Mycobacterium tuberculosis: playing hide and seek

When strolling through the streets of Utrecht, the town in the Netherlands that I live in, you sometimes hear people using 'Tering' as a swear word. What actually most people using this word don't know, is that it dates back to an ancient disease, which has been found in 4000-year-old. Such an old disease should have also been eradicated a long time ago already, right?

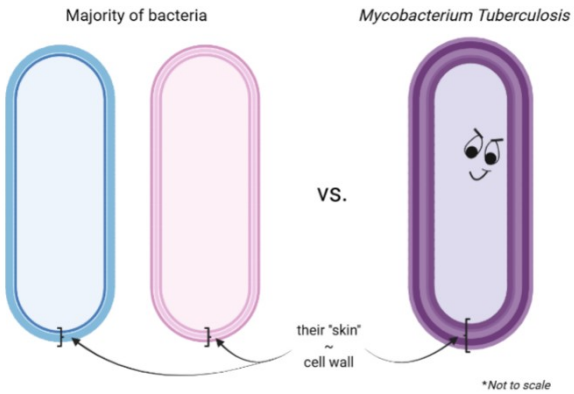
Actually no, it is not at all. 'Tering' refers to tuberculosis, or in short TB, and there are still 10 million new cases of active tuberculosis each year worldwide. This means that every 6 seconds, someone develops TB somewhere in the world, and every 21 seconds someone dies from this disease.

Tuberculosis was already present in the Roman and Greek civilizations, and great thinkers of that time described it as *phthisis* or consumption. The term 'consumption' came from the idea that the disease consumed people, leaving them weak and emaciated. Often TB was also referred to as 'Captain of all these men of death', illustrating the major wave of deaths it caused. There grew a great stigma and fear around TB, because not only did this disease cause death to so many, but people also did not understand how they would develop it.

It was only during the first half of the 19th century, that people really started to understand TB. On 24 March 1882, German doctor Robert Koch discovered the bacteria that cause the disease: *Mycobacterium tuberculosis (Mtb* in short). *Mtb* is spread from one person to another through tiny droplets in the air (the good old aerosols, which we've heard a lot about during COVID times) while talking, coughing, or singing. Initially, *Mtb* mainly affects the lungs, but from there it can spread through the whole body. In the years since its discovery in 1882, this bacterium has been extensively researched, making it one of history's most studied bugs. Nevertheless, *Mycobacterium tuberculosis* still poses many mysteries and unanswered questions that have not yet been revealed.

With 140 years of research behind us, what *do* we know about this bacterium? And what makes it so successful - at least from a bacterial point of view - that it lasts throughout centuries, despite our best efforts to eliminate the bug?

Actually, by looking at illustrations of *Mycobacterium tuberculosis* (see figure), you can already 'see' that this one seems a bit different than the majority of other bacteria (or if you don't notice, no worries, you will see it after having read the rest of this blog). Contradictory, for our bodies, this bacterium is not at all easy to 'see' - you will notice after reading further…



Let's start at the beginning. You can imagine that when you want to keep things inside, you need something that keeps things *inside*. And not unimportantly, also keeps the outside *outside*. Looking at your own body, your skin is a great example for this. Skin is the perfect barrier that keeps all your organs inside, while keeping dirt and potential invaders

outside. In fact, bacteria have something similar. But for bacteria, their 'skin' is called a cell wall.

Because the cell wall of bacteria is on their outside – their 'skin' – that is the part of the bacteria that our bodies can recognize. This makes sense, as this is the part of the bacteria that is in full contact with the human body – it's the only part of the bacteria that our immune systems can 'see'. So, what exactly happens when invading bacteria enter your body? Well, the immune system immediately senses that those little bugs are not part of your own body, mostly due to their cell wall 'looking' different from the parts of your body. A subsequent attack by the immune system follows, causing the bacteria to die, and the peace returns. And this is all the result of the initial response to the observed cell wall!

For *Mycobacterium tuberculosis,* however, it is a bit of a different story…

Mycobacteria – including *Mtb* - have a unique, very thick, waxy cell wall. Let me explain. Imagine pouring candle wax onto a very defined object. When solidified, the structures that were first very clear and easy to distinguish, are now covered in candle wax and turned into a big undefined block. You cannot feel or see any structures that were there before. This is actually how you can imagine the cell wall of *Mycobacteria:* a thick wax layer like candle wax, which covers the defined recognizable structures of the bacteria. Because of this, the human body has a hard time recognizing *Mycobacterium tuberculosis* as being an actual bacterium, a foreign invader. And as a result, it is difficult to kill…

Okay *M. tuberculosis*, I got you, very smart to build such a big waxy wall around you so that you're particularly hard to see, and the body cannot see what you are hiding. But imagine if you coated yourself in wax - your eyes, nose, and mouth would be clogged! How would you eat?

