Analysis of TB treatment studies identifies gaps in guidelines

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International guidelines for treating tuberculosis are due for specific improvements, according to two research papers published this week in the open access journal *PLoS Medicine*.

Public health programs in many countries adhere to World Health Organization (WHO) guidelines as the authoritative recommendations for treating tuberculosis (TB). But do these guidelines reflect the best available evidence? To answer this question, Dick Menzies of McGill University in Montreal and colleagues reviewed all available results from trials of currently recommended treatment regimens, first for initial treatment of TB, and then for individuals who had been previously treated without being cured, or had infections that were resistant to isoniazid, one of the main first-line anti-TB drugs.

In the first study, the researchers identified and analyzed 57 randomized, controlled clinical trials including more than 20,000 participants treated for TB. They found that regimens utilizing the drug rifampin for only the first 2 months, which have been recommended in 24 countries with high rates of TB infection, had significantly higher rates of failure, relapse, and acquired drug resistance compared with regimens that used rifampin for at least 6 months.

The second study analyzed trials of TB treatment in previously treated individuals, or those with isoniazid-resistant infection. The researchers found no randomized trials comparing the currently recommended WHO retreatment regimen against other approaches. In non-comparative

(cohort) studies, failure rates were generally low if participants were infected with strains that were sensitive to all antibiotics in the regimen. However, in studies in which participants were infected with a strain of Mycobacterium tuberculosis resistant to one or more drugs, failure rates ranged from 9% to 45%.

The researchers also analyzed the combined results of 33 trials that investigated the effect of various regimens on almost 2,000 patients (some receiving their first treatment for TB, others being retreated) with resistance to isoniazid alone. This meta-analysis found lower relapse, failure and acquired drug resistance rates to be associated with longer duration of rifampin treatment, daily therapy early in treatment, inclusion of the drug streptomycin, and regimens that included a greater number of drugs to which the patient's TB infection was sensitive.

Taken together, these findings will inform upcoming revisions of the WHO TB treatment guidelines, and identify an important need for clinical trials to evaluate dosing schedules, detection and management of isoniazid resistance, and the optimal duration of treatment to prevent relapse, as well as more effective approaches to retreatment of tuberculosis.

More information:

• Menzies D, Benedetti A, Paydar A, Martin I, Royce S, et al. (2009) Effect of Duration and Intermittency of Rifampin on Tuberculosis Treatment Outcomes: A Systematic Review and Meta-Analysis. PLoS Med 6(9): e1000146. doi:10.1371/journal.pmed.1000146

• Menzies D, Benedetti A, Paydar A, Royce S, Pai M, et al. (2009) Standardized Treatment of Active Tuberculosis in Patients with Previous Treatment and/or with Mono-resistance tdoi:10.1371/journal.pmed.1000150 and Meta-analysis. PLoS Med 6(9):

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