from mild to life threatening, and can require interruptions of treatment. This may predispose to the selection of resistant strains in patients, and thereby increase the risk of treatment failure and death. The ongoing expansion of treatment programmes worldwide increases the chances of these adversities and raises the need for proper surveillance of harm along with the scaling up of treatment efforts.

The introduction of new drugs for MDR-TB treatment that have not completed Phase 3 trials, starting with bedaquiline in 2012, makes this even more important. Guidance on the organization of spontaneous and active forms of pharmacovigilance have been produced by WHO in 2012 (7). The document also provides instructions on the interpretation of signals and causality associations. While the reporting of harms does not form part of the minimum indicators for MDR-TB programmes, the collection of additional patient data on type of

Box 5 - continued

adverse events, severity, onset dates and sequelae – together with the more standard data elements on demographics, previous history of treatment, site of disease, bacteriological endpoints and treatment outcomes – is important in quantifying drug-induced adverse effects and identifying risk factors.

Table 7 shows a good example of how such an analysis may be conducted to identify predictors of adverse events (quantified in terms of numbers using nominal regression in this case) (*21*). The same reference provides other descriptive methods that can be used to summarize the adverse experiences of the cohort. Such an analysis could help focus efforts towards addressing the patient or programmatic determinants that are associated with adverse events and thus improve the quality of care.

TABLE 7
Adjusted associations between demographic and clinical characteristics and number of different adverse events experienced per case during MDR-TB treatment (n=1015)*

Characteristic	1–3 vs. 0 events aOR (95%CI)[†]	≥4 vs. 0 events aOR (95%CI)[†]
Age in years at diagnosis	1.02 (1.0–1.04)	1.06 (1.04–1.07)
Sex		
Male	—	—
Female	1.94 (1.24–3.06)	3.61 (2.26–5.76)
TB symptoms at diagnosis		
<3 symptoms	—	—
≥3 symptoms	1.11 (0.79–1.55)	1.54 (1.07–2.20)
Bilateral pulmonary cavitations		
No	—	—
Yes	1.19 (0.77–1.85)	1.84 (1.18–2.89)
Number of days on treatment		
≤366	—	—
367–550	1.64 (1.05–2.58)	1.63 (1.00–2.68)
551–642	1.64 (1.04–2.58)	1.80 (1.10–2.96)
≥643	1.99 (1.22–3.23)	2.88 (1.73–4.80)

*The total *n* in this analysis is slightly less than the total number of cases because observations with missing information were eliminated from multivariate analysis.
[†]aORs and CIs are for the association between patient characteristics and experiencing one to three adverse events compared to none in the first column and four or more adverse events compared to none in the second column using nominal logistic regression.
MDR-TB = multidrug-resistant tuberculosis; aOR = adjusted odds ratio; CI = confidence interval; SD = standard deviation.

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Box 5 - continued

vii) Determinants of outcome among MDR-TB patients on treatment

More advanced analysis – to test hypotheses and quantify the influence of a risk or an intervention on a given effect – may be undertaken using surveillance data. These analyses require data to be available at the individual case level, as found in the treatment registers. The data should be first assessed to ensure they are complete, free of errors and updated.

When the data for all TB patients on treatment are analysed for the determinants of outcome, infection with drug-resistant strains is commonly found to be associated with failure or death regardless of setting. In some countries, the caseload of patients with DR-TB is large enough to permit separate analysis for MDR-TB cases. In the example shown below from Peru (Table 8) (*22*), analysis permitted a study of which associations between the composition of a drug regimen and risk of death were statistically significant. In this case, the hazard ratio was used to express the instantaneous risk of dying over the duration of patient observation (i.e. in contrast to the odds ratio used in the previous example which captures the cumulative risk for MDR-TB associated with the variables studied).

TABLE 8
Multivariable analysis of aggressive regimen and time to death, Peru (1999 to 2002) (n=699)

Variable	Hazard ratio, multivariable analysis	95% CI, multivariable analysis
Monthly exposure to aggressive regimen	0.63	0.43, 0.93
Received ≤2 previous regimens without CER	0.43	0.25, 0.74
Female	1.45	1.02, 2.07
Age	1.01	1.00, 1.03
Low BMI or malnutrition	2.45	1.63, 3.68
Tachycardia	2.19	1.50, 3.19
Extrapulmonary TB	1.68	1.05, 2.68
At least one comorbidity, other than HIV	1.71	1.21, 2.43
HIV infection	2.72	1.03, 7.24
Number of resistant agents	1.03	0.92, 1.15

doi:10.1371/journal.pone.0058664.t004

Aggressive regimen = at least five likely effective drugs, including an injectable drug for at least six months post-conversion and a fluoroquinolone; CER= standardized regimen used to treat MDR in Peru initially (containing Kanamycin-Ciprofloxacin-Pyrazinamide-Ethambutol-Ethionamide); BMI = body mass index; CI = confidence interval.

5.4 Conclusion

This chapter should provide the reader with a better understanding of the approaches to describe data on DR-TB, to analyse DR-TB surveys, to generate the main indicators for programme performance on MDR-TB care, and to perform some additional analyses to test hypotheses (e.g. risk factors for drug resistance or for particular outcomes).

To acquire advanced proficiency in the design and analysis of surveys, or to know which statistical tests are the most appropriate to answer a given question, reference to more specialist texts and the assistance of experts in survey methodology and biostatistics is recommended.

Readers are also encouraged to become more conversant in data analysis software, some of which are free to download and use, such as the one used to produce most of the graphics in this chapter (*23*).

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Chapter 6
HIV-associated TB: analysis of burden and response

Audience:

General readers, in particular, monitoring and evaluation officers in national TB programmes (NTP), and national programme managers.

Expected outcomes:

An increased awareness of how to:

- implement various analyses of HIV-associated TB surveillance data;
- assess the burden of HIV-associated TB;
- address data quality;
- understand the meaning of 'representativeness'.

Author:

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6.1 Introduction to HIV-associated TB

WHO estimates that of the 8.7 million new TB cases occurring in 2012, 1.1 million (13%) were in people also living with the human immunodeficiency virus (HIV). Infection with HIV greatly increases the risk of progressing to active TB disease. On average, the incidence of TB in HIV-infected people is approximately 30 times the incidence of that in people not infected with HIV and living in similar settings.

TB is the most common presenting illness among people living with HIV, including those who are taking antiretroviral therapy (ART). Around 75% of dually-infected people live in sub-Saharan Africa. TB is the leading cause of death among people with HIV, accounting for one in five HIV-related deaths. In 2012, an estimated 320 000 people died of HIV-associated TB.

There are several reasons for monitoring the number of newly detected TB cases, particularly in high HIV prevalence settings. Firstly, it provides a benchmark for ART needs. All detected TB/HIV cases should begin taking ART during the first eight weeks of TB treatment (*1*). Secondly, it gives information on the gap between detection and expected numbers of HIV-positive cases among reported TB cases. Thirdly, when collected at different points in time, it provides information on trends in the burden of TB/HIV coinfection, when combined with other information, such as HIV testing coverage among newly detected TB patients.

6.2 Analysis of programme data

The routine analysis of TB/HIV data should provide information on the strength of implementation of collaborative TB/HIV activities (*2*) and on the burden of TB/HIV and its time trends (*3*). This section will focus on the following particularly important aspects: The number of patients detected with HIV-associated TB over time, allowing comparisons with expected numbers; the number of detected patients receiving ART during the course of TB treatment (ART is a very important life-saving treatment and all TB patients infected with HIV should begin taking ART within eight weeks of initiating TB treatment); the outcome of TB care; data quality.

HIV/TB detection

Typically, national HIV care programmes maintain registers of people diagnosed with HIV infection and enrolled in care at the health facility level, including some information about their TB status. National TB programmes also maintain registers of TB patients,

including some information about their HIV status. The association of HIV infection and TB disease can be detected through the HIV care cascade when HIV-positive people are confirmed to have TB. The association may also be detected through the TB care cascade when newly diagnosed TB cases are tested for HIV at the time of TB diagnosis or during the course of TB treatment.

Ideally, the number of HIV-positive TB cases reported through HIV surveillance systems should match the number of HIV-positive cases reported through TB surveillance systems. In reality, the numbers seldom match as a result of miscommunication between the teams managing each of the disease information systems, and also due to misinterpretation of the indicators, and limitations in both information systems. However, if HIV and TB information systems are case-based (Chapter 2) and use unique national identifiers, then record linkage would allow an improved matching of records corresponding to patients with TB and HIV infection. Also, integrated TB and HIV services may maintain joint, interlinked information systems that effectively share information about the two diseases.

Figure 1 shows the number of detected and reported HIV-positive TB cases in Cambodia over time.

FIGURE 1
Number of HIV-positive TB cases detected and notified in Cambodia (2002 to 2012). *Source*: **WHO global TB database, 2013**
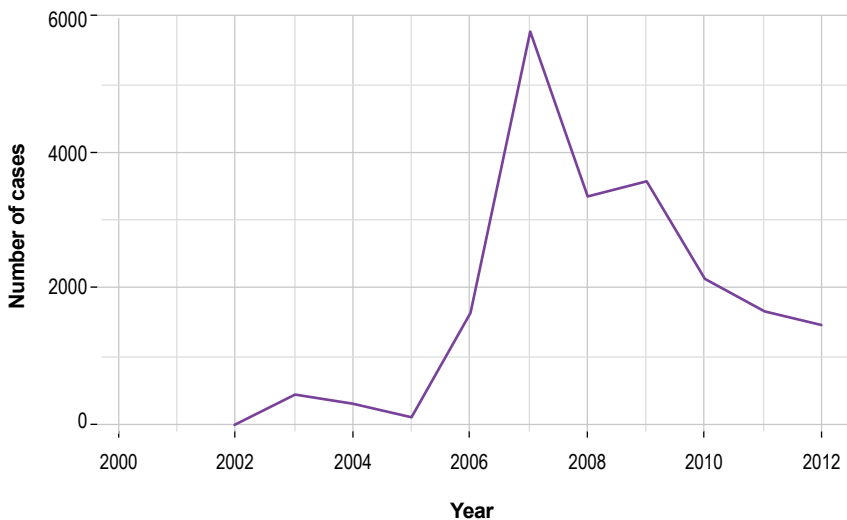
Before 2002, there was no systematic reporting of HIV test results among newly detected TB patients.