Turns out, *Mtb* might have thought of that…

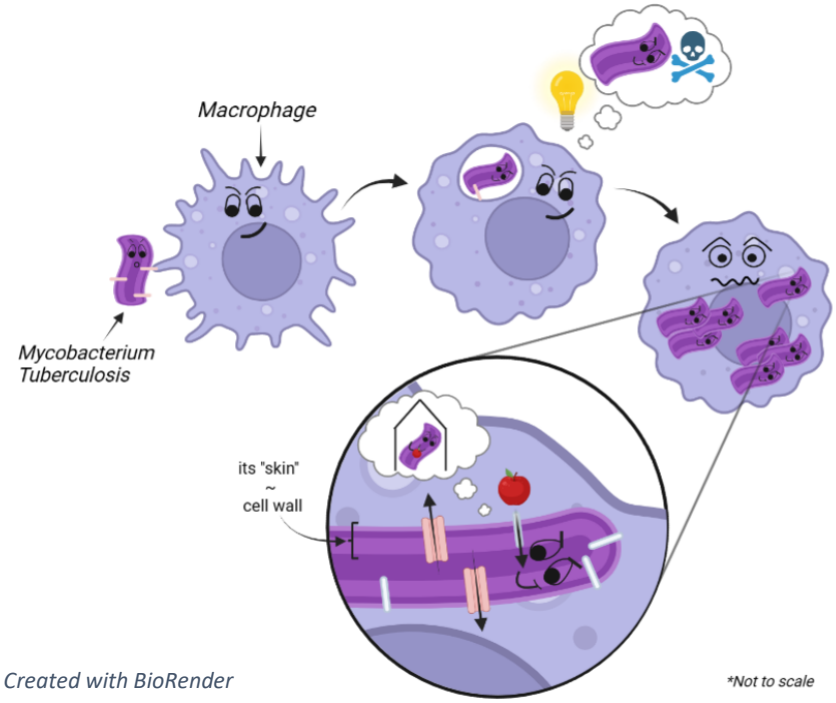
So, there has to be some entry to the inside of those bacteria, right? If you think back to the analogy of the candle wax layer, you can imagine it is really hard to take the wax off of the object. And that doesn't even get into the issue that this would uncover the whole defined structure of the object, something that *Mycobacterium tuberculosis* definitely does not want. You might have guessed it… *Mtb* has found a way to avoid taking big parts of his waxy coat off, and still be able to take up food from its environment. Recently, it has been found that the wax-like layer of the cell wall possesses little tiny gateways, through which the bacteria can selectively take up small nutrients from the environment. In this way, it can still hide its features under a cell wall as dense as a block of candle wax. Apparently, *Mtb* has created a perfect balance between staying nearly invisible and isolating itself, while still staying in contact with the environment for its own benefit.

But actually, I've only told you one part of the story… There are, in fact, particular structures that do stick out of the waxy layer of the cell wall. Those structures of *Mtb* are recognized by the first guards of the immune system: macrophages. Those macrophages engulf the *Mtb* bacteria and will eventually try to kill it…

Wait, what? I hear your question: why would *Mtb* put so much effort into creating a thick waxy wall, so it escapes the recognition by the immune system, but at the same time, stick things out

that partially undo this masking effect? And as a result, still fall into the trap of the immune system? Weird, right?

Of course, *Mtb* would not do it without a reason. Those structures that stick out will actually lead the bacteria to the place it really wants to be: inside those macrophages! When being engulfed by macrophages, the macrophages are totally ready to destroy the invader… but *Mtb* has another card up its sleeve! *Mycobacterium tuberculosis* uses other small channels to secrete proteins that block macrophages from doing their job: killing the bug! So, next to those 'in' channels for food take-up, *Mtb* also has 'out' channels to influence the behaviour and actions of macrophages. Within the macrophage, *Mtb* has abundant access to everything its heart desires: a shelter with lots of food (see the part that is zoomed-in in the figure). As a result, it can live, hidden inside the macrophages, happily ever after! Mission 'becoming invisible' accomplished again!



To sum up, *Mycobacterium tuberculosis* still leaves us with many questions unanswered, as it did in Koch's time. Nevertheless, we have also gained a lot of knowledge since his discovery. Today, we've seen at least some reasons why *Mtb* manages to stay with(in) us for such a long time already. It is just super smart. And in this post, I only pointed out a few of the many manipulatory mechanisms of this bacterium (many to come in the upcoming blogs). Because it has co-evolved with us for centuries, it knows our weak spots and acts on them. We have seen that, although *Mycobacterium tuberculosis* might 'look' different because of its cell wall, this feature in particular makes it nearly invisible to the body. On top of that, *Mtb* adds an extra layer of invisibility, by hiding inside the gatekeepers of our immune system: macrophages. So, this time's takeaway: although *Mtb* 'looks' different from other bacteria under a microscope to our *eyes,* it's all a trick to become invisible to our *immune systems* – and what we don't see, we can't catch.

Hope to see you in the next post of the mini-series about *Mycobacterium tuberculosis*! Next week, we dive deeper into what happens after *Mtb* bacteria hijack the macrophages. The *Mtb* story is not finished yet.

The fortress of *Mycobacterium tuberculosis*

Last November, I was in beautiful, sunny Lisbon, and as my parents and I looked back at the pictures we took there, something caught my eye. One of the iconic yellow trams shuttling between the tourist hotspots in the city had 'TBC' written on its front. TBC is, at least in Dutch (and in other languages as well, I noticed), the common abbreviation for tuberculosis. I myself am not an expert in graffiti slang, so I'm not sure if the creator of this graffiti was really referring to the disease tuberculosis (probably not), but my biomedical brain immediately linked it to this illness. For me, this was just a little reminder that tuberculosis is still incorporated into everyday life.

My dad took this photo of one of the yellow trams in Lisbon

Although the death rate of TB has dropped enormously in the last centuries, this yellow tram was only one sign that tuberculosis still *is* very present nowadays. The 'Captain of all these men of death' nickname might perhaps not be the most accurate anymore, but TB is still the second top killer in the category of infectious diseases (behind COVID-19), claiming 1.5 billion lives each year. And even more strikingly, according to the latest data almost 1 in 4 people in the world are infected with *Mycobacterium tuberculosis (Mtb)*. That is a quarter of the world's population… **a quarter**. Let that sink in. And who is noticing it? At least, not a lot of us… (including me before starting this project).

The question that arises is, why is tuberculosis so present but still so unseen?

It all comes down to how *Mtb* interacts with your body, and how your body reacts to *Mtb*. So, I will take you on a journey through the life of *Mtb* again. We are continuing the story where we left off the last time (if you didn't read the first blog, it's here).

Do you remember the contented *Mtb*, hiding inside its shelter - the macrophage? Seems perfectly fine for *Mtb*, don't you think? But from our human perspective, it is not at all beneficial. In fact, this is not where the *Mtb* life story ends.

We know by now that *Mtb* is good at sneaking into the first gatekeepers of our immune system – the macrophages – and disabling those cells to kill them. Interestingly, population data shows us that only 5-10% of people infected with *Mtb* develop actual TB disease. This means that even if *Mtb* gets into our immune cells, it might not have any immediate effect. So, there has to be more to the story of *Mtb* infection than we know at this point.

Let's see, can we explain this low rate of disease development, even in people who get infected?

