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Community based approaches to the control of multidrug resistant tuberculosis: introducing "DOTS-plus"

Paul Farmer, Jim Yong Kim

Tuberculosis remains the world's leading infectious cause of adult deaths, most of which are due not to multidrug resistant tuberculosis but to lack of access to effective treatment for drug susceptible tuberculous disease.[1] New data suggest, however, that multidrug resistant tuberculosis is emerging as an increasingly important cause of morbidity and death. In the United States, Europe, and Latin America, highly resistant strains of tuberculosis have caused explosive institutional outbreaks (in hospitals, prisons, and homeless shelters) with high case fatality rates among immunosuppressed people and high rates of transmission to other patients and to caregivers and their families.[2–8]

These outbreaks are not restricted to certain regions. The WHO/International Union Against Tuberculosis and Lung Disease's global survey of resistance to antituberculous drugs now reveals that multidrug resistant tuberculosis has already become established worldwide. In several countries—including Russia, Estonia, Latvia, Côte d'Ivoire, and the Dominican Republic—"hot zones" of ongoing transmission have been identified. Failure to follow the World

Summary points

Multidrug resistant tuberculosis is already a global pandemic, with focal "hot zones" of increased transmission

Although DOTS (directly observed treatment, short course) chemotherapy is the goal of global tuberculosis control, short course chemotherapy will not cure multidrug resistant tuberculosis

In settings of high transmission of multidrug resistant tuberculosis, "DOTS-plus" (a complementary DOTS based strategy with provisions for treating multidrug resistant tuberculosis) is warranted

Community based strategies designed to enhance local capacity are cost effective and make it possible to meet new medical challenges

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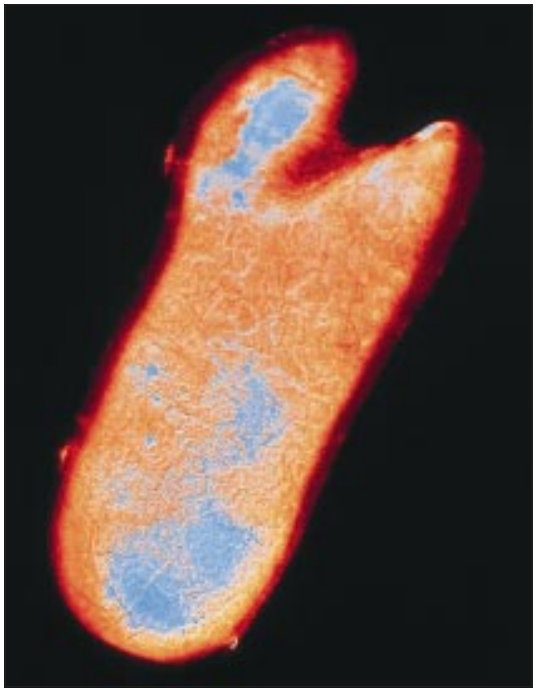
Health Organisation's guidelines was clearly associated with high rates of multidrug resistant tuberculosis; the survey was thus able to identify countries in which an increase in multidrug resistant tuberculosis was likely, given the current programme conditions.[9]

Unfortunately, treatment options have been limited for most people with multidrug resistant tuberculosis, largely because of the cost of drugs.[10 11] But the experience of a team based at the Harvard Medical School suggests that multidrug resistant tuberculosis can be treated even under adverse field conditions in countries with poor resources. In April, Harvard's programme in infectious disease and social change convened 50 experts in tuberculosis and public health to re-examine policies for controlling tuberculosis in the light of new epidemiological and clinical research. The meeting was cosponsored by the WHO's global tuberculosis programme, the American Academy of Arts and Sciences, and Partners in Health (a non-governmental organisation focusing on tuberculosis in Latin America). Also present were representatives of key foundations, multilateral aid agencies, and the pharmaceutical industry. Although most presentations cannot be summarised adequately here, highlights of the meeting are presented below.

