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New insight into the progression of tuberculosis infection

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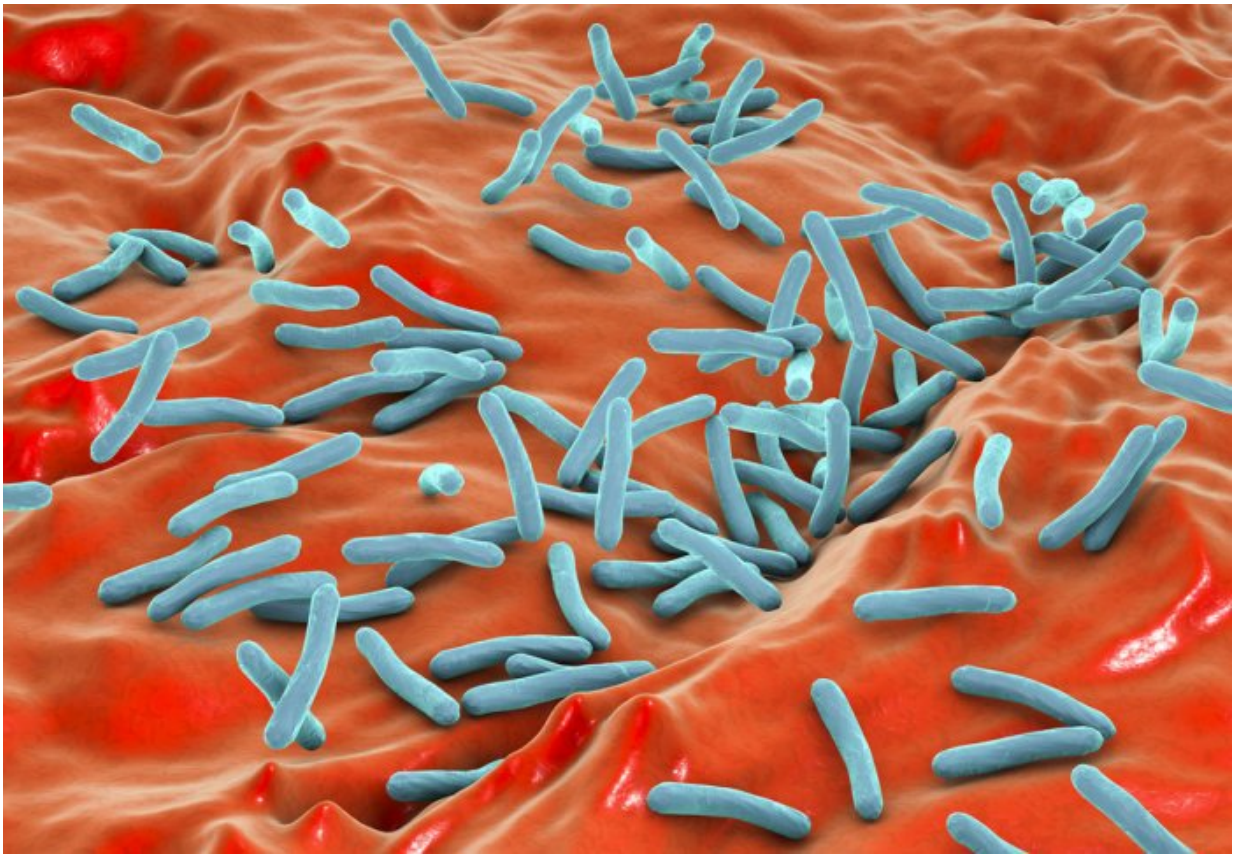

Myobacterium tuberculosis. Credit: Imperial College London

A new study suggests it may be possible to predict which people infected with TB will develop the disease.

Scientists have found evidence of a separate stage in tuberculosis (TB) infection, where people have no symptoms but are more likely to develop the full disease.

The findings, published in *Nature Medicine*, suggest it may be possible to identify which people are most at risk of developing TB. These patients could then be treated in a more targeted way.

Professor Robert Wilkinson, lead author of the study from Imperial College London and the Francis Crick Institute, said: "We have shown clear evidence for a TB stage in-between latent infection and active disease. It could lead to a way of predicting which infected individuals will develop TB disease and transmit it to others."

The results offer hope in controlling spread of disease, added Professor Wilkinson: "People ill with TB can infect up to 10–15 other people through close contact and if we can identify people in the transition stage, before they transmit the disease, that's potentially a game-changer in terms of TB eradication."

Conventionally, TB infection is classed into two stages: 'latent' and 'active'. People with latent infection test positive for an immune response to the TB bacteria, Mycobacterium tuberculosis, but do not have the symptoms of active disease.

Around 10 per cent of people with latent TB infection progress to active disease if left untreated. However, currently there is no accurate way to predict which infected individuals will develop the disease.

It is estimated that there are 2 billion people around the world with latent TB infection. Active TB kills an estimated 1.5 million people annually – with people with HIV being at greater risk.

The team, which included scientists from the University of Cape Town, South Africa, and the US National Institute of Health, screened 265 HIV-positive people for TB infection in a township in Cape Town where TB incidence is high. Of those who tested positive for latent TB, 35 were recruited to the study and were followed up over a period of six months.

The team used a combination of medical imaging techniques to study the lungs of the 35 patients – positron emission tomography (PET) and computed tomography (CT) scans – which highlighted areas of lung abnormalities as 'hot spots'.

Ten out of the 35 participants with latent TB infection had lung abnormalities consistent with a transitional or subclinical stage of TB progression. The other 25 participants had no hot spots and showed no signs of disease progression.

Over the course of the study, four of the 10 patients with lung abnormalities developed fully-fledged TB symptoms and started full treatment for TB. Two of these were found to have active TB confirmed by a standard sputum culture that tests for the presence of TB bacteria in the airways.

"We found evidence of differences in disease progression within a group of people that currently would all be diagnosed and managed as having the same latent TB infection, as none of them showed any outward symptoms of TB," explained Professor Wilkinson. "Those that had evidence of 'subclinical' disease on the PET/CT scans were at higher risk of developing the disease."

Imaging was continued during the treatment period for the four patients with active TB. This showed the lung abnormalities gradually diminishing over time.

Professor Wilkinson said: "These high-tech images provide us with new ways to evaluate whether treatment has cured an infection. Most importantly, it will show whether we need to treat for the full recommended duration of six months, as most patients find the standard six months regimen of two or three different antibiotics very challenging."

He added:"It would not be feasible to PET/CT scan everyone with latent TB as the majority of these people are in poor regions of sub-Saharan Africa and these particular scanners are expensive. Instead, the study is most promising in enabling other markers of this 'sub-clinical' stage of infection to be identified and be able to better predict those who will develop TB symptoms."

More information: Hanif Esmail et al. Characterization of progressive HIV-associated tuberculosis using 2-deoxy-2-[18F]fluoro-D-glucose positron emission and computed tomography, *Nature Medicine* (2016). DOI: 10.1038/nm.4161

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