Well, to begin, *Mtb* likes it so much within macrophages - there's plenty of food - that it starts growing and reproducing itself inside our cells. In most cases, the macrophages become kind of 'nauseous' from this feeling of something growing inside them, which they are not able to kill. So, what happens next?

Eventually, most infected macrophages die… However, because the *Mtb* bacteria just had their feast and are still feeling good when the macrophages die, they come out alive and kicking. Suddenly the immune system can sense the bacteria out and about in your body again. In response, new macrophages are called into the crime scene to do their duty. But unfortunately, a similar fate befalls them. The macrophages take up the bug, thinking they can kill it. But, *Mtb* counteracts and designates the macrophage as its shelter, where it starts growing and reproducing. Ultimately, most macrophages die and *Mtb* bacteria again go free. Same story over and over again.

But remember, most people who get infected with *Mtb* don't ever develop any noticeable disease. So, there must be something that the body can do to stop the annoying *Mtb* from growing and spreading, right?

Fortunately, the short answer is: YES, in most humans, there is. I'll explain. To succeed, the immune system calls in other types of immune cells. Those cells line up and surround the infected macrophages and *Mtb* bacteria, walling off the harmful *Mtb* bugs from spreading further. Let me clarify this with a real-life example. You can imagine the lining up of cells as the immune system building a fortress. And more specifically, a dirty medieval fortress with high brick walls, locking away pathetic prisoners. In the body of a TB patient, these prisoners are the infected macrophages and *Mycobacterium tuberculosis* bacteria. The surrounding walls of the fortress are made of burly immune cells. So that's it, a fortress built out of strong immune cells with imprisoned mischievous *Mtb* bacteria within, inside the lungs of TB patients. Scientists call this fortress a "granuloma".

Because there are hardly any gates to give access to the fortress – the granuloma -, and the walls composed of cells are firm and big, the inside of the fortress becomes desolate. Most left-over macrophages die, turning into a sticky, soft, white substance, which looks a bit like… cheese! Fun fact: the official scientific name for this desolated fortress is a "caseous granuloma". Caseous literally meaning cheesy. Sounds like a lovely place, am I right? (sarcasm)

And what is left over besides this?

Of course, the stubborn *Mycobacterium tuberculosis*… But there is some good news: the bug becomes less harmful than we've seen before. Because the macrophages die, there is less food

available for the bug population inside its fortress. And also, since the fortress is so secluded, there is very little exchange possible with outside of the fortress. As a result, the bacteria go into a sort of 'sleepy' state. Call it the energy-saving mode. Being in this sleepy state, the *Mtb* does not try its hardest to get out of the fortress. It chooses its battles. And once again, it reverts back to its best trick: HIDING. But this time, instead of hiding within living macrophages, it hides inside its filthy, cheesy, pesky medieval fortress.

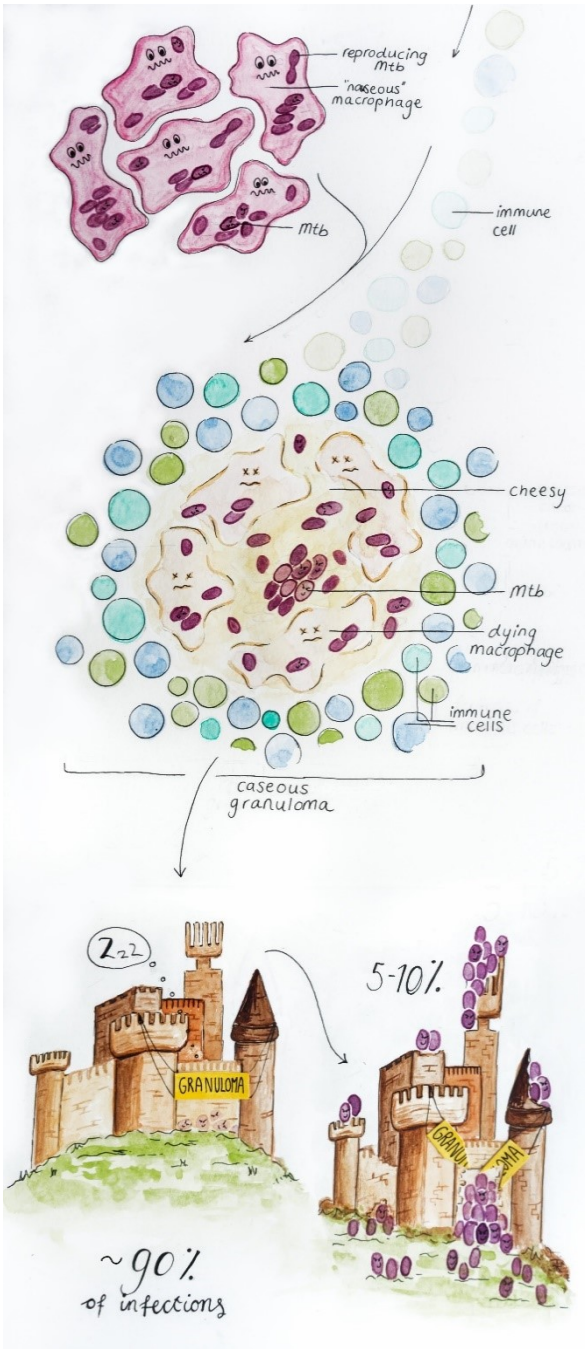
However, this fortress does do its job: *Mtb* stays within the big walls. Like real bricks-and-mortar fortresses, not all of these immune fortresses are exactly the same, but from our immune system's point of view, they all have the same purpose: keeping *Mtb* trapped within. In most TB patients, these fortresses containing *Mtb* will stay in their lungs for their entire lifetime. And actually, this is not that bad of a situation for either the human or the *Mtb*. The human and the bugs have reached some sort of agreement: *Mtb* bacteria can stay in the body, as long as they remain sleepy inside their fortress, and the body is not bothered by the bugs. Problem solved, right?

