Superbugs:

Investigating Drug-Resistant Tuberculosis

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~Problem~

About 25% of the world's population has tuberculosis (TB), either latent (dormant) or active. Compared to a COVID patient, who infects an average of 2 to 3 people, an active TB patient infects an average of 5 to 15 people. Although TB can be fully cured by taking medications regularly for 6 to 9 months, drug-resistant strains and other factors, such as underlying health conditions, make it harder to cure.

In my project, I researched tuberculosis, focusing on its diagnosis, transmission, prevention, and treatment. In addition, I investigated the biology of drug-resistant TB and explored the recent advancements in diagnostics and treatment.

The main purpose of this study is to raise awareness of tuberculosis and how it is becoming a growing problem in society — the number of cases of drug-resistant tuberculosis has been increasing. If more people become aware of this lethal disease, then we can all take proper steps to protect ourselves and others, and hopefully we can eradicate this disease once and for all.

~Method~

I used mainly three groups of sources for my research:

- Educational websites (such as Khan Academy)
- Educational YouTube channels (such as Kurgezagt—In a Nutshell and Ninja Nerd)
- Research articles from the National Library of Medicine, and Frontiers in Cellular and Infection Microbiology

Firstly, I watched the videos and read the articles a few times. Then, I took notes of anything that was relevant to my project. Finally, when writing the research paper, I reread all the notes a few times before choosing the most important ones to keep in the paper.

~Research~

What is Tuberculosis?

Tuberculosis, commonly known as TB, is an extremely infectious disease caused by the bacteria *Mycobacterium tuberculosis*. It is a pulmonary disease, which means it affects the lungs. TB spreads mainly via cough droplets when the infected person coughs or sneezes.

Overview of the Lungs

The lungs normally resemble balloons that expand when someone inhales air and contract when the person exhales. Their main job is to transport oxygen from the air into the bloodstream and release carbon dioxide from the body into the air. This process is called gas exchange.

TB Pathogenesis

If the tuberculosis bacterium were to enter someone's lungs, the macrophages[1] quickly attack the bacterium and trap it in their phagosome[2], which is flooded with acids. But the bacterium has a thick, waxy coat that makes the acids completely harmless. The bacterium then replicates inside the macrophage extremely slowly, doubling every 18 to 24 hours, which is at most 60 times slower than many other microbes, such as *E.coli*[3].

Eventually, the infected cells die, and the bacteria infect new cells. As more and more cells are infected and killed, an immune response is initiated. The immune system does its best to get rid of the bacteria. If the bacteria cannot be destroyed, the immune system does the next best thing, which is to form a granuloma[4] around the bacteria. As long as the bacteria are contained, the patient

will not show any symptoms. This is latent TB, which is kind of the stalemate version of TB. Roughly 2 billion people in the world have latent TB.

Active TB and Symptoms

Normally, the body is able to keep the disease under control. But if the body is unable to contain the growth of the bacteria, granulomas can burst, and the disease transitions from latent to active. 1 in 10 people may transition from latent to active TB.

The immune system 'panics' with the abundance of TB bacteria in the lungs, resulting in inflammation and difficulty breathing. Some other symptoms include:

- A bad, dry cough lasting more than 2 to 3 weeks with or without blood
- Severe weight loss
- A high fever
- Night sweats and chills
- Pneumonia
- *Erythema nodosum* [5]
- *Phlyctenular keratoconjunctivitis* [6]

Extrapulmonary TB

Tuberculosis is most commonly a pulmonary disease, but if it gets really severe, the bacteria can spread to other parts of the body (Figure 1). If it spreads, TB infects the lymph nodes, genitourinary system[7], bones, the nervous system, the gastrointestinal tract[8] and the heart.

Scrofula is a swelling of the lymph nodes, typically on the neck, caused when TB infects the lymph nodes. Urogenital TB happens when TB infects the genitourinary system and is one of the most common forms of extrapulmonary TB.

Pott's disease is when TB infects the bones, most commonly the spinal cord. Though TB does not normally affect the brain, if it does, it causes life-threatening meningitis TB, which is inflammation of the membranes covering the brain and spinal cord. Miliary TB is a severe widespread form of TB and is more common in the elderly or those who have a weakened immune system.

