# Module 1: Overview of tuberculosis (TB) and TB diagnostics

# Contents of this module

- What is TB and how is it treated?
- What is the global and national burden of TB?
- How is TB transmitted and who is at risk?
- WHO policy guidance on TB diagnostics
- Organization of TB laboratory services

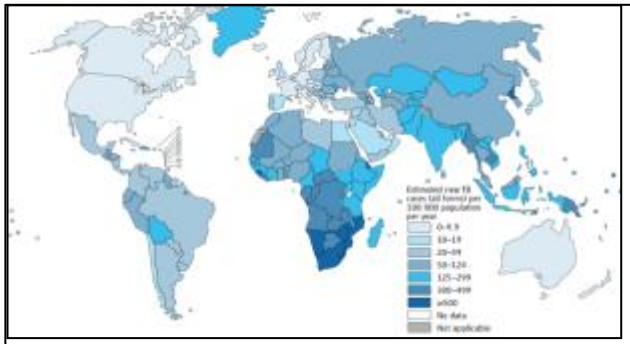
# Learning objectives

At the end of this module, you will be able to:

- Describe what is TB and how it is treated
- Explain the TB epidemic and national TB burden
- Describe how TB is transmitted and which factors influence the risk of infection
- Define and compare various methods of TB diagnosis
- Describe current WHO policies on TB diagnostics
- Describe levels of TB laboratory services and positioning of diagnostic tools

# The global TB situation

Update this slide annually using data from WHO's global report: http://www.who.int/tb/publications/global_report/en



| | Estimated number of cases | Estimated number of deaths |
|---|---|---|
| All forms of TB | 8.6 million (8.3-9.0 million)<br>• 0.5 million children<br>• 2.9 million women | 1.3 million<br>(1.0-1.6 million)*<br>• 74,000 children<br>• 410,000 women |
| HIV-associated TB | 1.1 million<br>(1.0-1.2 million)<br>(13% of cases) | 320,000 (300,000-340,000) |
| Multidrug-resistant TB | 450,000 (300,000-600,000) | 170,000 (102,000-242,000) |

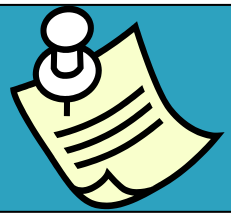
** Including deaths attributed to coinfection with HIV and TB*

*Source: WHO Global Tuberculosis Report 2013*

# TB burden in *(Country name)*

*To be customized by each country*

- Estimated TB incidence: X,XXX cases in 2012
  XX cases/100,000 population
- Estimated TB mortality: Y,YYY cases in 2012
  YY cases/100,000 population
- Estimated % of new TB patients with MDR-TB: Z.Z%



*Access WHO country profiles with epidemiological data and estimates:*
*http://www.who.int/tb/country/data/profiles/en/index.html*

# What is TB?

TB is an infectious disease that affects mainly the lungs (pulmonary TB) but can also attack any part of the body (extrapulmonary TB)

A person with pulmonary TB is infectious to others

# Symptoms of TB

- The most common symptom of pulmonary TB is a productive cough lasting for more than 2 weeks.
- Other respiratory symptoms may include shortness of breath, chest pains and haemoptysis (coughing up blood).
- People with TB may also lose their appetite, lose weight, have a fever or night sweats, or feel tired.
- Symptoms may vary depending on a person's age, HIV status and the site of the disease (pulmonary or extrapulmonary).

# Treating TB

- TB is curable!
- The standard treatment regimen for TB includes 4 first-line agents (rifampicin, isoniazid, ethambutol and pyrazinamide).
- Patients who have been previously treated for TB and who have a recurrence should undergo drug-susceptibility testing (DST) so their treatment regimen can be adjusted and optimized.
- TB treatment that is poorly managed can result in drug resistance. Drug-resistant strains of TB can be transmitted to others.
- Patients with rifampicin-resistant forms of TB require longer treatment (lasting up to 2 years) with expensive second-line agents that have more serious side effects.

# Drug-resistant TB

- Rifampicin-resistant TB (RR-TB) is TB with resistance to rifampicin, detected using phenotypic or genotypic methods, with or without resistance to other anti-TB agents (new definition).