At least, in most cases, the problem is solved. Around 90% of the people getting infected with *Mtb* do not get sick at all – they'll never develop active TB disease. However, in some cases (5-10%) the *Mtb* bacteria can wake up from their "sleepy" state and try their ultimate best to break through the walls of the fortress. And this is a problem.

Can you think of any reasons why the walls of the fortress would not serve as well as they used to? I will give you one example. With real fortresses, as time passes by, the walls erode because of the antiquity of the bricks. This is exactly what happens in the body. When the body ages, the immune cells - being the fundament of the walls - decay in quality. The walls become wobbly, and less force is needed to break through them. And you may think, but those *Mtb* were sleepy, right? How can sleepy bacteria have enough force to break through those walls? Okay, I agree, but sleepy *Mtb* are not dead *Mtb*. And sleepy *Mtb* are still alert. You know, they still are the same sneaky bugs we talked about in the first blog post in this series. Remember all those shifty actions it could perform with its cell wall? Well, *Mtb* always has more tricks up its sleeve…

When those fortress walls become unstable, *Mtb* starts to fire up from inside the fortress. It is not totally understood how *Mtb* is capable of reviving from its sleepy state. But what we *do* know is the result. The once perfectly closed wall is disrupted, enabling the bacteria to escape. Once on the loose, the bugs can patrol around, spreading through other parts of the lungs and even other parts of the body. It is when the bug starts affecting the essential organs in the body the real trouble starts… And this is when people start becoming really sick.

Fortunately, in societies where people have great healthcare, good hygiene, and healthy immune systems, this happens less often. In the majority of cases, *Mtb* stays peacefully in its well-guarded fortress. We actually now know that *because* of their fortress-based agreement, the bacteria and the human body can co-exist together for a long time. However, in most of those cases, the body is not able to totally get rid of the bacteria. This creates an ever-existing vulnerability for the human body when it's infected with *Mtb*. The immune system has to be well armed to sustain its protection – to keep its prisoners chained within the fortress. When environments make it easy for *Mtb* to jump from person to person, and it's difficult to access the medication that can give the immune system that extra boost to finally execute its *Mtb*



prisoners, it's more likely that *Mtb* will eventually win this long war. And unfortunately, this is also one of the reasons why tuberculosis has long been, and remains, such a big problem in less developed countries.

To wrap up this time, *Mtb* is the bacterium that goes unseen - both by the body *and* by society. It hides in human macrophages *as well as* in the human-built immune cell fortresses. Thanks to those fortresses, in the majority of people, *Mtb* infection never leads to actual TB disease. Therefore, the major part of *Mtb* infections are not visible for society, and it seems that this 90% of the infected people is perfectly fine - which indeed is the case for as long as they have a healthy immune system. But when the immune system is down, for instance, due to another infection or simply older age, *Mtb* makes its move. It attacks the body without holding back. So, by now, maybe you can imagine why they called TB 'Captain of all these men of death' in the past? First, it acts as a well-behaved prisoner, but in the end, stabs us in the back. Or rather, in the lungs.

Be sure to come back next week for the third and last instalment of this three-part series on *Mycobacterium tuberculosis.* Then we'll see how all of what I've told you about *Mtb* also hampers its treatment.

Hope to see you there and thank you for reading!

How diversity can be powerful: *Mycobacterium tuberculosis* and antibiotic resistance

The other day I visited my grandparents, and I told them about this mini-series I'm writing about tuberculosis (TB). We got into a conversation about the presence of TB in their youth. As they described the TB patients lying in hospital beds in the open air of a sanatorium (a specialised hospital to treat TB patients), I was reminded of the old idea that outdoor air was restorative for TB. With the lack of further knowledge on TB and TB treatment at that time, tuberculosis was often 'treated' by keeping patients in the fresh air, and this worked pretty well actually. But although it was the best medicine back then, it definitely wasn't curative.

Fortunately, we're well past that era. We know more about tuberculosis and the bacteria causing the disease nowadays. With the discovery that tuberculosis was caused by bacteria, came opportunities. Antibiotics - used to treat *bacterial* infections (as opposed to viral or fungal infections) - were introduced a few decades after the discovery of *Mycobacterium tuberculosis (Mtb)* and were directly applied to treat TB. This led to a major breakthrough in tuberculosis treatment, and antibiotics have been seen as *the* 'magic bullets' to treat TB ever since.

At this moment, the standard treatment for TB generally comprises a 6-month stretch of the use of various antibiotics. The combination of the different antibiotics is composed in a way that it unarms the bug on various fronts. If you've read the first blog of this mini-series, you might recall the undeniable importance of the cell wall for *Mtb* – *Mtb*'s 'skin', that thick, waxy layer on the outside of *Mtb*. With the cell wall being key for *Mtb*'s survival, it comes as no surprise that *this* particular feature of *Mtb* is often the target for antibiotics.

Isoniazid, one of the most powerful antibiotics used in TB treatment, tackles specifically this power feature of *Mtb*. It blocks the formation of *Mtb*'s thick, waxy 'skin' – and remember, that 'skin' is necessary for *Mtb* to stay so well in shape and isolated from our immune systems! With this layer unable to form properly, the *Mtb* is left uncovered and skinned (ew!). Without its skin, it can do nothing more than die eventually. Which is exactly want we want to achieve when giving this drug. Perfect!

However, with the introduction of - what was thought to be – our saviour from TB, also came trouble… A clear rise in multidrug-resistant (MDR) and extensively drug-resistant (XDR) strains of *Mtb,* which are resistant to at least two or four of the most effective drugs respectively, has been observed over the past years. These *Mtb* strains are becoming a major concern in the treatment of TB. Of course, *Mtb* managed to circumvent the directed attacks *again* - but this time not counter-attacks by the body but by drugs.

Let's take a closer look at the development of antibiotic resistance of *Mtb*. And in fact, it has everything to do with a common topic at this moment in time: diversity.