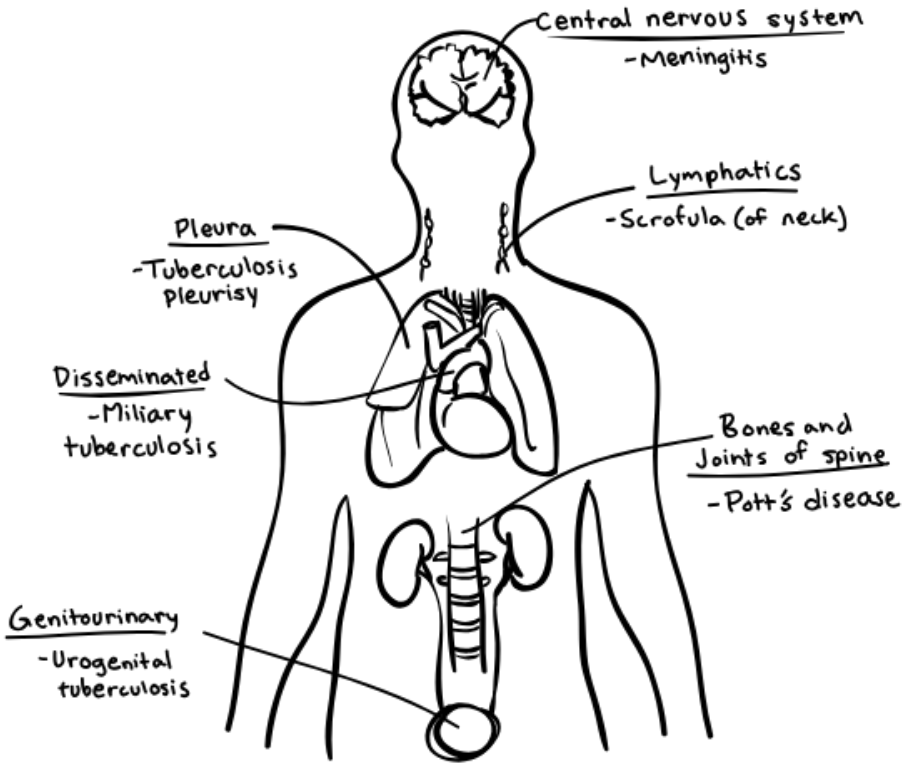


Figure 1 - Extrapulmonary TB

https://www.khanacademy.org/science/health-and-medicine/infectious-diseases/tuberculosis/a/what-is-tuberculosis

Who Is Most at Risk?

Tuberculosis is extremely contagious, especially if someone lives with an active TB patient, but other factors increase the chances of getting TB. Some include:

- Age
- Having certain diseases, such as HIV[9] or cancer, that reduce the function of the immune system
- Taking immunosuppressive medications[10]
- Living in crowded and/or poorly ventilated areas
- Living in poverty or being malnutritioned[11]
- Lacking access to proper medical care
- Substance abuse[12] (e.g. drugs)
- Living in prisons or jails.

Diagnosing TB

1/3 of the people with active TB don't get diagnosed. The most common way to test for TB is the tuberculosis/tuberculin skin test (Figure 2). A small amount (0.1 ml) of dead *Mycobacterium tuberculosis* is injected under the skin of the forearm. If a red bump appears after 48 to 72 hours, depending on the size of the bump and the patient's current health, it's considered positive. But this test is not always accurate.

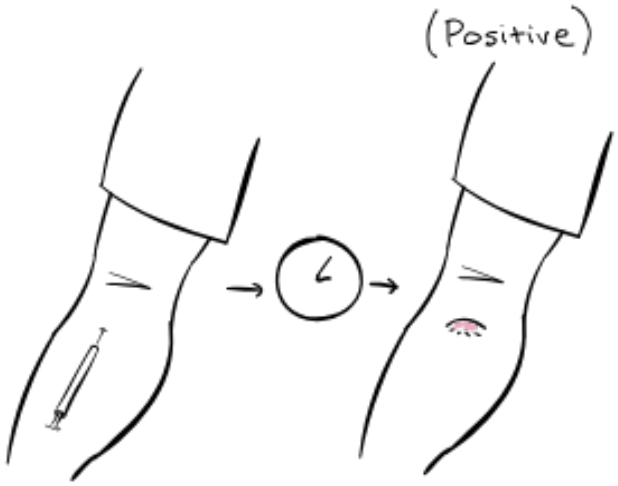


Figure 2 - Tuberculin Skin Test

https://www.khanacademy.org/science/health-and-medicine/infectious-diseases/tuberculosis/a/what-is-tuberculosis

Categorizing the Results of a Tuberculin Skin Test

	Conditions	Size of Bump
High Risk	• Suspect TB • Live with an active TB patient • Immunocompromised[13]	5mm - >15mm
Medium Risk	• Immigrated from a country with a high TB rate • Live/work in large-group settings • Healthcare worker • IV drug use • Under the age of 5 • Comorbidities[14]	10mm - >15mm
Low Risk	• Anyone else	>15mm

A chest x-ray or CT scan is used to check for granulomas or other signs of active TB in the lungs.

A sample of sputum, which is a thick mucus coughed up from the lungs, is sent to a laboratory, where it is checked for TB. While this test is accurate, it may take about 4 to 6 weeks.

A molecular test or a polymerase chain reaction test, known as a PCR, may also be used to detect TB.

