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Innovative Methods to Manage, Detect, and Prevent Tuberculosis

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Jones-López EC, et al. Cough Aerosols of *Mycobacterium tuberculosis* in the Prediction of Incident Tuberculosis Disease in Household Contacts. *Clin Infect Dis* (1)

Reviewed by Leonardo Martinez

The differential infectiousness of patients with tuberculosis has been studied for more than 50 years (2), and several research groups have shown that some cases are more infectious than others (2–5). Several methods of evaluating tuberculosis infectiousness have been used, including sputum smear status, cavitary lung lesions, tuberculin skin test (TST) conversion among contacts, and molecular epidemiological methods. Despite the diversity in methodology used, identifying the most infectious cases remains challenging. To prevent *Mycobacterium tuberculosis* transmission, accurate methods to identify highly infectious tuberculosis cases must be developed.

Colony-forming units (CFUs) found in cough aerosols, a relatively novel and distinct measure of tuberculosis infectiousness, have been reported in several recent studies (5, 6). Researchers found that household contacts of patients with tuberculosis with high CFU counts were 6 to 9 times more likely to have a positive TST compared with patients who had negative-aerosol tuberculosis. Jones-López and colleagues attempted to extend previous findings by conducting a retrospective cohort in Kampala, Uganda by investigating whether cough aerosols were able to predict incident tuberculosis disease among 369 household contacts of 85 patients with smear-positive tuberculosis.

Most contacts were female (56%), bacillus Calmette-Guérin vaccinated (76%), and had latent tuberculosis measured either through the TST (77% with induration >15 mm) or interferon- γ assay (80.9% with ≥ 0.35 IU/ml). The cohort was followed for a median of 3.9 years. After measuring CFUs found in cough aerosols of tuberculosis cases, household contacts were stratified by exposure to patients with aerosol-negative (215 of 369), low-aerosol

(78 of 369; defined as CFUs 1–9), and high-aerosol (76 of 369; defined as CFUs ≥ 10) tuberculosis.

Overall, eight contacts (8/369, 2.2%) developed incident tuberculosis disease: four contacts (4/76, 5.3%) of patients with high-aerosol tuberculosis; one contact (1/78, 1.3%) of patients with low-aerosol tuberculosis; and three contacts (3/215, 1.4%) of patients with aerosol-negative tuberculosis. Contacts of patients with high-aerosol tuberculosis had four times ($P = 0.05$) higher likelihood of incident tuberculosis disease compared with contacts of patients with low- or negative-aerosol tuberculosis. This was further strengthened after adjustment for potential confounders (odds ratio, 6.0; $P = 0.01$).

Study weaknesses included the retrospective design and the low number of incident tuberculosis cases, which limited the options for controlling confounding variables. In addition, molecular genotyping was not performed; therefore, incident cases might be due to community transmission. Lastly, this study included only smear-positive index cases; therefore, these findings were not relevant to contacts of smear-negative cases.

Despite these limitations, this study suggested cough aerosols might be an important prognostic biomarker for tuberculosis infectiousness. Clinical application of cough aerosols or other similar tools must be further studied, and prospective cohort studies are needed. ■

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Churchyard GJ, *et al.* Xpert MTB/RIF versus Sputum Microscopy as the Initial Diagnostic Test for Tuberculosis: A Cluster-randomised Trial Embedded in South African Roll-out of Xpert MTB/RIF. *Lancet Glob Health* (7)

Reviewed by María Eugenia Castellanos

The use of innovative technologies for the diagnosis of tuberculosis have recently dramatically increased in the developed and developing world. Xpert MTB/RIF (Xpert; Cepheid, Sunnyvale, CA) is an automatic molecular test that detects the presence of both *Mycobacterium tuberculosis* complex and rifampicin resistance in less than 2 hours. Xpert has been estimated to increase tuberculosis case detection by 23% compared with microscopy (8). In 2010, widespread implementation of Xpert was recommended by the World Health Organization (8). However, until recently, the population-level impact of using Xpert on patient clinical outcomes was unknown.

Churchyard and colleagues presented results of a pragmatic, parallel cluster-randomized trial conducted in South Africa among subjects suspected of having tuberculosis aged 18 years or older (7). Twenty laboratories were randomized to use either Xpert or sputum microscopy and 4,656 subjects were enrolled. The probability of a positive tuberculosis diagnosis was 50% higher if Xpert was used compared with microscopy (adjusted risk ratio, 1.5, 95% confidence interval, 1.0–2.2). However, after 6 months, overall mortality risk in both groups was similar: 3.9% versus 5.0% in the Xpert and microscopy arms, respectively. The adjusted mortality risk ratio was 1.1 (95% confidence interval, 0.5–1.6). There were also no differences between the groups in the proportion of subjects treated for tuberculosis and other secondary outcomes.

