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Results of a standardised regimen for multidrug-resistant tuberculosis in Bangladesh

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SUMMARY

SETTING: Individualised regimens based on drug susceptibility test results, generally used to treat multidrug-resistant tuberculosis (MDR-TB), require often unavailable expertise and resources.

OBJECTIVE: To evaluate a standardised regimen based on the susceptibility profiles of locally prevalent MDR-TB strains.

DESIGN: The activities of a successful DOTS programme in Bangladesh were complemented by offering treatment with a standardised 21-month regimen to patients with laboratory-confirmed MDR-TB disease. The regimen contained kanamycin, ofloxacin, prothionamide, pyrazinamide, ethambutol, isoniazid and clofazimine. Clinical and bacteriological progress was monitored quarterly until treatment completion, then 6 monthly for 2 years.

RESULTS: The status at the end of treatment of this cohort of 58 documented MDR-TB patients was as follows: eight (14%) deaths, seven (12%) defaults, three (5%) failures and 40 (69%) cures. One bacteriologically-confirmed relapse was recognised. Frequent and sometimes serious side effects proved to be the main problem, suggesting the need for a better tolerated but equally effective regimen.

CONCLUSION: A standardised approach may provide a reasonable alternative to individualised treatment of MDR-TB in resource-poor settings. However, DOTS-plus programmes in resource-poor settings may confront significant difficulties in the enrolment, diagnosis and management of MDR-TB patients.

KEY WORDS: multi-drug resistance; treatment; control; tuberculosis

TO ADDRESS the global tuberculosis (TB) epidemic, the World Health Organization (WHO) has recommended a multifaceted strategy known as DOTS, which includes directly observed treatment (DOT) with standardised short-course chemotherapy (SCC) using first-line drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin or ethambutol or both).[1,2] The DOTS strategy including SCC has proved effective in diverse settings and is the basis for the global TB control effort.[3]

The global TB epidemic has been complicated by the presence of multidrug-resistant tuberculosis (MDR-TB), defined as resistance to at least isoniazid (INH, H) and rifampicin (RMP, R).[4] A survey of 58 geographic sites found a median prevalence of MDR-TB among new TB cases of 1.0% (range 0–14.1%), but certain 'hot spots' of high prevalence were noted (e.g., the former Soviet Union, China and Iran).[4] The SCC component of the DOTS strategy does not provide acceptable cure rates in these 'hot spots'. For example, a retrospective cohort study in six countries described treatment success rates for SCC of only 52% (range 11–60%) and 29% (range 18–36%) among new and retreatment cases with MDR-TB.[5]

Farmer and others have therefore proposed that well-functioning DOTS programmes servicing MDR-TB-endemic populations should provide additional services to diagnose and treat MDR-TB patients (i.e., so-called DOTS-plus programmes).[6] Most MDR-TB treatment programmes have used individualised regimens based on drug susceptibility test (DST) results from the most recent isolate obtained from each patient.[6–13] This individualised treatment strategy requires ready access to reliable laboratory facilities, and medical specialists to interpret the results and to prescribe the tailored regimens. Such resources are not available in many low-income countries. The alternative strategy involves treating all MDR-TB patients with a standardised regimen based on the common DST profile of the prevalent MDR-TB strains.[14,15] This paper provides a detailed description of a DOTS-plus programme employing this standardised treatment strategy in a resource-poor setting.

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PATIENTS AND METHODS

Patients

The Bangladesh National Tuberculosis Programme (NTP) is supported by the Damien Foundation (DF), a Belgian non-governmental organisation (NGO), in eight districts containing 18 million people. The DOTS strategy is applied in these DF-supported districts. New and retreatment cases receive treatment with standard Category I, consisting of ethambutol (E, EMB), INH, RMP and pyrazinamide (Z, PZA) for 2 months, followed by INH and thioacetazone (T, Th_1) for 6 months (2EHRZ/6HT) and Category II (2SEHRZ/1EHRZ/5EHR) (S, SM = streptomycin) regimens, respectively.[2] In 2000, close to 10 000 smear-positive and over 1500 smear-negative cases were treated; the latest cure rates for new and retreatment cases are 88% and 85%, respectively. Two DST surveys comprising respectively 645 and 1041 isolates were conducted in the DF-supported districts in 1995 and 2001. They found a low overall MDR-TB prevalence that had fallen from 2.5% to 0.7% (from 0.7% to 0.4% in new, and from 6.8% to 3.0% in retreatment cases).[16] This successful DOTS programme decided to introduce standardised treatment of MDR-TB patients, and the present study reports on the first cohort of such patients enrolled between 1 April 1997 and 31 March 1999.