- Multidrug-resistant TB (MDR-TB) is TB with resistance to at least isoniazid and rifampicin.

- Extensively drug-resistant TB (XDR-TB) is MDR-TB plus resistance to a fluoroquinolone and at least one of three injectable second-line agents (amikacin, capreomycin or kanamycin).

# Transmission of TB bacilli

- *Mycobacterium tuberculosis* is almost always transmitted by patients who have active pulmonary disease.
  - A person with TB expels bacilli in small droplets of respiratory secretions.
  - The secretions quickly evaporate leaving “droplet nuclei” that are less than 5 μm in diameter.
  - Droplet nuclei of this size contain 1–3 bacilli and can remain in the environment for an extended time.
  - Following inhalation, droplet nuclei are able to travel deep into the lungs to produce infection.

# Risk factors for infection

- Approximately one third of the global population is *infected* with TB bacilli: infection is different than having active TB *disease.*

- A person's risk of acquiring TB infection depends on how long they were exposed to someone with pulmonary TB, the intensity of the exposure, as well as the strength of the person's immune system.

# Risk factors for disease

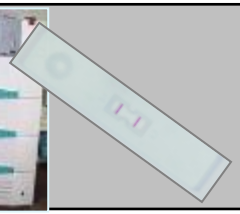
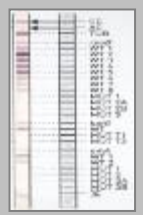
- Although one third of the world's population is infected with TB, only 10% of immunocompetent persons who are infected will develop active TB disease during their lifetime.
- Development of disease depends on an individual's susceptibility, and this can be influenced by conditions affecting the immune system as well as by other comorbidities.
- Being HIV-positive increases the risk of getting TB disease: people living with HIV who are also infected with TB have a 10% annual risk of developing active TB disease.

# Role of TB laboratories

**The TB laboratory network plays a critical role in TB control by providing:**

- Bacteriological confirmation of TB and drug-resistant TB
- Monitoring of treatment progress
- Support for surveillance studies (e.g., drug-resistance surveys and prevalence surveys).

# WHO's policies on diagnostics since 2007

| Year | Technology | Turnaround time | Sensitivity gain |
|---|---|---|---|
|   **Before 2007** | Ziehl-Neelsen microscopy; solid culture | <1 day, though often batched 30-60 days | Baseline |
|   **2007** | Liquid culture/DST; rapid speciation | 15-30 days | +10% compared with Löwenstein-Jensen solid culture |
|  **2008** | Line probe assay: in 2008 used only for smear-positive specimens or culture | <1 day, though usually batched and requiring transport | DST for rifampicin (RIF) and isoniazid (INH) only |

# WHO's policies on diagnostics since 2007

| Year | Technology | Turnaround time | Sensitivity gain |
|---|---|---|---|
|  **2009** | LED-based fluorescence microscopy | <1 day, though often batched | +10% compared with Ziehl-Neelsen microscopy |
| **Conditional 2009**  | Noncommercial methods for culture and DST [Microscopically observed drug susceptibility (MODS), Colorimetric redox indicator (CRI) methods, Nitrate reductase assay (NRA)]: To be used under clearly defined programme and operational conditions in reference laboratories and under strict laboratory protocols | 15-30 days | First-line DST only |
|  **Endorsed 2010, updated 2013** | Xpert MTB/RIF | <2 hours | +40% compared with Ziehl-Neelsen microscopy |

# Microscopy

- Microscopy is recommended for ALL levels of laboratories (that is, peripheral and higher levels).
- Microscopy can be done safely with minimal biosafety precautions.
- Microscopy has limited sensitivity, which is further reduced in HIV-positive individuals.
- Microscopy is required to monitor responses to anti-TB therapy.
- WHO recommends that in all settings LED fluorescence microscopy should be phased in to replace conventional bright-field microscopy and Ziehl-Neelsen staining.

