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Evaluation of tuberculosis control by periodic or routine susceptibility testing in previously treated cases

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SUMMARY

SETTING: A national tuberculosis control programme (NTP) disposing of baseline drug resistance rates and using 2EHRZ/6TH in the treatment of new cases.

OBJECTIVE: To estimate the extent of drug resistance created by the NTP.

DESIGN: Resistance rates in 2EHRZ/6TH failure and relapse cases were compared to baseline, and resistance profiles of repeat isolates were checked. Numbers of observed resistant failures were compared to numbers expected due to pre-existing resistance. Trends of resistance in combined new and previously treated cases were extrapolated.

RESULTS: High drug resistance rates were observed. Changes in resistance to streptomycin, the virtual absence of documented acquired resistance and a close match of observed with expected resistant failures all indicated accumulation of primary drug resistance as the main mechanism. Resistance in relapse/failure cases showed a significantly declining trend, and estimated combined drug resistance decreased rapidly.

CONCLUSIONS: Drug resistance in previously treated cases seems to consist of passed-on primary rather than true acquired resistance. A one-time survey is thus confusing, but continuous routine testing may constitute the best drug resistance monitoring method. Cases previously treated with short-course chemotherapy may show drug resistance much more frequently than generally assumed, and all should receive a re-treatment regimen. The 2EHRZ/6TH regimen proved very safe under field conditions, causing no 'amplification' towards multidrug resistance and almost no acquired isoniazid resistance. Implementation of this regimen, together with a standardised re-treatment regimen, seemed to rapidly reduce isoniazid as well as multidrug resistance levels, despite the fact that directly observed treatment was not strictly applied.

KEY WORDS: tuberculosis; drug resistance; acquired resistance

THE GLOBAL objectives of any tuberculosis control programme must be to cure the maximum possible number of patients, at the same time avoiding the creation of acquired drug resistance (ADR).[1] Surveillance of drug resistance rates should thus be an integral part of programme monitoring. Both repeated representative drug resistance surveys measuring primary drug resistance (PDR), as well as systematic drug susceptibility testing (DST) for all first-line failure cases and relapses (failures/relapses) have been proposed.[1,2] Although unnecessary for standard re-treatment, testing of failures is assumed to reveal ADR relapses caused by a poorly functioning programme.

Failures/relapses have been attributed mainly to faulty regimens and irregular drug intake, as they were infrequently related to drug resistance in early controlled clinical trials.[3,4] The subject of 'amplified' drug resistance and the creation of multidrug resistance (MDR, defined as resistance to at least isoniazid and rifampicin), even when the standardised regimens recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD) and World Health Organization (WHO) are applied, has recently been raised.[5,6] Despite indications that MDR-TB generally dies out under a good DOTS (directly observed treatment, short-course) programme,[5] a DOTS-plus strategy comprising MDR-TB treatment has been advocated. Moreover, in some parts of the world systematic DST followed by individualised regimens has been suggested for all cases.[7]

Since 1994, the Damien Foundation has implemented TB projects for the Bangladesh National Tuberculosis Programme (NTP) in a working area consisting of eight of the 64 districts not covered by the NTP before that time. The following regimens

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are used: 1) 2(3)EHRZ/6HT* as first-line regimen for new smear-positives; in line with NTP guidelines,[8] up to early 1997 this regimen was also prescribed for 'not-new' cases, who had used R for less than 1 month; 2) 2SEHRZ/1(2)EHRZ/5$(EHR)_3$ for re-treatment cases; until 1997 the first-line regimen was given to re-treatment cases who had used rifampicin for less than 1 month, after which the NTP allowed us to prescribe the re-treatment regimen for these cases also; and 3) 2EHZ/10HT for new smear-negative and extra-pulmonary cases.

In 1995, at the start of the Damien Foundation's involvement in the Bangladesh NTP, baseline resistance rates in new or previously treated cases were determined for a representative sample of patients who had never been treated under the programme, as published earlier.[8] We report here on the subsequent follow-up of drug resistance in failures/relapses of treatment in the NTP. Criteria for failure or relapse followed standard NTP guidelines,[1] and were thus essentially based on confirmed positive sputum smear results at 5 months or later during treatment (for failures), or after treatment had been completed (for relapses). New and re-treatment cases had received TB treatment previously for respectively less than 1 month and 1 month or more.