Treatment regimen

After reviewing the relevant medical literature, the prevalent drug resistance profiles, and the cost and availability of various drugs, the following standardised regimen was devised and prescribed for all enrolled patients. Phase I consisted of daily supervised treatment with kanamycin (K, KM), clofazimine (C, CLF), ofloxacin (O, OFL), prothionamide (P, PTH), INH, PZA and EMB given for 3 months during compulsory hospitalisation; Phase II consisted of 12 months of daily ambulatory treatment with the same drugs except KM and C; this was followed by Phase III treatment with EMB and P for 6 months (3KCOPHZE/12OPHZE/6EP). Phase II treatment had to be supervised by a health worker as often as feasible, depending on distance, transport costs, etc., but at least once weekly. An average 33% of the doses were observed; in three patients a few weekly supervisions of intake were missed, and only ten had at least half their doses observed. Phase III treatment was unsupervised, but with fortnightly or monthly out-patient reviews. Standard dosages were prescribed for EMB, PZA and INH,[2] but as over 90% of adult patients in Bangladesh weigh between 33 and 45 kg, the standard dose of 300 mg INH was in fact moderately high. Patients weighing $\leqslant$54 kg received 500 mg daily of P; otherwise, 750 mg daily was prescribed. Ofloxacin dosages were 600 mg daily for patients up to 50 kg, and 800 mg daily for heavier patients, while KM dosage was 750 or 1000 mg. Clofazimine was given at a uniform dosage of 100 mg daily.

KM, OFL, PTH, PZA and EMB are recognised components in various recommended MDR-TB treatment regimens, and are relatively non-toxic.[17–19] Other second-line agents, such as cycloserine and para-aminosalicylic acid (PAS), were not included due to cost, weak activity and concerns about this resource-poor programme's inability to monitor or manage the adverse effects of these drugs. Two agents (INH and CLF), which were relatively non-toxic, readily available, and familiar to the treating doctors, were included to supplement the regimen, although the evidence for their effectiveness in treating MDR-TB is limited. Epidemiological and animal studies suggest some benefit from inclusion of INH in MDR-TB treatments, perhaps because susceptible or borderline resistant sub-populations within the patient's total burden of *M. tuberculosis* organisms may be treated (reviewed in reference 19). Moreover, levels of resistance to INH below the usual serum levels have been reported for a considerable proportion of MDR strains.[20,21] CLF has demonstrable in vitro and in vivo activity against *M. tuberculosis*,[22] and it has recently been shown to lower the minimal inhibitory concentration of isoniazid in both susceptible and resistant strains.[23] CLF also provided a potentially active third drug in cases that might exhibit INH- and Th_1-induced cross-resistance to PTH.

Inclusion criteria were pulmonary tuberculosis, age 18–65 years and residence in a district supported by DF or an associated NGO. Consenting patients with smear-positive failure or relapse after a fully-supervised Category II regimen administered in a DF-supported health facility were started on the standardised regimen without laboratory confirmation of their MDR-TB status. However, to remain in the study and to be eligible for final analysis, MDR-TB disease had to be confirmed by DST in the reference laboratory in Antwerp, Belgium. Patients refusing hospital admission during the initial 3-month intensive phase of treatment were excluded. All services, including food, were provided at no expense to the patient during this mandatory hospitalisation. Each participant provided written informed consent.

Methods

On admission, patients were seen by a medical officer, and baseline chest X-ray (CXR), biochemical and haematological investigations were performed. Two sputum specimens were collected for microscopy and culture. Two further sputum specimens for microscopy were collected at the end of the first and second months of treatment. Clinical and bacteriological follow-up was then conducted quarterly until treatment completion, with two sputum samples collected for microscopy and one for culture on each occasion. Six-monthly reviews with similar investigations continued for 2 years after treatment completion.