Agenda: new control strategies

The goal was to assess the scope and dynamics of the emerging problem of multidrug resistant tuberculosis, the strengths and limitations of existing control strategies, and the potential contribution of community based treatment efforts.[12] Since the presence of multidrug resistant tuberculosis signals a failure to adhere to a tuberculosis programme, the key need in global control of tuberculosis remains the adoption of DOTS (directly observed treatment, short course). In settings where multidrug resistant tuberculosis is already a problem, however, DOTS alone will be insufficient for three reasons: *(a)* those already ill with the disease would not be cured with short course chemotherapy based on isoniazid and rifampicin; *(b)* nosocomial transmission is likely when untreated patients continue to seek care in clinics and hospitals; and *(c)* patients with primary resistance to isoniazid and rifampicin who receive standard, short course chemotherapy are likely to develop resistance to pyrazinamide and ethambutol as well. Since empirical retreatment regimens are often based on the same four drugs plus a short course of streptomycin, patients initially resistant to two drugs may become resistant to as many as five. This "amplifier effect" of short course chemotherapy has contributed to a large outbreak of multidrug resistant tuberculosis in urban Peru.[13]

Quantified, the results of this observation are sobering. A mathematical model of likely scenarios resulting from control that does not eradicate tuberculosis—in which the efficacy of treatment for drug susceptible disease is relatively high but that for drug-resistant disease is nil—projects a short term (50 year) surge in multidrug resistant tuberculosis.[14] The model shows that empirical short course chemotherapy and inadequate treatment regimens will lead to a distinct amplification of first line drug resistance. HIV coinfection, furthermore, is likely to accelerate the natural dynamics of tuberculosis epidemics.



DR KARI LOUNATMAA/SPL

Mycobacterium tuberculosis is a rod shaped bacillus bacterium; here the cell wall has split, as occurs when antibiotic drugs kill the bacterium

The WHO's policy on tuberculosis has improved outcomes in settings around the world,[1] although the claim that multidrug resistant tuberculosis will simply disappear if DOTS is established widely is open to challenge. In Algeria and parts of China, where the introduction of DOTS has resulted in a prompt decline in drug resistance, resistance to rifampicin was not yet known or exceedingly rare when better control programmes were introduced.[15 16] In other countries in which DOTS programmes were introduced, however, rates of multidrug resistant tuberculosis either remained steady or increased. In Korea, for example, overall drug resistance has declined since the start of a good programme—the paper making this claim none the less states that rates of multidrug resistant tuberculosis have increased between 1980 and 1995.[17] A critical re-evaluation of several studies suggests that, where multidrug resistant tuberculosis is established, incidence falls only if patients with active disease are treated effectively—that is, with longer courses of second line drugs, selected in keeping with drug susceptibility patterns. In no setting in the world with an established problem of multidrug resistant tuberculosis have case rates fallen when DOTS with short course chemotherapy was introduced.

Reports from hot zones

Between 1990 and 1996, the incidence of tuberculosis in Russia rose by more than 300%, with 250 000 cases registered in the latter year alone.[18 19] A substantial proportion of these are infected with drug resistant strains: the study by the WHO and the International Union Against Tuberculosis and Lung Disease conducted in the Ivanovo region showed 12% of all culture positive cases to be resistant to one or more first line drugs.[9] Currently Russian prisoners with

multidrug resistant tuberculosis are estimated to constitute 10-20% of all active cases of tuberculosis in some prisons.

A recent population based survey from Mexico confirms the impression of widespread drug resistance.[20] Evidence from the district of Orizaba, Mexico, suggests that ongoing transmission of drug resistant strains of *Mycobacterium tuberculosis* is to be expected when effective treatment is not available. Studies on restriction fragment length polymorphism by the Instituto Nacional de Salud Pública de México show that some 10% of all linked cases are due to multidrug resistant strains, suggesting that patients with multidrug resistant tuberculosis—11% of all patients in this cohort—were efficient transmitters of their disease.

