

# **Is antibiotic resistance in tubercle bacillus a threat to humans?**

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*About two million people are killed every year by the bacterial infection disease tuberculosis (Tb), which makes it the second leading infectious cause of death, next after HIV (human immunodeficiency virus). Mycobacterium tuberculosis is the agent that causes the infection and is spread through the air. An airborne bacterium can cause an enormous distribution and therefore it is of great interest to cure Tb so the global health issue is reduced. Different therapy strategies, of which the main one was antibiotics, were introduced in the late 19<sup>th</sup>- and the following 20<sup>th</sup> century and managed to restrict and reduce the disease. Nowadays we have reached a critical point since M. tuberculosis evolved a defense against many antibiotics and no longer is eliminated in our attempt to cure the disease. This summary will elucidate the mechanisms of the tuberculosis infection, how the bacteria evolved a defense and how we can prevent it. Should we be worried?*

## **Tuberculosis and its treatment**

The infectious disease tuberculosis is thought to be one of the oldest recorded human disorders. Since the disease is so old, one might think that we'll never get rid of it? Well, we made some progresses so don't despair.

The bacterium transfers through the air and can therefore infect anyone, especially people with a lowered immune system. Luckily, the bacterium was identified 1882 which led to the introduction of different treatment strategies in the purpose to eliminate, or at least reduce the infectious disease and its dispersal. Sanatorium, vaccination and surgery of the lung were thought to be successful methods but the main treatment for curing tuberculosis were the "medicine sent from above": the antibiotics. The real value of the first named strategies has been discussed and one is not sure whether or not they actually were effective. Antibiotics on the other hand proved that they were reliable and worked effectively against the bacteria. They inhibit the growth or totally eliminate the bacteria by killing them off. This was such a successful therapy that the other treatment strategies seemed unnecessary and was soon to be phased out.

Thanks to these various types of therapy treatment, cases of tuberculosis started to decline and continued to decline until 1984. After this year the battle against Tb started to fail and the amount of infected people suddenly started to increase. This was due to increased cases of HIV-infected people (who had a defect immune system). Not only did we gain more cases of the disease, but the treatment also started to be ineffective. Something happened that should not happen - some strains of *M. tuberculosis* had evolved a resistance against antibiotics, making the drugs useless in the treatment of tuberculosis.

## **Resistance**

It is well known that a cell can develop some side steps that can modify the organism in various ways. Some side steps, in form of mutations, gives rise to cancer and some gives a bacterium a super quality. The last-mentioned mutation created the bacteria we today fear. If a mutation provides the bacteria with a resistant quality and if it survives an exposure to antibiotics, it could lead to the development of resistant bacteria. This happens if the favored

gene is selected to the future bacteria generation. Since mutations occur spontaneously and independently of the environment, mutated and resistant individual bacterium will always exist due to this spontaneous and natural mechanism. However, mismanage of the antibiotics gives the mutated bacteria an advantage versus non-mutated bacteria, which will be killed whereas the mutated will survive. An increased usage and mismanage of the drugs will therefore improve the resistance of bacteria. Thus, resistant bacteria have been more common nowadays. To a certain extent, I guess we have our self to blame.

### **Antibiotic mechanism and the developed resistance**

Even if an antibiotic is a miracle medicine, one might think that the drugs are complex compounds. They are in a way, but they work through only four different mechanisms when inhibiting or killing off the bacteria. They can (1) inhibit the bacterial cell wall synthesis, interact with either the (2) key enzymes in the folic acid metabolism, (3) protein synthesis or (4) nucleic acid synthesis. Tb is commonly treated with five primary antibiotics: Isoniazide, Streptomycin, Rifampicin, Pyrazinamide and Ethambutol. Secondary drugs can also be used but they are less effective and can also give rise to side effects. These are especially administered in the presence of resistant bacteria or if the patient does not tolerate other drugs.

These five drugs work in various ways and gives rise to two different mechanisms: affecting the bacterial protein- and cell wall synthesis.

**Table 1.** Shows how the primary drugs used to cure Tb and their mechanism against the bacteria.

<b>Antibiotics</b>	<b>Mechanism</b>
Streptomycin	Inhibit bacterial protein synthesis
Rifampicin	Inhibit bacterial protein synthesis (blocks RNA-synthesis)
Isoniazide	Inhibit cell wall synthesis
Ethambutol	Inhibit cell wall synthesis
Pyrazidamine	Probably a part of the cell wall synthesis (is believed to be involved in the fatty acid synthesis)

Resistance against antibiotics involves five different mechanisms. The bacteria can (1) produce enzymes that destroy the drug, (2) change their permeability to the drug, (3) alter the structural target for the drug, (4) alter the metabolic pathway that bypasses the inhibition produced by the drug or (5) alter the enzyme so it still can perform its metabolic function but is much less affected by the drug.

### **Natural progress of the disease**

The course of a tuberculosis disease is divided in two stages: the primary- and post primary tuberculosis. Primary tuberculosis is subscribed by a primary complex, meaning that the organism enters the lung (via the air), attacks and infect the lung tissues and at least one lymph node. Every step afterwards is involved in the post primary tuberculosis and includes

spreading of the bacteria and causing various types of infections. *M. tuberculosis* lives in an aerobic environment and has a maximum growth in tissues with a high oxygen supply. Since it is a poor flow of venous blood in the upper part of the lungs, the gas exchange between the blood and the alveoli is reduced and thereby the oxygen concentration is higher in this area. Therefore the bacteria prefer to grow in the apex of the lung. Even though this will imply that the lungs are the main targets to infect, the bacteria can infect every organ and tissue in the human body.