OBJECTIVES

The main objective was to obtain an in-depth view on the safety (as regards creation of drug resistance) of the regimens as applied in the NTP, by 1) comparing the drug resistance rates among failures/relapses to baseline rates found before the Damien Foundation's involvement in the NTP; 2) comparing drug resistance before and after treatment, for the few available pairs of isolates; 3) correlating resistance, treatment outcome and regularity of attendance for drug collection or DOT; 4) comparing numbers of observed and expected drug-resistant failures by applying rates reported from clinical trials; and 5) estimating the trends of combined drug resistance.

METHODS

A drug resistance survey representative of the eight-district working area was conducted shortly after the start of the Damien Foundation's activities in Bangladesh. Analysis of only those cases new to the programme resulted in a baseline profile of drug resistance in 'new' and 'previously treated cases', as published earlier.[8] Thereafter, sputum samples from relapse and failure cases were sampled systematically, with repeat history taking to detect hidden previous treatment in all cases classified as 'new' at the start of the first course of treatment. The samples were then sent for DST to the supranational reference laboratory in Antwerp, Belgium, and tested as described previously.[8] Resistance rates found in these samples were compared to those obtained in the baseline survey that covered patients who had never been treated by the NTP. Baseline rates in previously treated cases were compared to those of first-line relapses/failures with a drug intake history of at least 1 month before 2EHRZ/6HT ('not new before first-line treatment'), while rates in those without such a history ('new before first-line treatment') were compared to baseline rates found earlier in new cases. For analysis, drug resistance patterns were further classified into two major groups, those resistant to INH and its combinations, excluding MDR (Hr = resistance to INH only or with other drugs, but not with RMP), and MDR. Considering that streptomycin (S, SM) was not used in first-line treatment, and SM resistance could thus not be acquired, analysis focused on changes in rates of resistance to SM and its combinations within the Hr and MDR classes, namely SH(E) and SHR(E). Rate ratios of relapses/failures to baseline were calculated for SH(E) or SHR(E). The product of total baseline Hr, or MDR, with these ratios was compared to the corresponding rates actually observed in the failures/relapses, to check the hypothesis that all Hr or MDR could represent pre-existing rather than acquired resistance. This was first done separately for the 'new before first-line treatment' and 'not new before first-line treatment' groups. Overall first-line treatment failure/relapse ratios and their multiplication products for total Hr and MDR were then calculated, using proportional prevalences of 'new before' and 'not new before' within our study population, and the corresponding results for the respective groups.

Resistance patterns of all available paired (pre- and post-first-line treatment) isolates were checked for ADR to INH and/or RMP after repeat DST.

Treatment data from 1995, 1996 and 1997 were computerised and updated regularly for relapses occurring up to mid-1999 (1–4 years after the end of treatment). Regularity was expressed as expected divided by actual duration of treatment, both measured as number of days, for the intensive and the continuation phase. Computerised DST results were linked to patient treatment data. All data entered were verified by one of the authors (AVD).

Numbers of registered and expected resistant failures of first-line treatment were compared. The total number of drug-resistant failures registered was extrapolated from the drug resistance rates found in the present follow-up study, using stratification into 'new before first-line treatment' and 'not new before first-line treatment'. The numbers of initially resistant

* E, EMB = ethambutol; H, INH = isoniazid; R, RMP = rifampicin; Z, PZA = pyrazinamide; T, Th = thioacetazone. Numbers preceding the letters indicate the duration in months of the phase of treatment, while numbers in subscript indicate the number of times the drug is taken each week.

cases among all those treated with the first-line regimen were estimated, applying the rates from our baseline survey. Failure rates after 2SEHRZ/6HT, reported from the British Medical Research Council (BMRC) clinical trials,[4,9] were used to calculate failures expected among cases with initially resistant tuberculosis.

Finally, the prevalence of resistance and its trend over time were calculated for each year from the start of the Damien Foundation's activities in tuberculosis control. Registrations were classified by type (new, re-treatment after non-programme treatment, re-treatment after programme treatment) and the number of each type was multiplied by its observed rate of resistance. For new cases and non-programme re-treatments, these were the corresponding rates from the baseline survey. For programme failures/relapses, the rates observed during the respective years and reported here were applied.

For statistical analyses Epi-Info version 6.04 was used. Rates were compared using Pearson's χ^2 test or Fisher's exact test.

