Failure of Directly Observed Treatment for Tuberculosis in Africa: A Call for New Approaches

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(See the article by Lawn et al. on pages 1040–7)

The tuberculosis pandemic continues to evolve. In some parts of the world, tuberculosis case rates have decreased to historically low levels, whereas, in other parts of the world, the incidence of tuberculosis is increasing. In sub-Saharan Africa, tuberculosis continues to be a major threat to individual and public health as incidence rates surpass 1000 cases per 100,000 population in some regions. In 1994, the World Health Organization (WHO) declared tuberculosis a global emergency and introduced the directly observed treatment, short course (DOTS), strategy for global tuberculosis control, but the plan has produced variable success. In the face of this intensified effort to diagnose and treat tuberculosis, the rates in sub-Saharan Africa continue to climb. Various experts have argued that the failure of the DOTS strategy to control tuberculosis results from failed implementation, poor public health infrastructure, poverty, the lack of interventions that are sensitive to personal preferences, and the HIV epidemic. Although each of these reasons may contribute, the problem with the DOTS strategy may be even more fundamental. What is the rationale for the DOTS strategy? Is it a public health intervention designed to curb the spread of tuberculosis, or is it a treatment guideline for tuberculosis?

The DOTS strategy was introduced in 1994 as a comprehensive plan for tuberculosis control built around 5 strategic activities [1]. First, governments must commit to control tuberculosis and provide the human resources and infrastructural capacity to deliver care for persons with tuberculosis. Second, case detection is performed through passive case-finding, with microscopic examination of sputum samples used as the diagnostic standard. Third, treatment consists of the standard short-course regimen and must be given using directly observed therapy. Fourth, there must be a regular supply of medication to the national tuberculosis-control program. Fifth, a system must be in place for monitoring and tracking cases throughout the country. As part of the strategy, the WHO also proposed a performance target of identifying 70% of tuberculosis cases and curing 85% of them.

The article by Lawn et al. [2] is an ecologic study that describes coincident tuberculosis and HIV epidemics in a township near Cape Town, South Africa. The study is unique because it examines a population in a well-defined geographic region that was characterized by 2 population census surveys 8 years apart, so disease rates could be adjusted for demographic changes. The community is served by a single community health clinic, making it likely that the means of diagnosing and reporting cases of tuberculosis and HIV infection were uniform, thereby avoiding detection and reporting biases. The most striking feature of the design is that DOTS was implemented in an optimal way in the district, and the program achieved cure rates of >80% in smear-positive cases of tuberculosis.

In this setting, the authors were able to show that the tuberculosis rates increased 2.5-fold during the study period and continued to increase even after the prevalence of HIV infection had leveled off. Tuberculosis rates increased most among adolescents and individuals aged 20–39 years—the age groups most likely to be affected by HIV infection in this population. The authors conclude that the DOTS strategy alone was ineffective in this community because of the population effects of HIV infection on tuberculosis.

Although it is important to herald the successes of the DOTS strategy around the world [3, 4] and to acknowledge its role in preventing the emergence of multidrug-resistant strains of Mycobacterium tuberculosis [5], we may learn more about tuberculosis control from examining where the DOTS strategy has failed. By understanding the reasons for failure, we may
be able to modify and improve current approaches and to design new strategies. The study by Lawn et al. [2] offers some insight into why the DOTS strategy failed, at least in this small, well-studied African community. Some experts have stated that the main reason for the DOTS strategy's failure is lack of proper implementation [6–8]. But that is not likely here, because all tuberculosis care was offered through a single clinic that achieved WHO treatment goals. Lawn and colleagues argue that the HIV epidemic fueled the tuberculosis epidemic in the township, citing the temporal association between the 2 epidemics and its biologic plausibility as evidence. As an ecologic study, however, it is possible that an unmeasured factor, such as population migration, has produced the results we observe. In the United States, for example, we witnessed a resurgence of tuberculosis from 1986 to 1993 that was initially attributed to the "new" AIDS epidemic but was later attributed to tuberculosis in foreign-born individuals, with HIV infection playing a lesser role [9]. In this township, we find ourselves confronting a similar interpretation. Detailed molecular epidemiology of tuberculosis cases and HIV serostatus of individuals would help to clarify the transmission dynamics among individuals in this population.

So where does the DOTS strategy falter? DOTS is not optimally designed to interrupt the spread of tuberculosis. Epidemics result from the transmission of a microorganism from infectious persons to \( \geq 1 \) susceptible individual. The force of this transmission is captured in the basic reproductive rate of an epidemic, a parameter that can be understood as the number of new infections among susceptible individuals during the infectious period of a case. Only 3 determinants underlie this important parameter: (1) the number of contacts (per unit time) between an infectious patient and susceptible contacts; (2) the probability of infection (or disease), given adequate contact for transmission from the patient to a susceptible individual; and (3) the duration of infectiousness of the index case.

When one examines the elements of DOTS, only the treatment of disease directly alters one of these key epidemic parameters by reducing the duration of infectiousness. The DOTS strategy does not address the number and frequency of contacts or the likelihood of disease after infection. For tuberculosis, it is estimated that a single patient may infect \( \sim 10 \) contacts before receiving treatment [10]. With a lifetime risk of tuberculosis of \( \sim 10\% \) [11], then each case of tuberculosis will be replaced by another, at some point in the future. In the presence of HIV infection, however, the dynamics are altered, because HIV infection is associated with a high risk for progressive primary tuberculosis [12] and reactivation of disease [13]. A single tuberculosis case will likely yield \( >1 \) subsequent case, thereby accentuating an epidemic.

Our experience with DOTS teaches us that treatment of tuberculosis alone is ineffective in containing its spread in some communities, particularly where HIV infection is endemic. New approaches should be developed that interrupt the spread of M. tuberculosis in the community. These public health interventions may aim to alter contact patterns of infected patients through real-time geographic mapping of disease incidence or through social development programs. Other interventions might aim to reduce the risk of disease after infection, either by treating latent tuberculosis infection in high-risk groups (e.g., HIV-infected persons and household contacts), or by the systematic treatment of HIV infection with antiretroviral therapy [14]. As suggested by Lawn et al. [2], age-specific, active case finding in high-risk populations might also preempt tuberculosis spread by reducing the duration of infectiousness. The common theme for these approaches is to target transmission as the main goal of the intervention.

In summary, a framework for tuberculosis control requires clearly defined goals—that is, whether an intervention targets primarily transmission or treatment. The DOTS strategy is an excellent and well-orchestrated set of treatment guidelines that provide governments, ministries of health, and health care professionals unambiguous advice on how to treat patients with tuberculosis. And for this reason, it should remain a centerpiece in our efforts to treat tuberculosis disease. The study from Cape Town illustrates the urgent need to develop novel strategies to act as companions to DOTS. These novel public health strategies should have as their primary goal to interrupt the spread of tuberculosis. Because of the potential effect of HIV infection on tuberculosis control, these strategies must also integrate with the HIV prevention and treatment programs.

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**References**