# Culture

- Culture is recommended for national or regional level laboratories.
- Both solid culture and liquid culture are recommended by WHO, but they require a high level of biosafety precautions.
- Liquid culture is more expensive than solid culture but results are available more rapidly and it is more sensitive.
- Rapid identification of species is recommended.
- Culture (either solid or liquid) is required to monitor MDR-TB patients' treatment.

# Phenotypic (culture-based) drug-susceptibility testing (DST)

- Phenotypic DST is recommended for national or regional-level laboratories.
- Phenotypic DST requires a high level of biosafety precautions.
- In many settings and patient groups, rifampicin resistance is a good proxy for MDR-TB.
- DST for second-line agents should be performed for all patients with MDR-TB.
- Phenotypic DST for second-line agents is required to confirm or exclude XDR-TB.

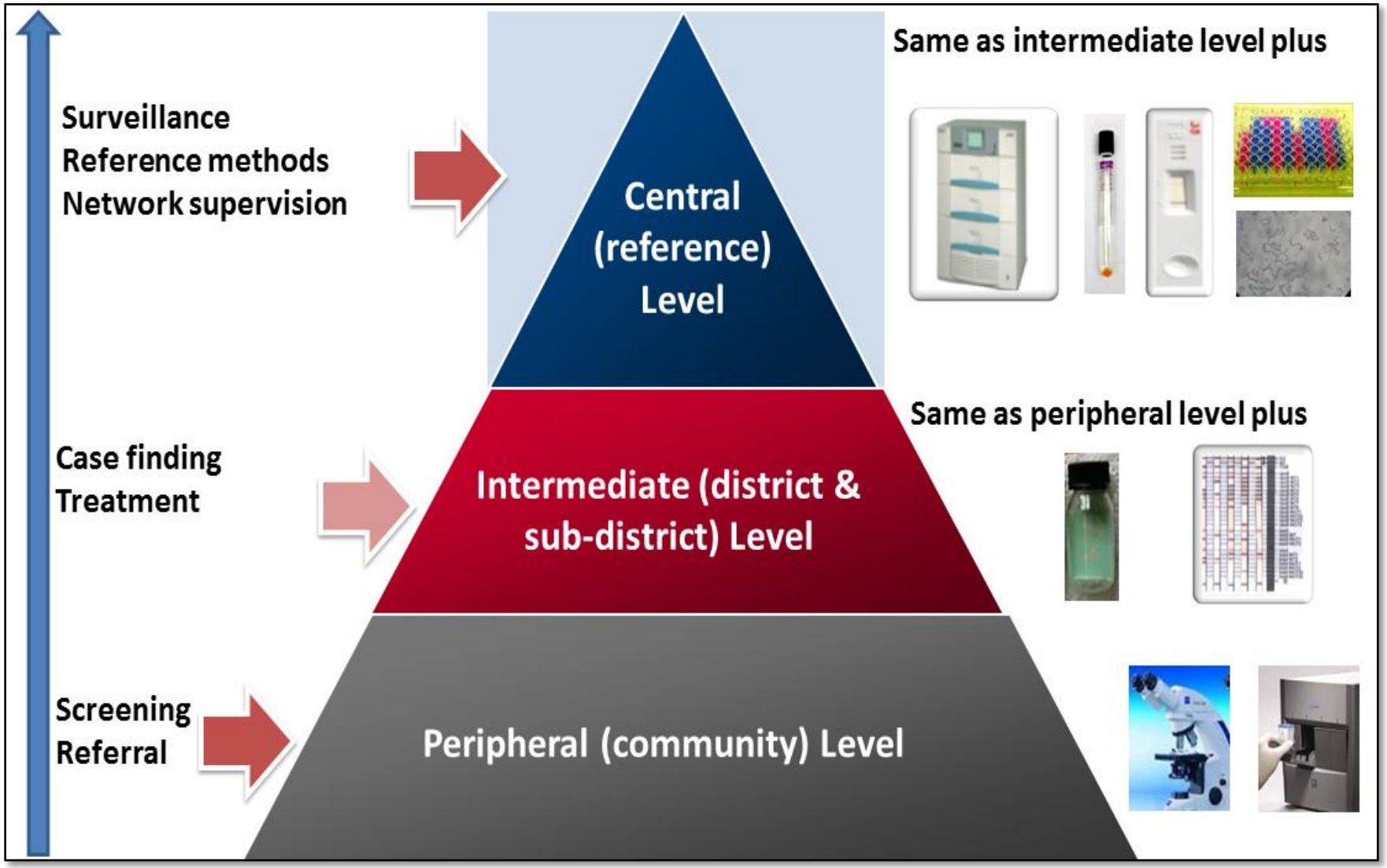
# Line probe assay (LPA)