Direct smears were stained by the Ziehl-Neelsen method and read for 100 fields at ×1000. Sputum specimens for culture were placed in 5 ml of transport medium (1% cetylpyridinium chloride and 2% sodium chloride in distilled water),[24] and sent to the Belgian reference laboratory. In Antwerp, the specimens were decontaminated,[25] cultures were done on Löwenstein-Jensen medium, and DST performed for INH, RMP, SM and EMB using the proportion method.[26] As scanty growth was regularly obtained due to prolonged transport times, any number of colonies isolated was considered positive. Part of the isolates were also tested for susceptibility to KM and OFL on Middlebrook 7H11 agar using a critical proportion of 1% and critical concentrations of 6.0 and 4.0 μg/ml, respectively.[27] Susceptibility tests for PZA, PTH and CLF were not performed.

Endpoints and analysis

Patients who failed or relapsed after receiving a fully-supervised retreatment regimen but who could not have MDR-TB confirmed by DST, due to culture failure or contamination, or isolation of non-MDR-TB or another mycobacterium, were excluded from analysis. The same was done for patients with an MDR-TB isolate in the recent past, but who were negative on smear and culture at the start of this treatment. Non-MDR-TB patients were changed back to Category II treatment (or a variant thereof, depending on the DST profile of their isolate). 'Cure' was defined as completion of treatment and persistently negative smears and cultures at the end of treatment and on at least two previous examinations. 'Bacteriological failure' was persistently positive sputum cultures for *M. tuberculosis* after at least 6 months of treatment, without taking into account colony counts. A patient developing positive cultures with the same strain after successful treatment completion, as documented by IS*6110* restriction fragment length polymorphism (RFLP), was defined as a 'bacteriological relapse'.

Data handling and statistical analyses (e.g., Fisher's exact test) were performed using Epi Info (version 6.02, Centers for Disease Control and Prevention, Atlanta, GA, USA).

RESULTS

During the 4 years (1995–1998) during which DF supported TB services in the eight districts of Bangladesh and treated 23 000 cases, 172 patients were detected with MDR-TB infection on laboratory investigation or were recognised as having failed or relapsed after Category II treatment based on clinical grounds and/or smear microscopy (Figure). Of these patients eligible for the study, 25 (15%) with laboratory-confirmed MDR-TB infection were apparently cured on Category II treatment, 18 (10%) died before study entry, 13 (8%) were lost to follow-up and 52 (30%) refused treatment. Seventy patients were enrolled and began the standardised treatment regimen, including six additional cases from an adjoining region serviced by an associated NGO. Seventeen of the 70 patients had MDR-TB infection documented by DST performed 2–28 months (median 7 months) prior to study entry, with repeat DST at enrolment. Of 46 cases who had failed Category II treatment and seven relapses after Category II treatment admitted to the study pending laboratory confirmation of MDR-TB status, eight (17%) failure and four (57%) relapse cases were removed from the study because MDR-TB infection could not be confirmed by DST (Figure).

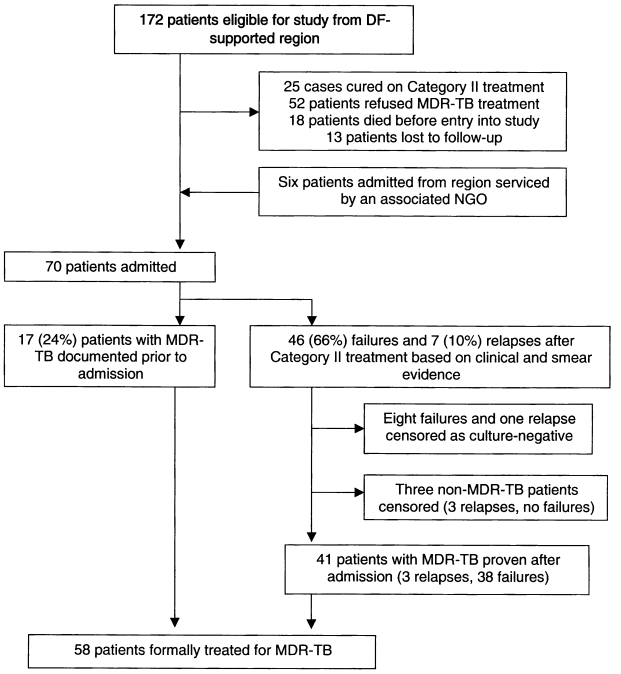

Figure Study profile. DF = Damien Foundation; MDR-TB = multidrug-resistant tuberculosis; NGO = non-governmental organisation.