RESULTS

Table 1 shows the rates of resistance found in the baseline survey compared to those of 435 re-treatment cases (204 failures and 231 relapses after first-line treatment), representing all such cases sampled up to the end of 1999. Sampling covered all treatment centres, and reached 69% of failure and 82% of relapse registrations for the cohorts entered into the computer. Missing samples were due to staff forgetfulness or refusal by the patient to supply a sample, as there were no exclusion criteria. Separate rates are shown for 'new before first-line treatment' patients (333 cases), versus 'not new before first-line treatment' patients (102 cases).

In 'new before first-line treatment' cases, total Hr had risen from 5.58% baseline drug resistance to 39.63%. For MDR, this rate had changed from 0.64% to 8.1%. Remarkably, there was not a single case of resistance to RMP only, and only one (0.3%) to EMB. Resistance to SM only decreased slightly (non-significantly) to 4.2% vs. baseline 5.15%, but drug resistance to SH(+E) increased out of proportion, from 1.72% baseline to 13.81%. Similarly, drug resistance to SHR(+E) changed considerably, from 0.21% (baseline) to 5.1%. The bottom part of Table 1 shows the rate ratios for drug resistance profiles, including SM, observed in the failures/relapses vs. baseline. The SH(+E) and SHR(+E) increments, by a

Table 1 Resistance in failure and relapse cases of first-line treatment compared to baseline profiles

Drug resistance	Baseline study, new cases	Relapse + failure new before first-line treatment	Baseline study not new cases	Relapse + failure not new before first-line treatment	All relapse + failure after first-line treatment
No. of patients examined	466	333	179	102	435
Pan-susceptible (%)	88.20	47.77	63.67	10.79	39.10
Resistant to H only (%)	3.86	24.02	14.53	42.16	28.27
to R only (%)	0.43	0.00	0.56	1.96	0.46
to S only (%)	5.15	4.20	5.03	3.91	4.13
to E only (%)	0	0.30	1.68	0.00	0.23
to RS (%)	0	0.00	1.12	0.00	0.00
to HE (%)	0	1.80	1.68	3.92	2.30
to HR (%)	0.43	1.80	1.12	8.82	3.45
to HRE (%)	0	1.20	2.23	4.90	2.07
to SH/SHE (%)	1.72	13.81	6.15	13.73	13.79
to SHR/SHRE (%)	0.21	5.10	2.23	9.80	6.20
All H except MDR (%)	5.58	39.63	22.36	59.80	44.36
Total MDR (%)	0.64	8.10	5.58	23.53	11.72
Ratios of resistance compared to baseline					
For S/RS only		0.82		0.64	0.77
For SH(E)		8.03		2.23	6.67
For SHR(E)		24.29		4.40	19.62
Resistance expected applying the above ratios observed for SH(E) and SHR(E)					
% total H resistance expected using the observed SH(E) ratio		44.80		49.90	46.0
% total MDR expected using the observed SHR(E) ratio		15.54		24.53	17.65

Relapse or failure cases without TB drug intake for at least one month prior to Cat 1 are called 'new before first-line treatment', and compared to new cases from the baseline survey. The others are shown separately as 'not new before first-line treatment', and compared to 'not new' cases from the baseline survey.
H = isoniazid; R = rifampicin; S = streptomycin: E = ethambutol; MDR = multidrug resistance (resistance to at least H and R).

factor of 8.03 or 24.29, are both highly significant ($P < 0.0001$). The products of the baseline rates for new-case Hr and MDR, with their respective ratios, were 44.8% for Hr and 15.54% for MDR.

Rates of resistance observed among 'not new before first-line treatment' failures/relapses were higher, but showed similar changes (Table 1). Total Hr rose from 22.36% baseline to 59.8%, while MDR rates increased from 5.58% to 23.53%. Also in this group, resistance to SM decreased only slightly, while drug resistance to SH(+E) and to SHR(+E) increased by factors of respectively 2.23 ($P = 0.03$) and 4.40 ($P = 0.005$). The products of these factors with their respective rates in previously treated cases from the baseline study were 49.90% total Hr and 24.53% MDR. Combining both new and not new patients before first-line treatment, our 435 failures/relapses showed an overall rate ratio to baseline drug resistance of 0.77 for SM, 6.67 for SH(+E) and 19.62 for SHR(+E). Overall multiplication products were 46% total Hr and 17.65% total MDR.

Considering first-line failures and relapses separately, the rate of Hr was high in both (36.8% in relapses vs. 52.4% in failures). The difference was more pronounced for MDR, with only 4.3% in relapses vs. 19.9% in first-line failure cases.