Now, there is a rapid diagnostic test for TB called the Xpert MTB/RIF (MTB → *Mycobacterium tuberculosis*; RIF → Rifampin). This test requires a sample of sputum to determine whether the patient has TB and whether it's resistant to Rifampin, which is a drug used to treat TB.

Preventing Transmission of Active TB

As TB is an airborne disease, coughing is the most common way it spreads. If someone with active TB coughs, lots and lots of bacteria will be floating in the air.

When preventing the transmission of active TB, lots of components are important, including:

- Wearing a mask, especially in the first 2 to 3 weeks after diagnosis (e.g. when around other people, when leaving the house for medical appointments, when healthcare providers are present and during transport)
- Isolating oneself, especially in the first 2 to 3 weeks after diagnosis (e.g. from general public/public transportation, from visitors, from household guests and from high-risk individuals)
- Diluting (i.e. opening doors and windows, turning on the fan, etc.)
- Social distancing

- Taking medication at proper times consistently

The Four I's

The 'four i's' method is used for preventing and treating TB. It stands for intensified case finding, Isoniazid, isolation and immunization.

Intensified case finding is to keep in mind certain populations that are affected the most by TB. These include immigrants or migrant workers from countries with a high TB rate, prisoners, homeless people, IV drug users and patients with HIV/AIDS.

Isoniazid is one of the 4 main drugs used to treat active TB. It is also used against latent TB with a 90% success rate. Even though it significantly reduces the chances of getting progressive secondary TB[15], it still takes 9 to 12 months to fully cure the latent TB infection.

Isolation is used to prevent the transmission of active TB. Typically, the patient is contained in a single room with protected airflow, and any visitor is required to wear a N95 mask[16].

Immunization (BCG vaccine) is available for TB, but it is not very effective for adults. However, a systematic review and meta-analysis conducted in 2014 demonstrated that the BCG vaccine reduced infections by 19–27% and reduced progression to active tuberculosis by 71%. Vaccination is widely used in countries with high rates of TB and shown to be highly effective when applied to children.

Treatment

Treating tuberculosis prevents it from spreading and causing disabilities or death. A TB patient takes medication for about 6 to 9 months, although sometimes the regimen can be longer or shorter. A different set of medications is needed depending upon:

- If the patient has latent or active TB
- Where the infections are located
- The general health of the patient
- Whether the case is a drug-resistant strain or not

Normally, after a patient is diagnosed with active TB, they undergo therapy with 4 different drugs: Rifampin (RIF), Isoniazid (INH), Pyrazinamide (PZA) and Ethambutol (EMB) for about 2 months. Then they take only RIF and INH for approximately another 4 months. Sometimes, longer treatment is needed for certain reasons, including:

- Having meningitis TB[17] or miliary TB[18]
- Having HIV/AIDS
- Being pregnant
- Having drug-resistant TB

Also, the drugs may cause some side effects. Rifampin may cause hepatitis[19], thrombocytopenia [20] or drug interactions[21]. Isoniazid may cause hepatitis or peripheral neuropathy[22]. Pyrazinamide may cause high uric acid levels[23] or overt gout[24]. Ethambutol may cause optic neuritis[25].

What is Drug-Resistance and How Does it Occur?

Drug-resistance occurs when the micro-organism is able to withstand the drug used to treat it, making it harder to treat. It occurs in TB when the drugs are used incorrectly, either because the prescription was incorrect, the quality of the drugs was poor, or the treatment was stopped too early. Drug-resistance also occurs because the bacteria are continuously evolving.

Types of Drug-Resistant TB

There are many types of drug-resistant TB. Some include:

- Multiple drug-resistant TB (MDR-TB), which occurs when TB is resistant to at least Rifampin and Isoniazid.
- Rifampin-resistant TB (RR-TB), which occurs when TB is resistant to at least Rifampin.
- Extreme drug-resistant TB (XDR-TB), which is an extreme version of MDR-TB, where TB is resistant to:
    - Any Fluoroquinolone, which is a group of drugs (Levofloxacin and Moxifloxacin)
    - Any second-line drug (Capreomycin, Kanamycin, Streptomycin, Polypeptides and Amikacin)

Although patients with drug-resistant TB face a challenge in treatment, cure is likely with early identification and proper drug management.

Multiple Drug-Resistant TB:

There were many outbreaks of MDR-TB in the 1900s, and they were initially thought to be caused by nosocomial transmission[26]. While it is one of the main reasons for outbreaks, especially in busy hospitals, it is not the only reason.

In the 1900s, chaotic treatment was the main reason for MDR-TB outbreaks, since in most countries there were not proper systems for treating TB. Once drug-resistant TB became more common, directly observed therapy (DOT)[27] efficiently helped in treating TB.

In the early 2000s, scientists thought that gaining drug-resistance meant that the bacteria were weaker in other ways and that drug-resistance could not spread from bacterium to bacterium.