The demographic characteristics and drug resistance patterns of the final cohort of 58 patients are given in Table 1. The patients had had TB for a median of 24 months (range 6–133). Forty-three (74%) patients had radiological evidence of extensive disease affecting more than one lobe. Medical examinations and screening biochemical investigations on study entry detected the following co-existing conditions: impaired liver function (one patient), mild renal impairment (two patients), and probable diabetes mellitus (one patient). As the human immunodeficiency virus (HIV) is not a recognised problem in Bangladesh, serological investigations were not performed.

The progress of the study cohort at 3 and 21 months of treatment is shown in Table 2. Notably, 51 (88%) patients became culture-negative during the initial 3-month intensive phase of treatment. Only one patient had intermittently positive cultures after the third month of treatment, presumably caused by prolonged

Table 1 Baseline characteristics of 58 patients formally treated for multidrug-resistant tuberculosis using the standardised regimen

Characteristic	*n* (%)
Demographic	
Median age, range (years)	35 (18–57)
Sex (M/F)	49/9
Clinical	
Median disease duration, range (months)	24 (6–133)
Extent of illness*	
Extensive	43 (74%)
Lobar	5 (9%)
Not quantified	10 (17%)
Antibiogram	
Resistant to INH and RMP	14 (24%)
Resistant to INH, RMP and EMB	15 (26%)
Resistant to INH, RMP and SM	5 (9%)
Resistant to INH, RMP, SM and EMB	24 (41%)

* Extensive disease was defined as radiological evidence of cavities and/or moderately dense infiltrates involving more than one lobe; lobar disease was defined as radiological evidence of disease restricted to one lobe.
M = male; F = female; INH = isoniazid; RMP = rifampicin; EMB = ethambutol; SM = streptomycin.

treatment interruption due to severe stomach problems at the end of intensive phase. According to protocol criteria he was declared cured, but he relapsed within 6 months. Two more cured patients had one positive isolate after the third month, one with a few colonies at 6 months and the other at 12 months of treatment. However, they later remained persistently negative on smear as well as culture on respectively nine and seven specimens collected up to 24 months post treatment. Only one cured patient remained smear-positive up to the sixth month, but was clinically well and cultures were negative from the third month onwards. At the completion of the 21-month treatment regimen, eight (14%) patients had died, seven (12%) had defaulted, three (5%) had failed treatment and 40 (69%) were cured.

Of the eight deaths, two occurred in the first 6 months of treatment: one patient developed fulminant hepatic failure, while the other had a brief psychotic episode, lapsed into a coma and died. Both of these deaths were attributed to adverse drug effects because many of the medications in this regimen can cause hepatic dysfunction, while prothionamide, the quinolones and isoniazid have been associated with neurological side effects. The remaining six patients died later on treatment, one from a complication of pleurocentesis; the other five died of respiratory insufficiency and cor pulmonale secondary to their extensive pre-existing lung damage (all six were smear-negative with presumed inactive or cured TB at the time of death).

The seven (12%) defaulters abandoned treatment because they could no longer tolerate the drug regimen. Many of the 58 patients reported adverse drug effects, most of them minor (Table 3). These did not lead to treatment modification in the intensive phase. However, one of the deaths attributed to side effects occurred then, and treatment may have been interrupted too late. Nausea and vomiting were common adverse effects and were effectively managed in hospital by dietary modifications and symptomatic treatment, but after discharge these interventions proved more difficult to implement. Seven patients required treatment modification because of persisting gastrointestinal symptoms between months 4 and 15 of the regimen: prothionamide was reduced (in five) or ceased (in one patient), and ofloxacin was stopped in the other (clofazimine replacing the offending medication in each case).