This data can be interpreted as follows:

The number of detected and reported HIV-positive TB cases remained very low between 2002 and 2005, then peaked at nearly 6000 in 2007, followed by a steady decline.

The rise in coinfected cases during the period 2005–2007 could be due to changes in the epidemiology of TB, improvements in either case detection or simply increased reporting and notification of detected cases. For example, improvement could come from any one of the following: Better coverage of HIV test result reporting in notified TB cases; increased coverage of HIV testing; increased coverage of TB screening and testing among people living with HIV; increased burden of HIV among TB patients.

Similarly, the decline after 2007 could be due to: decreased reporting of HIV test results; decreased coverage of HIV testing; decreased coverage of TB screening and testing among people living with HIV; decreased burden of HIV among TB patients.

It is also important to understand the total number of TB cases that were tested for HIV. If the number of TB cases tested for HIV in a given year was very low, for example, then the proportion of cases found with HIV among those tested could vary from year to year due to chance fluctuations.

Also, when relatively few patients are tested for HIV out of a large number of TB patients, it is possible they were not chosen at random. Some patients may have been systematically prioritized for testing, for example if their physician felt they were sicker than others. When interpreting time trends of the prevalence of HIV among tested individuals, it is very important to consider whether the population that was tested was systematically different to the population that was not tested. Figure 2 shows a time series of new TB cases with a documented HIV test result available at time of TB diagnosis, or during the course of TB treatment.

 The number of tested TB cases increased very rapidly between 2006 and 2010 and then reached a plateau.

If we divide the first indicator by the number of tested TB cases, we obtain the prevalence of HIV among tested TB cases, which is plotted below (Figure 3).

FIGURE 2
Number of TB cases tested for HIV in Cambodia (2003 to 2012)
Source: WHO global TB database, 2013
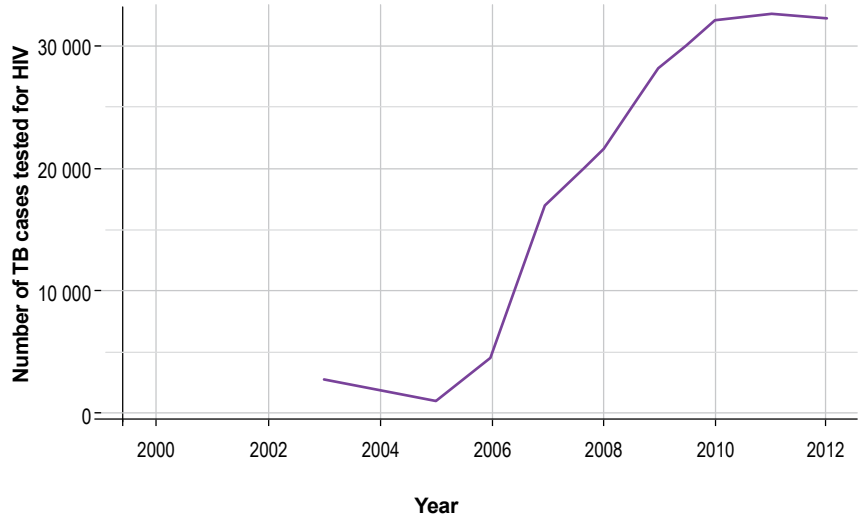
FIGURE 3
HIV prevalence among tested TB cases in Cambodia (2003 to 2012)
Source: WHO global TB database, 2013
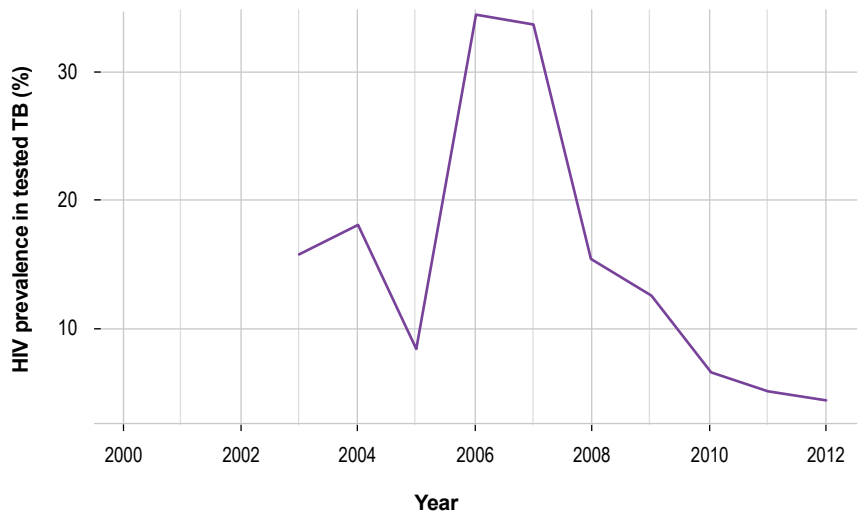
The coverage of HIV testing is an important factor in interpreting these figures. If the coverage is less than 100% of TB cases and tested individuals are not selected at random, then the prevalence of HIV in tested individuals could be different from the prevalence of HIV in untested individuals. Figure 4 shows the coverage of HIV testing among TB patients, expressed as a percentage of total TB cases reported.

FIGURE 4
HIV testing coverage among TB cases in Cambodia (2003 to 2012)
Source: WHO global TB database, 2013
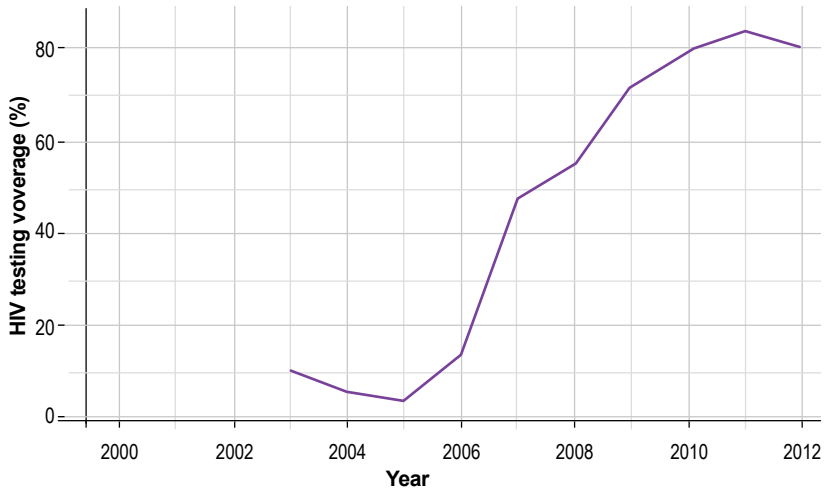
HIV testing coverage was less than 20% until 2006 and then gradually increased to around 80% in 2010–2012. Since 2010, the coverage of testing was high and therefore, we can have more confidence about the information provided by routine testing in terms of HIV prevalence among TB cases. This is because the tested population is likely to be statistically representative of the total population of TB patients. But prior to 2010, the quality of the information was lower. When testing coverage was lower than 80%, differences in HIV prevalence between tested and untested individuals could have a large impact on the result, and on the difference between the measured prevalence of HIV and the true prevalence of HIV among detected TB cases.

It is important to know the prevalence of HIV among TB patients in order to direct resources and provide optimal care to patients. Any predictions based on routine testing results with incomplete coverage are likely to be incorrect due to patient selection bias, as explained above.

It is possible to obtain an unbiased estimate of the prevalence of HIV among detected TB cases. This can be achieved by testing every newly detected TB case. However, if resources are scarce and logistics insurmountable, it may be preferable to conduct a survey and *randomly select*[a] a sample of new TB cases (e.g. 1000 cases in the country) and test those cases for HIV. If the sample selected is truly random, then the survey result would

a. Individuals randomly selected from a larger population have the same probability of being selected. Simple random sampling, which requires a complete national list of all TB patients, is the most basic type of unbiased sampling of TB patients. Simple random sampling can be a component of a more complex random selection design. For instance, when a complete list of TB patients is not available at the national level but a list of TB clinics is available, then TB clinics may be randomly selected. Within clinics, lists of patients can be compiled for patients to be randomly selected (Smith PG and Morrow RH. *Field trials of health interventions in developing countries: a toolbox*. Macmillan Education 2005. ISBN 0 333 64058 6.

theoretically be unbiased. The survey estimate of HIV prevalence could still differ from the true value among all TB cases, but if the survey is repeated a large number of times under similar conditions, on average the survey estimate would match the true value. Cambodia completed a survey in 2003 and then again in 2005 (4). Table 1, reproduced from the survey findings, shows that HIV prevalence in people with TB was not as high as suggested by the routine testing data shown above.

As can be observed from the survey results, the two surveys also allowed a comparison of HIV prevalence rates among TB cases and between different sub-population groups. It can be observed that HIV prevalence was highest in the 25–44 year-old age group in both surveys. This type of finding allows programmes to prioritize routine HIV testing to populations most in need, particularly in conditions of scarce resources.