- LPA is recommended for national or regional laboratories to detect rifampicin resistance alone or in combination with isoniazid resistance.
- LPA is recommended for use only on smear-positive specimens and *M. tuberculosis* isolates.
- LPA requires at least 3 separate rooms to avoid cross-contamination.
- LPA requires moderate to high levels of biosafety precautions.
- LPA cannot be used to monitor treatment.
- LPA for second-line DST is not recommended; phenotypic DST is still required to detect XDR-TB.

# Xpert MTB/RIF assay

- The Xpert MTB/RIF assay is suitable for all levels of laboratories where appropriate infrastructure is available and there is a case-load that matches the capacity of the instrument.
- The test detects both TB and rifampicin resistance.
- It can be used as a stand-alone diagnostic test.
- The test requires an uninterrupted and stable electrical power supply, yearly calibration of the modules, and an ambient temperature of 15–30 ˚C. Cartridges and reagents should be stored at 2–28 ˚C.
- The test cannot be used to monitor treatment
- DST is required to detect resistance to anti-TB agents other than rifampicin.

# A well functioning, tiered laboratory network is a key component in TB control



# Peripheral laboratory

**Peripheral laboratories:**

- Are located within a general dispensary, clinic or hospital
- Have limited services for TB diagnosis that may include
  - Sputum specimen collection
  - Sputum-smear microscopy
  - Xpert MTB/RIF testing
- Should participate in external quality assurance (EQA) programmes

# Intermediate laboratory

**Intermediate-level laboratories:**

- Are in regional or large hospitals
- Have expanded services for TB diagnosis that may include
  - Sputum specimen collection
  - Sputum-smear microscopy
  - Xpert MTB/RIF testing
  - Culture and identification of *M. tuberculosis*
  - LPA
- Provide support for peripheral laboratories
  - Supply reagents and materials
  - Offer training, supervision, EQA of sputum-smear microscopy and Xpert MTB/RIF testing.

# Central laboratory

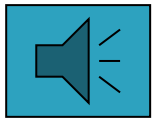
**Central laboratories:**

- Are at the country, provincial or state level
- Provide comprehensive services for TB diagnosis that may include
  - Sputum specimen collection
  - Sputum-smear microscopy
  - Xpert MTB/RIF testing
  - LPA
  - Culture and identification of *M. tuberculosis*
  - DST for first-line and second-line anti-TB agents
- Provide support for the laboratory network
  - Organizing and participating in training, providing supervision and EQA of sputum-smear microscopy, Xpert MTB/RIF testing and culture; offering advice on procurement
- Engage in other activities
  - Participate in operational research, drug-resistance surveillance.

# Summary

- TB is an infectious disease that mainly affects the lungs but can affect any part of the body.
- Although one third of the world's population is infected, only 10% of immunocompetent people infected with TB will develop active TB disease during their lifetime. Being HIV-positive increases the risk of developing TB disease: people coinfected with HIV and TB have a 10% annual risk of developing active TB.
- WHO recommends using the Xpert MTB/RIF assay to diagnose pulmonary TB, and on selected specimens to diagnose extrapulmonary TB.
- The TB laboratory network plays a critical role in TB control, and is generally organized into 3 levels: central, intermediate and peripheral. Each level has well defined technical or managerial tasks, or both.
- Since 2007 WHO has endorsed different technologies, and defined for each technology the appropriate level of implementation within the laboratory network.

# Assessment



- How is TB transmitted and which factors influence the risk of infection?
- What are WHO's recommendations for using the Xpert MTB/RIF assay?
- For which specimens does WHO recommend using LPA testing?
- Describe the general organization of a TB laboratory network, and at which levels different diagnostic tests should be used.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