There are a few risk factors for getting MDR-TB. These include:

- A relapse of the infection after being treated
- Continuing treatment after a pause in treatment

- Living with someone who has MDR-TB
- Living in areas or countries with high chances of getting MDR-TB
- A HIV coinfection.

MDR-TB is difficult to treat because it's resistant to the first-line drugs (RIF, INH, PZA and EMB) and the second-line drugs tend to be weak and toxic. As a result, MDR-TB normally takes 18 to 24 months to be fully cured.

Biology of Drug-Resistance

When it comes to drug-resistance, there are two types: intrinsic and acquired. Intrinsic drug-resistance is when the bacteria are able to make the drug less effective and is usually present in all members of the bacterial family. Acquired drug-resistance is when bacteria have specific mutations that make them resistant.

The main mechanisms of drug-resistance in *Mycobacterium tuberculosis* are a thick cell wall and efflux pumps (Figure 3). In addition to these two, some bacteria may have cytosolic resistance.

The Cell Wall:

Mycobacterium tuberculosis has three layers: a base layer, called the *peptidoglycan*; the middle layer, called the *arabinogalactan*; and a thick, waxy coat made by mycolic acids. Water-dissolvable drugs cannot get past the waxy coat and fat-dissolvable drugs tend to get stuck in the wax. Hence multiple drugs are used so that one drug, such as Ethambutol, can crack the thick cell wall and other drugs, such as Rifampin and Isoniazid, can easily enter the bacterium and kill it from the inside.

Efflux Pumps:

Efflux pumps are proteins that are shaped as tunnels or pumps. Some efflux pumps use cellular fuel[28] while others use electrical gradients[29] to push out drugs.

Since the medications are ejected very quickly, they do not have enough time to kill the bacterium. Efflux pumps are a major reason for drug-resistance because *Mycobacterium tuberculosis* naturally has lots of them, and some strains develop mutations[30] that keep these pumps on permanently.

Cytosolic Resistance:

Cytosolic resistance is when the bacterium targets the medications that specifically attack the bacterium's ribosomes[31]. An enzyme[32] adds a small chemical to the bacterium's ribosome and as a result the drugs can no longer attack the ribosome, making them ineffective. The bacterium also produces enzymes that stick extra molecules onto the drug, changing its chemical shape[33], making it harmless. Some proteins in the bacterium are able to sense certain medications, and when they do, they instantly turn on a whole team of defense genes, including the efflux pumps.

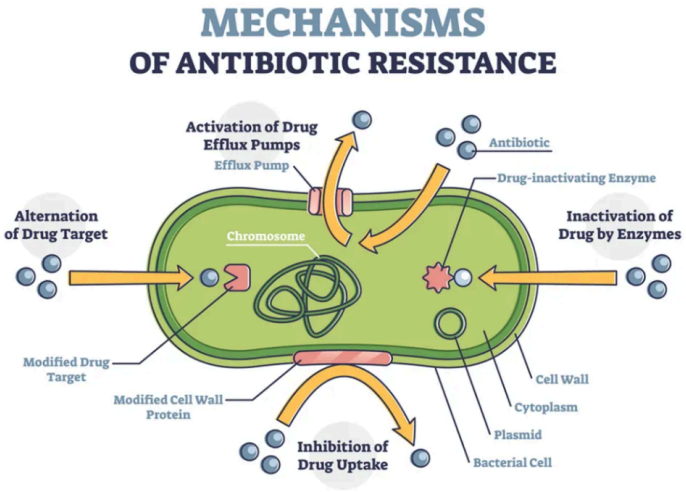


Figure 3 - Mechanisms of TB Drug-Resistance

https://cellmicrosystems.com/blog/experts-overcoming-obstacles-in-biofilms/

New Treatments and Diagnostics

One recent advancement in TB treatment is the 6-month BPaLM regimen, which includes Bedaquiline, Pretomanid, Linezolid and Moxifloxacin. It has a 89% success rate against MDR-TB and RR-TB.

New diagnostics include:

- Molecular tests
- Interferon gamma release assay tests (IGRA)
- Computer-aided detection (CAD)
- New skin tests that are more accurate in diagnosing TB

There are also new vaccines for TB in the making. There are 16 vaccines in progress and in clinical trials, with 6 in final phases. Some of them include M72/AS01E, which has a 50% efficacy[34], and the MTBVAC, which is targeting prevention in adolescents and adults.

New Treatments Against Drug-Resistant TB:

Recent advancements in treatment for TB focused on shortened, more effective, and less toxic and inconvenient treatments. New drugs, such as Bedaquiline and Pretomanid, are combined with older ones, such as Linezolid and Moxifloxacin, to make new treatment regimens.

