The global rise of extensively drug-resistant tuberculosis: is the time to bring back sanatoria now overdue?

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Before effective treatment for tuberculosis became available thousands of people spent time in sanatoria (figure) in the hope of a cure through fresh air, sunlight, adequate nutrition, and micronutrients such as calcium.[1] Surgical techniques to promote part or complete lung collapse (eg, artificial pneumothorax, plombage, and thoracoplasty) were also used.[1] Although no controlled studies have established the effectiveness of these interventions, the existence of sanatoria led to long-term removal of infectious patients from the community.[2,3] The need for sanatoria lessened when therapy led to cure rates in outpatient settings similar to those in inpatient settings and when disease burden fell because of improved living conditions and effective national tuberculosis programmes.[4]

After three to four decades of rifampicin use, cases of multidrug resistant (MDR) and extensively drug-resistant (XDR) tuberculosis have appeared. Worldwide, 5–10% of the roughly half a million prevalent cases of MDR tuberculosis are extensively drug resistant.[5]

XDR tuberculosis in particular is a grave threat since mortality rates are substantially higher than for other forms of the disease;[6–8] it greatly increases the costs of running a tuberculosis programme and can thus weaken well or modestly functioning national treatment programmes. In South Africa, for example, the annual mortality rate in patients with XDR tuberculosis in a non-outbreak setting approaches 40%;[6] despite treatment of about half a million drug-susceptible cases and less than 10 000 MDR and XDR cases every year, MDR and XDR disease uses up more than 50% of the annual tuberculosis drug budget.

Since the revised definition of XDR tuberculosis and widespread publicity that followed the Tugela Ferry outbreak in 2006,[7] drugs such as capreomycin and para-aminosalicylic acid and extended drug susceptibility testing have become available in several developing countries including South Africa. In that country, line-probe assays (and the Gene Xpert MTB-RIF assay) are now also available within the national treatment programme. Thus, since late 2006 an estimated 2000–3000 people with XDR tuberculosis and an equal or higher number of people with MDR disease in whom treatment has failed, have been detected and treated with second-line drugs. Consequently, treatment-related outcome data have become available in programmes using second-line drugs such as capreomycin and para-aminosalicylic acid in settings of intensive inpatient therapy.[6,9–11] However, data from retrospective studies have shown that outcomes in high-burden settings such as South Africa for both MDR[12] and XDR tuberculosis[6] are poorer than outcomes achievable in settings of intermediate to low burden.[9–11] These data also show that in a non-outbreak setting, unlike Tugela Ferry,[7] and with the availability of antiretroviral drugs and injectable second-line drugs such as capreomycin, mortality rates in XDR tuberculosis, even in HIV-infected patients, are much better than previously estimated.[6] Nevertheless, overall outcomes and the programmatic capacity to render these cases non-infectious remain poor. For example, studies in five provinces of South Africa showed that the overall 6-month sputum-culture conversion rate in patients with XDR tuberculosis was about 20%.[6] Thus, large numbers of treatment failures exist.

In South Africa, the designated treatment facilities for XDR tuberculosis in most provinces do not have or have very few individual isolation rooms and limited access to infection control technology, and are filled to capacity. Thus, long waiting lists for beds facilitate disease transmission within the community. Services for MDR but not XDR tuberculosis are being decentralised in South Africa. This laudable change will create more capacity for cases of XDR tuberculosis, but the burden of disease means that in some provinces such as the Northern Cape outpatient treatment of XDR disease is already occurring because of restricted bed capacity. Treatment has failed for many patients—ie, sputum culture conversion has not occurred after 12 months of intensive inpatient treatment for XDR tuberculosis with regimens including an injectable drug such as capreomycin. In addition to low culture-conversion rates, a substantial proportion of patients whose sputum cultures convert to negative, sooner or later revert back to being culture positive (Dheda K, unpublished). Whereas some patients die within several weeks, many survive for months or years. This observation is not surprising since in prechemotherapeutic times the tuberculosis mortality rate was roughly 50%, and about 25% had chronic disease.[1,13,14] How should we deal with these people who are living with failed treatment and who still have the capacity to transmit disease?

In several provinces, including the Western Cape, multidisciplinary review committees decide about discharging patients for whom treatment for XDR disease has failed.[15,16] After a social assessment and a home visit, culture-positive patients are discharged back into the community. Few resources to track these patients are available, and work is continuing to establish their longevity and outcomes. Is the discharging of these patients, who often live in a single room with many other family members, into impoverished communities justifiable? The situation represents an ethical equipoise (unblock

Lancet 2012; 379: 773–75

Published Online
October 26, 2011
DOI:10.1016/S0140-6736(11)61062-3

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Figure: **The 3500 bed Sondalo Tuberculosis Hospital in Italy (A) and the Saint-Hilaire du Touvet Sanatorium in France in the early 1930s (B)**

beds and reduce hospital transmission but increase community-based transmission and burden of disease).

