Computer model predicts potential impact of short-course therapy against multidrug-resistant tuberculosis

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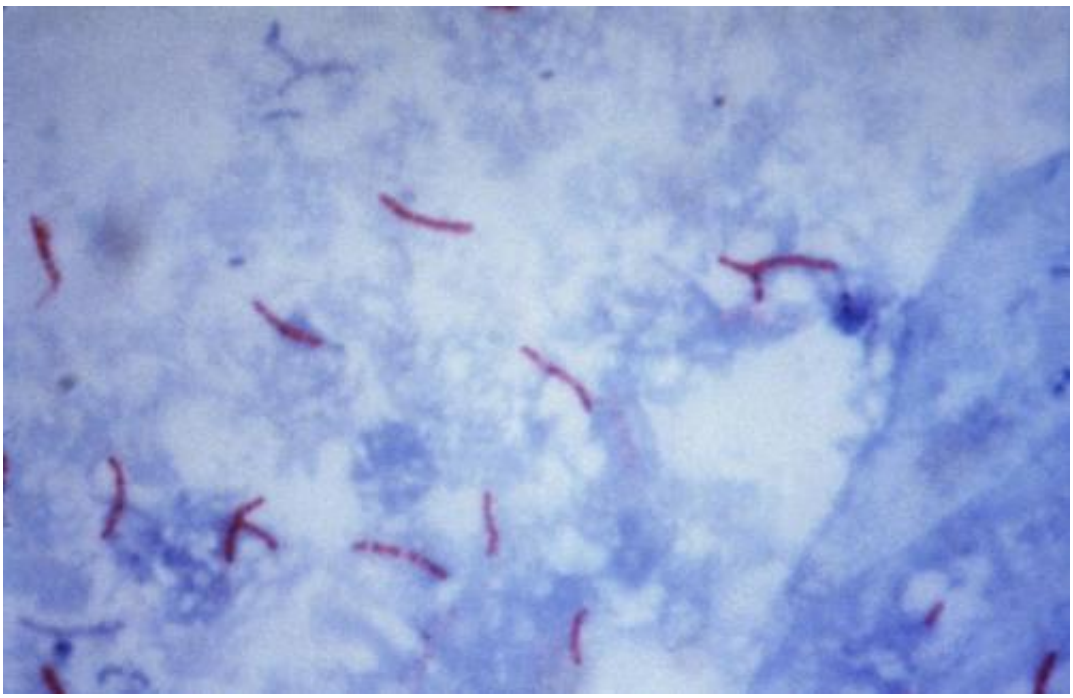

This photomicrograph reveals Mycobacterium tuberculosis bacteria using acid-fast Ziehl-Neelsen stain; Magnified 1000 X. The acid-fast stains depend on the ability of mycobacteria to retain dye when treated with mineral acid or an acid-alcohol solution such as the Ziehl-Neelsen, or the Kinyoun stains that are carbolfuchsin methods specific for M. tuberculosis. Credit: public domain

Johns Hopkins researchers have developed a computer simulation that helps predict under which circumstances a new short-course treatment

regimen for drug-resistant tuberculosis could substantially reduce the global incidence and spread of the disease.

The computer model was developed to help understand the impact of a recommendation issued in May by the World Health Organization for wider use of a new nine- to 12-month treatment regimen for multidrug-resistant tuberculosis (MDR-TB). The conventional treatment regimen takes 18 months to two years.

Tuberculosis, which is spread through the air from one person to another, is the No. 1 cause of infectious disease deaths in the world, with an incidence of approximately 10 million new cases and 1.7 million deaths each year. MDR-TB is strains of TB bacteria that cannot be killed by the strongest-available TB drugs, rifampin and isoniazid. These strains alone are estimated to cause almost 500,000 new TB cases and over 100,000 deaths each year.

In the study, described in the Dec. 15 edition of *The Lancet Respiratory Medicine*, the researchers found that the new regimen could lower the incidence of MDR-TB in Southeast Asia by 23 percent more than conventional treatment over eight years. Importantly, they describe the types of situations where this number might be an over- or underestimate. If the new regimen could achieve this same impact on a global scale, over 100,000 new cases of MDR-TB could be averted every year.

Conventional treatments for MDR-TB are costly and uncomfortable. The drugs used include a daily injection that must be taken for the first eight months of the regimen, followed my many more months of pills. These drugs frequently cause severe side effects, such as nausea, headache, chest pain and rash. MDR-TB costs five to 10 times more to treat than other TB cases, and the costs of drugs and time are a burden to health systems and patients worldwide. In the U.S., treating MDR-TB

can cost anywhere between $17,000 to $482,000 per person. As a result, compliance with the regimen and its availability in poorer countries is limited, leading to further spread of the disease.

"About 15 to 20 percent of patients who start conventional treatment for drug-resistant TB don't finish, mostly because of the length, expense and discomfort associated with it," says Emily Kendall, M.D., an instructor in the Department of Medicine at the Johns Hopkins University School of Medicine. "The short-course regimen could cut both treatment time and cost of treatment in half."

Promising outcomes of preliminary studies in patients in Southeast Asia and parts of Western and Central Africa led the World Health Organization to make the recommendation, but safety and efficacy have not yet been proven in large-scale clinical trials. Kendall says uncertainty about the new regimen's role prompted her group's interest in creating a computer model to assist health care groups and governments in deciding whether or not to switch to the new regimen, which uses a combination of seven drugs.

Kendall says the model her team created allows researchers to "virtually" explore the new regimen's impact in a simulated population. By tuning the model to replicate population data, such as the number of people at risk for developing TB and the fraction of TB patients who have drug resistance, the model can predict changes in the TB disease burden—or number of cases—over many years.

For the test study, Kendall's team based the model on experience in Southeast Asia, where the short-course regimen was originally developed by a group of researchers in Bangladesh. They found that, compared to using the conventional treatment in this population, which only reduced current MDR-TB incidence by 14 percent, using the new short-course treatment decreased the incidence of MDR-TB by 23 percent in eight

years in the model.

The Johns Hopkins investigators caution, however, that the short-term treatment's impact is dependent on several assumptions, including that no more than 10 percent of possible patients are excluded from treatment by additional drug resistance and that using the new regimen actually increases the number of MDR-TB patients treated. If these assumptions do not play out in actual practice, using the new regimen could have substantially less impact—and even lead to more cases—than using the conventional regimen, in some cases. The model is helpful in describing the situations where the new regimen is likely to have large impact, small impact or no impact at all.

"Several important factors are still uncertain, but if we can keep the number of excluded patients down to around 10 percent, if treatment of the other 90 percent of patients is as successful as preliminary studies suggest and if cost savings from the shorter regimen allow more patients to be treated, then this regimen is likely to have a really big impact," says Kendall.

Kendall also cautioned that there are some populations in which the short-course regimen may not work well. For example, the regimen is not yet recommended for children or for TB infections outside of the lungs. "Our computer tool can help guide certain decisions about the short regimen," Kendall says, "but scientists and health care workers still need to be really vigilant about gathering more data on how it's working and for whom it is working best as we begin to use it more widely."

Provided by Johns Hopkins University School of Medicine

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