In 2008 and 2009, two more nationally representative surveys of HIV in TB cases were conducted, showing a prevalence rate of 6.4% and 6.3%, respectively. The survey results were then much lower than results obtained from two rounds of routine testing (15% and 13%, respectively), suggesting that the HIV prevalence among routinely tested TB cases was higher than the true value. Often, when freely available HIV tests are scarce, doctors tend to reserve them for patients who are very sick or who they believe are the most likely to have acquired HIV infection. As a result, the proportion of HIV-positive cases in the sub-set of tested cases may be higher than in all TB cases. Figure 5 shows time trends in HIV prevalence among routinely tested TB patients, and also shows the underlying TB population HIV prevalence as determined from four consecutive national representative surveys.

FIGURE 5
HIV prevalence among tested TB cases in Cambodia (solid line) and as determined from consecutive national representative surveys (X symbol in red) (2002 to 2012). *Source*: WHO global TB database, 2013
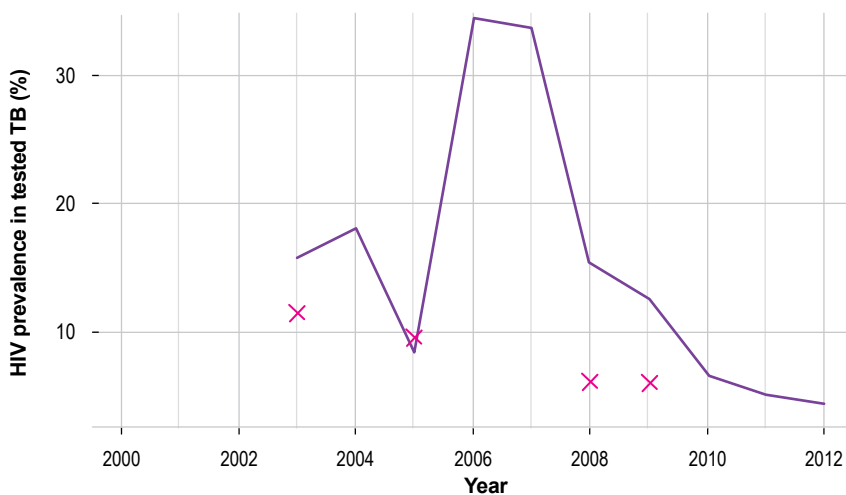
TABLE 1
HIV seroprevalence among TB patients in Cambodia, 2003 and 2005 surveys (*4*)

	2003		2005	
	HIV-pos (%)	95% CI*	HIV-pos (%)	95% CI*
All TB tested	11.8	10.5 – 13.2	9.9	8.8 – 11.1
Males	13.5	11.7 – 15.6	10	8.4 – 11.6
Females	9.9	8.2 – 11.9	9.8	8.2 – 11.5
Age group				
0-14	15	7.1 – 26.6	7.7	0.4 – 14.9
15-24	9.7	6.1 – 14.5	6.2	3.1 – 9.3
25-34	27.2	22.6 – 32.2	24.8	20.6 – 28.9
35-44	16.9	13.8 – 20.5	17.5	14.5 – 20.6
45-54	5.7	3.8 – 8.4	5.2	3.3 – 7.2
55-64	4.7	2.9 – 7.4	1.7	0.5 – 2.9
65+	4.3	2.2 – 7.4	0.5	0 – 1.3

* 95% Confidence interval (CI). The significance of the 95% CI is the following: If the survey had been repeated a large number of times and the 95% confidence interval was calculated each time, then the true value of prevalence would be found within 95% of the confidence intervals. Since each survey was done only once, it cannot be known if the true value was really within the interval.

The care cascade

The HIV treatment cascade is a system to monitor the number of individuals living with HIV who are actually receiving medical care and the treatment they need. It was developed to recognize the various steps necessary for everyone who needs HIV care to remain engaged in it – from an initial stage of getting tested for HIV to being able to suppress the virus through treatment.

The HIV treatment cascade provides a way to examine critical questions, including:

- How many individuals living with HIV are getting tested and diagnosed?
- Of those, how many are linked to medical care?
- Of those, how many are retained in care?
- Of those, how many receive ART?
- Of those, how many are able to adhere to their treatment plan and achieve viral suppression?

By closely examining these separate steps, policy-makers and service providers are able to pinpoint where gaps may exist in connecting individuals living with HIV to sustained, quality care. Knowing where the drop-offs are most pronounced, and for what popula-

tions, helps national, state and local policy-makers and service providers to implement system improvements and service enhancements that better support individuals as they move from one step in the care continuum to the next. Figure 6 provides an example of the HIV care cascade in the United States (*5*) and illustrates the key points of drop out for patients undergoing treatment.

FIGURE 6
The HIV care cascade in the United States (2010)

Out of the more than one million Americans with HIV:

82%

902 000 know they are infected

86%

726 000 were linked to HIV care

37%

407 000 have stayed in HIV care

33%

363 000 are receiving treatment

25%

275 000

have a very low amount of virus in their body
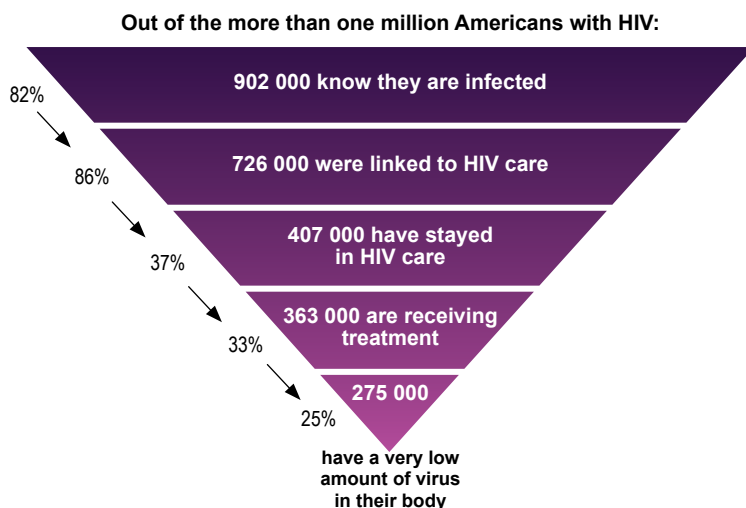
The WHO-recommended TB/HIV response (*2*), includes, from a TB diagnosis entry point:
- early testing of newly diagnosed TB patients for HIV infection;
- treatment of HIV+ TB patients with cotrimoxazole;
- treatment of HIV+ TB patients with ART within eight weeks of TB treatment initiation (within two weeks in severe HIV cases).

And from an HIV diagnosis entry point:
- systematic screening for symptoms leading to TB investigation, diagnosis with Xpert MTB/RIF and corresponding treatment, as necessary;
- isoniazid preventive therapy for patients in whom active TB was ruled out.

From a health facility management point of view:
- infection control to prevent transmission of TB.

Figure 7 shows the TB/HIV care cascade in Viet Nam as of 2012, with shortcomings highlighted in red: a quarter of newly registered TB patients were not tested for HIV and more than half of cases identified with HIV infection did not receive ART.

FIGURE 7
TB/HIV care cascade in Viet Nam (2012)
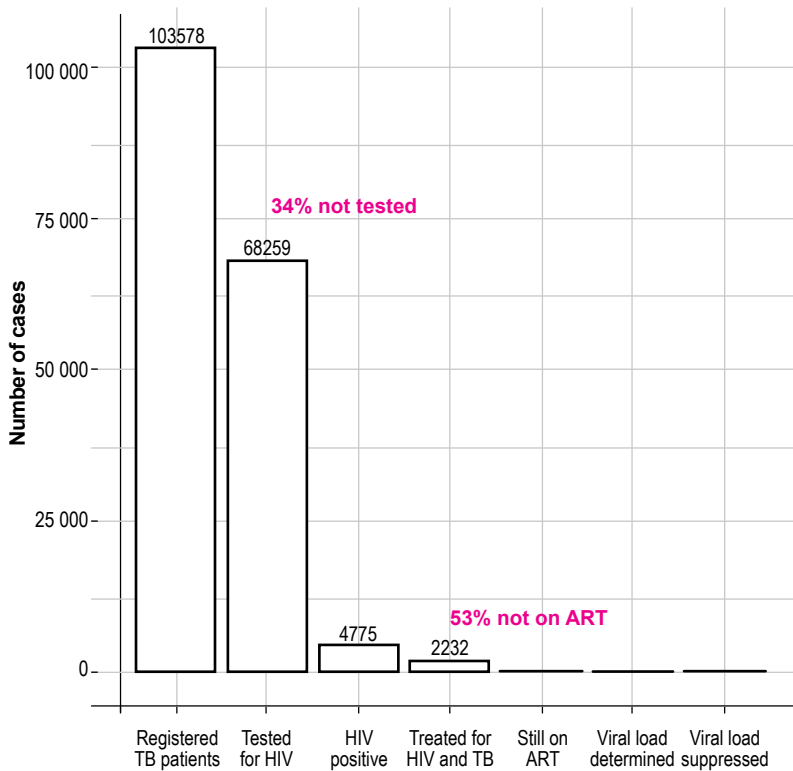
The TB/HIV care cascade may also be examined from the HIV diagnostic entry point as all newly diagnosed HIV-positive patients should be screened for TB symptoms, then investigated for TB in case of symptoms and treated for TB and HIV where TB is confirmed.