By December 2002, all 40 patients defined as 'cured' had completed 24 months of follow-up. As shown in Table 2, only one patient has relapsed smear- and culture-positive (at 6 months post treatment completion), while on microbiological and molecular investigations one late recurrence proved to represent reinfection with a fully drug-susceptible strain. Three other 'cured' patients died of pulmonary insufficiency

Table 2 Evolution and outcome of treatment for patients with multidrug-resistant tuberculosis receiving the standardised regimen

	n (%)
Status at end of intensive phase (3 months), $n = 58$	
Died by 3 months	1 (2)
Defaulted by 3 months	2 (3)
Smear-negative	47 (81)
Culture-negative	51 (88)
Smear-positive	8 (14)
Culture-positive	3 (5)
Culture-contaminated	1 (2)
Status at end of treatment (21 months), $n = 58$	
Died	8 (14)
Defaulted	7 (12)
Bacteriological failure*	3 (5)
Cured smear- and culture-negative†	40 (69)
Status 24 months after declaration of cure, $n = 40$‡	
Died of TB sequelae or other causes	3 (7.5)
Relapsed smear- and culture-positive	1 (2.5)
Reinfected with a different drug-susceptible strain	1 (2.5)
Remained bacteriologically negative	35 (87.5)

* Bacteriological failure defined as repeatedly positive sputum culture for *M. tuberculosis* after 6 months of treatment.
† Cure defined as repeatedly negative sputum cultures upon completion of 21 months treatment.
‡ Status of the sub-cohort of cured patients followed up for the full 24 months.

Table 3 Number and frequency of presumed side effects reported during treatment with the standardised regimen

Side effect*	*n* (%)
Nausea, vomiting	41 (71)
Arthritis	14 (24)
Neuritis	7 (12)
Mental confusion	7 (12)
Skin rashes	2 (3.5)
Jaundice	2 (3.5)
Miscellaneous	4 (5.9)

* More than one side effect was reported for some patients.

or an unrelated cause after treatment completion, having been smear- and culture-negative on at least seven occasions since the third month of treatment. The other 35 patients remained smear- and culture-negative.

Of the 58 pre-treatment isolates, 43 (74%) were cultivable from −20°C storage and were subjected to KM and OFL susceptibility testing. One strain was KM-resistant, while all were susceptible to OFL. The KM-resistant patient became culture-negative after the 3-month intensive treatment phase, but defaulted from therapy at 6 months. Isolates obtained from the three failure cases after 10–18 months of treatment remained susceptible to KM and OFL. The single patient who relapsed within 6 months of treatment completion had acquired resistance to OFL but not to KM.

The drug and hospitalisation costs (including food) to the NTP of the 21-month regimen were respectively US$500 and $200 per patient.

DISCUSSION

Individually tailored regimens based on the infecting organism's drug susceptibility profile remain the standard of care in affluent countries. The original evaluation of individually tailored regimens conducted at the National Jewish Centre for Immunology and Respiratory Medicine in Denver, Colorado, between 1973 and 1983 reported a culture conversion rate of 65%, with a final success rate of 56% after a mean follow-up of 51 months.[7] Subsequent studies in Korea, Turkey and the US have achieved better results,[8–10,13] with clinical response rates as high as 96% among HIV-negative patients.[8] These studies had access to extensive medical, laboratory and surgical facilities. A community-based treatment programme using individualised regimens in Peru recently reported that cure rates of more than 80% can also be achieved in low-resource settings. However, the Peruvian project had extensive external support.[28] Interestingly, disappointing results using a standardised approach in the same country have also been reported.[15]

Individualised treatment has several theoretical advantages compared with a standardised approach.[14] For example, improved selection of effective drugs may optimise cure rates, and acquisition of additional resistance may be avoided because at least three effective drugs will always be administered. However, this study has demonstrated that a DOTS-plus programme employing a standardised treatment strategy with only minimal reference laboratory support and no access to surgical facilities can achieve similar results (i.e., a sputum culture conversion rate of 88% after 3 months of treatment, and a final cure rate of 69%). Acquisition of additional resistance (to ofloxacin) was demonstrated only for the single early relapse case, but may have been underestimated because of our fairly high critical concentration. In terms of relapse-free survival, our long term results are similar to those obtained with the expensive individualised treatment in the Lima study. Of total cohorts enrolled, 36 of our 58 patients (62%) were alive and seemingly cured of MDR-TB at 24 months follow-up, compared with 48 of 75 (64%) at a median of 40 months (range 7–66) in Lima.[28]

