DER SPIEGEL

Tuberculosis patient in India: *Poor nutrition, ignorance and poverty allow the disease to spread easily*

MEDICINE

Injection against consumption

Two billion people worldwide are infected with the pathogen which causes tuberculosis. Only a new vaccine could halt the spread of the disease. Hope is now pinned on five vaccines which are currently being clinically tested.

Since the Football World Cup in South Africa two years ago, "Turbo Boots" has been visiting the country's primary schools – a football superstar who embodies everything that children want to be. He appears strong, good, radiant – in short: A winner.

But Turbo Boots' goal is not to encourage the children to play football. He is the mascot of the "Kick TB" campaign. His goal is to explain to the children the dangers and symptoms of the – together with aids and malaria – most devastating epidemic in the world.

"The people here know far too little about this disease," says Mark Cotton from the Stellenbosch University who conducts research into infectious diseases among children in the huge complex of Cape Town's Tygerberg Hospital. In some districts of the town, tuberculosis breaks out in almost one percent of the population every year – that is the highest rate worldwide.

Confined living conditions, poor nutrition, ignorance and poverty together with tobacco smoke and the dust in factories and mines – those used to be the reasons why pulmonary consumption became rampant in Europe; today, a century later, we have exactly the same breeding ground in South Africa, but also in India, Russia and China. Added to that is the large number of AIDS victims who are practically defenceless against the TB pathogen – HIV has enabled tuberculosis to flare up like tinder.

Several hundred children suffering from severe TB are treated every year in Tygerberg Hospital alone, says Cotton. For researchers this makes the hospital the ideal place to test new therapies or vaccines against the disease. This means that one of the worst centres of the epidemic is also a great source of hope for doctors worldwide: Cotton is currently conducting a study with a very promising and innovative TB vaccine. Stefan Kaufmann from the Max Planck Institute of Infection Biology in Berlin has developed it together with his team.

"The immune response to the vaccine used to date is simply too weak," says Kaufmann. He is talking here about the "BCG vaccine" with which doctors have been trying to combat the TB pathogen for 90 years. But that vaccine protects only infants, and then only against the "disseminated" forms of tuberculosis. It provides absolutely no protection against pulmonary tuberculosis, the most widespread and most contagious variant of the disease.

The aim of the Max Planck researchers is to stimulate the immune system as selectively as possible. They therefore inserted a gene of "listeria" into the old BCG vaccine. This gene was intended to make it easier for the immune system to recognise the vaccine. And indeed: First trials on voluntary subjects have shown that the new TB vaccine also activates the killer cells of the immune system – the scientists hope that this will significantly boost the protective effect.

In Cape Town the researchers are first testing their substance on 48 healthy babies. 36 of them receive the new vaccine, the other 12 for comparison the old BCG vaccine – without the doctors knowing which of the two they are administering. "The children receive an injection in the right shoulder during their first week of life," explains Cotton. "The typical pustule then forms there." The last child in the study is to be vaccinated at the end of May, then doctors and scientists will monitor the health and immune response of the children for six months. If the small participants respond well to the vaccine, it will then be tested on around 9000 children and – if the result of this study is also positive – thereafter in a large-scale efficacy study on several tens of thousands of children.

"If everything goes as we hope, then that would be simply wonderful," says Cotton, and the enthusiasm in his voice is unmistakeable. A vaccine that provides reliable protection against pulmonary tuberculosis. A greater step forward for world health would be almost inconceivable. Without the long-awaited injection, on the other hand, pulmonary tuberculosis will be almost impossible to overcome. "A modelling study shows that without an innovative vaccine, we will not significantly reduce the spread of the disease," says Michael Brennan from Aeras, a non-profit organisation for the development of a new TB vaccine.

Tuberculosis is probably the oldest documented disease in humanity. Traces of the pathogen can even be found in Egyptian mummies; Hippocrates – who called the illness "phthisis", or wastage – described TB in detail. Finally, 130 years ago, Robert Koch also discovered the pathogen that caused the disease: A bacterium which he named *Mycobacterium tuberculosis.*

The study of microbiology founded by Koch succeeded in conquering most bacterial scourges, but failed in the face of the TB pathogen. Even today, an estimated two billion people are infected with mycobacterium tuberculosis. In the vast majority of cases, the pathogen withdraws into the body's own macrophages where it often remains in a latent state until the person dies, but in one case in every ten the disease breaks out at some time. That applies to around nine million people every year; someone dies of TB every 22 seconds.

"Tuberculosis still exists even in Germany," says Joachim Ficker, who heads a special ward for TB patients at the Nuremberg North Clinic. A total of 4330 cases of the disease were reported to the Robert Koch Institute in 2010. Many of Ficker's patients come from Eastern Europe, Asia and Africa. But the disease is also breaking out again now in numerous German people who became infected as children during the war. "That is due in particular to the fact that more and more "biologicals" are being prescribed for rheumatism patients which suppress the immune system," says Ficker.