The following diagram (Figure 8) shows the TB/HIV care cascade in South Africa (6) in 2011, showing that one third of eligible TB patients did not initiate ART (in 2011, eligibility criteria for ART in TB patients in South Africa included a CD4 count >200 cells/μl, but this criterion is now no longer relevant globally: all TB patients should begin taking ART within eight weeks of TB treatment (1,2) regardless of CD4 count). Examination of the TB/HIV care cascade should prompt corrective action to ensure adequate provision of care to all patients.

FIGURE 8
TB/HIV care cascade in a clinic in South Africa (2011)
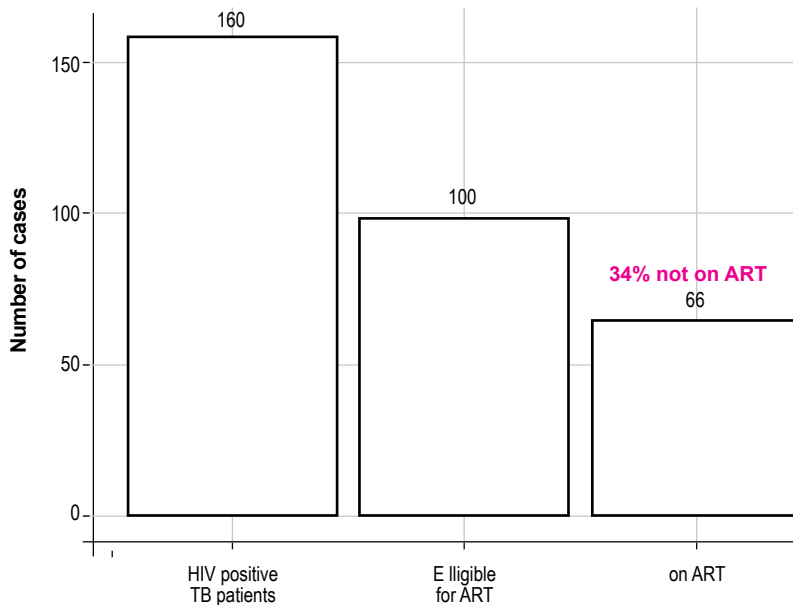
Cohort analysis of treatment outcomes

A traditional approach to documenting the performance of TB treatment and care (including patient support) is through the analysis of HIV-positive TB treatment outcomes. WHO recommends that treatment outcomes are reported separately for the cohort of HIV-positive TB patients (*2,7,8*).

Figure 9, reproduced from the *Global TB report 2013* (*3*) shows the difference in the distribution of treatment outcomes between HIV-positive and HIV-negative TB patients globally (*9*).

A more complete analysis of treatment outcomes would need to examine the proportion of patients with confirmed TB who were not started on treatment as well as the true proportion of case fatalities among those that were lost to follow-up during treatment. In settings with case-based information systems (Chapter 2), understanding the factors associated with negative outcomes would require cross-tabulating outcomes by age groups, sex, and key population groups such as prisoners, people who inject drugs, etc. The understanding of such factors can help inform corrective action.

FIGURE 9
Global TB treatment success and death rate (patients lost to follow-up during treatment are included in the death rate), by HIV status (2011 cohort)

a. Treatment success, 2011

Percentage of cohort (%)

HIV+ (117 094)	HIV- (959 174)	HIV+ (163 300)	HIV- (845 907)	HIV+ (79 817)	HIV- (385 748)
New smear-positive patients (data from 88 countries)		New smear-negative and extrapulmonary patients (data ftom 72 countries)		Retreatment patients (data from 59 countries)	

b. Death rate among evaluated cases, 2011

Percentage (%)

HIV+ (109 137)	HIV- (925 024)	HIV+ (148 798)	HIV- (811 586)	HIV+ (73 354)	HIV- (370 385)
New smear-positive patients (data from 88 countries)		New smear-negative and extrapulmonary patients (data ftom 72 countries)		Retreatment patients (data from 59 countries)	

Treatment success is much lower in HIV-infected patients (Figure 9, panel a, top) as a result of a higher case fatality rate (panel b, bottom). Early treatment with ART considerably decreases the risk of death during the course of TB treatment (1, 10–13).

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Chapter 7
Estimating TB mortality using vital registration and mortality survey data

Audience:

1. Epidemiologists, statisticians and monitoring and evaluation officers working in NTPs.
2. Staff in NTPs who are interested in learning about estimation of TB mortality and how interpretation of its trends could be useful to their programmes.

Expected outcomes:

By the completion of this chapter, the reader should be:

- familiar with key available data sources on mortality, including the International Classification of Diseases (ICD) system for classification of causes of death;
- able to understand how estimates of TB mortality, both among HIV-negative and HIV-positive sub-populations, are produced;
- able to interpret time trends in, and geographical distribution of, tuberculosis mortality;
- familiar with the mortality to notification (M/N) ratio indicator;
- able to understand how mortality attributable to multidrug-resistant TB is estimated.

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7.1 Sources of mortality data

International Classification of Diseases

The International Classification of Diseases (ICD) system is the international standard tool to systematically code mortality and morbidity data (*1*). Currently in its tenth revision (ICD-11 will be released in 2015), the ICD provides a comprehensive standardization of clinical care and research activities, such as: the definition of diseases; managing health care; the allocation of resources and the monitoring of outcomes. It also includes standard codes for causes of death (COD).

The main TB-related cause of death codes, as well as non-specific or so-called 'ill-defined' causes of deaths codes (e.g. TB sequelae, i.e. pathological complications resulting from TB disease such as chronic obstructive pulmonary disease), from the past two ICD iterations are shown in Table 1. Use of the ill-defined causes should be avoided if possible.

TABLE 1
Standard codes for TB-related cause of death

Cause of death	ICD-9 codes (1979-1998)	ICD-10 codes (1999-Present)
Tuberculosis	010-018	A15-A19
Respiratory tuberculosis	010-012	A15
Other tuberculosis	013-018	A17-A19
Ill-defined causes	137.0-137.4	R00-R99, B90.9, P37.0 and J65

Civil registration and vital statistics systems

'Civil registration' is defined as the recording of the occurrence and characteristics of vital events, such as: live births; deaths with information on COD and civil status events (e.g. a marriage record).

A 'vital statistics' system records vital events from civil registration system with the purpose of producing statistics (*2*).

Effective civil registration and vital statistics (CRVS) systems produce data on a continuous basis that are consistent and comparable with data from the whole population. Data should be recorded by trained professionals as close to the event as possible (*3*). Such CRVS systems can produce statistics consistently on COD. Deaths that occur in health

facilities or under the supervision of a health worker can be medically certified and coded in accordance with the ICD (Figure 1). Where a death occurs outside a health facility, verbal autopsy (VA) methods can be used to determine the probable cause of death. The monitoring of a cause of death makes CRVS systems a significant resource, such as for disease-specific programmes (e.g. TB), to identify priorities, guide policy, allocate resources and to measure progress.

FIGURE 1
## Example of a medical certificate showing the cause of death (*4*)

Cause of death		Approximate interval between onset and death
I Disease or condition directly leading to death*	(a) *Respiratory failure*	*< 2 weeks*
	due to (or as a consequence of)	
Antecedent causes Morbid conditions, if any, giving rise to the above cause, stating the underlying condition last	(b) *Pulmonary fibrosis*	*2 years*
	due to (or as a consequence of)	
	(c) *Pulmonary tuberculosis*	*6 months*
	due to (or as a consequence of)	
	(d)	
II Other significant conditions contributing to the death, but not related to the disease or condition causing it	*Chronic bronchitis*	*10 years*

*This does not mean the mode of dying e.g. heart failure, respiratory failure. It means the disease, injury, or complication that caused death.

The medical certificate provides an aetiological description of the sequence of events that led to death. In this example: (a) is the immediate cause of death, preceded by contributory cause (b) that itself was preceded by (c), the underlying cause of death that started the sequence of events. In this example, (c) is the cause that is reported in the CRVS.

Despite these obvious benefits of CRVS systems, many countries have not invested in them, resulting in a lack of high quality output (*5*). As a result, most countries where TB is highly endemic are currently not producing reliable information on the underlying causes of death (Figure 2). The quality of VR data is documented globally by WHO (*6*). Statistical methods can be used to account for incomplete coverage or miscoding. Political commitment in the international community is now strong with the *Global Call for Partner Action on CRVS* highlighting the need to develop CRVS systems in Africa and Asia where there is significant need because of the high disease burden due to TB (*7*).

FIGURE 2
Countries with national vital registration systems (sample VR systems) reporting mortality data with the distribution of causes of deaths to WHO since May 2012 (in purple)
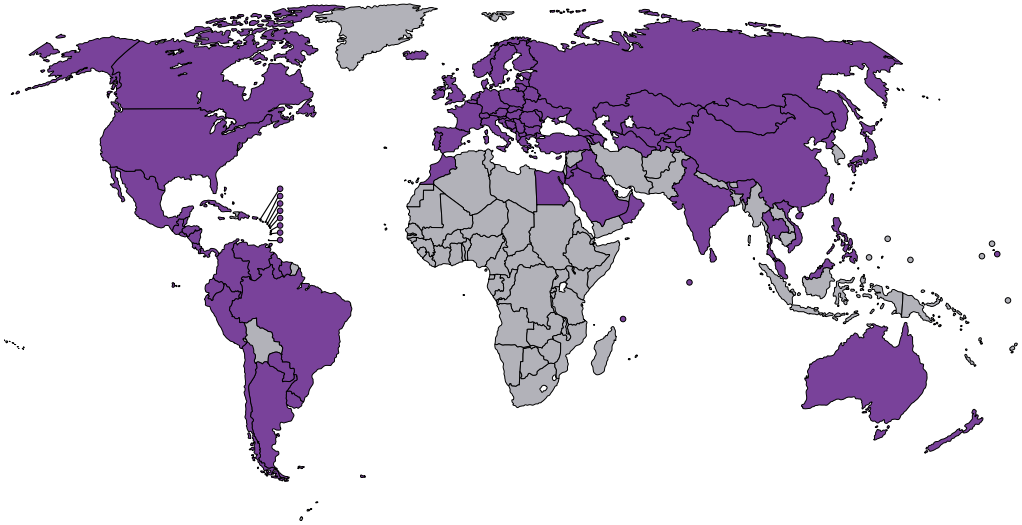
TB deaths reported through VR systems are limited to TB deaths among HIV-negative individuals. Deaths among people living with HIV with TB as a contributory cause are coded within the HIV chapters of ICD-10. However, contributory causes of death in HIV-positive individuals are often difficult to analyse due to the high frequency of miscoding.

