An overview on tuberculosis and on anti-tuberculosis drug safety's issues, monitoring and management (aDSM)

1 The pathology of tuberculosis

1 E-learning objectives

The general objectives of this module are:

• Increase student's knowledge on key features of tuberculosis (TB) and its causative agent, M. tuberculosis;

• Increase student's knowledge on TB epidemiology and pathophysiology.

2 Personal stories from TB Survivors

Thandiwe, from Ethiopia

My name is Thandiwe, I am Ethiopian and I have a form of tuberculosis (TB) which is resistant to many different drugs – known as 'multidrug resistant TB', or 'MDR-TB'. Since then I have received very good counselling, have learnt a lot about TB, and have begun to recover. I now know that TB is curable and preventable and I am hopeful for the future.

……ending the TB epidemic by 2030 is one of the health targets of the Sustainable Development Goals (WHO 2019) (Figure 1) (1,2)

Figure 1: The End of Tuberculosis (WHO Image)

Floyd, from Zambia

When I was six years old, I suffered from tuberculosis. When I walked, I would fall down after every two steps. I was seriously malnourished; my stomach was also completely bloated because of the TB. I was born with HIV. My parents both died of

AIDS. After their death I was brought to other members of my family, but nobody wanted to take care of me. They shunned me because I was covered with stinking sores and wounds. I was also mistreated. Fortunately, I ended up in the Transit Home. I became healthy again. They gave me TB medication and AIDS inhibitors. They made sure I finished my treatment. I felt good and happy again." (3)

You can see his story on You-Tube (4)

3. Key facts

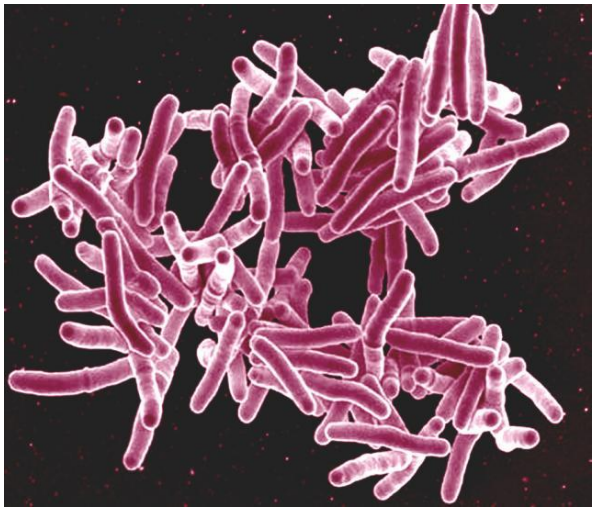
- Tuberculosis (TB) is a human disease caused by the bacteria *Mycobacterium tuberculosis*. It mainly affects the **lungs**.
- The pulmonary disease is the most common presentation, but many other organs (, gastrointestinal system, lymphoreticular system, skin, central nervous system, musculoskeletal system, reproductive system, and liver) can be affected, since TB is a multi-systemic disease.
- TB is curable and preventable.
- TB is spread from person to person through the air.

4. Etiology

M. tuberculosis has the following characteristics (1,2):

- is an alcohol and acid-fast bacillus (neither gram-positive nor gram-negative because of very poor reaction with the Gram stain).
- is a non-spore forming, non-motile, obligate-aerobic, facultative, catalase negative, intracellular bacteria.
- has the presence of several lipids in the cell wall including mycolic acid, cord factor, and Wax-D.
- has **resistance** to several antibiotics
- has ability to survive under extreme conditions such extreme acidity or alkalinity, low oxygen situation and intracellular survival (within the macrophage)
- two TB-related conditions exist: **latent** TB infection and TB **disease**. Latent TB infection means people have been infected by TB bacteria but are not (yet) ill with the disease and cannot transmit the disease.

These features explain why tuberculosis is difficult to treat.



5. Epidemiology

Key facts:

- **In 2016:**
  - The World Health Organization (WHO, 2016) reported a 22% drop in global TB mortality from 2000 through 2015. There is a need to accelerate to a 4–5% annual decline to reach the 2020 milestones of the End TB Strategy. TB still accounts for a huge burden of morbidity and mortality worldwide and it is one of the top 10 causes of death worldwide (1,2).
- **In 2017**:
  - **10 million people fell ill with TB (about 0.15% globally)**
  - 1.6 million died from the disease (including 0.3 million among people with HIV)
  - 1 million children became ill with TB
  - 230 000 children died of TB (including children with HIV associated TB).
  - About 54 million lives were saved through TB diagnosis and treatment between 2000 and 2017.
  - In 2017: about 0.2% of African People had TB with about 2480000 (Nigeria about 20% with about 418000 cases, Ethiopia 9% with about 172000, Tanzania about 5% with about 108000, Eswatini, 0.15% with about 3500 cases) (see fig.2,3).