You might think of the population of *Mycobacterium tuberculosis* bacteria as being one homogenous group of annoying little bugs. Like a little army of ants, all seemingly alike. Indeed, I also presented it like this in the other blog posts for clarity – my bad. But in fact, there dwells a huge variety in the *Mtb* population within *and* across individual human patients. A beautiful

collection of diversity, actually – just as we have in our human population. Our human population has an amazing variety of different appearances *and* behaviours. And this is nothing different from the population of *Mtb* bacteria in the body during infection. Turns out, being greatly diverse is *Mycobacterium tuberculosis'* major superpower when it comes to resistance to external attacks, from our own body – our immune system – and from prescribed drugs.

To explain how this diversity drives resistance, we go back to our beautiful human population.

Look at the humans around you, on the streets, in the library. All our appearances differ. Only to name one example: there are people with more light-toned skin, and people with a more dark-toned skin. There are, however, some environments in which specific skin tones may be more advantageous – biologically speaking - than others. For example, people with more dark-toned skin are less prone to get a sunburn after a long day in the burning sun, compared to people with light-toned skin (like me, a typical Dutchie who is very likely to get sunburned…). Just like humans, each individual *Mtb* also has a slightly different 'skin'. And what represented the 'skin' of *Mtb*, again? Right, the cell wall. So, like every human's skin tone, every *Mtb*'s cell wall differs slightly. The building blocks of the cell wall just slightly differ from one *Mtb* to another, for example. And it just happens that some 'skin tones' of *Mtb* will be more susceptible to a given antibiotic, while other skins will be more resistant.

This comes with some – not all so fun - consequences. When introducing an antibiotic drug to *Mtb,* the bacteria with more susceptible skin will be killed by the antibiotic – great! However, some of the *Mtb* could have a more 'resistant' skin, and stay alive. The father of evolution, Darwin, would say: 'survival of the fittest'. The fittest – in this case, the ones with a more resistant type of skin - survive. Those bacteria can enjoy the 'joie de vivre', grow and reproduce. Eventually, we end up with a population composed of more *Mtb* bacteria with resistant skins, and fewer with susceptible skins. And in that case, the treatment will not be effective…

And that's not the only trick up *Mtb*'s sleeve. *Mtb* is versatile, just like humans. Besides differences in people's appearances, humans also differ in behaviour. There are people that like to stay in, whereas others prefer a walk in the fresh forest air. People with an eternal overloaded agenda - the busy bees - and people that like to take it more slowly. The different *Mtb* bacteria present in the body at the time of infection are just like that. They vary in behavioural traits as well.

By behaving differently, the ones that are not accidentally blessed with a great skin can still take their shot at surviving the antibiotics. This is just another example of *Mtb* being smart - and we've already seen how smart *Mtb* can be in the last articles in this mini-series.

So, how do *Mtb* bacteria differ in behaviour? Actually, perhaps without noticing, you've already come across two examples of behavioural changes in the previous blog posts. Do you remember the big fortress containing sleepy *Mtb* bacteria?

Well, smart *Mtb* simply like to stay in. And specifically, inside the filthy, desolated, well-guarded fortress that they build inside the lungs of infected humans - the caseous granuloma. In this fortress, they are way harder for the antibiotics to reach. The drugs have to go *inside* the secluded fortress to act on the *Mtb*. And we've just seen in the last blog post that immune cells try to do their ultimate best to build a big, firm wall to lock up the bacteria. So, it seems that

the solution of the body to achieve a truce between the body and *Mtb* – the building of a granuloma fortress - is also complicating the total killing of the bacteria by antibiotics. Darn it!

Fortunately, some drugs do have the capability to sneak through the backdoors of the fortress. However, it could be that they are still not able to kill off all of the *Mtb* inside the fortress. Why? Because of *Mtb*'s behaviour inside the fortress: sleepy, bland and non-growing. When you're like this inside a big fortress, you can imagine that people won't notice your presence that much. In contrast, you can't miss the busy bee-*Mtb*. With the sleepy, energy-saving mode turned on in those *Mtb* bacteria, a lot of general processes - which are up and running in more active *Mtb* bacteria - are switched off. Simply, to save energy. The problem is that some of our antibiotics work against proteins that are only switched on when these general processes are switched on, which means they kill only the busy bee-types of *Mtb* bacteria. With those processes running on the back burner, the antibiotics do not work as well for sleepy ones…

And this is particularly the case for isoniazid. Isoniazid blocks the creation of new cell walls of *Mtb* bacteria. The only thing is... making new cell walls mostly happens when the *Mtb* are active and reproducing. Unlike the busy bees, the sleepy bacteria are in energy-saving mode, so they don't actively need to make new wax. This means that only the active busy bee-type *Mtb* bacteria are tortured by antibiotics like isoniazid...