The Nuremberg-based lung specialist sees mainly the serious cases in his special ward. Only seldom does he treat patients with simple pulmonary tuberculosis. Instead the TB pathogens have frequently taken root in his patients' bones, lymph nodes, kidneys or meninges. "Furthermore," says Ficker, "we often have problems with drug resistance." Although the doctors have antibiotics at their disposal – and since the introduction of streptomycin in 1946, medicine is no longer unarmed to fight the pathogen of pulmonary tuberculosis – nevertheless the antibiotics have been unable to take away the terror of this disease. The pathogen is far too clever for that.

The bacteria attack the body in inconceivable numbers. That is why only a combination of several – generally three – antibiotics administered simultaneously have an effect. Otherwise the development of drug resistance is practically unavoidable due to the high probability of mutations.

Another characteristic of the pathogen, however, is even more perfidious: When the disease finally breaks out, the mycobacterium awakes only gradually from latency. Since the medication kills off only the active part of the pathogen, however, the medication has to be administered for a long time, generally between six and nine months.

The battle against the pathogen is often too slow and too short. The unavoidable consequence: Multi-drug resistant strains of tuberculosis which have become resistant to the two most important standard antibiotics are spreading worldwide (see graph on page 119). Even extensively drug-resistant strains which are additionally resistant to at least two further drugs have already been discovered in around 60 countries. A total of around 150,000 deaths a year are attributable to resistant pathogens.

They stubbornly resist the treatment, and often even the most aggressive treatment is ultimately in vain. "The therapy," says Anneke Hesseling, director of the paediatric research programme at the Desmond Tutu TB Centre in Cape Town, "takes at least eighteen months, and we are unable to cure one in six patients." Added to this are the side-effects of the drugs: Around a quarter of children suffer – in some cases severe – hearing damage.

So the need for an effective vaccine becomes ever more urgent – a goal that was criminally neglected for decades. "Ten years ago, all the TB vaccine researchers in the world would have fit into a minivan," says Peter Small from the Bill and Melinda Gates Foundation in New Delhi.

In the meantime, however, some 500 researchers worldwide are working on the subject. "The awareness has changed," says Small. Market analyses showed that several hundred million Euros a year can be earned with a new vaccine. "From then on," says Small, "the interest grew." In the meantime five new TB vaccines are being clinically tested. And in the laboratories the scientists are already working on the next generation.
The Gates Foundation, in particular, set the pace. The Foundation donated some 400 million dollars to the fight against tuberculosis, more than half of which for the development of a vaccine – and many others followed suit. Not only the German Ministry of Research and the American National Institutes of Health, but also Norway, the Netherlands and

Great Britain are now supporting the search for a vaccine. The EU contributed over 30 million Euros. In industry, the British pharmaceuticals giant GlaxoSmithKline, in particular, is taking a lead.

The researchers are investigating two main approaches:

~ The genetic modification of the old BCG vaccine. This is the approach being followed in particular by the Max Planck Institute in Berlin. A similar approach by another team has been stopped for the time being due to side effects.

~ The "booster strategy". A second injection with a new vaccine is intended to strengthen the effect of the old BCG vaccine.

It may be possible to combine the different vaccines with one another. "TB researchers are increasingly coming to the conclusion," says Michael Brennan from Aeras, "that we need different vaccines for the different phases of the disease: Some could block the infection, others prevent the bacteria from being awakened and others again could shorten the duration of the antibiotic treatment."

But a number of questions still remain unanswered. In particular the researchers would like to know how exactly the immune system actually combats the tuberculosis pathogen. What role do the helper cells play? When do the killer cells come onto the scene? And how important is the innate immune system?

Peter Small from the Gates Foundation sees this as a central problem: "Until now it seems as though the scientists were following their expedition to the TB vaccine without a map. Only when we really understand the reactions of the immune system will we know in which direction we need to be heading."

It is still not clear, however, where the 40 to 80 million dollars are to come from that are needed for the efficacy studies on the first generation of vaccines. "Compared with HIV," says Brennan, "TB research is miserably under-financed."

"We are at the crossroads," says Small. "If we don't now succeed in bringing a new tuberculosis vaccine over the finishing line, then all the money and effort that has been invested to date will have been in vain."

VERONIKA HACKENBROCH

BCG VACCINATION
Generally protects only infants against certain forms of tuberculosis. Vaccinated persons can nevertheless become ill later.

TREATMENT
Possible, but difficult, with antibiotics. Several antibiotics have to be administered simultaneously and over a period of at least six months.

DRUG RESISTANCE
Resistant strains have developed as a result of misuse of antibiotics. They have spread worldwide.