There was a trial in South Africa called the Nix-TB (2015 to 2019) (Ravikoti et al., 2025) showing that the 6 month regimen of Bedaquiline, Pretomanid and Linezolid (BPaL) had a 90% success rate against MDR-TB and XDR-TB, but noted that high doses of Linezolid caused significant side effects. Another trial called ZeNix (2017 to 2019) (Ravikoti et al., 2025) reported that lower doses of Linezolid was still effective with less side effects. Other trials showed that adding Moxifloxacin (BPaLM) resulted in better success rates (89%) and fewer side effects than longer treatments, which had 52% success rate. Other trials, like

endTB, endTB- and BEAT India, have shared promising results, mainly shorter and more effective treatments for MDR-TB and XDR-TB. New WHO guidelines include 6 months of the BPaLM regimen for those with MDR-TB or RR-TB and the BPaL regimen for those with pre-XDR-TB.

The BPaLM/BPaL regimen represents advancements in TB treatment, but there are still a few notes to keep in mind. Firstly, the safety of Pretomanid has not been studied for those 14 and under and for pregnant women. Secondly, patients with a history of QT prolongation[35] or electrolyte imbalances[36] are at a higher risk of getting QT interval prolongation[37] when treated with Bedaquiline and Moxifloxacin. Also, Linezolid can cause severe side effects, such as myelosuppression[38]. Thirdly, a low CD4 count[39] in TB patients may impact the tolerance and increase the risk of severe side effects. Finally, while effective for most types of TB, the BPaLM regimen is not recommended for TB affecting the central nervous system, osteoarticular TB[40] or miliary TB.

New Diagnostics:

There are also many recent advancements in diagnostics for TB, which include:

- Molecular tests for testing TB and drug-resistance
- IGRAs for detection
- Biomarker-based assays for detecting, diagnosing and monitoring TB
- CADs for TB screening
- Aerosol-capture technologies to prevent transmission
- 3 skin tests for TB were approved in 2022, mainly improving the specificity[40]

Glossary

1. ***macrophages*** – a large phagocytic cell found in stationary form in the tissues or as a mobile white blood cell, especially at sites of infection
    1.1. ***phagocytic*** – the ability of certain cells (phagocytes) to engulf, ingest and destroy foreign particles, microorganisms or dead cells via a process called phagocytosis
2. ***phagosome*** – a membrane-bound sac (vesicle) formed inside a cell to surround and trap large ingested particles, such as bacteria or debris
3. ***E.coli*** – a common type of bacteria that lives in the intestines and can be helpful or harmful
4. ***granuloma*** – a small, organized cluster of immune cells produced in response to infection, inflammation or the presence of a foreign substance, such as micro-organisms
5. ***erythema nodosum*** – a skin condition causing painful, red and tender bumps most commonly on the shins
6. ***phlyctenular keratoconjunctivitis*** – a hypersensitivity immune reaction of the cornea and conjunctiva to foreign antigen
7. ***genitourinary tract*** – both the urinary organs and the reproductive organs
8. ***gastrointestinal tract*** – the system, starting at the mouth, that digests food, absorbs nutrients and gets rid of waste
9. ***HIV (human immunodeficiency virus)*** – a virus that attacks the immune system
10. ***immunosuppressive medications*** – drugs that inhibit or reduce the strength of the body's immune system
11. ***malnutritioned*** – deficiencies, excesses or imbalances in a person's intake of energy and/or nutrients

12. ***substance abuse*** – *a harmful addiction to a specific substance, especially alcohol and drugs*
13. ***immunocompromised*** – *having an impaired immune system*
14. ***comorbidities*** – *the simultaneous presence of two or more diseases or medical conditions in a patient*
15. ***progressive secondary TB*** – *an active form of TB that occurs when a previous, latent infection, which is commonly from years prior, reactivates due to a lowered immune system*
16. ***N95 mask*** – *a tight-fitting mask that filters at least 95% of all airborne particles*
17. ***meningitis TB*** – *a severe, often fatal form of inflammation of the membranes (meninges) surrounding the brain and spinal cord*
18. ***miliary TB*** – *a severe, widespread form of tuberculosis where bacteria enter the bloodstream and spread throughout the body*
19. ***hepatitis*** – *an inflammation of the liver*
20. ***thrombocytopenia*** – *an abnormally low number of platelets in the blood*
21. ***drug interactions*** – *when a substance changes how a medication works in the body, potentially making it less effective, more potent or causing new side effects*
22. ***peripheral neuropathy*** – *damage to the peripheral nervous system, which consists of nerves outside the brain and spinal cord*
23. ***high uric acid levels*** – *when the body produces too much uric acid or fails to filter enough out through the kidneys*
24. ***overt gout*** – *the active, clinically apparent stages of gouty arthritis with noticeable signs of inflammation*
    24.1. ***gouty arthritis / gout*** – *a painful form of inflammatory arthritis caused by high uric acid levels in the blood*