Verbal autopsy

In the absence of a well-established CRVS with continuous and high-quality output, or when a death occurs outside a health facility, VA methods can be used to determine the probable cause of death. These methods involve interviews with family members and/or people who cared for the deceased person prior to death, in order to ascertain the cause (8). This is sometimes conducted in the course of a demographic and health questionnaire survey. There are limitations to VA, such as that the method does not perform equally well for all causes of death. In fact ascertaining death from TB based on VA often presents challenges, especially when the evidence of TB (e.g. bacteriological, chest X-ray) is not available in existing patient records.

7.2 Monitoring TB mortality among HIV-negative individuals

Among countries for which VR data can be used (see Figure 2), it is possible to monitor TB mortality by plotting TB deaths as captured by the CRVS and reported to WHO on an

annual basis (*9*). Data of questionable quality, such as outliers and data points obtained from systems with very low coverage, are excluded or adjusted for analytical purposes. Reported TB mortality data are adjusted upwards to account for incomplete coverage (i.e. the amount of estimated deaths with no cause documented) and ill-defined causes of death (Box 1).

The total number of so-called estimated deaths in a country for a given calendar year is derived from estimated death rates obtained from life tables applied to United Nations (UN) population estimates (*10, 11*). It is typically assumed that the proportion of TB deaths among those not recorded by the VR system is the same as the proportion of TB deaths in VR-recorded deaths. For VR-recorded deaths with ill-defined causes, it is assumed that the proportion of deaths attributable to TB is the same as the observed proportion in recorded deaths.

The adjusted number of TB deaths d_a is obtained from the VR reported number of deaths with TB as the documented cause (*d*) as follows:

$$d_a = \frac{d}{c(1 - g)}$$

where *c* denotes coverage (i.e. the number of deaths with a documented cause divided by the total number of estimated deaths) and *g* denotes the proportion of ill-defined causes (Box 1).

The uncertainty related to this adjustment is estimated with standard deviation:

$$SD = \frac{d}{4}\left[\frac{1}{c(1 - g)} - 1\right]$$

The uncertainty calculation does not account for miscoding, for example HIV deaths miscoded as deaths due to TB.

BOX 1
Adjusting TB mortality for deaths in CRVS with ill-defined causes: Thailand

During a 2013 national health review of the TB programme in Thailand, routinely collected surveillance data were studied in detail as part of an epidemiological assessment of TB disease in the country. Among these data were national CRVS records with cause of death information (Table 2).

TABLE 2
National CRVS data on cause of death

| year	(1)	(2)	(3)	(4)	(5)	(6)	(7)	(8)	(9)
1990	399134	252512	109184	0.63	0.43	3937	10964	6.96	19.38
1991	414130	264347	113536	0.64	0.43	3663	10041	6.41	17.59
1992	434683	275313	117130	0.63	0.43	3595	10011	6.23	17.13
1994	450482	305526	111137	0.68	0.36	3473	7980	5.94	13.76
1995	459558	324842	114598	0.71	0.35	4144	8979	7.03	15.36
1996	490440	342643	121648	0.70	0.36	4622	10317	7.76	17.22
1997	436101	298084	103739	0.68	0.35	3697	8364	6.14	13.78
1998	447274	310512	116981	0.69	0.38	4252	9939	6.98	16.14
1999	524710	362607	151140	0.69	0.42	5265	13156	8.54	21.20
2000	514438	365583	149567	0.71	0.41	6246	14910	10.02	23.86
2002	514526	380364	143060	0.74	0.38	6751	14714	10.58	22.94
2003	533220	384131	127487	0.72	0.33	6906	14316	10.71	22.25
2004	565150	393592	149212	0.70	0.38	6076	14000	9.34	21.59
2005	528387	395374	151096	0.75	0.38	5534	11901	8.44	18.26
2006	526734	391126	149918	0.74	0.38	5214	11364	7.91	17.28

(1)   Estimated number of total deaths in the country
(2)   Number of deaths with a documented cause of death
(3)   Number of deaths with an ill-defined cause of death
(4)   Coverage, expressed as a proportion (c): (2)/(1)
(5)   Proportion of ill-defined causes of deaths out of all those with a documented cause of death: (3)/(2)
(6)   Number of deaths (d) with TB as the documented cause
(7)   Adjusted (for coverage and ill-defined causes) number of deaths (da) with TB as the documented cause
(8)   'Raw' TB mortality rate per 100 000 population: (6)/national population estimate
(9)   'Adjusted' TB mortality rate per 100 000 population: (7)/national population estimate

HIV-negative TB mortality was plotted over time (Figure 3). The x symbol denotes raw TB mortality rates (data shown in column (*8*) of Table 2) measured through CRVS records. Raw numbers were adjusted to account for incomplete coverage of CRVS as well as for ill-defined ICD-10 codes for cause of death, represented by the blue line (data shown in column (*9*) of Table 2). Values with no CRVS data

Box 1 - continued

(2007–2010) were projected using the same rate of decline for the years 2004 to 2006. The blue ribbon shows the uncertainty range in estimated mortality and the dashed line represents the international target of 50% reduction in TB mortality by 2015 compared to 1990 level. The increase in TB mortality after 1997 is possibly related to the severe economic crisis that affected the country before the implementation of Thailand's universal health coverage scheme.

FIGURE 3
Time trends in TB mortality (excluding HIV) in Thailand
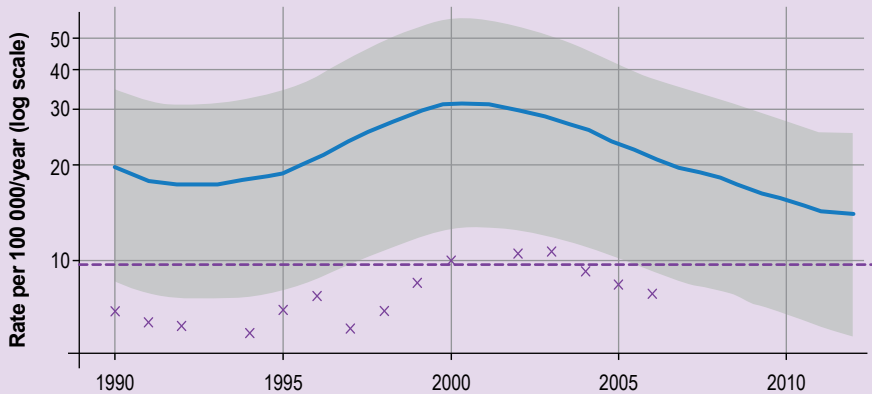
Levels of TB mortality were also studied at the sub-national level in an attempt to better understand the distribution of deaths due to TB in the country and whether these were associated with the amount of TB cases notified. The adjusted mortality rate per 100 000 was calculated for each province in the country and compared against the all-forms, all-ages TB case notification rate per 100 000, (Figure 4). No obvious association can be observed, making a definitive interpretation difficult (also see section 7.4).

Box 1 - continued
FIGURE 4
Scatterplot of TB mortality rate against case notification rates in Thailand, by province

Misclassification of deaths is also a problem of CRVS system data. A well-documented example is that of the VR data on TB deaths from South Africa and Zimbabwe where a large number of HIV deaths are miscoded as TB deaths in an attempt to avoid HIV-related stigma. Improved empirical adjustment procedures have recently been published (*12*) and options for specific post-hoc adjustments for misclassification errors in the measurement of TB mortality need to be reviewed.

Missing data between existing CRVS data points can be interpolated, while trailing missing values can be predicted using exponential smoothing models for a time series (*13*). In the absence of CRVS data, time series of TB mortality could also be estimated from repeat VA surveys (Box 2).

7.3 Monitoring TB mortality among people living with HIV

HIV is registered as the underlying cause of death when a person dies from TB, while TB is recorded as a contributory cause. Since one third of countries with VR systems report only the underlying and not the contributory causes of death to WHO, VR data usually cannot be used to estimate the number of TB deaths in HIV-positive people.

BOX 2
Case study: Viet Nam

Data from repeat nationwide-representative verbal autopsy surveys conducted in 2006 (*14*) and 2009 (*15*) were used to determine the level of TB mortality (excluding HIV-associated TB deaths) and the trend over time in Viet Nam. The cause of death data obtained from the surveys were adjusted to account for ill-defined causes and incomplete coverage. TB mortality was projected back-wards in time based on the adjusted 2006–2009 trend, assuming a constant rate of change per year based on the exponential decline in TB incidence. Figure 5 shows trends in TB mortality (excluding HIV). The lack of direct measurement of mortality over 1990–2005 is detrimental to the accuracy of estimates of time trends in mortality. The year 1990 is used for reference, as dictated by the Stop TB Partnership international target for TB mortality (halving of TB mortality in 2015 compared to 1990).

