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Beyond DOTS: Avenues ahead in the management of tuberculosis

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ABSTRACT

India has almost 30% of the global burden of tuberculosis (TB)—one person dies of the disease every minute in our country. India has mounted the second-largest DOTS programme in the world to control this disease. However, DOTS has its limitations and newer approaches have been developed over the years to overcome the global burden of tuberculosis.

Problems with health facilities, patients, drugs and the disease itself constitute some of the hurdles in the implementation of the DOTS programme. In an attempt to go beyond DOTS, the WHO launched the 'Stop TB Initiative' in 1988. Against the background of irrational antituberculosis drug use, which contributes to increasing drug resistance, the effective involvement of private healthcare providers is imperative to achieve better geographical and patient coverage for the implementation of DOTS. The WHO is currently addressing the issue of involving private practitioners in tuberculosis control in a programme called Public-Private Mix DOTS (PPM DOTS). The Stop TB Initiative is also active in the area of dual infection with HIV and tuberculosis, and the initiatives that have been taken in this area include 'ProTEST', community contribution to tuberculosis care, and development and dissemination of training materials and guidelines. The DOTS-Plus strategy for the management of multidrug resistant (MDR)-TB and the establishment of the Green Light Committee to review project applications in this area are initiatives taken to curb the problem of drug resistance in tuberculosis.

Even decades after the introduction of the DOTS strategy, much needs to be done to expand the services to the entire population; it is now essential to develop strategies that go beyond DOTS.

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INTRODUCTION

The Southeast Asia Region (of the WHO) accounts for nearly 38% of the world's tuberculosis cases, with 3 million new cases and nearly 750 000 deaths occurring annually. Among adults in this Region, tuberculosis is the commonest cause of death from infectious disease; 75% of the mortality and morbidity due to the disease occurs in the age group of 15–45 years. The scourge of HIV infection and the emergence of drug resistance have further complicated the issue.[1]

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Pioneering studies from India have earlier demonstrated the effectiveness of ambulatory treatment of tuberculosis.[2] The necessity and feasibility of direct observation of treatment,[3] the efficacy of intermittent treatment with antituberculosis drugs,[4] and the feasibility of case detection by sputum-smear microscopy in primary healthcare institutions[5] have also been demonstrated in India.

Unfortunately, in spite of these contributions, India has the unique and unwanted honour of housing almost 30% of the total tuberculosis cases in the world. In India, 2 million people develop the disease every year[6] and one person dies of the disease every minute.

The financial burden of these statistics on an already economically strapped country is tremendous. Every year, tuberculosis costs India more than Rs 13 000 billion in the public sector while patients spend more than Rs 645 billion annually on private care. Patients suffering from tuberculosis incur a total loss of Rs 3469 (US$ 99) on expenses for diagnosis and treatment.[7] Studies carried out in different parts of India have also shown a high percentage of tuberculosis-related debts—67% of rural and 75% of urban patients incur debts on account of treatment for tuberculosis.[8]

This led Dr Mahler, the previous Director-General of WHO to comment, 'The whole world benefits from the fruits of Indian (tuberculosis) research—the whole world, except India.'[9]

The forty-fourth World Health Assembly in 1991 recognized the growing importance of tuberculosis as a public health problem and the potential for cost-effective control using currently available tools.[10] A new global framework for effective tuberculosis control called DOTS (directly observed treatment, short-course) was then developed.[11] Today India has the second-largest DOTS programme in the world, and places about 50 000 patients on treatment every month (*http://www.tbcindia.org/*). Nearly 200 000 healthcare workers have been trained and more than 3000 laboratories have been provided with electricity and water connections, binocular microscopes and reagents.[12]

However, the limitations of the DOTS programme are accepted[13,14] and therefore other approaches have been developed over the years to overcome the global burden of tuberculosis. We briefly discuss these avenues.

CURRENT SCENARIO

Currently, there are two major treatment programmes: self-administered therapy (SAT) and DOTS. In SAT, the patient obtains all the treatment medications initially and takes them at home without supervision. In DOTS, every dose of antituberculosis medication taken by the patient is directly observed and recorded by a healthcare worker or some other responsible individual. Table I summarizes these approaches.

