The Emerging Crisis of Drug-Resistant Tuberculosis in South Africa: Lessons from New York City

Richard A. Murphy

Division of Infectious Diseases, Massachusetts General Hospital and Brigham and Women's Hospital, Boston, Massachusetts

Multidrug-resistant tuberculosis and extensively drug-resistant tuberculosis have emerged as important infections in South Africa among patients infected with human immunodeficiency virus (HIV). In the face of this new epidemic, South Africa must rededicate itself to the task of tuberculosis control and treatment with a rapid, multifaceted approach. Priorities include expansion of second-line treatment capacity, investment in clinical laboratories, a system to ensure supervised treatment for all patients, and enhancement of infection control procedures. In New York City, where drug-resistant tuberculosis emerged 2 decades ago—also in the context of a large HIV-infected population and an underfunded public health infrastructure—similar steps were successful in leading to the rapid decrease in rates of drug resistance among tuberculosis isolates. With refinements based on local resource constraints, urgent measures could potentially arrest the alarming increase in multidrug-resistant and extensively drug-resistant tuberculosis cases in South Africa. Unlike many countries in sub-Saharan Africa, South Africa has the capacity to mount a rapid and large-scale response before drug-resistant tuberculosis envelops a much larger and far poorer region.

The rise of multidrug-resistant tuberculosis (MDR-TB) and extensively drug-resistant tuberculosis (XDR-TB) in South Africa among patients with HIV infection is a grave and urgent threat. As South Africa takes steps to respond, there are important lessons to be drawn from New York City (NYC), where, 2 decades ago, drug-resistant tuberculosis also emerged among patients with HIV infection [1, 2]. It is striking that many of the same conditions that fueled the rise of drug-resistant tuberculosis in NYC also underlie the current epidemic of MDR-TB and XDR-TB in South Africa. These include a large and undertreated HIV-infected population, inadequate infection control in hospitals and clinics, and a public health infrastructure not equipped to ensure that patients complete treatment courses. Although important differences should not be minimized, the experience of NYC provides potentially important insights for South Africa as it shapes its own unique response.

MDR-TB AND XDR-TB IN SOUTH AFRICA

When I arrived in KwaZulu-Natal, South Africa, in August of 2006, it was already apparent, from published reports, that drug-resistant tuberculosis was deeply embedded in the province [3]. But the dimensions of the crisis on the ground were not apparent to me until one day in January 2007, when I met Precious Cele (fictitious name), a 35-year-old woman with HIV infection who, 2 months before, had received a diagnosis of smear-positive pulmonary tuberculosis. It was her first episode of tuberculosis, and she had been prescribed standard 4-drug chemotherapy, which she had dutifully taken. However, during treatment, her cough persisted, and her weight fell by 7 kg (15 lb). The day I met her, the laboratory confirmed that she had MDR-TB (defined as infection with *Mycobacterium tuberculosis* with resistance to isoniazid and rifampicin), and we sought urgent initiation of second-line tuberculosis treatment at the only public hospital in the province where it was available. However, we learned that in front of her were ~100 other patients also waiting for initiation of treatment for MDR-TB and XDR-TB.

Although South Africa has committed substantial resources to respond to the growing crisis of drug-resistant tuberculosis, for doctors and nurses caring for patients with drug-resistant tuberculosis in clinics, major barriers undermine prompt diagnosis and referral. To improve the outlook for patients in South Africa with drug-resistant tuberculosis, the NYC experience suggests some crucial investments that should be considered in the

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Reprints or correspondence: Dr. Richard A. Murphy, Medecins Sans Frontieres/Doctors Without Borders, 333 7th Ave., 2nd Fl., New York, NY 10001 (richard.murphy@newyork.msf.org).

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short term, including (1) the creation of enough MDR-TB and XDR-TB treatment capacity such that, after microbiological diagnosis, therapy can begin immediately; (2) the development of improved laboratory capacity to guarantee rapid, accurate, and accessible results of culture and susceptibility tests; (3) the creation of a public health infrastructure capable of ensuring that patients complete tuberculosis therapy; and (4) the institution of measures in hospitals and clinics to decrease the nosocomial transmission of drug-resistant tuberculosis.

EXPANDING TREATMENT CAPACITY

One very important lesson from the NYC outbreak of MDR-TB was that, in HIV-infected hosts, MDR-TB follows an accelerated course and has a very high case-fatality rate [2]. However, evidence from the NYC epidemic also shows that outcomes, at least for patients with MDR-TB, can be better when active, second-line agents are promptly initiated [2, 4]. Although not yet well studied, XDR-TB (defined as infection with *M. tuberculosis* with resistance to isoniazid and rifampicin as well as resistance to any fluoroquinolone and 1 of the second-line injectable agents) in patients with HIV infection may follow the same essential principle. It is therefore vital, during the short window of time when second-line tuberculosis therapy can improve clinical outcomes—for patients such as Precious Cele—that it not be delayed.

A particularly urgent issue in South Africa involves how to expand second-line treatment capacity to prevent potentially avoidable deaths and ongoing transmission from untreated disease. If the inpatient model is used, expansion of capacity will be slow and expensive, and queues may remain the mechanism by which second-line treatment is allocated. An important alternative model for South Africa to consider for selected patients is community-based treatment of drug-resistant tuberculosis. Compelling data that support community-based treatment for drug-resistant tuberculosis—by use of peer support and multidisciplinary teams—have been generated in other resource-constrained settings, which suggests that such a model can be both cost-effective and efficacious [5]. Furthermore, outpatient models can be scaled up quickly as the need escalates and can include antiretroviral therapy (>60% of patients in South Africa with tuberculosis have concomitant HIV infection), and resources can be reallocated for other purposes once the crisis abates.