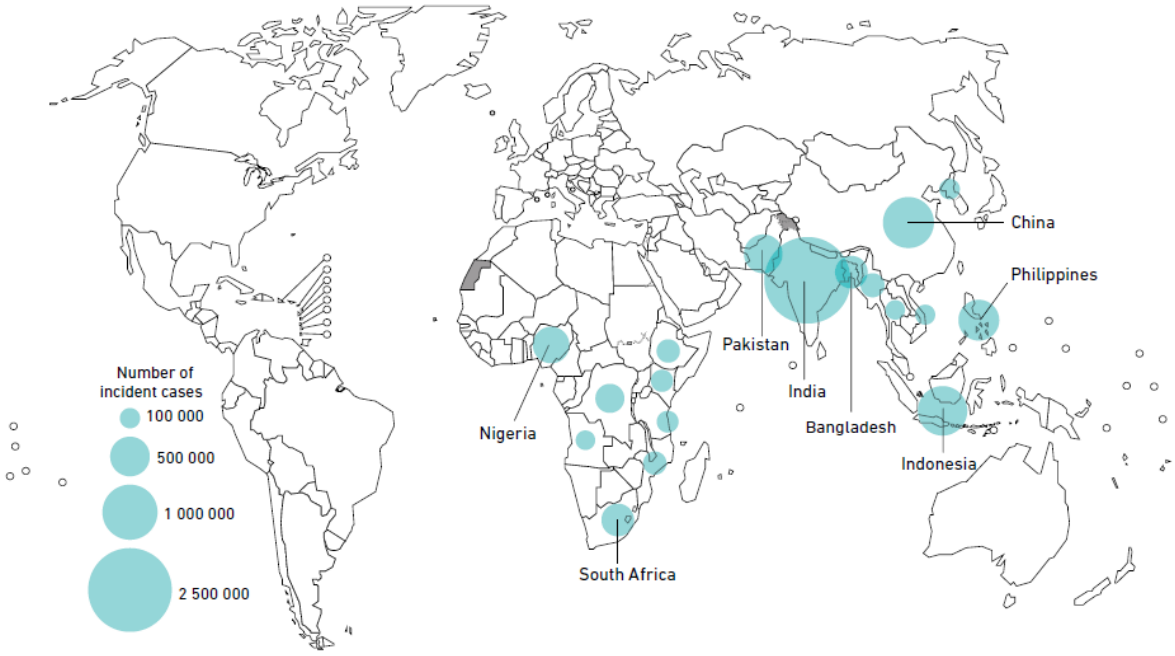


Fig. 2: Estimated TB incidence in 2017, for countries with at least 100 000 incident cases (WHO Report 2018)

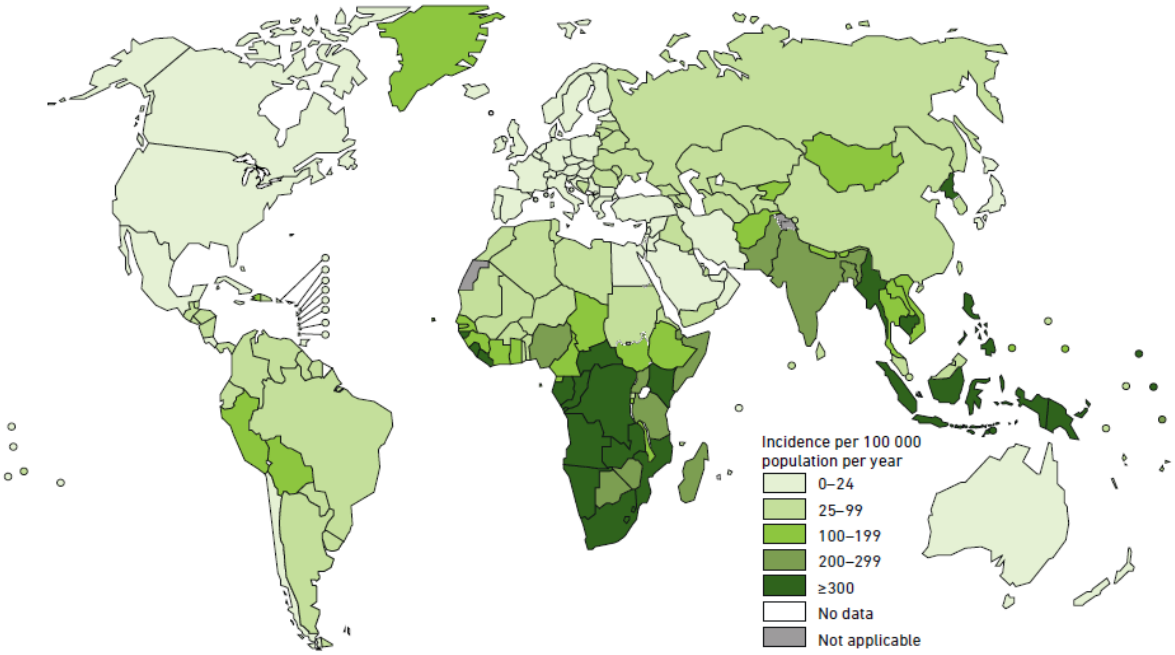


Fig. 3: Estimated TB incidence in 2017

- Six countries (India, Indonesia, China, Nigeria, Pakistan, and South Africa) account for 60% of TB death in 2015 (WHO, 2017). In addition to the six countries listed above, several