Similar conclusions were drawn by workers in urban Peru, demonstrating that multidrug resistant tuberculosis can emerge even in a setting in which DOTS has been well established: of 258 patients who had complied with DOTS and failed to respond to treatment or were close contacts of patients with drug resistant disease, 55% were confirmed to have multidrug resistant tuberculosis.[21] These data, which drew on both conventional and molecular epidemiology, pointed to high rates of intramural transmission of multidrug resistant tuberculosis within households and clinics. Furthermore, primary resistance was amplified through repeated courses of DOTS in two thirds of a smaller cohort of more than 75 patients with disease due to highly resistant strains.

In cooperation with Peru's highly successful national tuberculosis programme, Partners in Health has initiated a novel attempt to treat patients with multidrug resistant tuberculosis in northern Lima. Working largely with poor families living in a slum area, this community based effort initiated directly observed, individualised treatment for more than 50 patients with longstanding disease. Most of the cohort are resistant to all four of the drugs used in Peru's tuberculosis programme; most had substantial parenchymal destruction when they entered treatment through this project. With aggressive individualised treatment regimens, however, all of the patients became "smear negative"—that is, had no evidence of tubercle bacilli on microscopy—and in more than 85% of patients results of smears and cultures remained negative a year into treatment.

What is to be done?

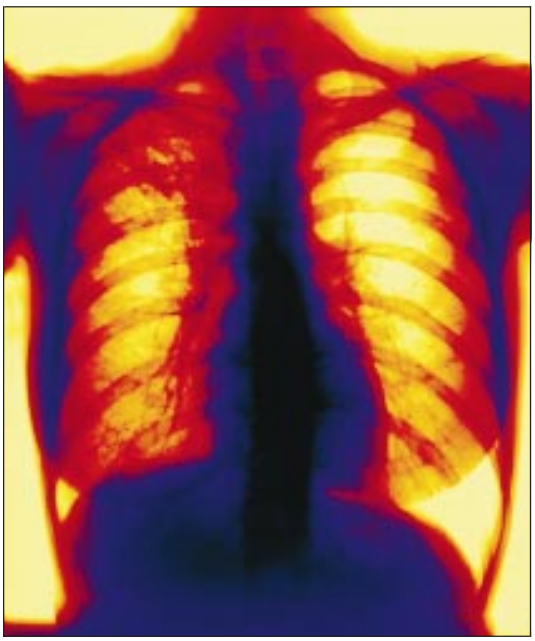
Establishment of cohorts and isolation practices may be the least defensible policies during an era in which our therapeutic armamentarium, though weak, contains drugs that can cure most patients infected with multidrug resistant tuberculosis. The clinical outcomes in the community based effort in Peru seemed to be at least as good as those registered in US medical centres, where long hospital stays and surgery have been central to the cure of many patients with similar drug resistance patterns.[21]

Although striking inequalities of access mean that treatment is available to some patients and not others, these inequalities also mean persistent transmission of drug resistant strains well beyond the confines of an initial focus of transmission: outbreaks of tuberculosis are only briefly local. In 1996, for example, Bifani and colleagues showed the molecular similarity of 273 strains of multidrug resistant tuberculosis isolated in New York City—259 of which were resistant to four or more antituberculosis drugs—to strains of patients living in Atlanta (Georgia) and Denver (Colorado).[22] The authors argued that the multidrug resistant phenotype of these organisms stemmed from a single W strain, which had been transmitted between these three metropolitan areas, all major hubs of car and air travel.