IMPROVING LABORATORY INFRASTRUCTURE

The rapid initiation of second-line treatment for patients infected with drug-resistant *M. tuberculosis* in South Africa will depend on a close relationship between doctors and mycobacterial laboratories. Although South Africa has the benefit of more facilities for culture and sensitivity testing than any other sub-Saharan African nation, the increased demands created by the current epidemic of drug resistance have stretched this hard-working sector and have highlighted its limitations. Currently, delays in the reporting of results and difficulties in locating data for individual patients hinder the early diagnosis and rapid referral of patients for treatment of MDR-TB and XDR-TB, which directly affect patient outcomes. As the epidemic escalates, the number of clinical specimens that South African laboratories will receive will vastly increase. Investments made now will help laboratories to handle this elevated demand more efficiently and accurately. If clinical laboratories are supported and improved, they can also become important platforms for testing various novel diagnostics that may ultimately shorten the time needed to diagnose drug-resistant tuberculosis.

ENSURING TREATMENT COMPLETION

Leading up to the growth of drug-resistant tuberculosis, both NYC and South Africa experienced an underinvestment in the vital public health infrastructure needed to ensure completion of tuberculosis treatment among patients [6]. The implications of this underinvestment in NYC were vividly illustrated by a study at Harlem Hospital, conducted early in the outbreak, which showed that, among 178 patients discharged with standard tuberculosis treatment in 1988, only 11% completed it [7]. Similarly, each year, South Africa reports >400,000 cases of tuberculosis, but high rates of default and loss to follow-up result in a low treatment-success rate of only 70% [8]. The lowest rates of treatment completion are found in the province of KwaZulu-Natal—not coincidently, the apparent epicenter of drug-resistant tuberculosis in South Africa [3]. Indeed, for patients with resistant disease, the need for intensive adherence support and close patient follow-up is especially great because second-line therapy is associated with more adverse effects and requires a longer treatment course. Moreover among patients with MDR-TB and XDR-TB, the implications of treatment default for both the individual and society are particularly grave.

In NYC, the expansion of directly observed therapy with community-outreach workers and intensive case management was associated with marked improvements in the incidence of tuberculosis and rates of drug resistance [9]. At the clinic level, programs that were particularly effective were "patient-centered" and included relevant incentives and peer-based support [10, 11]. Likewise, an improvement in treatment adherence and a reduction in the number of new cases of drug-resistant tuberculosis in South Africa will require a strong commitment from central health authorities and a rethinking of the way in which tuberculosis therapy

is delivered at the most local levels. In South Africa, patient-centered approaches that include peer support (already used with great success in the antiretroviral therapy rollout sector) and relevant incentives could improve adherence to treatment. A commitment by health authorities and by local clinics to patient-centered strategies may result in higher rates of treatment completion (and may reduce the incidence of drug resistance), because such approaches address, rather than ignore, the difficult social and economic circumstances in which tuberculosis is most commonly encountered.

CONFRONTING NOSOCOMIAL TRANSMISSION

In NYC, it was demonstrated that, among hospitalized HIV-infected patients, drug-resistant tuberculosis can spread efficiently [12]. Furthermore, patients infected with drug-susceptible strains who enter health care settings can be reinfected with drug-resistant strains [13]. Although no longer in existence in NYC, tuberculosis wards—comprised almost entirely of HIV-infected patients—remain commonplace in South Africa (and throughout sub-Saharan Africa), and few experts were surprised to learn that the majority of patients with XDR-TB in Tugela Ferry, South Africa, had recently been admitted to a hospital [3]. Outpatient clinics are another key setting where drug-resistant tuberculosis can be transmitted [14]. At antiretroviral therapy rollout clinics and outpatient departments in South Africa, it is common for immunocompromised patients like Precious Cele to line up for hours in poorly ventilated rooms. The nosocomial transmission of drug-resistant *M. tuberculosis* in hospital wards and outpatient clinics is undoubtedly contributing to the current crisis in South Africa. It is imperative that current tuberculosis infection-control protocols in South Africa be redesigned in cost-effective ways. In addition to reconsidering the practice of clustering patients with suspected tuberculosis in open wards, other steps potentially within reach include (1) the separation and prioritized evaluation of patients who present as outpatients with symptoms compatible with tuberculosis, (2) the implementation of basic environmental controls in wards and waiting areas to ensure the circulation of outside air (or the treatment of recirculated air), (3) the isolation of patients with suspected or definitive drug-resistant tuberculosis, and (4) the provision of respiratory protection devices for medical staff involved in the care of patients with tuberculosis [15]. Medical staff, with the support of occupational health departments, should be offered voluntary HIV testing, and HIV-infected staff should be offered access to early antiretroviral therapy, as well as positions that do not involve close contact with patients with tuberculosis.

CONCLUSIONS

In the face of MDR-TB and XDR-TB, South Africa has acted rapidly and admirably, but more must be done. South Africa must rededicate itself to the task of tuberculosis control and treatment with a rapid, multifaceted approach. This must include expansion of second-line treatment capacity, investment in clinical laboratories, assurance of supervised adherence support for all patients, and enhancement of infection control procedures. In NYC, similar steps were successful in leading to the rapid decrease in rates of drug resistance [9]. With refinements based on local resource constraints, these measures could potentially arrest the alarming growth of MDR-TB and XDR-TB in South Africa. Unlike many countries in sub-Saharan Africa, South Africa has the capacity to mount a rapid and large-scale response before drug-resistant tuberculosis envelops a much larger and poorer region. Support for South Africa's efforts from donor nations is a moral imperative and will avoid the erosion of hard-won gains that have accrued since the antiretroviral therapy rollout.

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