How can tuberculosis be so powerful and kill so many people? Well, this is due to two things: the infections and their ability to be persistent in the human body.



**Figure 1.** X-ray of a Tb-infected lung. The white area is damaged, non-functional lung tissue.

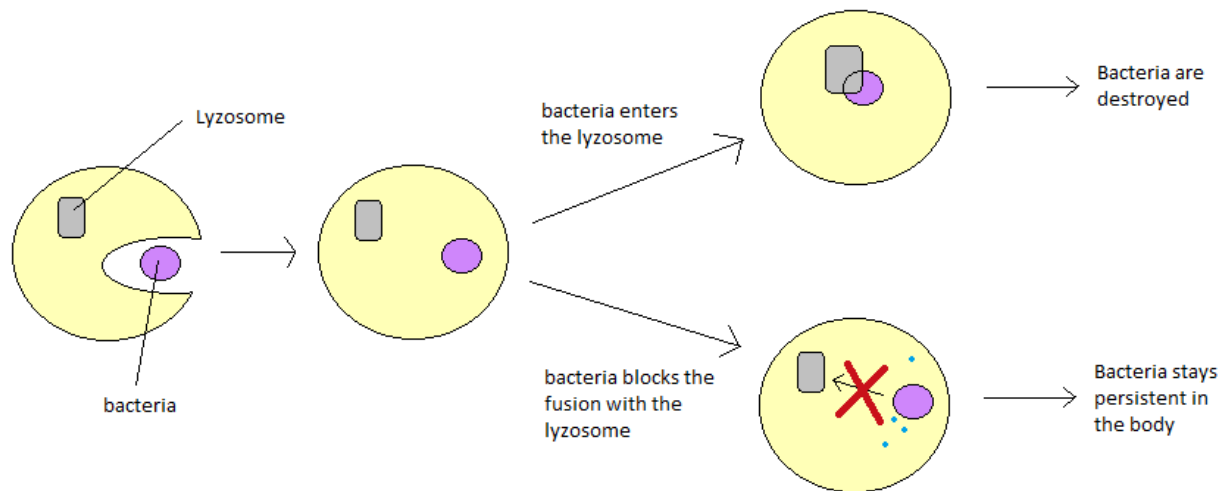
latest described state, the lung will have fragments of damaged tissue and the transmitted abscess can also lead to a further distribution of the bacteria, and that is if all bacteria has not died from the corpuscles-attack. Overall, the lung capacity is lowered. Further distribution of the bacteria throughout the body can give rise to enormous damage, for example meningitis.

Second of all, the bacteria have both a structure and different proteins that make them more resistant to antibiotics. The structure of the cell wall contains certain kinds of proteins that regulate the influx and efflux of substances, called the efflux-system. These proteins have the ability to “spit out” the drugs, which then makes the drugs useless. *M. tuberculosis* also has proteins that block the pathway that destroys them. To understand this a little background story must be told (see figure 2): when a bacterium enters the body, the human macrophages (part of the human immune system) will “eat them up”. Inside of the macrophage, a membrane, called a phagosome, surrounds the bacterium. The phagosome will mature which will make it enter the lysosome, which can be described as a trash can. It is inside the lysosome that the bacterium actually gets killed.

First of all, the infections *M. tuberculosis* can result in two different disorders. It can either give rise to an overproduction of mucus or lead to an inflammatory exudation of liquid in the lung tissue. An increased production of mucus is a chronic state and will partly result in a diminished gas exchange. The exudation state will instead be more acute and have a worse lapse. When the inflammatory exudation of liquid is present in the lung, the white corpuscles in the human immune system will attack and eliminate the bacteria in the liquid. This results in abscess that will be coughed up in the tree of bronchus and leave a cavern behind. This cavern consists of non-functional lung tissue. To summarize the

non-functional lung tissue.

A bacterium can secrete proteins that block the lysosomal delivery and therefore be persistent in the human body for decades. Even if the bacterium is trapped in the macrophage and thus be in a dormant state, it is still important to eliminate the bacteria since they easily become active.



**Figure 2.** Describes how *M. tuberculosis* can escape the macrophages attempt to destroy it.

### How promising or threatening is the future?

Even though we should be aware of the problems that follow with resistance and also be careful with the instructions that are given in the treatment of tuberculosis, one can be a bit hopeful for the future. Studies have shown that there are some disadvantages that follow with the mutation that creates a resistant gene. For example, an altered genome can imply an extra cost for the bacteria and can lead to that essential processes also get altered. For instance: a change in the ribosome can result in a slower protein synthesis. It is also believed that resistant bacteria has a slower growth, and can therefore easily be outtrived by those bacteria that are sensitive to antibiotics.

At last but not at least, the research for new and effective drugs are in progress. To produce new antibiotics has not been a priority for a long time since it brings out a high research cost and the drugs have been fully useful until recently. One example of these new drugs is thioridazine, which in combination with antibiotics has cured patients with resistant bacteria.

This implies that we in the future can overcome the antibiotic resistance of *Mycobacterium tuberculosis* but we must not forget our responsibility: a decreased amount of antibiotics and a correctly administrated cure can reduce resistant bacteria.

For more information see: Blomberg L. 2012. Är antibiotikaresistens hos *Mycobacterium tuberculosis* ett hot mot människan? Självständigt arbete i biologi. Uppsala universitet.