25. ***optic neuritis*** – inflammation of the optic nerve, the cable connecting the eye to the brain
26. ***nosocomial transmission*** – the spread of pathogens within a healthcare setting (e.g. hospitals)
27. ***DOT (directly observed therapy)*** – a strategy where a healthcare worker or designated person watches a patient take each dose of their medication to ensure they swallow it, confirming adherence and monitoring for side effects
28. ***cellular fuel*** – biochemical substances, primarily Adenosine Triphosphate (ATP), that provide the necessary energy for all biological processes within an organism's cells
29. ***electrical gradients*** – the difference in net electrical charge between two regions, such as across a cell membrane, resulting in a force that drives the movement of ions
30. ***mutations*** – a permanent alteration in the DNA sequence of an organism or virus, acting as the raw material for genetic variation and evolution
31. ***ribosomes*** – a complex cellular machine, composed of ribosomal RNA (rRNA) and proteins, responsible for protein synthesis in all living cells
    31.1. ***protein synthesis*** – the fundamental biological process where cells generate new proteins — essential for structure, function, and regulation — by assembling amino acids into polypeptide chains based on genetic instructions from DNA
32. ***enzyme*** – a substance produced by a living organism which acts as a catalyst to bring about a specific biochemical reaction.
33. ***chemical shape*** – defines the three-dimensional arrangement of atoms and chemical bonds within a molecule
34. ***efficacy*** - the ability to produce a desired or intended result

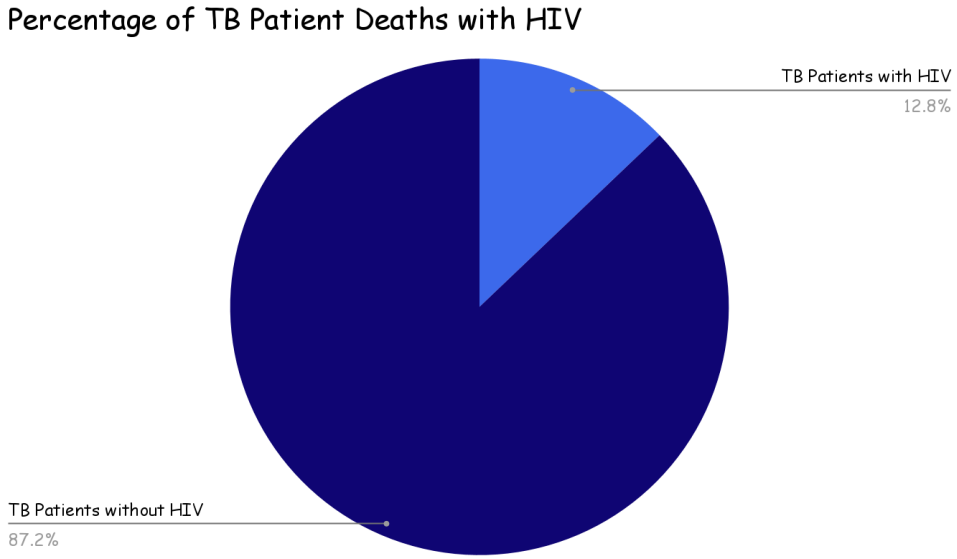
35. ***QT prolongation*** – the heart's lower chambers (ventricles) take longer than normal to recharge between beats. (*QT prolongation* is a more general term, whereas *QT interval prolongation* is a more specific term)
36. ***electrolyte imbalances*** – the levels of essential minerals — such as sodium, potassium, calcium, magnesium, etc. — in your body become too high or too low
37. ***QT interval prolongation*** – the heart's lower chambers (ventricles) take too long to recharge electrically between beats
38. ***myelosuppression*** – a form of bone marrow suppression where bone marrow activity decreases, reducing the production of blood cells
39. ***low CD4 count*** – fewer than 500 cells/mm^3, indicating a weakened immune system
40. ***osteoarticular TB*** – a form of extrapulmonary TB characterized by the infection of bones and joints
41. ***specificity*** – measures a diagnostic test's accuracy; high specificity identifies true negatives (i.e. healthy patients) and minimizes false positives
    41.1. ***sensitivity*** – measure a diagnostic test's accuracy as well; high sensitivity identifies true positives (i.e. sick patients) and minimizes false negatives
    41.2. ***true positives*** – the person is ill with a condition and the diagnosis correctly identifies that they are ill
    41.3. ***true negatives*** – the person is healthy and the diagnosis correctly identifies that they are healthy
    41.4. ***false positives*** – the person is healthy, but the diagnosis incorrectly identifies that they are ill with a condition
    41.5. ***false negatives*** – the person is ill with a condition, but the diagnosis incorrectly identifies that they are healthy