Resistance rates found in first-line failures/relapses showed a clear decrease over time (Table 2). Hr decreased from 62.1% in 1995/1996 to 30.6% in 1999 ($P < 0.0001$). For MDR these figures were 20.7% and 6.8% ($P = 0.016$). The proportion of pan-susceptible cases increased from 13.8% to 56.5% ($P < 0.0001$). Considering only the period after the change of the re-treatment regimen indication from 1997 onwards, the trend of pan-susceptible and Hr failures/relapses remained significant ($P = 0.0002$ and $P = 0.003$), but the trend of MDR among these failed to reach significance ($P = 0.31$).

During this period, drug resistance among the failures/relapses of the re-treatment regimen did not show any trend, fluctuating around an average of 16.7% Hr and 55.0% MDR in relapses, and 7.3% Hr and 86.9% MDR in failures (data not shown).

Ten first-line relapse and seven failure cases had also been examined by DST before treatment (detailed data not shown). Of these 17 pairs, except for some variations in resistance to EMB, 16 had the same pattern both before and after treatment: 10 were Hr, four were MDR, and two were sensitive to INH and RMP. One strain was borderline resistant to INH before and fully resistant after first-line treatment. No cases of acquired RMP resistance were found.

Mean regularity and supervision of treatment for all failures/relapses of the 1995/1996/1997 cohorts were also studied (detailed data not shown). The difference in mean regularity between the 8710 successfully treated cases and the original first-line treatment of 140 relapses was not significant, but it just reached significance for the 192 failure cases. Mean regularity was 97.6% in the intensive and 95.7% in the continuation phase for cured or completed cases without registered relapse during the next 1–4 years (mean follow-up 714 days, median 668). For the original treatment of relapses, mean regularity was 96.5% in the intensive ($P = 0.15$) and 95.7% in the continuation phase. For failures, these figures were 96.6% ($P = 0.03$) and 94.6% ($P = 0.04$), respectively. Compared to those who were definitively cured, relapsing cases did not show a significantly lower proportion of regular cases. However, in the intensive phase the failure group had only 87.0% highly (>90%) regular patients vs. 91.7% for those who were successfully treated ($P = 0.02$), while in the continuation phase this was 75.5% vs. 82.6% ($P = 0.01$). The average number of supervised doses was not significantly lower (16.8 for cured/completed, 16.9 for relapsed and 17.3 for failures), nor were there fewer intensively supervised cases with these adverse outcomes.

The numbers of first-line failures recorded, and the Hr and MDR among them, were compared to expected numbers derived from the rates reported from clinical trials, as shown in Table 3. According to Mitchison and Nunn, the failure rates of the first-line regimen used in Bangladesh and tested in BMRC trials in East Africa were 0.3% among fully susceptible and 14% among initially H- or HS-resistant cases.[4] This corresponds closely to our own Bangladesh data for pre-existing Hr. The estimated rate of failure among initially MDR cases was set at 50%, based on our own results using either first- or second-line treatment (data not shown).

Table 2 Trend of acquired resistance patterns by year

	First-line failures + relapses combined				
Resistance profile	1995–1996	1997	1998	1999	Total
Sensitive	13.8%	29.2%	44.8%	56.5%	39.1%
Hr (not MDR)	62.1%	52.1%	41.9%	30.6%	44.4%
MDR	20.7%	12.5%	10.5%	6.8%	11.7%
No. of strains studied	87	96	105	147	435

Hr = resistance to isoniazid (only or with other drugs but not with rifampicin); MDR = multidrug resistance (resistance to at least isoniazid and rifampicin).

Table 3 Drug resistance observed in failure cases of first-line treatment: cohorts 1995–1997, comparison of observed and expected numbers

	Rates applied	Total cohort treated by first-line treatment 1995 to 1997
New cases treated with first-line treatment		10 001
'Not new' cases treated with first-line treatment		1 153
Hr present among new cases, MDR excluded (baseline survey rate)	5.6%	560
Hr present among 'not new' cases, MDR excluded (baseline survey rate)	22.36%	258
Total Hr cases in the cohort		818
MDR among new cases (baseline survey rate)	0.64%	64
MDR among 'not new' cases (baseline survey rate)	5.58%	64
Total MDR cases in the cohort		128
Failures of first-line treatment expected because of Hr (refs. 7 and 8 and own data)	14%	114 (a)
Failures of first-line treatment expected because of MDR (own data)	50%	64 (b)
Failures of first-line treatment registered from 1995 to 1997		285
Hr (MDR excluded) among registered failures, applying rates found in present study	53%	151 (c)
MDR among registered failures, applying rates found in present study	20%	58 (d)
Excess Hr failures (= c − a)		37
Excess Hr failures as % cohort		0.33%
Excess MDR failures (= d − b)		−6
Excess MDR failures as % cohort		−0.06%

MDR = multidrug resistance (resistance to at least H and R); Hr = resistance to INH (only or with other drugs but not with R).