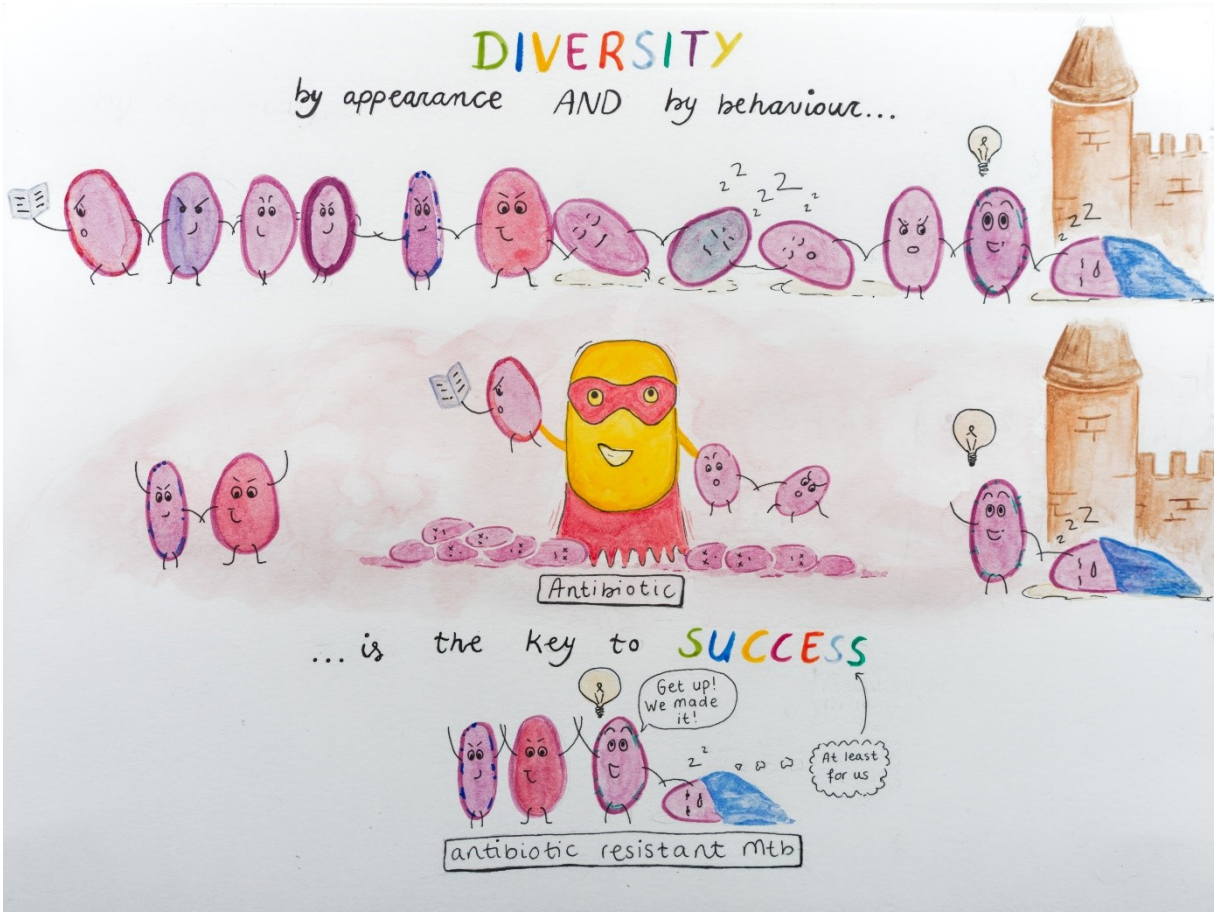
But we have a solution here. This is exactly the reason why we always treat patients with a good mixture of different antibiotics that all target different processes. Combining forces is always a good idea!

Nonetheless, because of this massive variety in *Mtb* bacteria – in appearance *as well as* in behaviour – it could still occur that a few bacteria are totally fine and compatible with the total combination of different antibiotics. And those are exactly the ones that can continue to grow, reproduce, and take over. Leaving us with a population of highly resistant bacteria…

There is also one major societal aspect that we're missing in the antibiotic resistance story. And that is that MDR and XDR strains often arise from misuse and mismanagement of TB antibiotics. The reason TB treatment takes so long is because it takes time and effort to kill the whole population of diverse *Mtb* bacteria. Without finishing the full months-long treatment period, more *Mtb* are likely to persist. Low-income countries often lack access to the right amount of drugs, as well as guidance and support to facilitate regular drug intake. Patients facing a months-long treatment with at least four different drugs are likely to drop out after some time of noticed improvement. You might have experienced something similar yourself – if your doctor prescribes you 10 days of antibiotics but you feel better after 5, you might be tempted to stop taking the drugs. You can imagine this could be even more the case when treatment takes up to 6 months (or more) and when you are not aware of the dangers. However, not finishing treatment is exactly what gives rise to the development of MDR and XDR *Mtb* strains.

To end, with the introduction of new antibiotics, new antibiotic resistant strains will always pop up. Although we are getting better at seeing the pitfalls of certain antibiotics and know how to manage those, this is not the sole solution. As stated in Cell (one of the most respected biological journals): "To truly stem the tide of tuberculosis, we need new and effective vaccines." We have to look for a new 'magic bullet'.

Just a few weeks ago, the WHO announced plans to establish a new TB Vaccine Accelerator Council. With the century-old BCG vaccine – the current TB vaccine – on its decline, it is time for something new. Vaccines are different from antibiotics in that they help our immune systems to gain some artillery, so they can fight off the bacteria themselves. And in addition, with a vaccine you prevent disease on a population level, rather than problem-solving on an individual level with antibiotics - to which *Mtb* can develop resistance. While we don't have a new vaccine yet, we are on our way. But until then, *Mtb* is still the big winner in this constant battle. And diversity is its key to success. Maybe we can learn from *Mycobacterium tuberculosis* in that perspective.



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If you've been with me for the whole mini-series, you might have noticed how everything I told you about *Mtb* is interconnected. This is a perfect example of biology, in fact. Everything is complex. But that's also why it is so cool. I hope I've sparked some enthusiasm for this fascinating microbe and you enjoyed reading the posts!

Thanks a lot for reading (a part of) the mini-series, it has been a great joy!
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Other resources used to write this blog:

Types and functions of heterogeneity in mycobacteria | Nature Reviews Microbiology

Frontiers | The evolving biology of *Mycobacterium tuberculosis* drug resistance (frontiersin.org)

Anti-tuberculosis treatment strategies and drug development: challenges and priorities | Nature Reviews Microbiology

Tuberculosis: a problem with persistence | Nature Reviews Microbiology

Guide: How to translate complicated science into accessible jargon-free blog articles?

Dear science communicators,

On this webpage, you can find a guide on how to transform science articles or/and scientific concepts into an accessible jargon-free blog post. Below you'll find all possible steps you can incorporate in your writing process towards great blog posts.

How does this webpage work?

In the table below, you'll find all the possible steps in the process of writing a science-based blog post. Each step is an individual page you can open by going to the title with your cursor (Click OPEN). On the individual pages, you'll find some more in detail

information about that particular step. Each step is labelled with to which part of the process the step belongs: 1) Structuring 2) Writing 3) Reviewing 4) Figure creating. The figure-creating step is totally optional! (I included this because I made additional figures for each post) The bookmark icons in front of the page titles are corresponding with the colours of the label, and indicate that there is more detailed information when you open the page.