FIGURE 5
TB mortality excluding HIV-associated TB deaths, log scale
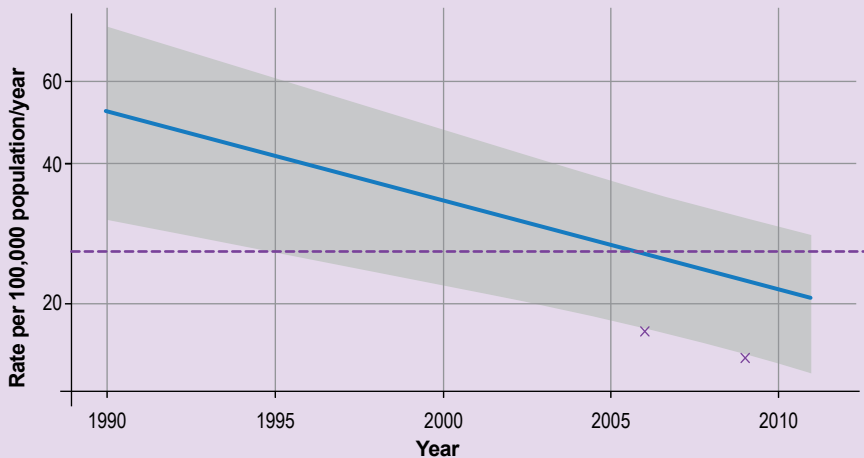
The blue ribbon denotes the uncertainty range. The x symbol denotes the raw data from verbal autopsy studies. Raw data were adjusted to account for ill-defined causes of deaths and for incomplete coverage (blue line). The horizontal dashed line (purple) represents the target of havling the 1990 level of TB mortality by 2015.

TB mortality among HIV-positive people must then be estimated indirectly, such as using methods implemented in the Spectrum software.[a] TB mortality is calculated as the product of HIV-positive TB incidence and case fatality ratios:

$$M = (I\text{-}N)F_u + NF_n$$

a.   http://www.futuresinstitute.org/spectrum.aspx

where *I* represents incident TB cases among people living with HIV, *N* represents HIV-positive cases that are notified, (*I-N*) represents HIV-positive TB cases that are not notified and M represents TB mortality among HIV-positive people. F_n and F_u are the case fatality ratios for notified and non-notified incident TB cases, respectively.

7.4 Mortality to notification ratio

The ratio of TB mortality measured from CRVS systems (among HIV-negative individuals) to TB case notifications could be a useful indicator for the identification of populations with higher mortality for targeted action. Figure 6 provides a global picture of this indicator, among countries with high-quality COD data. High levels of TB mortality in Eastern Europe could be associated with high drug-resistant TB (DR-TB) levels, while in South East Asia, high levels of TB mortality could be explained by the large estimated amount of untreated TB.

FIGURE 6
Country-level TB mortality to notification ratios (2012)
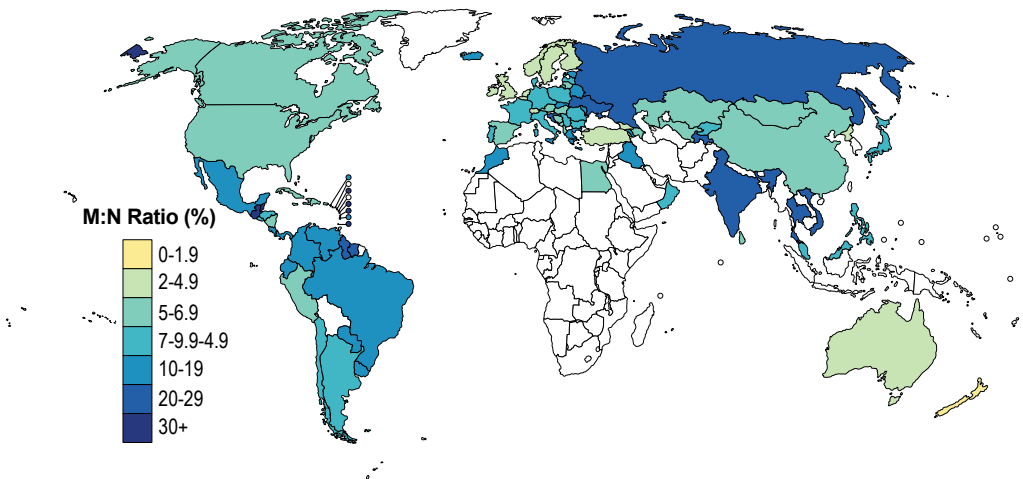
Analyses of TB mortality can also be conducted based on population sub-groups and their associated risk factors, such as race, ethnicity, socioeconomic status, age, sex and geography (*16*). Linkage of mortality with notification data could thus be helpful to identify sub-populations at greater risk of dying within a country.

7.5 MDR-TB mortality

Differentiation between death from drug-susceptible and DR-TB is currently not available in ICD. User-defined codes are required (e.g. in South Africa U51 and U52 classify deaths

from MDR-TB and XDR-TB respectively, as shown in Table 3). However, even in South Africa the drug susceptibility testing coverage among all pulmonary TB cases is quite low, which could mean that DR-TB deaths are likely to be misclassified. Therefore, although certainly possible, direct measurement of DR-TB deaths from CRVS systems requires further investment to produce high quality data.

TABLE 3
User-defined COD codes for DR-TB deaths in South Africa (*17*)

	2006	2007	2008	2009	2010
MDR-TB U51	604	597	712	1184	856
XDR-TB U52	3	84	135	151	171
DR testing coverage among pulmonary TB	NA	NA	27%	10%	12%

Indirect estimation of MDR-TB mortality derives the number of deaths from MDR-TB as the product of total deaths from TB, the overall proportion of TB cases that have MDR-TB, and the relative risk (RR) of death (among people with MDR-TB compared with those without MDR-TB). While estimates of total TB mortality and the prevalence of MDR-TB have been available for several years from VR data (i.e. for total TB deaths) and representative surveillance or survey data (for the proportion of cases with MDR-TB), an estimate of the RR is not. A systematic review and meta-analysis (*18*) of the published literature was undertaken to estimate the relative risk of dying from MDR-TB compared with non MDR-TB. There were 25 studies conducted that included data about mortality among patients enrolled on treatment for MDR-TB and TB (without MDR-TB), during and after treatment. These allowed for the calculation of a global estimate of the RR of dying from MDR-TB. The studies had a broad geographical coverage and included countries with both high and low burdens of MDR-TB and HIV but were insufficient to estimate the regional or other sub-group-specific RRs.

The global estimate of MDR-TB deaths was based on the following formula:

$$m = M*p*r$$

m = global MDR-TB mortality;
M = global TB mortality;
p = overall proportion of MDR-TB among prevalent TB cases, approximated by the weighted average of the proportion of new and retreated cases that have MDR-TB = 0.06, range (0.04-0.07);
r = the relative risk of dying from MDR-TB versus non-MDR-TB = 2.36, range (1.67-3.05).

For the year 2012, M=1 300 000 and p=0.057 (*19*). This led to 170 000, range (100 000–240 000).

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Chapter 8
Combining surveillance and survey data to estimate TB burden

Audience:

1. Epidemiologists, statisticians and monitoring and evaluation officers working in NTPs.
2. Staff in NTPs who are interested in learning about estimation of TB burden and how interpretation of its trends could be useful to their programmes.

Expected outcomes:

By the completion of this chapter, the reader should be able to:

- Understand how data from different sources can be used to help interpret observed trends in TB case notifications and TB mortality.
- Interpret variation among population groups.
- Understand how estimates of TB incidence, prevalence and mortality can be produced or estimated from available sources of data.
- Be aware of some of the main issues when trying to make indirect estimates of the TB burden in a population.

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8.1 TB incidence

TB incidence is at the core of the Millennium Development Goals (MDG) – Target 6C: Have halted by 2015 and begun to reverse the incidence of malaria and other major diseases (*1*). The goal of reversing TB incidence may be especially relevant in countries that also have substantial HIV epidemics and experienced a rapid rise in TB incidence during the 1990s. However, in most parts of the world TB has been slowly declining since 1990 (*2*). Case notification rates (assumed to be a proxy for TB incidence) in England and Wales were already declining well before any effective intervention for TB became widely available, suggesting that TB incidence is associated with multiple factors, including improvements in socioeconomic and living conditions (Figure 1, see also Chapter 1).

FIGURE 1
Trends in all forms TB case notification rate (log scale) in England and Wales (1913-2011). *Source:* **Public Health England (TB section)**
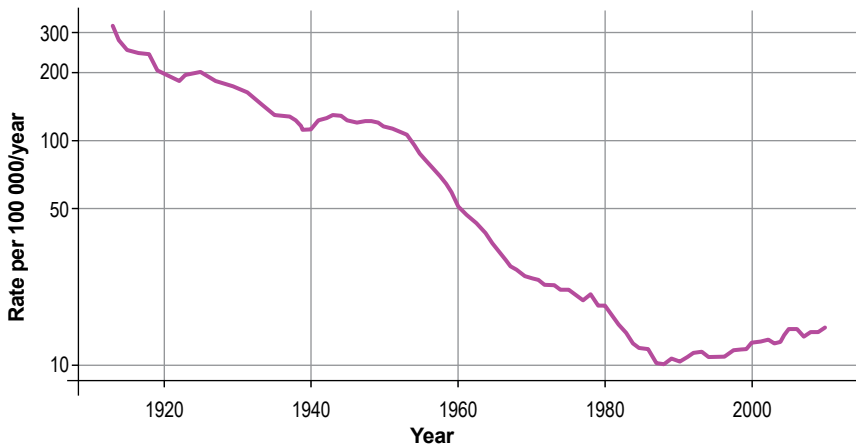
TB incidence has proved difficult to measure or estimate in most countries. Surveys measuring TB incidence require large population-based cohort studies. This type of survey is resource intensive and logistically demanding, making it highly impractical to conduct in most settings, where incidence surveys would need to follow a very large cohort of individuals (e.g. in excess of 50 000 people), over a period of at least one year. During this time, the cohort has to be actively followed to ensure minimal loss to follow-up and in order to ensure the validity of results. As a result, to date, no country has conducted a nationally representative TB incidence survey.