~Data~

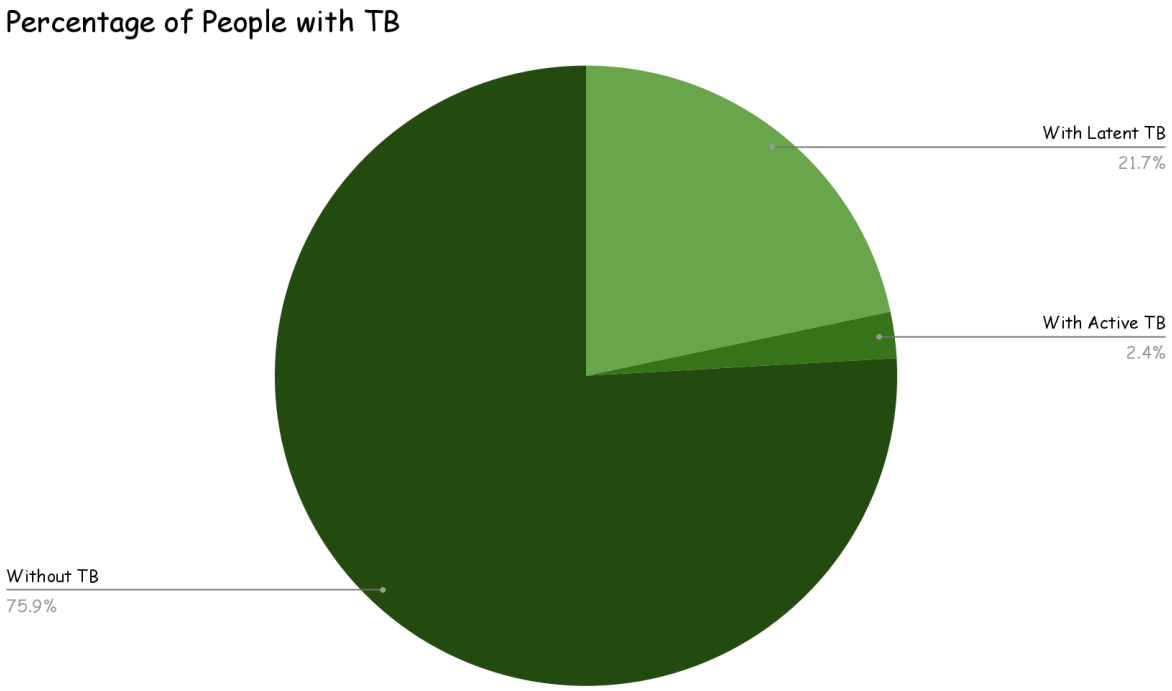
Real-World Statistics:

1) A COVID patient infected an average of 2 to 3 people. An active TB patient infects 5 to 15 people on average (Green, 2024).

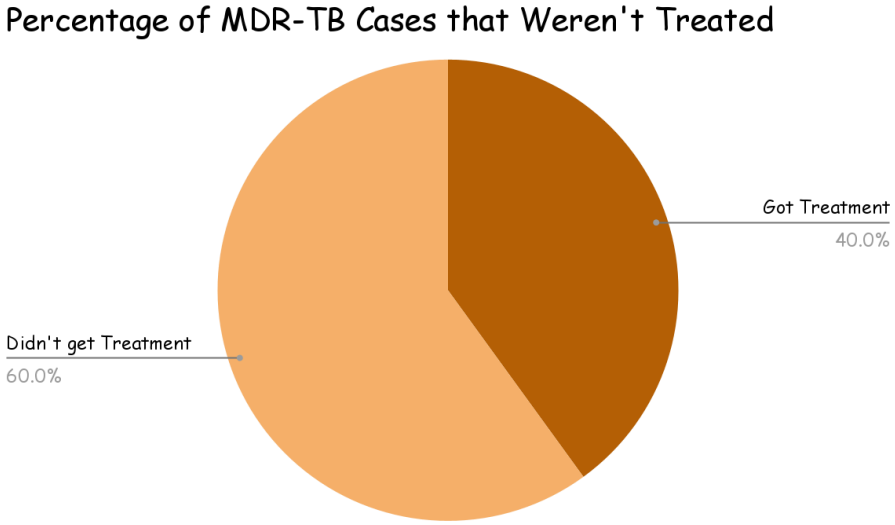
2) 1.3 million people died of TB in 2022. Out of those, 167 thousand people had HIV (~1/8 of the total who died of TB) (Green, 2024).



3) An estimated 2 billion people have latent TB (~1/4 of the total population) and an estimated 1 in 10 people with latent TB will progress to active TB (200 million people; ~1/40 of the total population) (Green, 2024).