Blogpost workflow

# Step in the process	Aa Step	Part of process	Select
1	Choose your topic and read about it	Structuring	Not started
2	Brainstorm	Structuring	Not started
3	Decide on the key message	Structuring	Not started
4	Create a short storyline	Structuring	Not started
5	Create an outline	Structuring	Not started
6	Write the introduction	Writing	Not started
7	Write the main text	Writing	Not started
8	Write the ending	Writing	Not started
9	Check the structure of the blog	Reviewing	Not started
10	Check for the flow of the blog	Reviewing	Not started
11	Check for jargon in the blog	Reviewing	Not started

# Step in the process	Aa Step	Part of process	Select
12	Add foreshadowing		Not started
13	Ask for feedback and improve your work	Reviewing	Not started
14	Decide on the topic for your supplementary figure	Figure creating	Not started
15	Sketch the figure	Figure creating	Not started
16	Create the figure	Figure creating	Not started
	Read literature	Figure creating Reviewing Structuring Writing	Not started

Notes on the workflow

Important to note is that **not all the steps have to be used**! This is more of a total overview of all the possibilities. Especially for the structuring part, you could pick the steps that work best for you. Feel free to try different (combination of) steps and take out the ones that suit you best. The steps you're using could also depend on which topic you are writing about. For a more though topic or complicated message, it could help to have a clearer structure and well-defined outline that you could stick to, while for an easier topic, you could perhaps lean more on your creativity during the writing process.

I myself also varied which steps I used for my different blog posts. The order of steps that worked best for me was:

1. Choosing a topic
2. Deciding on the key message
3. Deciding on three key points supporting the key message
4. Write a short storyline in about 100-200 words based on your key points.

5. Write down thoughts and ideas about the topic and structure them under Introduction, Main Text, and Ending in a more or less logical order.
6. Start to write the introduction
7. Write the main text
8. Write the ending
9. Check structure
10. Check flow
11. Check jargon
12. Ask for feedback and process it
13. *Decide topic figure*
14. *Try different sketches of the figure*
15. *Create figure*

Notes:

- Reading on the topic was included along the whole process of structuring, writing and reviewing - not specifically in particular steps.
- Steps 13-15 are in italics because this is an addition I did in my blogs, but it is separate from the blog-writing process itself.
- For the writing part: I liked to start at the actual beginning of the blog, the introduction. In this way, you follow the structure and flow of the actual story you're about to write. When doing this, the connecting sentences between the introduction part and the main text came more naturally to me. However, for other people, it will work better to start with the core of the blog - the main text - and afterwards add the introduction and ending of the blog.

Use this page as a tool during your writing process

This webpage is created with the idea that you could actually also use the page as a hands-on tool while being in the process of translating science into accessible blog

posts. When you have a Notion account yourself, you can duplicate the page (top right corner) and paste it into your own Notion. In this way, you can edit the steps and pages however you prefer and what works best for you. When you click on ‘Board’ in the top left of the table, you can see that all the individual steps are ordered according to ‘Not started’, ‘In progress’ and ‘Done’. While writing, you can drag the particular steps to the part of the process they are in. In this way, you can keep track of where in the process you are and what you have to do. Additionally, you could press Filter (top right); Part of Process, and filter for the specific step that you’re in (for example, Structuring). Then, only the Structuring steps will be visible and it is easier to keep track.

Looking back on the process

This kind of writing forces you to make all your sentences super clear and there is no room for different interpretations. I think this skill is really something you can use in scientific writing as well. Also, the creative process of writing and thinking of analogies enables you to see scientific concepts in a broader perspective. You learn to see similarities between real-life situations and molecular or cellular biological processes. For the scientist, this adds a new layer of thinking about a particular biological process, which may also help to come up with new research ideas.

I hope this guide will help you with creating a more accessible way to spread your science. Thank you for using it!

Science isn’t finished until it’s communicated - Sir Mark Walport, U.K. Government Chief Scientific Adviser

Elective Science Communication project - Master's program Infection & Immunity - Merel Sijbranda - 2023.

Supervisor: Alex Cloherty - Ph.D. Candidate AMC; Science Communicator; MicrobialMondays.com

Source cover: Public engagement and science communication: A waste of time? | Earlham Institute

Choose your topic and read about it

Part of process	Structuring
Select	Not started
# Step in the process	1

1. Choose your topic
2. Read general reviews about the topic, or other recent field-chancing articles, depending on how well you know the topic already and on your purpose of the blog post.

Brainstorm

Part of process	Structuring
Select	Not started
# Step in the process	2

1. Brainstorm about all possible concepts and ideas related to the topic you want to capture in the blog post. You could use scientific articles or your own research/knowledge as a resource for the main text. For the introduction and ending of your blog post, you could also use other blog posts, news items, YouTube videos, etc. - everything that gives you any inspiration for concepts or stories you would like to incorporate.
2. Put all your ideas in a mind map or list.
3. Categorize and structure all the concepts and ideas in the mind map/list.

This process of brainstorming and ordering your thoughts could be as extensive as you want. It is more of an invitation to be creative and think about all possible things that are connected to the topic you want to write about.

Decide on the key message

Part of process	Structuring
Select	Not started
# Step in the process	3

1. Decide on the key message of your blog post
2. Decide on the three main points to make in the blog post, supporting this key message.
    a. In this way, you diminish the change you put too much ‘new’ information in your blog post. Because you are probably an expert in the field you’re writing about (or at least more than most of the readers), it is sometimes hard to distinguish between what is ‘new’ information for the reader and what is common knowledge. By sticking to three main points, you’ll create a clear and understandable story with a few key messages you’ll leave the reader with.

Create a short storyline

Part of process	Structuring
Select	Not started
# Step in the process	4

1. Write a short storyline of around 100-200 words which includes the key points to make in your blog.
    a. When writing a short story, you can already connect the key points. You can see this as a before-written summary of your post. This forms the basis for your future outline.

Create an outline

Part of process	Structuring
Select	Not started
# Step in the process	5

1. Use the created mind map, the three main points, and the storyline to create a general outline of your blog.
    a. During this process, read more into the topic. Based on what you've read, you can fill in the outline more and more.