There were limitations to this trial. First, as a pragmatic trial, bias in enrollment or follow-up might have occurred differentially in study arms. Second, the study was designed to detect a 50% reduction of mortality in the Xpert arm, so it might have been underpowered to detect smaller differences. Lastly, the effect of Xpert on drug resistance could not be assessed owing to a low proportion of rifampicin-resistant cases.

Study strengths included that it was conducted as part of a nationwide roll out of Xpert testing in South Africa, which allowed real-world assessment of the benefit of Xpert. Moreover, the

randomization procedure allowed the researchers to provide more robust and valid findings than observational studies.

Based on this and other recent randomized trials (9, 10), new technologies as promising as Xpert might not improve health outcomes in countries with a high tuberculosis burden where diagnosis is not linked to proper and effective tuberculosis treatment. Until issues in tuberculosis clinical management are improved in low-income settings, the decision to implement high-cost Xpert testing remains controversial. ■

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Heemskerk AD, *et al.* Intensified Antituberculosis Therapy in Adults with Tuberculous Meningitis. *N Engl J Med* (11)

Reviewed by Benjamin D. Hallowell

Tuberculous meningitis is the most lethal form of *Mycobacterium tuberculosis* infection, and even with early diagnosis and treatment, nearly one in three patients die (11). Two small randomized trials found that increasing rifampicin dosage (12) or supplementing standard treatment regimens with fluoroquinolones (13) improved mortality outcomes.

Heemskerk and colleagues (11) aimed to validate these findings and to determine if a short-term (8 week) intensified anti-tuberculosis treatment regimen (increasing rifampicin dosage to 15 mg/kg/day and adding 20 mg/kg/day of levofloxacin) followed by 9 months of standard tuberculosis treatment significantly reduced mortality at 9 months compared with standard treatment alone. For this purpose, they conducted a pragmatic, randomized, double-blind, placebo-controlled trial that enrolled patients from two Vietnamese hospitals. Before randomization, patients were stratified by site, HIV status, and disease severity. A total of 43% of the study population were HIV seropositive; 408 subjects were assigned to intensive treatment, and 409 subjects were assigned to standard care. After 9 months of follow-up, 113 subjects in the intensive treatment group and 114 subjects in the standard treatment group died (hazard ratio, 0.94; 95% confidence interval, 0.73–1.22). There were

no significant differences found in mortality among the subjects subgroups, secondary outcomes, or adverse events.

Intensive treatment at the selected dosage is unlikely to reduce mortality at 9 months, which contradicts previous findings (12, 13). Because the prescribed dose of fluoroquinolones was sufficient to achieve adequate levels in the cerebrospinal fluid, fluoroquinolones are unlikely to improve survival outcomes (13). In a similar study conducted by Ruslami and colleagues, intensified rifampicin treatment at 13 mg/kg/day was given intravenously and resulted in three times higher drug concentrations in the blood and cerebrospinal fluid than a similar oral dose (12, 14). Other studies showed that oral doses of rifampicin as high as 35 mg/kg/day were tolerated and were associated with bacterial load decline (15). Although a short-term oral rifampicin dosage of 15 mg/kg/day is unlikely to improve survival, higher drug concentrations could significantly improve survival outcomes.

Despite no significant differences at 9 months, Kaplan-Meier curves for subjects in the intensive treatment arm did not converge with the standard treatment group until after 8 weeks, which suggested that longer intensive treatment might improve outcomes, although this was not demonstrated with other drug regimens (16, 17).

Diagnosis of tuberculous meningitis is challenging, and the criteria used in this study might have permitted the inclusion of nondiseased or other types of tuberculosis cases (such as tuberculomas without meningitis) (18). The potential for misclassification might have reduced statistical power to detect a difference between groups. In addition, disease severity was assessed by the British Medical Research Council staging system which, although widely used, relies exclusively on clinical evaluation. Recently, a severity score that used a series of variables, such as imaging and other comorbidities, was shown to be superior to the Medical Research Council staging system (19).

Further trials with higher rifampicin doses and longer follow-up must be performed to investigate whether an effective drug regimen can successfully reduce mortality. Until effective treatment regimens are found for individuals with tuberculous meningitis, early diagnosis and treatment remain the most effective methods to maximize survival. ■

Author disclosures are available with the text of this article at www.atsjournals.org.

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