Instead, incidence is typically derived from routine case notifications. However, there are two sources of uncertainty in such estimates: 1) Not all cases that are diagnosed are reported; and, 2) not all TB cases are detected. In high-income countries with

high-performance TB surveillance and health systems, case notification systems are assumed to capture all, or almost all, incident cases of TB. In other settings, however, routine case notifications do not provide accurate estimates of incidence. There are several reasons for this. Firstly, the private sector does not always report newly detected cases. For instance, a recent study in India suggested that about 46% of detected cases are not reported (3). Secondly, not all cases may be detected, particularly in countries with no health insurance and social protection (or equivalent mechanisms), or where the coverage and performance of health services and laboratories are weak. Results from national population-based prevalence surveys in high TB burden countries consistently show that most cases were not diagnosed with TB prior to the survey. Common reasons for not seeking care include the following: lack of symptoms; symptoms not judged severe enough to seek care; and poor access to health services. Thirdly, only about half of reported TB cases in low- and middle-income countries are confirmed microbiologically, as in many countries diagnosis is limited to sputum smear microscopy, which has limited sensitivity. The quality and accuracy of diagnostics for clinically-diagnosed cases (cases with no bacteriological confirmation of TB) is difficult to quantify, and likely to vary between settings. Not all reported clinically diagnosed cases are necessarily true TB cases. The introduction of more sensitive and specific diagnostics should increase the proportion of bacteriologically-confirmed cases among all reported TB cases and reduce the magnitude of diagnosing TB incorrectly.

The incidence of sputum smear-positive pulmonary TB cannot be reliably derived from results of tuberculin surveys in school children. Although this was a method used in the past, it has recently come under scrutiny and the underlying assumptions are no longer considered satisfactory (4).

Measuring TB incidence in low- and middle-income countries is a challenge. The main solution for the future is to increase coverage of TB surveillance to all providers of health care and minimize the level of under-reporting (i.e. the proportion of cases not reported to public health authorities out of the total number of detected cases) and over-diagnosis (i.e. false-positive TB cases). High levels of under-reporting call for corrective action so that the information provided by routine case notifications reflects the burden of disease in absolute terms and trends.

Inventory studies

To help better measure and address the problem of under-reporting of TB, a priority of the WHO Global Task Force on TB Impact Measurement in 2011–2012 was to develop guidance on the design, implementation and analysis of inventory studies to measure TB

under-reporting (5).[a] Inventory studies are increasingly being used, and can help to plan and implement public–private mix (PPM) activities. An inventory study aims to quantify the number of TB cases meeting standard case definitions in all, or in a sample of public and private health facilities, and compares those data with the records of TB cases notified to local and national authorities. Comparisons are made through a process called 'record-linkage', in which duplicate and unique records are identified. Depending on existing systems for data management, records can be linked either using existing databases or linkage may need to be preceded by special efforts (for a limited time period) to collect data on the number of cases diagnosed by all health care providers in the country, or by all health care providers in a random sample of well-defined geographical areas.

Capture-recapture analysis

In certain circumstances, the results from inventory studies can be combined with a type of modelling called 'capture-recapture' analysis in order to estimate TB incidence.

An inventory study from the Republic of Iraq showed that TB under-reporting was 16% of the total number of detected cases (Figure 2) (6). Private providers and public providers that were not under the NTP authority diagnosed these cases. Capture-recapture modelling estimated that an additional 473 cases (95% confidence interval: 394–565) had not been detected by any of the three types of health providers. The capture-recapture analysis thus allowed for the updating of national estimates of TB incidence. A low level of under-reporting is an important characteristic of a high-performance TB surveillance system.

It should be noted that capture-recapture methods have inherent limitations and are not reliable in many countries due to critical underlying model assumptions that do not hold in practice (5).

## Deriving incidence from prevalence

It is theoretically possible to derive TB incidence from data on TB prevalence. TB incidence can be approximated as the ratio of TB prevalence divided by the average duration of disease. The difficulties in estimating incidence from prevalence include:

- A typically limited precision of TB prevalence estimated from a population-based survey (standard deviation is usually about 20–25% of the best estimate).
- Limited data on disease duration. Disease duration is affected by multiple factors, including the performance of case finding, the prevalence of HIV and

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a. The main purpose of the guidelines on inventory studies is to describe and explain how to design, implement and analyse an inventory study to measure TB under-reporting. The guide also explains how to apply capture-recapture methods to estimate TB incidence, emphasizing the conditions that must be fulfilled for these methods to be used.

the prevalence of multidrug resistance among TB patients. While data on the duration of symptoms can be collected during a population-based prevalence survey, three considerations limit their usefulness in estimating the national average of disease duration. Firstly, the natural history of disease is shortened by the investigation (active case finding during a prevalence survey) compared with the longer average duration of disease of patients not participating in the survey. Secondly, prevalence surveys typically find a large proportion of bacteriologically-confirmed pulmonary TB cases with no or only few symptoms. Thirdly, some of the most frequent symptoms caused by TB, such as chronic cough, are common in the general population, particularly among smokers, and are not specific to TB.

FIGURE 2
Inventory study showing where TB patients were diagnosed in Iraq (2011)
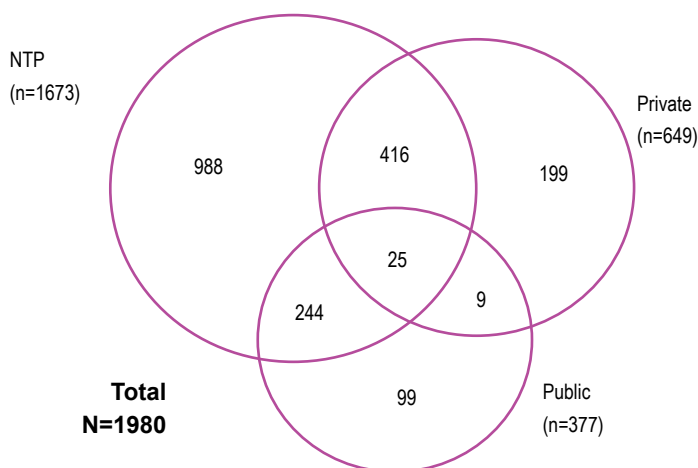
8.2 TB prevalence

TB prevalence is a very useful indicator of the burden of TB disease and it provides an indication of how much ongoing transmission there may be in the population. It is directly measurable through population-based surveys (7). There has been considerable progress in recent years to plan and implement prevalence surveys in a large number of countries in Asia and Africa, based on methods recommended by WHO (Figure 3). Prevalence surveys have proved extremely useful for designing and adapting national TB control programme strategies.

FIGURE 3
**Countries in which national population-based surveys of TB prevalence have
been implemented using currently recommended screening and diagnostic
methods, since 1990 or are planned in the near future (July 2013) (2)**
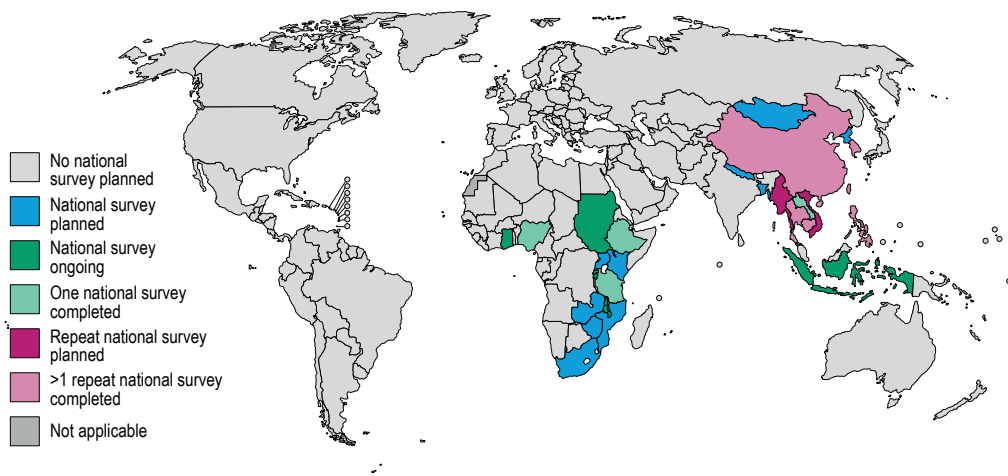

For the past two decades, Cambodia has been known to have one of the highest levels of
TB prevalence (expressed as a proportion of the total population) in the world. TB control
in Cambodia was reinstated in 1994 following decades of civil conflict and economic
hardship. TB services were first limited to provincial and district hospitals. At the early
stage of DOTS expansion to health centres in 2002, the NTP decided to directly measure
the burden of TB through a nationwide prevalence survey. The prevalence for all forms
of TB was estimated at 1.5% (range 1.2% to 1.8%) of the population, one of the highest
levels of prevalence observed in recent history. A second, nationally representative survey
was conducted in 2011. The prevalence for all forms of TB was estimated at 0.8% (range
0.69% to 0.96%) of the population, showing a statistically significant difference with the
findings from the first survey (95% confidence intervals did not overlap).