A further difficulty is that there are no, or restricted, palliative care facilities. Thus, patients are unable to die in a dignified surrounding while infection control is ensured. Some patients are also recurrently non-compliant with their treatment, and treatment can be withheld when a risk of resistance amplification exists and no further therapeutic options are available. Forced detention of a few patients when deemed appropriate is a contentious issue that has been debated but cannot currently be meaningfully enforced within South Africa.[15,16] Pregnant women who have no family support pose a dilemma because there are no or few social services or community stay facilities to look after isolated infants who are at high risk of contracting tuberculosis.

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The situation, though of different proportions, is also of concern in low-burden and intermediate-burden settings, which have rapidly dismantled their sanatoria and curtailed their dispensary networks[1,17] in view of the decreasing tuberculosis incidence, availability of effective short-course chemotherapy, and need to increase cost-effectiveness of health interventions. The current model in most resource-rich settings consists of isolation rooms in respiratory or infectious disease departments that admit a decreasing number of patients with sputum-smear positive tuberculosis (for the short time necessary to render them non-infectious) and a few complicated cases (eg, patients co-infected by HIV or with comorbidities). Because of its chronicity and poor response to treatment, XDR tuberculosis is also creating capacity problems in these settings. For example, the first two cases resistant to all known drugs (totally drug-resistant tuberculosis[18]) led to inpatient stays for up to 21 months, with the patients remaining sputum-smear positive during the entire course of treatment (about 94 months) before death.[8,19] Apart from developing countries in Africa, China, and India, countries of the former Soviet Union are facing the same difficulties: heavy burden of disease and hence increasing numbers of treatment failures, and lack of adequate isolation and infection control facilities due to resource constraints.[20] Results from a survey in five reference centres within the European Union show that infection control standards are far from ideal,[21] thereby generating a risk of nosocomial transmission both to patients and to health-care workers who now have high rates of MDR and XDR tuberculosis in some parts of the world.[22,23]

Clearly, the building of robust national treatment programmes that include new facilities with good infection control, improved laboratory and clinical capacity, and introduction of newer rapid diagnostic technologies, is a priority in the medium to long term, but what are the other more immediate and pressing needs in South Africa and other settings of high, intermediate, and low burden? One immediate priority is to build community stay and palliative treatment care facilities by adapting existing structures, to prevent continuing transmission within hospitals and the community by untreatable or dying patients with XDR tuberculosis or by patients with MDR disease for whom treatment has failed. In South Africa, hospitals exist where patients with complicated tuberculosis are treated and convalesce, and in most cases with few infection control measures. However, there are no sanatoria, as in prechemotherapeutic times, that cater for chronically ill people who are not on treatment or when there are no further therapeutic options. Thus, we are advocating for facilities where state-of-the-art palliative care and laboratory facilities can be provided to dying patients in a safe and dignified setting; there, destitute people for whom treatment has failed could voluntarily reside on a long-term basis with social, educational, and recreational facilities, and receive good nutrition and care from support groups and a multidisciplinary team within an infection-controlled setting, thereby reducing transmission within the community and to family members, including children.

Investment in such infrastructure now will be worthwhile in the medium to long term. That appropriate funding is ring fenced is crucial, so that adequate human and financial resources can be directed at addressing this crisis. The main costs will be those of construction or adaptation of existing buildings, providing continuing treatment if indicated, and staffing and running of these facilities, which are all country specific. Training of appropriate health-care workers, already in short supply, educational initiatives directed at patients, and appropriate cost analysis studies will be needed.

The time for rebuilding so-called new sanatoria under a new vision has come and is overdue. A step in the right direction in South Africa is the appointment of a National Drug-Resistant TB Advisory Committee, the development of a strategic plan to fight drug-resistant tuberculosis, and the recent announcement by the South African Minister of Health Aaron Motsoaledi of a R100 million (US$14 million) commitment to start building new designated MDR tuberculosis treatment facilities.[24] Whether these strategies will also include palliative care and long-term community stay facilities remains unclear. Other encouraging policies are the expansion of intensive drug-resistant tuberculosis case-finding programmes to other provinces and piloting of the use of innovative approaches such as use of smartphone mapping technology.

Several newer diagnostic technologies (including the Gene Xpert MTB-RIF assay) and drugs have or will soon become available in high-burden settings.[25] However, the challenge is not only to harness these technologies with other public health strategies—such as strengthening of laboratory capacity, programmatic tuberculosis and HIV management, engagement of all tuberculosis care providers, improvement of infection control and allocation of human resources, and advocacy—but also to prevent the emergence of further resistance and the rapid diminution of the effectiveness of newly introduced antituberculosis drugs. We have now come full circle and once again there are large numbers of patients for whom there are no effective antituberculosis drugs. The pool of untreatable cases is accumulating and will need swift action to avoid a human catastrophe.

Contributors
KD and GB both conceived the idea for and wrote this report.

Conflicts of interest
We declare that we have no conflicts of interest.

Acknowledgments
We thank Norbert Ndjeka, Director of the Drug-Resistant-TB, TB and HIV at the South African National Department of Health, for his comments and input.

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