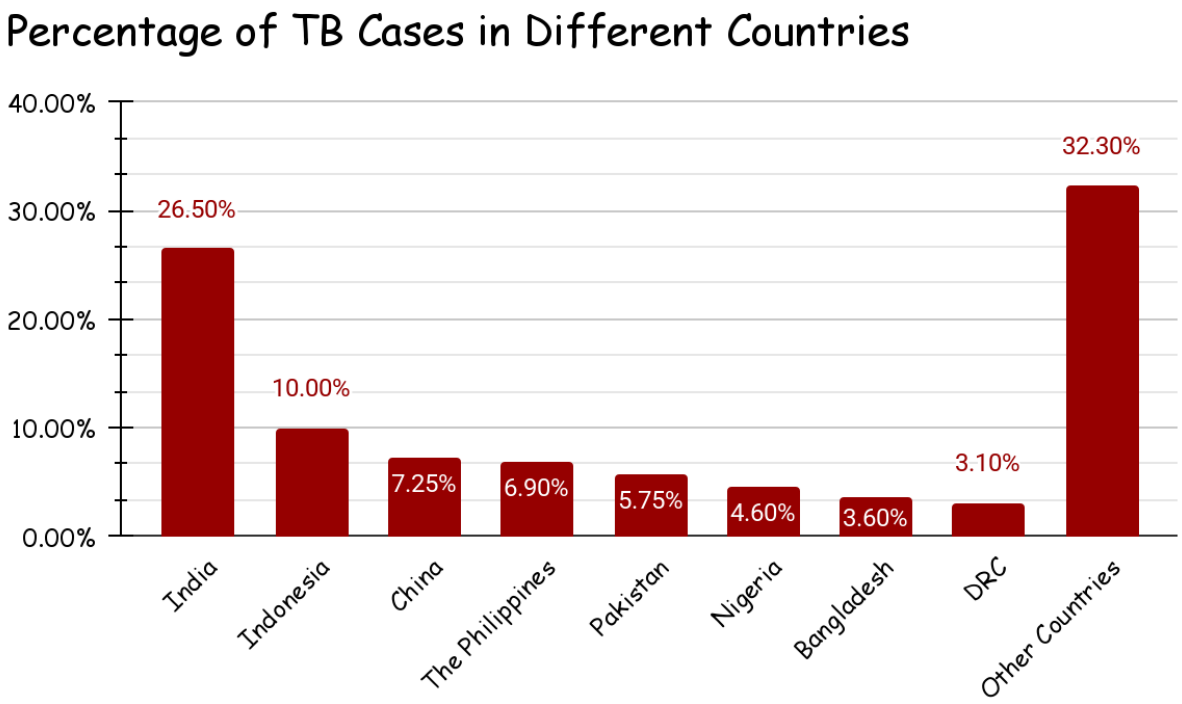


4) An estimated 3 in 5 people with MDR-TB did not get treatment (World Health Organization, 2025).



5) In Canada, there were 1971 cases of active TB reported in 2022 (5.1 per 100 thousand people) (Public Health Agency of Canada, 2025).

6) India, Indonesia, China, the Philippines, Pakistan, Nigeria, Bangladesh and the Democratic Republic of the Congo (DRC) are responsible for ~2/3 of all global TB cases (Ravikoti et al., 2025).



~Conclusion~

Tuberculosis, commonly called TB, is an extremely contagious pulmonary disease caused by Mycobacterium tuberculosis and generally takes about 6 to 9 months to cure. However, the drug-resistant variant provides an extra challenge to cure.

Drug-resistance is when the micro-organism is able to combat against the medicine used to treat the disease, making it harder to cure. Mycobacterium tuberculosis has 2 main factors for drug-resistance — a thick cell wall and efflux pumps — with an addition of cytosolic resistance in some bacteria. The thick, waxy cell wall prevents some drugs from getting inside the bacterium, and the efflux pumps eject the drugs out of the bacterium before the drugs can do any harm. Cytosolic resistance is when the bacterium targets specific drugs that attack its ribosome.

While drug-resistant TB may seem difficult to cure, humanity is taking a stand against it. Recently, 4 new drugs — Bedaquiline, Pretomanid, Linezolid and Moxifloxacin — were created to fight against drug-resistant TB. These 4 drugs make up the BPaLM regimen, which has a 89% success rate against multiple drug-resistant TB and Rifampin resistant TB. There were also many new diagnostics created in the past decade, including 3 new skin tests, improving the detection and specificity.

Although humanity has made many advancements in TB diagnostics and treatment in the past few decades, more research still has to be done to eradicate this lethal disease, once and for all.

~Acknowledgements~

I would like to thank my parents for their continuous support, my science fair teachers for their guidance, and my mentors for their help and guidance as well. Finally, I would like to thank you for taking the time to read my project and learn more about this deadly disease.

~Citations~

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Images -

Figure 1: Extrapulmonary TB

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Figure 2: Tuberculin Skin Test

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Figure 3: Mechanisms of TB Drug-Resistance

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