Our study has some limitations. First, the design did not include a second study arm. As explained, the setting was deemed unsuitable for comparison with individualised treatment, and other second-line drugs were unaffordable or considered too toxic or inferior to replace one of those we used. The limited cohort size is a second limitation, allowing for wide confidence intervals (95%CI) (i.e., cure rate 69%, 95%CI 55–80%). However, the bacteriological effect of our regimen is a more remarkable feature, with only 7% (four patients) combined failure and relapse rate. The difference with the standardised protocol used by the Peru NTP (32% failure rate and unknown relapses among 298 proven MDR-TB cases[15]) is clearly significant ($P = 0.0001$). Moreover, since our first cohort, more proven MDR-TB cases have been treated with variants of the described regimen, using fewer drugs and/or a shorter treatment regimen, with similar results: 86 of 126 (68%) patients started before 1 April 2002 were cured. The relative insensitivity of our cultures due to transport delays is a third limitation, compensated for by considering any number of colonies isolated as positive. This may have led to false declaration of MDR-TB in early failures due to transient resistance; however, only one isolate was obtained after 4 months of Category II, for which MDR-TB treatment failed, as proven by several MDR isolates. Two more patients were included with isolates obtained before the end of Category II treatment, i.e., after respectively 5 and 6 months, which is rather late for transient resistance. We also believe that repeated testing by smear as well as culture over a sufficiently long follow-up period has prevented failures and relapses from being missed due to lower culture sensitivity. A final limitation of this study may be that the results are not applicable to some other MDR-TB-endemic populations. Though conducted in poor communities in Bangladesh, this study was aided by several favourable factors: there was a low rate of MDR-TB in a stable HIV-negative population; second-line drugs (apart from the quinolones) had not been used for TB; and there was a well-established NTP supported by a well-resourced NGO and highly motivated personnel. Programmes servicing some other MDR-TB endemic populations, such as prisons in the former Soviet Union, do not have all of these favourable factors. Furthermore, the use of standard dosage INH may be slightly misleading, as it corresponded to an average of 7 mg/kg in this exceptionally low-weight population, and there may have been a INH-synergistic effect from clofazimine.

Our treatment regimen (3KCOPHZE/12OPHZE/6EP) was meant to be a maximal combination, using all possibly still active first-line drugs besides the selected second-line drugs for which the rationale has been described. Although, according to the literature, the effectiveness of INH and C remains uncertain, we included them because they have *not* been shown to add nothing in combination with second-line drugs. Their contribution to the success of this combination cannot be determined, but the addition of INH and CLF was the main difference between our standardised regimen and that one used in Peru.

The bacteriological effectiveness of our regimen was to some extent offset by its sometimes serious side effects. Our staff was trained in their recognition and management, with clear instructions as to when to stop the possibly offending drugs, but the side effects of second-line drugs nevertheless pose a problem that is difficult to overcome, especially in resource-poor countries. The biochemical and other tests required to investigate adverse reactions are not available, and cause of death is difficult to ascertain. Two deaths in the first 6 months of treatment were attributed to adverse drug reactions, but mild side effects were more common and more troublesome. Another seven patients could not tolerate the medications and defaulted, mainly during the later phases of treatment; the most common offending drug was prothionamide, which caused severe nausea and vomiting. These side effects could be relieved by dietary manipulation and symptomatic treatment in hospital, but after discharge to poor households unable to provide such support, many patients complained of worsening gastrointestinal symptoms. For these reasons, further cohorts have been enrolled on variations of the same regimen, each time omitting a single drug. No further deaths from drug toxicity have been recorded in over 100 other patients enrolled after the present cohort.