DOTS

It is worth examining the DOTS scheme in some detail before discussing the avenues beyond DOTS. DOTS consists of 5 elements—government commitment, diagnosis primarily by

TABLE I. Comparison of the salient features of Self-Administered Therapy (SAT) and Directly Observed Treatment, Short Course (DOTS)

SAT	DOTS
More time- and cost-efficient	Requires adequate and quality drug supply, supportive laboratory services, and equipment—therefore, high initial investment
No extra costs (salaries, manpower and travel expenses)	Demands increased human resources and time
Patient needs to make only one trip to the healthcare facility for the medication	May stigmatize patients in various cultural and social settings, drawing attention to them as they have to go to the DOTS centre
Patients or relatives are not obliged to take additional time off from work	Prevents travel during the course of treatment
Populations that are mobile or from remote areas can be easily targeted	Method is far more complete, effective and cost-efficient
At home, administration of drugs also allows relatives to become more involved in the patient's healthcare	Enables high detection rates, which breaks transmission to other non-infected people
Supporters of SAT argue that implementation and reaching high coverage rates with DOTS is difficult	Dosages easy to administer, monitor and evaluate, and maintaining high cure rates of up to 95%. Increases compliance and minimizes the chances for MDR
Without monitoring, poor, non-compliant, or faulty self-administration can have detrimental or fatal results for both the patient and community at large (there may be an increase in MDR-TB or mass transmission)	Can be implemented in unstable or stressed environments
With a 12-month course of treatment, SAT also involves a rigorous time commitment from the patient. This, some argue, may be the cause of SAT's high percentage of drop-outs	Non-compliant patients, under supervision, can also be successfully treated
	Creates community awareness by encouraging local involvement

MDR-TB multidrug-resistant tuberculosis

microscopy, regular supply of good quality drugs, direct observation of treatment, and surveillance and monitoring.

The number of countries implementing the DOTS strategy increased by 21 during 2000, bringing the total to 148, and 27% of the tuberculosis cases worldwide were treated under DOTS.[15] In India, the Revised National Tuberculosis Control Programme (RNTCP) and DOTS were implemented in 1993 and, by 2001, coverage by DOTS was about 40%, allowing about 450 million people to have access to DOTS. The states of Rajasthan, Kerala and Delhi report 100% coverage, while Gujarat, Tamil Nadu and Himachal Pradesh are approaching full coverage. Maharashtra and West Bengal have covered more than two-thirds of their population (*http://www.tbcindia.org/*).

In the RNTCP, physicians are trained to make a diagnosis in patients with cough for more than 3 weeks primarily by sputum microscopy, treatment is directly observed, and standardized regimens and methods of recording and reporting are used. Patients who complain of a chronic cough undergo 3 sputum smear examinations over a 2-day period. If 2 or 3 of the smears are positive for acid-fast bacilli, antituberculosis treatment is initiated. If all 3 smears are negative, 1–2 weeks of broad-spectrum antibiotics are prescribed. If only 1 of the 3 smears is positive or if symptoms persist after the administration of broad-spectrum antibiotics, a chest X-ray is obtained, usually at a larger health centre, and the patient is evaluated.[12]

On the basis of their clinical features, patients are grouped into 3 categories and accordingly, drug treatment is given twice-weekly (Table II).[15]

TABLE II. Treatment according to the DOTS programme

Category	Characteristics	Therapy
I	Patients who have not previously been treated, who have new sputum smears positive for acid-fast bacilli and seriously ill patients with negative sputum smears	Four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) for 2 months and then 2 drugs (isoniazid and rifampicin) for 4 months
II	Previously treated patients	Four drugs (isoniazid, rifampicin, pyrazinamide and ethambutol) with streptomycin for 2 months, then the first 4 drugs for 1 month, then 3 drugs (isoniazid, rifampicin and ethambutol) for 5 months
III	Smears are negative for acid-fast bacilli, patients have abnormal X-rays, and who are not seriously ill, including those with extrapulmonary tuberculosis	Same treatment as for those in Category I, except that ethambutol is omitted

Notes: Patients in categories I and II, whose smears are positive for acid-fast bacilli at the end of the intensive phase of treatment (the first 2 or 3 months in categories I and II, respectively), receive another month of intensive-phase treatment.

Every dose of medication in the intensive phase is directly observed, either by a health worker or by a community member who is not a family member. In the 4–5 month continuation phase, when the bacterial load is far lower, at least the first of each of the thrice-weekly doses is directly observed. Medications for both phases of treatment are kept in an individual box containing the entire course of treatment for a single patient. Diagnosis and treatment are free of charge. Recording and reporting are performed according to WHO recommendations, with the progress and outcome of every patient recorded and reported quarterly.