For the 1995, 1996 and 1997 cohorts combined, 10 001 new and 1153 not new cases were treated with 2EHRZ/6HT. Applying the rates for new (5.60% Hr, 0.64% MDR) and not new (22.36% Hr and 5.58% MDR) cases from our baseline survey, there should have been 818 Hr and 128 MDR cases among them. An excess of 37 Hr failures was observed compared to those calculated (n = 151 vs. 114), corresponding to 0.33% of the 3-year treatment cohort. For MDR the excess calculation returned a negative value of six cases (n = 58 observed vs. 64 expected), or 0.06% of the cohort.

Figure 1 shows the evolution in registration of types of cases (n = 19 042) from the start of the Damien Foundation's TB control activities. Figure 2 shows the corresponding estimates for registration of Hr and MDR cases. Especially obvious is the fast decline of non-NTP re-treatment cases (mostly from the private sector), from 35% to less than 7% of total registrations. Re-treatment after NTP treatment remained at an almost constant level, and is about 3% at present. Both because of this shift and because of the decreasing proportion of resistant first-line failures/relapses, the calculated decrease of Hr cases was almost linear, from 13.2% to 7.6% after more than 5 years of functioning. MDR seemed to have remained stable at 2.4% to 2.9%, decreasing to 1.4% of all cases only after more than 5 years.

DISCUSSION

The BMRC clinical trials have shown that virtually no ADR is created by the 8-month regimen 2SHRZ/6HT,[4] later extensively used in IUATLD programmes and thus often called the 'IUATLD regimen', and that relapses retained their original (usually sensitive) susceptibility pattern. This has at times been over-simplified, with all short-course chemotherapy relapses being considered as pan-susceptible. Unpublished continuous monitoring in the Tanzanian NTP (Martin Chonde, personal communication, Arusha 1998) as well as a recent survey in Benin[10] indicate continuing low levels of PDR and virtually no MDR after long-term use of the regimen. Used with intensive DOT, the IUATLD regimen seemed not to cause an increase in drug resistance rates in new cases in Karonga District (Malawi), where in previously treated patients INH resistance fell from 44% to 10% in about 12 years,[11] although repeat post-treatment DST revealed the emergence of Hr in 9/47 failure/relapse cases. Unfortunately, several reversions to INH susceptibility cast some doubt on the interpretation of the Karonga report.

In South Africa, INH resistance rates dropped over 25 years of supervised use of 6-month (E)HRZ throughout, from 14% to 9.5% in new cases, and from 54% to 15% in previously treated cases.[12]