countries in Asia, Africa, Eastern Europe, and Latin and Central America continue to have an unacceptably high burden of tuberculosis.
- About one-quarter of the world's population has latent TB

6. Pathophysiology

The first contact of the Mycobacterium organism with a host leads to manifestations known as primary tuberculosis. This primary TB is usually localized to the middle portion of the lungs, and this is known as the Ghon focus of primary TB. In most infected individuals, the Ghon focus enters in a state of latency (latent TB infection). Secondary tuberculosis (TB disease) usually occurs because of reactivation of a latent tuberculosis infection or due to a re-infection. The lesions of secondary tuberculosis are in the lung apices (1,2)

Many people who have latent TB infection never develop TB disease. But some people who have latent TB infection are more likely to develop TB disease than others. Those at high risk for TB disease include:

- People with HIV infection
- People who became infected with TB bacteria in the last 2 years
- Babies and young children
- People who are sick with other diseases that weaken the immune system
- Elderly people
- People who were not treated correctly for TB in the past

7. Who is most at risk?

Major risk factors are:

- *Socio- economic factors*: Poverty, malnutrition, wars, children, people who use tobacco (7.9% of TB cases worldwide are attributable to smoking) (1,2).
- *Immunosuppression*: Persons with compromised immune systems, such as people living with HIV (people who are infected with **HIV** are 20 to 30 times more likely to develop active TB) (1,2).
- *Occupational*: Mining, construction workers, pneumoconiosis (silicosis) (1,2).

8. Key-points
- *M. tuberculosis* is an intracellular bacterium known to cause TB, a serious infectious disease that generally affects the lungs and that can be fatal;

- TB is one of the top 10 causes of death worldwide. In 2017, 10 millions cases of TB were reported globally and TB was estimated to have affected 2% of the whole Africa population;

- *M. tuberculosis* infection often leads to the development of primary TB. Secondary TB occurs after the disease becomes reactivated. TB major risk factors include socio-economic, occupational and health factors.

9. References

(1) https://www.who.int/tb/post2015_strategy/en/
(2) https://www.who.int/tb/en/
(3) https://www.kncvtbc.org/en/
(4) https://www.youtube.com/watch?v=YLo9MH2naMc

10 Intermediate Questionnaire

Which one of these systems of the human body is mainly affected by tuberculosis?

a. the central nervous system
b. the respiratory system
c. circulatory system
d. the urinary system

Teaching:

"It mainly affects the lungs. The pulmonary disease is the most common presentation, but many other organs (respiratory system, gastrointestinal system, lymphoreticular system, skin, central nervous system, musculoskeletal system, reproductive system, and liver) can be affected, since TB is a multi-systemic disease.".

***M. Tuberculosis* is:**

a. a non-spore forming, non-motile, gram-positive bacterium

b. a non-spore forming, non-motile, gram-negative bacterium

c. a non-spore forming, non-motile, intracellular bacterium

d. a spore forming, motile, intracellular bacterium

Teaching:

"*M. Tuberculosis* is … is an alcohol and acid-fast bacillus (neither gram-positive nor gram-negative because of very poor reaction with the Gram stain). (It) is a non-spore forming, non-motile, obligate-aerobic, facultative, catalase negative, intracellular bacteria.".

2 TB Drugs

1. E-learning objectives

The contents of this module are aimed at:

- Increasing student's knowledge on the different kinds of drugs that are used to treat TB and to the Active Drug Safety Monitoring and management Programme, a useful tool to monitor the usage of recently developed anti-TB drugs;

- Increasing student's knowledge on different types of drug-resistant TB, including multidrug-resistant TB and extensively drug-resistant TB.

2. First and second line drugs

More than twenty drugs have been developed for the treatment of TB (see medication cards for more information). Several TB drugs are often combined together in one tablet or pill in a Fixed Dose Combination.
There are two lines drugs:

- ✓ the **first line drugs**: only used for the treatment of new patients who are very unlikely to have resistance to any of the TB drugs.
- ✓ the **second line drugs**: only used for the treatment of drug resistant TB.

3. Drug-resistant tuberculosis

Drug-resistant TB continues to be a public health crisis.