CHALLENGES IN IMPLEMENTING DOTS

Khatri and Frieden[12] identified several challenges in the implementation of the DOTS programme in India. Apart from these, there are other challenges that have impacted on the success rates of the DOTS programme globally. They have been classified into the following four broad categories:

Health facilities

1. Suboptimal functioning of the general health services, including health worker lethargy to administer DOTS to patients in absolute poverty, those who are socially marginalized or poorly integrated in the city, and itinerant labourers;[16]
2. Variable effectiveness of the state government;
3. Poor collaboration and synergy among the public, private and voluntary health sectors;
4. Lack of well trained and committed health services personnel;
5. Poor laboratory resources;

6. Lack of coordination between public health systems and academic institutes where new doctors are trained.

Patients

1. A large and mostly unregulated private sector provides a substantial proportion of the outpatient care (50%–60%), which is of inconsistent quality;[17]
2. Varying socioeconomic status of patients;
3. Establishing patient-friendly services is difficult;
4. Poor community involvement in tuberculosis care and a patient-centred approach.

Drugs

1. Ensuring the quality of drugs is difficult.

Disease

1. The increasing impact of HIV infection on the incidence of tuberculosis;
2. A surge in drug-resistant forms of tuberculosis;
3. Lack of operational research regarding the impact of the DOTS programme;
4. Relatively poor assessment of the impact of DOTS on extrapulmonary tuberculosis.

EXPANDED DOTS FRAMEWORK

In late 1998, the WHO launched a global partnership called the 'Stop TB Initiative' linking the health, social and economic sectors in the fight against tuberculosis. In 2000, the Amsterdam Declaration by a high-level Ministerial Conference of Ministers of Health and Finance endorsed this initiative.

The expanded framework reinforced the 5 essential elements of the DOTS strategy, and included in its fold the problems of HIV-related and drug-resistant forms of tuberculosis. The 5 elements of the expanded framework included (i) sustained political commitment to increase human and financial resources and make tuberculosis control a nationwide activity integral to the national health system; (ii) ensuring access to quality-assured sputum smear microscopy for case detection, standardized short-course chemotherapy for all cases of tuberculosis under proper case-management conditions including direct observation of treatment; (iii) uninterrupted supply of quality-assured drugs with reliable drug procurement and distribution systems; (iv) an operational recording and reporting system enabling outcome assessment of each and every patient; and (v) assessment of the overall programme performance.

A few approaches to tackling some of the challenges in tuberculosis control are discussed below.

PRIVATE PRACTITIONERS IN THE CONTROL OF TUBERCULOSIS

In India, about 80% of all qualified doctors, 75% of dispensaries, 60% of hospitals, and 75% of the country's health expenditure are in the private sector.[18,19] Unfortunately, little information is available on patients with tuberculosis in private clinics and very few studies have investigated the tuberculosis management practices of private practitioners.[20] The relative advantages of a private practitioner are convenience of location and working hours, confidentiality, their personal rapport with patients, and 'better' treatment adherence among patients under their care, compared to patients under the RNTCP. However, these advantages are countered by the reluctance of doctors to use sputum examination for diagnosis, their disregard for recommended drug regimens, their virtual inaction with regard to treatment default, and their failure to keep even the minimum essential records.[21] In addition, many patients cannot afford to pay for a full course of treatment.[22]

Patients are prescribed a variety of drug regimens, some of which are inappropriate and may include a single drug or two drugs. Moreover, private practitioners practising in low income areas in India have been found to have a gross lack of knowledge about the diagnosis and treatment of tuberculosis.[17] A study of tuberculosis patients and private practitioners in India showed that the median delay in the diagnosis of tuberculosis was about 3 weeks and 2 weeks in urban and rural patients, respectively, after they consulted the doctors. About 33% of urban patients and 36% of rural patients had not been diagnosed even 4 weeks after they had approached a practitioner.[20] Irrational practices such as administration of the wrong drugs, or the right drugs in the wrong doses or combinations may contribute to the rise in multidrug-resistant (MDR) tuberculosis in India.[23]

We found similar results in a recent survey conducted in Mumbai (unpublished data). Questionnaires were mailed to private practitioners regarding the management of patients with tuberculosis. Of the 1000 doctors to whom the questionnaires were mailed, 210 responded. Only 53 doctors (25.3%) diagnosed and followed up patients by using sputum smear positivity for acid-fast bacilli. Symptom criteria such as cough (45, 21.4%), increased appetite (60, 28.5%), weight gain (90, 42.8%) and absence of fever (57, 27.1%) were used for prognosis as well as changing the treatment regimen. Eighty-five doctors (40.5%) depended on the erythrocyte sedimentation rate as a diagnostic criterion!