Cost efficacy analyses do not capture the true strengths of community based approaches to the treatment and control of tuberculosis, which build local capacity for addressing the health and social problems that beset many communities in which tuberculosis is endemic. The experiences in urban Peru and rural Haiti, where the yield on healthcare investments in poor communities is as evident in increased local capacity as in morbidity and mortality data, suggest that "community capacity building" should be a central part of control strategies.[23]

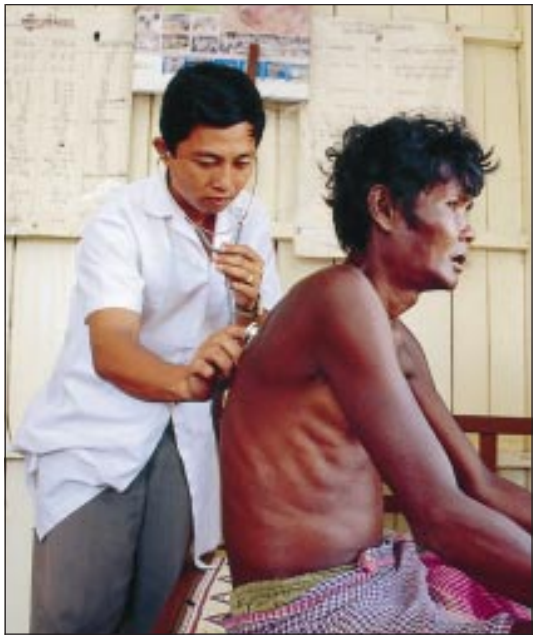
Although many participants expressed concern about diversion of funds from the treatment of drug susceptible disease to drug resistant cases, a "zero sum" approach to the problem (which presumes competition for scarce resources between those with resistant and those with susceptible strains) was deemed unwise; a far larger investment in global control of tuberculosis is clearly warranted. But because aggressive treatment of multidrug resistant tuberculosis would require a substantial infusion of new resources, advocates outside the tuberculosis and public health communities are needed.

The multidrug resistant tuberculosis epidemic in New York City showed that, although it was clear from the outset that the decay of the care and control infrastructure for tuberculosis had contributed to the gravity of the problem, it was not until the efforts of the public health community were backed by the clout of political figures and the support of other sectors,



SCOTT CAMAZINE/SPL

Chest *x* ray film showing evidence of pulmonary tuberculosis (red areas) in the upper lobe of the right lung



SEAN SPRAGUE/PANOS PICTURES

Individualised treatment may be needed for multidrug resistant tuberculosis

including organised labour, that sufficient funds were made available for aggressive treatment and control.[24] Positive outcomes were also founded on an improved capacity to identify patients with multidrug resistant tuberculosis and alter treatment accordingly.[25]

Resolutions of the meeting: introducing "DOTS-plus"

Several resolutions were elaborated at the meeting. All patients with active tuberculosis, regardless of drug susceptibility patterns, have a right to treatment. Furthermore, resistance to antituberculous agents is an urgent problem demanding prompt attention. The current situation calls for a focused and concerted effort which, together with the global implementation of DOTS, can bring the eradication of tuberculosis finally within our grasp.

Participants agreed that in some settings DOTS alone is clearly insufficient; complementary efforts to treat multidrug resistant tuberculosis are desirable in the hot zones with the technical capacity and political will necessary for success. What was called for in these instances might well be termed "DOTS-plus." A consensus was reached that a DOTS-plus approach to multidrug resistant tuberculosis would be most likely to succeed where DOTS was already established or being established. In such settings patients with multidrug resistant tuberculosis could be triaged to individualised treatment regimens or, if possible, into empirical retreatment schemes appropriate to the local epidemiology.

To help to initiate and oversee pilot DOTS-plus schemes, the meeting resolved that a new WHO working group on multidrug resistant tuberculosis would be created. The goals of the working group are straightforward, if challenging: to bring new resources to tuberculosis; to identify sites in which to replicate community based approaches to controlling multidrug resistant tuberculosis; to place the requisite technical assistance at the service of these and other pilot projects.

As regards the importance of timing to an initiative to combat multidrug resistant tuberculosis, it was noted, "you can pay now, or you can pay later." The costs will only rise with delay.

For more information on the meeting or on the WHO working group on multidrug resistant tuberculosis, please contact the programme in infectious disease and social change at Harvard Medical School (00 1 617 441 6288; ihsj@igc.org) or the global tuberculosis programme at the WHO (00 41 22 791 2675).

Competing interests: None declared.

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