The repeat surveys provide robust evidence of a decline in TB burden in Cambodia,
following DOTS expansion in 2002. Results indicate a 45% reduction in prevalence of
bacteriologically-confirmed cases over a period of only nine years (Figure 4).

As the burden of TB falls and surveillance systems are strengthened, prevalence surveys will
no longer be efficient ways to measure the burden of TB and are likely to be discontinued.
For example, the Republic of Korea implemented seven surveys at five-year intervals from
1965 to 1995. Repeat surveys were discontinued when the required sample size became

unreasonably large due to low TB prevalence levels, and as a result of the gradually declining overall acceptability of survey investigations by a population with a high level of income and access to health care (*8*). Having completed a fifth survey in 2010, China may also discontinue the practice of repeat surveys for similar reasons. In the absence of population-based survey data, TB prevalence is difficult to estimate with accuracy (*2*).

FIGURE 4
Trends in TB prevalence per capita in Cambodia
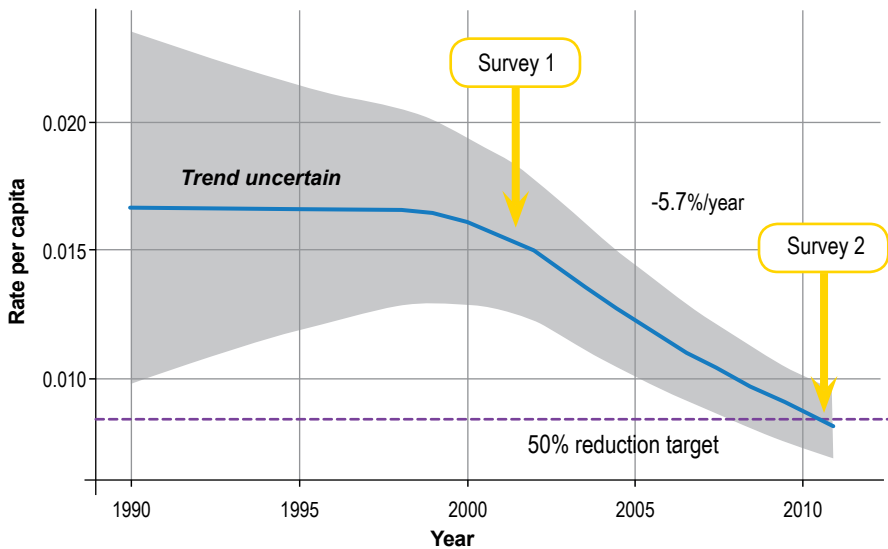
The dashed line shows the international target of halving prevalence by 2015 compared with the estimated level of 1990.

8.3 TB mortality and case fatality ratio

Chapter 7 details sources of data on TB mortality. The ratio of TB mortality to estimated TB incidence is termed TB case fatality ratio (CFR). The CFR may be calculated excluding HIV-positive TB deaths or including HIV-positive TB deaths.

Data from the 20th century in England and Wales can be used to consider this ratio over time (Figure 5). The dashed line displaying the TB mortality rates ran parallel to the solid line showing the case notification rates until around 1945, indicating that both mortality and case rates declined at about the same annual rate. Until the Second World War, about 40–50% of people who had contracted TB died from the disease. However, TB mortality fell at a faster rate on average thereafter. The CFR dropped dramatically with the advent of effective chemotherapy, with further slow improvements during the 1990s and 2000s (Figure 6). TB mortality rates continued to decrease in the 1990s and 2000s despite a concurrent

increase in TB notification rates, suggesting a lower risk of death among immigrants that nowadays account for the majority of TB cases in the country.

FIGURE 5
TB case notification rates (solid line) and TB mortality rates (dashed line), England and Wales (log scale), from 1913 to 2010. *Source:* **Public Health England (TB section)**
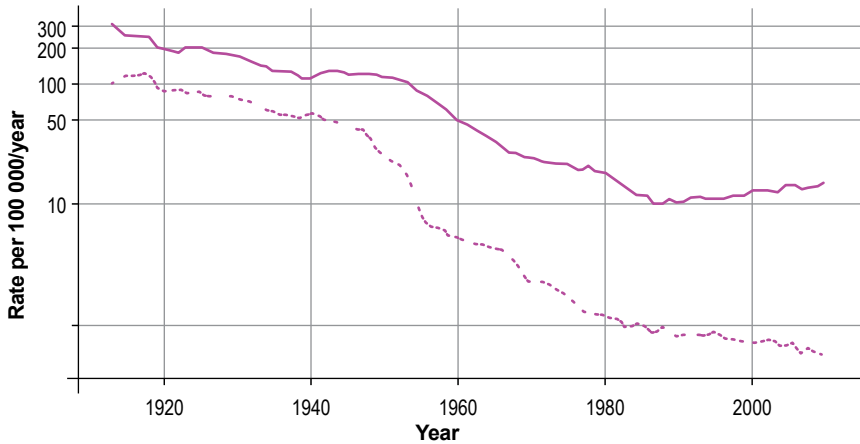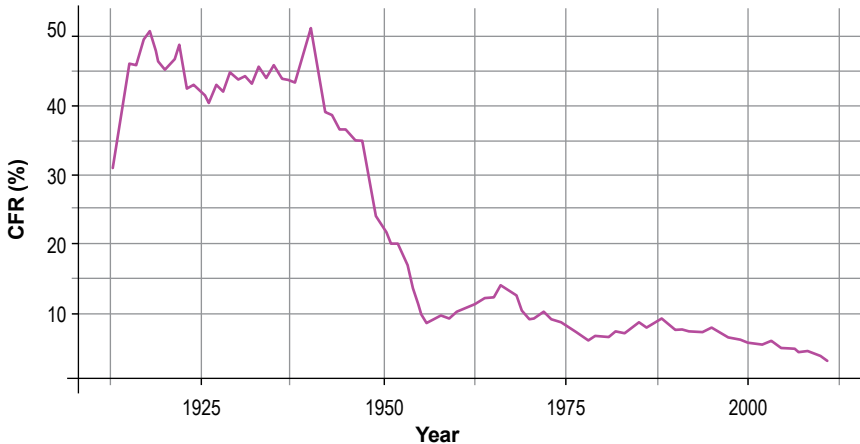

FIGURE 6
TB case fatality ratio estimated as the ratio of TB deaths over TB cases, England and Wales, from 1913 to 2010. *Source:* **Public Health England (TB section)**

The CFR is a powerful indicator of the efficacy of TB detection and TB programme success. Using TB mortality data from national vital registration systems, the CFR (excluding HIV-positive TB deaths) can be analysed at the sub-national level, (e.g. the provincial level), thus allowing the identification of areas with the weakest programme performance. In a similar manner, the CFR can be compared between age and sex groups, allowing better targeting of interventions.

Globally, the CFR including estimated TB deaths in HIV-positive individuals declined from 20% (range: 18–23%) in 2000 to 16% (14–18%) in 2010, explaining why mortality fell on average 3.5% per year, a higher rate of decline than observed for incidence over the same decade (1% per year). ART is expected to play an increasing role in preventing TB deaths as coverage expands (approximately 16% of notified TB cases estimated to be infected with HIV globally when on ART in 2010). ART and isoniazid prophylaxis will also increasingly contribute to the prevention of TB in individuals with both HIV infection and latent TB infection.

The CFR is also affected by the prevalence of MDR in TB cases and by the performance of programmatic management of MDR-TB. A higher CFR will be observed if the performance of programmatic management of MDR-TB is weak.

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Epilogue

Chapters 1, 2 and 3 presented analyses that interpret trends in case notification rates from information systems generating aggregated and individual data on cases, respectively. Major determinants of TB were discussed in Chapter 4, and to some extent in Chapter 5, providing insights into changes in cases over time and a better understanding of factors affecting trends in TB case notification. In turn, trends in TB incidence can be deduced from trends in case notifications, changes in the main drivers of a TB epidemic (such as HIV, Chapter 6), trends in mortality (Chapter 7) and in TB prevalence.

The WHO Task Force on TB Impact Measurement has developed a set of standards and benchmarks to assess the performance of TB surveillance systems, identifying data gaps and data quality problems, and describing unmet monitoring and evaluation needs.[a] It is possible to estimate indicators of TB burden in countries with missing data on incidence, prevalence or mortality (Annex 2 of WHO *Global TB Report 2013*)[b] but generally at the expense of considerable uncertainty.

The ideal situation is one where data generated by TB case notifications provide a reliable proxy of TB incidence, and cause of death data from national vital registration systems that accurately measure TB mortality, including AIDS deaths with TB as an underlying cause of death.

a.   TB surveillance expert group. Geneva: World Health Organization; 2011. Available at: http://www.who.int//tb/advisory_bodies/impact_measurement_taskforce/meetings/surveillance_expert_group_meeting_sept2011/en/index.html
b.   Global tuberculosis report 2013. Geneva: World Health Organization; 2013. Available at: http://www.who.int/tb/publications/global_report/en/index.html

Surveillance data collected in vital registration and TB notification systems provide essential information about the TB epidemic and programmatic efforts to control the disease at both national and local levels. Analysis of these data can help programme managers and other staff to track the level of and trends in TB disease burden, detect outbreaks of disease and identify ways to improve existing TB prevention, diagnostic and treatment services. This book provides practical guidance on the analysis and use of such surveillance data, and is suitable for a wide range of people engaged in TB control. It was produced as a major collaborative effort as part of the work of the WHO's Global Task Force on TB Impact Measurement.

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