As many as 35 different regimens were prescribed for the treatment of fresh cases of tuberculosis. The regimens differed with regard to the use of various first-line drugs, their combinations and the duration for which they were prescribed. Only 96 (45.7%) of the 210 doctors prescribed the standard regimen of rifampicin, isoniazid, ethambutol and pyrazinamide (HERZ). During the continuation phase, 2 (40, 19%) or 3 (56, 26.6%) drugs were being given for a duration ranging from 4 to 24 months. Four of the doctors reported using HERZ continuously for a period of 6–12 months. Twenty doctors (9.5%) prescribed 5 drugs and, interestingly, second-line drugs (ciprofloxacin or sparfloxacin) were also used in the intensive phase.

Forty-four doctors (20.9%) preferred sending their patients to a specialist for treatment of a relapse and only 19 doctors asked for antibiotic sensitivity reports in such patients. Many different strategies were being used for the treatment of a relapse. These ranged from extending the duration of first-line drugs with or without the addition of 2 new drugs in the first 2 months, and adding 2–4 new drugs to the previous regimen. The new drugs that were being used or added to the previous regimen were ciprofloxacin, ethionamide, para-aminosalicylic acid (PAS), cycloserine, kanamycin, amikacin, ofloxacin or sparfloxacin.

Various strategies were used for the treatment of non-responders, including the addition of 1–5 new drugs to the ongoing treatment, starting drugs not used previously, using the same drugs for a longer period of time and trying out new drugs for a period of 15–30 days initially.

The major arguments put forward by private practitioners against participating in public sector programmes were doubts regarding national guidelines and quality of care at DOTS centres, loss of revenue if they participated in the DOTS programme, loss of patients for follow up and infrastructural limitations for public health tasks such as defaulter tracing.[24]

TABLE III. Summary of action plans for promoting public–private mix (PPM)-directly observed treatment, short-course (DOTS)

Action-oriented communication and information gathering to establish links with the private health sector
Collaboration with the private health sector within the DOTS framework. In this private practitioners are invited to participate as DOTS centres and they are given the necessary laboratory back-up while their patients are given medicines through the DOTS programmes and the doctors are trained in diagnosis and therapy. The response and practicability of this project is being evaluated in some parts of India. There has to be an availability of public funding for provision of tuberculosis care by private providers.
Undergraduate and postgraduate medical students need to be encouraged to spend time working with the Revised National Tuberculosis Control Programme (RNTCP) as part of their training.
Coordinate research on public–private mix models.
Solicit representation of private providers on advisory and monitoring bodies of the RNTCP.
Initiate and maintain dialogue with private healthcare providers at all levels.

Against this background, the effective involvement of private healthcare providers is imperative to achieve better geographical and patient coverage for the implementation of DOTS. The private health sector—comprising private practitioners, voluntary and for-profit organizations, professional societies, private hospitals and corporate health providers—offers immense opportunities to further the implementation of DOTS. By involving them, the DOTS programme can enhance patient access and acceptance, increase case detection and improve treatment outcomes.[25]

Involvement of the private sector in the implementation of DOTS may be achieved through a variety of approaches. WHO is currently addressing the issue of involving private practitioners through Public–Private Mix DOTS (PPM DOTS). As a first step, a global assessment in 23 countries across 6 WHO Regions was undertaken. This helped to identify issues and interventions to facilitate private practitioner involvement in DOTS implementation.[25] Specific recommendations have been made, some of which are highlighted in Table III.

PATIENT COMPLIANCE

One of the challenges identified by Khatri and Frieden[12] regarding the success of implementation of the RNTCP in India is the difficulty in 'establishing patient-friendly services, with the patient as the "VIP" of the program'.

In Mumbai we conducted a study to evaluate the effect of an educational intervention in patients with tuberculosis. The pre-intervention study, conducted at 45 randomly selected DOTS centres in Mumbai covering 1708 patients, indicated a lack of knowledge about antituberculosis medicines as well as the transmission of tuberculosis.