The adverse reactions and prolonged therapy associated with MDR-TB treatment increase the risk of non-adherence. DOT is therefore vital to support patients with these adverse reactions, to ensure adherence to treatment, and to avoid the acquisition of resistance to additional agents.[14,18,19] Community-based projects using trained local residents to perform DOT have reported good results.[6,12,28] However, relying on local residents and family members to provide DOT had previously yielded disappointing results in Bangladesh. Instead, a network of DOT providers, using largely uneducated 'village doctors', had been developed with good results, but for this more complicated treatment, also requiring intensive patient counselling, they were thought to be insufficiently reliable. Full DOT was therefore instituted in the intensive phase of MDR-TB treatment, as recommended by WHO authorities.[14] Out-patients receiving phase II treatment then had on average one third of their doses observed by a health worker. Closer observation of treatment was impossible when servicing these isolated populations, and many future MDR-TB treatment programmes in resource-poor rural areas are likely to encounter similar difficulties in attaining higher levels of supervision.

MDR-TB has recently gained increasing notoriety, and NTPs in resource-poor endemic countries may feel pressured into instituting DOTS-plus programmes.[4,6] This study demonstrates that the strategy of using a standardised regimen provides acceptable results, but it also highlights the practical difficulties in establishing MDR-TB treatment programmes in resource-poor settings which may have been understated to some extent by other authors.[6,11] Firstly, there are problems in enrolling patients. The DF-supported NTP was aware of 172 eligible patients, but only 70 were ultimately admitted to the study (Figure). Fifty-two (30%) patients refused treatment, and this proportion has not decreased in more recent cohorts. Some refuse because of the fear of the possible side effects that were explained to them, or because they cannot leave work. Many patients have lost faith and prefer other treatment providers (herbal or private western-type doctors, about 40% of refusals). The mandatory 3-month period of hospitalisation is also a recognised disincentive for almost 40%, although all hospital services, including meals, are provided free. The NTP continues to require this hospitalisation period as proof of commitment on the part of the patient, to ensure adherence during the critical intensive phase of treatment, and to monitor and treat any adverse effects. This policy is supported by international authorities and guidelines.[17,18]

Accurate diagnosis of MDR-TB presents a second set of problems for DOTS-plus programmes that do not have ready access to specialised laboratory facilities. An MDR-TB treatment trial in Rwanda found that nearly 50% of eligible patients died or were lost to follow-up while awaiting DST results from a distant reference laboratory.[29] Failure or relapse after Category II treatment was therefore an inclusion criterion in the present study to avoid such losses. Only 31 (17%) patients died or absconded before entering the present study (Figure). However, failure of Category II treatment proved a better predictor of the presence of MDR-TB than relapse in this well-run DOTS programme. Eighty-three per cent of 'failure' cases, but only 43% of relapses, proved to have MDR-TB. Hence, access to laboratory services is clearly required to accurately diagnose MDR-TB in relapse cases. Ideally, these resources should be even more widely applied in MDR-TB endemic areas because the clinical diagnosis of MDR-TB based on failure of Category II treatment exposes patients to unnecessary, ineffective treatment and the risk of acquiring resistance to additional agents (i.e., the amplifier effect).[6,30] When failing Category II treatment, MDR-TB patients also represent a reservoir of infection for the community.

Finally, justification of DOTS-plus programmes may prove problematic in resource-poor countries where the prevalence of MDR-TB is low. While the results of this DOTS-plus initiative in Bangladesh are gratifying, this study probably contributed little to TB control in a region of Bangladesh where the prevalence of primary MDR-TB is around 0.5% and over 10 000 non-MDR-TB cases are treated annually.[16] However, the absolute need to treat all TB patients, including those with MDR-TB, is evident on ethical, clinical and public health grounds.[6] The funds necessary to achieve this ideal may no longer be the main limiting factor, as additional funding is now often available and drug costs on the international market have fallen. In Bangladesh, a wide range of cheap, locally manufactured fluoroquinolones has been available for some time, which explains the moderate cost of the regimen we used. These drugs are being intensively promoted for treatment of TB, and quite a few MDR-TB patients can afford the US$100 presently needed for 1 year of levofloxacin prescribed in the private sector. The decision of whether or not to treat MDR-TB under the NTP is thus further complicated by the rapidly increasing misuse of and creation of resistance to second-line drugs, especially fluoroquinolones, in the private sector in these countries.[31] The identification of a truly effective standard regimen, together with guidelines for its proper use, would greatly facilitate this decision.