Order all your ideas under:

- Introduction
- Main text
- Ending

Note:

Also, for this step of the process, you can continue detailing the paragraphs to a level that works best for you. For some people, it might work better to make a more general outline and let more room for creativity while writing, while for others it might be helpful to detail the outline more (to the level of having a key message for individual paragraphs for example), so you have a clear structure you can fall back on. Try out different levels of detailing the outline and see what works best for you!

For me, it worked best to write down all the ideas and concepts that came to mind while reading papers/blog posts/other resources, etc., and order them in a more or less logical order under Introduction, Main text, and Ending. From this, I started writing the blog.

Write the introduction

Part of process	Writing
Select	Not started
# Step in the process	6

While writing the introduction, keep in mind that:

- The introduction is really important to capture the reader’s attention for the topic. It has to spark the curiosity of the reader to read more about this topic. If the introduction is boring, the reader is less likely to read the whole blog post. And that is of course not at all what we want!
- Especially the first sentence of the introduction has to be very appealing to the reader. This determines already for a big part whether people are going to read your whole blog or quit reading after the introduction. Readers have to get a clear idea of the topic and mostly it has to be a fun and easy read.
- The introduction has to be a maximum of 10% of the blog.
- Choose for yourself when you want to write the introduction. You could start with it and continue with the main text, and ending after, but you could also write the main text first and then see what kind of introduction would fit with your main text. This is totally up to you.
- Ask yourself: How is the introduction facilitating the main topic?

How to make an introduction appealing to the reader: Start your story with a…

- Anecdote of a personal story:
  - A place, book, movie/series, or conversation with someone reminded you of the topic or introduced you to the topic.
  - What was your personal reason to write this blog?
- A topical news item related to the topic of your blog post

- Comparison of the topic with a real-life situation: how does my story relate to everyday life?

End the introduction with:

- A question: to what question is the reader to get an answer after reading this blog?
- A problem

Write the main text

Part of process	Writing
Select	Not started
# Step in the process	7

Based on your key message, your three main points, the detailed outline, and the storyline, start writing actual your story.

Important while writing:

- Make sure each paragraph has a clear beginning and end.
- Every paragraph consists of one main idea.
- Connect your paragraphs with the beginning and/or ending sentences of the paragraph.
- Use direct and active language instead of passive language (what we used to do with scientific writing).
- Don’t couch your main message in an abundance of difficult words or sentence constructions, this only distracts from your real message. Keep your message clear and snappy. In this way, it is obvious what your message is. Use more simple terminology that cannot be misunderstood.
- Make your sentences as explicit as possible.

Build the story by:

- Introducing the simpler concepts first
- Gradually take the reader into more complex concepts.

How to spice up your writing:

- Use emotion
- Use humour
- Make it personal where ever possible. Examples:
  - Use, ‘your/our body’ instead of ’the body’
  - ‘You can imagine that… ’
  - ‘I noticed this too’
  - Bring the reader into the story: for example by using, ‘**We** gained knowledge, …’ or ‘it left **us** with …’

Write the ending

Part of process	Writing
Select	Not started
# Step in the process	8

To end the blog you could:

- Summarize and conclude the content and key message of the blog.
- Return to the anecdote used in the introduction, making the story circular. By doing this, you put the introduction in perspective after the knowledge the reader gained from reading the blog.

Make sure that:

- Your take-home message is clear and concise
- You add one or a few last sentence(s) to leave the reader with an idea/action/room for thought.

Check the structure of the blog

Part of process	Reviewing
Select	Not started
# Step in the process	9

Check the structure:

- Read your written text and judge whether every paragraph is in a logical place within the article.
- Keep in mind: first, introduce the simpler concepts, and gradually take the reader into more complex concepts.

If the structure is not clear:

- Keep in mind what your key messages are.
- Rearrange the paragraphs and see if it improves.

Check for the flow of the blog

Part of process	Reviewing
Select	Not started
# Step in the process	10

While checking the flow of the article:

- Check if every paragraph nicely flows into the next paragraph. If this is not the case, add connecting sentences at the beginning and/or end of the paragraphs.
- Get rid of everything that is unnecessary and distracts from the main message.
- Check if the language for analogies and jargon words is consistent throughout the article. If you have used a particular word in one place, make sure that the same word is used again when you refer to the same analogy or jargon. Repetition is key when explaining more difficult concepts. In contrast, it’s generally best to vary the words you use in ‘normal’ sentences to make the story more enjoyable to read.
- Make sure that the length of the sentences varies throughout the text, to make it more enjoyable to read. Use shorter sentences for explaining tough concepts, and longer sentences for flair and going into more detail.

Check for jargon in the blog

Part of process	Reviewing
Select	Not started
# Step in the process	11

Check for jargon:

- Avoid using any jargon that your readers are not familiar with as much as possible.
- If the jargon is necessary for the story you're telling, provide a very clear explanation for it.
    - Often you can do this by explaining the concept with a simple analogy. When explaining the analogy: keep it direct, clear, and snappy.
        - In this way, people can envision what the process/concept, etc looks like without going into the biological details. → The goal is always to keep it simple for the reader. So, don't add complicated words to make the sentences 'prettier', if that means the essence of the sentence is lost.
    - Explain the jargon in a clear way: For example, ''…., microbiologists call this a …".
- If there are more jargon-like words in one sentence: cut the sentence into two short ones. In this way, it is easier to grasp for your reader.
- Be aware that words that do not sound jargon to you, can be for the reader.

Decide on the topic for your supplementary figure

Part of process	Figure creating
Select	Not started
# Step in the process	14

This part is totally up to you! I liked to create figures with my blogs to explain the biological concepts even more (visualizing complicated processes is more helpful to some people than reading them) or to capture the main take-home message of the blog.

When creating figures for your blog, ask yourself:

- What parts of the written blog would be understood better when adding a figure?
- What is the main concept/idea you want to capture in a figure?

Read literature

Part of process	Figure creating, Reviewing, Structuring, Writing
Select	Not started
# Step in the process	

Literature reading is always fundamental to all the above-mentioned steps.