In the second phase, 10 DOTS centres (130 patients) were selected for intervention by systematic sampling, representing various areas of Mumbai. Ten randomly selected centres served as controls (150 patients). One social worker gave a lecture in a local language (Marathi or Hindi) to all patients registered at each centre regarding tuberculosis and its treatment (including the general course of the disease, misconceptions that patients have, role of the patient in the spread of the disease, importance of completion of treatment, drug information, hazards of incomplete treatment and importance of diet and hygienic lifestyle). Patients were informed in advance about the lecture and interviewed on the same day, 1 week and 1 month after the lecture to assess the knowledge gained regarding the disease and drug therapy. The questionnaire was field-tested and validated in advance and consisted of 8 broad questions that were asked to the patient in the local language. These questions covered their knowledge about the disease, its spread and treatment. The answers given by the patients were analysed using a scoring system in which positive scores were given to correct answers. Since the group consisted of both literate and illiterate patients, the results of the illiterate group were analysed separately as well.

TABLE IV. Responses of patients at the intervened and control DOTS centres

Time points	Intervention (n=130)	Control (n=150)
	Correct responses (%) (n=1040)	Correct responses (%) (n=1200)
Pre-intervention	513 (49.3)	589 (49.1)
Immediate	864 (83.1)*	589 (49.1)
1 week	855 (82.2)*	582 (48.5)
1 month	864 (83.1)*	580 (48.3)

*$p<0.001$ *v.* pre-intervention group (chi-square test)
Values expressed as percentages of all correct answers (positive scores) to the questionnaire

Before the intervention, of the responses obtained from the patients at DOTS centres only 49.3% were correct. Immediately after the intervention, correct responses increased to 83.1%. Patients gave a similar level of correct responses even 1 week and 1 month after the intervention (82.2% and 83.1%, respectively). As expected, at the control DOTS centres, the percentages of correct responses remained nearly the same after an interval of 1 week and 1 month. These data are summarized in Table IV.

After the intervention, there was a significant improvement in the knowledge of the patients; 88% of patients knew that tuberculosis was caused by droplet infection. While before the lecture only 75% of patients said that tuberculosis could be cured with proper treatment, subsequently 96% of patients knew that the disease was curable with proper treatment. Before the intervention, 40% of patients felt that tuberculosis could be treated with a 4-week course of drugs while after the intervention 92% of patients said that it could not be treated with a 4-week course. This type of knowledge is important in preventing default in therapy.

The beliefs and attitudes of the patients form a very important part of therapy. Knowledge about the dosages of drugs and duration of treatment was unknown to 27% and 14% of patients, respectively. After the intervention, only 8% and 4% of patients, respectively, did not know about the dosages and duration of treatment. Only 4% of patients knew about the common adverse effects of antituberculosis drugs before the intervention. After the intervention, 50% of patients knew about these.

Before the intervention none of the patients knew that they could develop resistant strains if they defaulted on treatment. After the intervention, about 50% of patients knew of the possibility of developing resistant strains after default of treatment.

To find out whether the illiterate group of people (n=44) responded in a similar manner as the literate group, data for the illiterate patients were analysed separately. The response rate in the illiterate group was similar to that of the whole group. There was a 68.4% improvement over the pre-intervention values and this improvement remained the same, i.e. 66.2% and 66.2% after 1 week and 1 month post-intervention. The illiterate group showed similar results, i.e. 70.2%, 66.2% and 66.2% improvement immediately, 1 week and 1 month post-intervention, respectively.

There was no difference in the number of patients who defaulted on treatment at both the intervened and control centres (approxi-

mately 8%). Several reasons were identified for default of treatment, including difficulty in follow up at the DOTS centre, patients returning to their native place, homelessness, alcoholism, etc.

The results of this study indicate that patient knowledge needs to be improved to ensure better compliance. However, the socio-economic problems that influence completion of treatment also need to be addressed to ensure a lower default rate.

Community participation in improving access to diagnostic and treatment facilities as well as completion of treatment is well known.[26–28] In general, successful community approaches have been the result of good collaboration between general health services, the tuberculosis control programme and the community; good education of the patient and his or her family; training for community supporters as well as health workers; and good systems of supervision of community supporters by tuberculosis programme staff.