CONCLUSION

This study has shown that standardised treatment of MDR-TB can provide satisfactory results and can be implemented as part of a successful DOTS programme. The standardised treatment strategy may be a justifiable alternative to the expensive, resource-demanding approach of individually tailored regimens that international agencies and national authorities should consider when establishing DOTS-plus programmes. This study has also highlighted the problems in enrolling, diagnosing and managing MDR-TB patients in resource-poor countries.

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RÉSUMÉ

CONTEXTE : Les régimes individualisés basés sur les résultats des tests de sensibilité aux médicaments, généralement utilisés pour traiter la tuberculose à germes multirésistants (TB-MR), dépendent d'une expertise et de ressources qui ne sont pas toujours disponibles.
OBJECTIF : Evaluer un régime standardisé basé sur les profils de sensibilité des souches localement prévalentes de TB-MR.
SCHÉMA : Les activités d'un programme de DOTS couronné de succès au Bengladesh ont été complétées par l'offre d'un régime de traitement standardisé de 21 mois aux patients atteints d'une maladie TB-MR confirmée par le laboratoire. Le régime comportait kanamycine, ofloxacine, prothionamide, pyrazinamide, éthambutol, isoniazide et clofazimine. On a suivi l'évolution clinique et bactériologique chaque trimestre jusqu'à l'achèvement du traitement, puis tous les semestres pendant 2 ans.
RÉSULTATS : La situation en fin de traitement pour cette cohorte de 58 patients TB-MR documentés a été la suivante : huit (14%) décès, sept (12%) abandons, trois (5%) échecs et 40 (69%) guérisons. On a découvert une rechute bactériologiquement confirmée. Le problème principal a consisté en effets collatéraux fréquents et souvent sérieux, ce qui indique la nécessité d'un régime mieux toléré mais avec une efficacité bactériologique égale.
CONCLUSION : Une approche standardisée peut représenter une alternative raisonnable au traitement individualisé de la TB-MR dans les contextes à faibles ressources. Les programmes DOTS-plus dans les contextes à faibles ressources peuvent néanmoins être confrontés à des difficultés significatives dans l'enrôlement, le diagnostic et la prise en charge des patients TB-MR.

RESUMEN

CONTEXTO : Los regímenes individualizados, basados en los tests de sensibilidad a los medicamentos, generalmente utilizados para tratar la tuberculosis multirresistente (TB-MR), requiere recursos y una pericia que no se encuentran a menudo.
OBJETIVO : Evaluar un régimen estandarizado basado en los perfiles de sensibilidad de las cepas localmente prevalentes de TB-MR.
DISEÑO : Las actividades de un programa exitoso de DOTS en Bangladesh fueron complementadas con la disponibilidad de un régimen estandarizado de 21 meses para los pacientes con enfermedad TB-MR confirmada por el laboratorio. El régimen contenía kanamicina, ofloxacina, protoniamida, pirazinamida, etambutol, isoniacida y clofazimina. Se realizó un seguimiento de la evolución clínica y bacteriológica trimestralmente hasta el término del tratamiento y luego semestralmente durante 2 años.
RESULTADOS : La situación al final del tratamiento en este cohorte de 58 casos documentados de TB-MR era la siguiente : ocho (14%) muertes, siete (12%) abandonos, tres (5%) fracasos y 40 (69%) curaciones. Se constató una sola recaída bacteriológicamente confirmada. El principal problema fue el de los efectos adversos de los medicamentos que fueron frecuentes y a veces serios, lo que indica la necesidad de un régimen con medicamentos mejor tolerados y de eficacia similar.
CONCLUSIÓN : Un enfoque estandarizado puede ser una alternativa razonable al tratamiento individualizado de la TB-MR en los contextos de escasos recursos. Los programas DOTS-plus también pueden verse enfrentados a dificultados significativas en el enrolamiento, diagnóstico y manejo de los pacientes TB-MR.