- ✓ The best estimate is that, worldwide in 2017, 558 000 (mean value) people **0.008% globally**) developed TB that was resistant to rifampin (RR-TB), the most effective firstline drug, and of these, 82% (circa 457000) (**0.006 globally**) had multidrug-resistant TB (MDR-TB) (resistance to isoniazid and rifampin) (1,2).
- ✓ In 2017: about 0.008% of African People had MDR/RR-TB with about 80000 cases (Nigeria about 0.01% with about 24000 cases, Ethiopia 0.005% with about 5000, Tanzania about 0.003% with about 2000 cases, Eswatini 0.03% with about 340 cases) (see fig.4) (1,2).

Fig. 4: Estimated incidence of MDR/RR-TB (multi-drug resistance, rifampin resistance) in 2017 for countries with at least 1000 incident cases.

4. Extensively drug - resistant tuberculosis (XDR-TB)

It is a form of TB which is resistant to at least four of the core anti-TB drugs (1,2). It involves resistance to:

- the two most powerful anti-TB drugs (isoniazid and rifampin), also known as **multidrug-resistant** (MDR-TB):
- o and any of the fluoroquinolones (such as ofloxacin or moxifloxacin)
- o and at least one of the three injectable second –line (amikacin, capreomycin or kanamycin).

5. The treatment with new drugs

- ✓ Two new drugs (bedaquiline and delamanid) are in confirmatory phase 3 trials, having received accelerated approvals for MDR tuberculosis based on phase 2 data in 2012, and 2014, respectively.

- ✓ An active surveillance is needed to obtain a more complete picture of such new products' safety profiles and provide guidance on their (contra)indications (1,2).

- ✓ By the end of 2017, globally 68 countries reported having imported or started using bedaquiline and 42 countries had used delamanid. Most (79%) of the patients treated with bedaquiline were reported by two countries: the Russian Federation and South Africa (1,2).

6. Active Drug Safety Monitoring and management (aDSM) Programme

A special and new form of PV is aDSM for patients with drug-resistant (DR) forms of tuberculosis. Since 2013, after introduction of two new TB drugs (**bedaquilline** and **delamanid**), WHO recommends active TB-drug safety monitoring and management (aDSM) when using one of these drugs. aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs (part of which have not yet received full approval from international Food & Drug/Medicinal Authorities), novel MDR-TB regimens or extensively drug-resistant (XDR)-TB regimens to detect, manage and report suspected or confirmed adverse drug reactions.
The overall objectives of aDSM are to reduce risks from drug-related harms in patients on treatment for drug-resistant TB and to generate data to inform future policy updates on the use of such medicines.aDSM is seen as an active and systematic way of patient monitoring to be incorporated in the programmatic management of patient with DR-TB.
The WHO presents three different aDSM packages: in the core package, only serious adverse events are to be reported. In the intermediate package, apart from the serious adverse events, also adverse events of special interest should be reported, and the advanced package targets all adverse events of clinical interest. Full cohort event monitoringis not deemed feasible for routine monitoring of DR-TB patients. There is also an aDSM WhatsApp group which is currently used for planning of meetings, sharing the minutes of these meetings and for dissemination of PV information.

7. Key-points

- **TB can be treated effectively by using first line drugs or second line drugs, according to the different types of TB that are to be treated;**

- **The usage of new anti-TB drugs should be monitored with active TB-drug safety monitoring and management programmes aimed at reducing the risks associated to drug-related harms in patients who take new anti-TB drugs.**

8. References

(1) https://www.who.int/tb/post2015_strategy/en/
(2) https://www.who.int/tb/en/

9 Intermediate Questionnaire

What is extensively drug-resistant tuberculosis (XDR-TB)?

a. a type of TB that is resistant to first line drugs only

b. a type of TB that is resistant to second line drugs only

c. a type of TB that is resistant to at least three of the anti-TB core drugs

d. a type of TB that is resistant to at least four of the anti-TB core drugs

Teaching:

"It is a form of TB which is resistant to at least four of the core anti-TB drugs.".

An active Drug Safety Monitoring and management (aDSM) Programme is:

a. a clinical trial specifically designed to assess the efficacy of new anti-TB drugs

b. a clinical trial specifically designed to assess the safety of new anti-TB drugs

c. a new methodology used to detect, manage and report suspected or confirmed ADRs in patients on treatment with new anti-TB drugs

d. a new database used **to collect reports of anti-TB drugs-related ADRs**

Teaching

"**aDSM is defined as the active and systematic clinical and laboratory assessment of patients on treatment with new TB drugs (part of which have not yet received full approval from international Food & Drug/Medicinal Authorities), novel MDR-TB regimens or extensively drug-resistant (XDR)-TB regimens to detect, manage and report suspected or confirmed adverse drug reactions.".**