Peer leaders should be identified among patients who are on, or have received, antituberculosis treatment. Such leaders can coordinate patient meetings and discuss problems associated with drug therapy. In addition, patient *melas* at regular intervals (social gatherings), social workers' support systems to deal with the social aspects of patients on therapy so as to decrease the defaulter rate (such as home visits if necessary), involvement of community health workers and even tuberculosis clubs[29,30] are some of the other ways to improve patient compliance. Several incentives are being used in many programmes worldwide to enable and stimulate participation by patients and providers in DOTS-based care, for example, provision of monthly food packages and monetary and non-monetary incentives to community-based providers.

TUBERCULOSIS AND HIV INFECTION

The human immunodeficiency virus (HIV) epidemic is one of the most important threats to tuberculosis control globally. It has been estimated that there are about 4 million HIV-infected people in India,[31] about half of whom are also infected with *Mycobacterium tuberculosis*. Active tuberculosis will develop annually in about 7% of these,[32] leading to 140 000 cases of tuberculosis each year from reactivation of the disease alone. This means that approximately 200 000 additional new cases will occur each year, representing a 10% increase, even at the current relatively low rate of HIV infection.[12]

The problems with coexistence of the two diseases are many. HIV is a powerful known risk factor for reactivation of latent tuberculosis infection; HIV-infected persons who become newly infected by *M. tuberculosis* rapidly progress to active tuberculosis. Further, tuberculosis is the commonest cause of HIV-related death. The nutritional status of patients with HIV and tuberculosis is markedly worse than that of HIV patients without tuberculosis and may contribute to a decreased survival in these patients.[33]

Unfortunately, tuberculosis also has an adverse effect on HIV infection. Studies indicate that the transcriptional activity of HIV-1 is enhanced in patients with the two diseases, and this might accelerate the natural progression of HIV infection.[34] Further, drug interactions make the management of such patients difficult. It has been reported that nitric oxide production (which is elevated in patients with HIV infection, especially those co-infected with tuberculosis), declines significantly following 4 weeks of antitubercular therapy, therefore perhaps influencing recovery.[35]

For many years, those involved primarily with tackling tuberculosis and those involved primarily with tackling HIV have pursued largely separate courses. Tuberculosis programmes have concentrated mainly on ensuring that all patients have access to the basic treatment and control measures, while HIV programmes have formulated their own strategies. It is obvious, however, that both programmes have a common cause. There is a growing recognition that increased collaboration between tuberculosis and HIV programmes will yield benefits for more effective and efficient training, drug supply, case management and surveillance.[36]

The WHO has evolved its own strategy to improve such coordination. The Stop TB Initiative, particularly through the TB/HIV Working Group and consisting of representatives of partners involved in tackling TB/HIV, is specifically active in this area.[37] This group first met in Geneva in April 2001 and now provides a forum for the coordination of activities to decrease the burden of TB/HIV. The initiatives they have taken range from policy development to innovative approaches such as the 'ProTEST' Initiative, community contribution in the care of tuberculosis, and development and dissemination of training materials and guidelines.[38]

The ProTEST Initiative launched by the WHO in 1998 aims at making the collaborative links between HIV and tuberculosis programmes operational and, delivering appropriate interventions for prevention and care of tuberculosis and HIV along with general health services. The name 'ProTEST' suggests the provision of voluntary counselling and testing (VCT) for HIV and the demand for VCT as an entry point for access to a range of HIV and tuberculosis prevention and care interventions. This Initiative has paved the way for a subsequent wave of expansion of collaborative programme activities in priority countries most hit by the dual infection. This programme is functional mainly in Africa.

THE PROBLEM OF MULTIDRUG-RESISTANT TUBERCULOSIS

The problem of drug resistance is a major threat to the tuberculosis control programme. MDR-TB is a specific form of drug-resistant tuberculosis due to a strain of bacillus resistant to at least isoniazid and rifampicin, the two most powerful drugs. Guidelines for the management of drug-resistant tuberculosis have been developed but are in a state of flux, with new data on resistance emerging from different parts of the world.

A deteriorating public health infrastructure, reduced funding for tuberculosis control, population growth, increasing poverty, poorly managed tuberculosis programmes, HIV, migration, etc. all contribute to drug-resistant tuberculosis.

However, improper use of antibiotics in the treatment of drug-susceptible patients remains the most preventable and common cause of development of resistant strains. Irrational prescribing is rampant and has been documented in various parts of India,[20,39,40] Bolivia,[41] Korea,[42] the USA[43,44] and Pakistan.[45] Pharmacies in India[46] and abroad[47] are involved in irrational dispensing practices. Compliance in patients is often poor and can also contribute to incomplete treatment and emergence of drug resistance.[48]

Between 1% and 3.4% of new patients have been reported to have MDR-TB in India.[49] In New York city the figure was estimated to be 7% in the early 1990s[50] and 10%–15% in areas of Russia.[51] However, if even 2% of new patients in India have MDR-TB, this represents 20 000 new infections every year. The financial and human resources required to treat 1 patient with MDR-TB are greater than those required to treat 100 drug-susceptible patients. More than 1 million new patients with tuberculosis still do not have access to the basic programme package in India. [12]

While drug-susceptible tuberculosis can be cured within 6 months, MDR-TB requires extensive treatment for up to 2 years.

It is also less effective, more toxic and expensive, compared to the treatment of drug-susceptible tuberculosis (second-line drugs are 300 times more expensive than first-line ones), making this an urgent problem for governments to tackle.

The WHO recognized the seriousness of this problem and, in 1998 along with several global partners around the world, conceived the DOTS-Plus strategy for the management of MDR-TB. A Working Group was established in 1999 to approve, conduct and oversee projects in this area. DOTS-Plus is a comprehensive management strategy that includes the 5 tenets of the DOTS strategy and takes into account issues such as the use of second-line drugs in areas where there is a high prevalence of MDR-TB. While DOTS prevents the emergence of drug-resistant and MDR-TB by ensuring that patients adhere to the full course of treatment, DOTS-Plus is designed to cure MDR-TB using second-line drugs.

It is important to note that DOTS-Plus is not 'a universal cook-book strategy' and should only be implemented in areas with moderate to high levels of MDR-TB. Identifying patients with MDR-TB saves costs by providing effective treatment protocols without wasteful, unnecessary and ineffective treatment. Furthermore, the primary cycle of MDR-TB transmission gets controlled, thereby saving future funds and indirect costs that would otherwise have to be diverted for treatment of both sick individuals and those they infect.

One of the major obstacles to the implementation of DOTS-Plus is the lack of access to second-line drugs. To address this issue, the Working Group has made arrangements with the pharmaceutical industry to provide second-line drugs to DOTS-Plus pilot projects (only for projects that are validated by the Green Light Committee—see below) at reduced prices (up to 99% lower than prices in the open market).[51,52] The Green Light Committee is a subgroup of the Working Group and has been established by the Working Group for the purpose of reviewing project applications and determining whether projects are in compliance with the guidelines developed by the Working Group. The WHO is a permanent member of the Green Light Committee and houses the Secretariat.

A recent study by Sterling *et al*.[53] made an effort to compare the impact of DOTS with DOTS-Plus on tuberculosis deaths in the developing world. The cumulative number of tuberculosis deaths per 100 000 population over 10 years, was the main outcome measure. The authors reported that under DOTS, 276 people (of whom 24 were MDR) would die from tuberculosis over 10 years, while the optimal implementation of DOTS-Plus would result in 4 (1.5%) fewer deaths. The authors further reported that if implementation of DOTS-Plus was associated with even minimal decreases in the effectiveness of DOTS, substantially more patients would die than under DOTS, further emphasizing the importance of optimal implementation of any of the programmes at the grassroots levels.

CONCLUSION

Since the introduction of DOTS in the early 1990s, much progress has been made in global tuberculosis control. By 2000, 148 countries had adopted the WHO DOTS strategy for tuberculosis control and 27% of the tuberculosis cases worldwide were treated under DOTS. However, this is not enough. About one-third of the world's population is already infected with tuberculosis. Each year, an estimated 8.4 million new cases are produced from this reservoir of infection and 1.9 million people die of the disease. The poor and marginalized in the developing world are the worst affected: 95% of all cases and 98% of deaths from tuberculosis occur in resource-poor countries.

Even within countries adopting the DOTS strategy, much needs to be done to expand the services to the whole population and it is essential to develop strategies that go beyond DOTS.

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Obituaries

Many doctors in India practise medicine in difficult areas under trying circumstances and resist the attraction of better prospects in western countries and in the Middle East. They die without their contributions to our country being acknowledged.

The National Medical Journal of India wishes to recognize the efforts of these doctors. We invite short accounts of the life and work of a recently deceased colleague by a friend, student or relative. The account in about 500 to 1000 words should describe his or her education and training and highlight the achievements as well as disappointments. A photograph should accompany the obituary.

—Editor