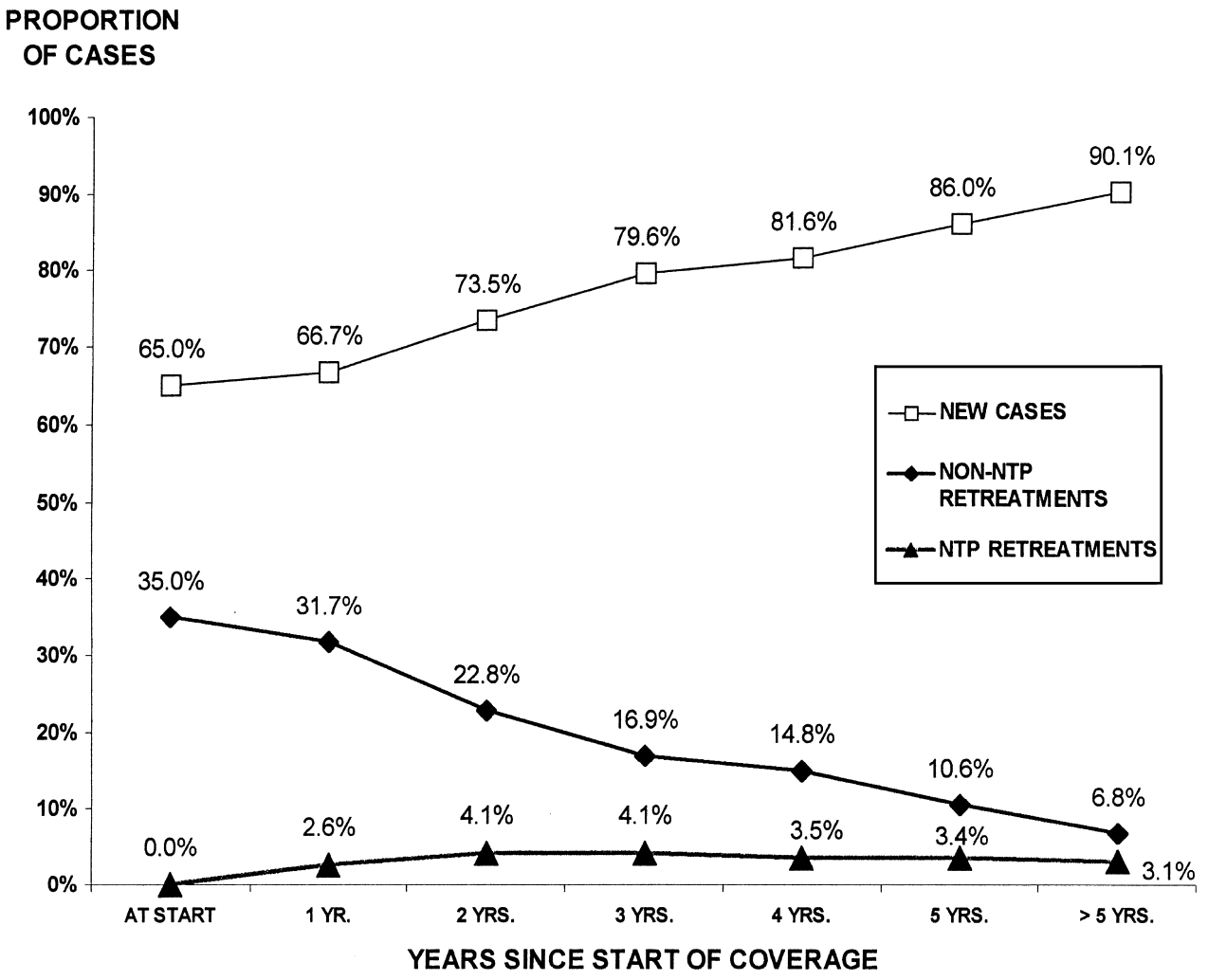

Figure 1 Evolution in type of cases presenting for treatment by year of coverage under the NTP. Only smear-positive pulmonary TB cases have been included. Registrations have been regrouped according to the number of years since the NTP started in a particular thana (diagnostic and treatment centre). NTP = National Tuberculosis Programme.

Decreases in drug resistance in both new and previously treated cases under a well-organised NTP, or after introduction of DOT, has also been reported from Korea, Algeria and the USA.[13–15] In contrast, chaotic treatment in the state of Gujarat (India) caused an increase of drug resistance in previously treated cases: resistance to INH rose from 34.5% to 55.8%, and that to RMP from 2.8% to 37.3% in only 6 years.[16]

Thanks to the virtual absence of human immunodeficiency virus (HIV) infection, the Bangladesh NTP was able to continue to use the IUATLD regimen without many difficulties. However, although cure rates approached 85%, DST of failures/relapses showed alarming levels of resistance. Of note were the changes in resistance to SM, although it was not being used at all in NTP treatment regimens (EHRZ/HT). Although drug resistance to SM only did not change significantly compared to baseline study levels (only 1% decrease), we did observe a highly significant and disproportionate increase in resistance to S+H and S+H+R (eight to 12 times, and five to eight times the SM only drop, Table 1). We hypothesise that a major part of the resistance observed is not ADR on top of pre-existing SM resistance, but PDR carried on throughout treatment, a phenomenon that has already been reported earlier.[17] Frieden and colleagues have also found some pre-existing resistance in 60% of resistant, previously treated cases.[18] Starting from moderately high PDR levels, the far higher rates of failure/relapse among initial Hr compared to sensitive cases[4,9] would logically result in such an accumulation of resistance in this group. Applying the ratios of SH(E) and SHR(E) resistance patterns to baseline total Hr and total MDR, all resistance observed in 'new before first-line treatment' failures/relapses could be explained. In the 'not new before treatment' group about 16% of observed Hr could not be explained as a concentrated residue, but all MDR was accounted for. Overall, our interpretation

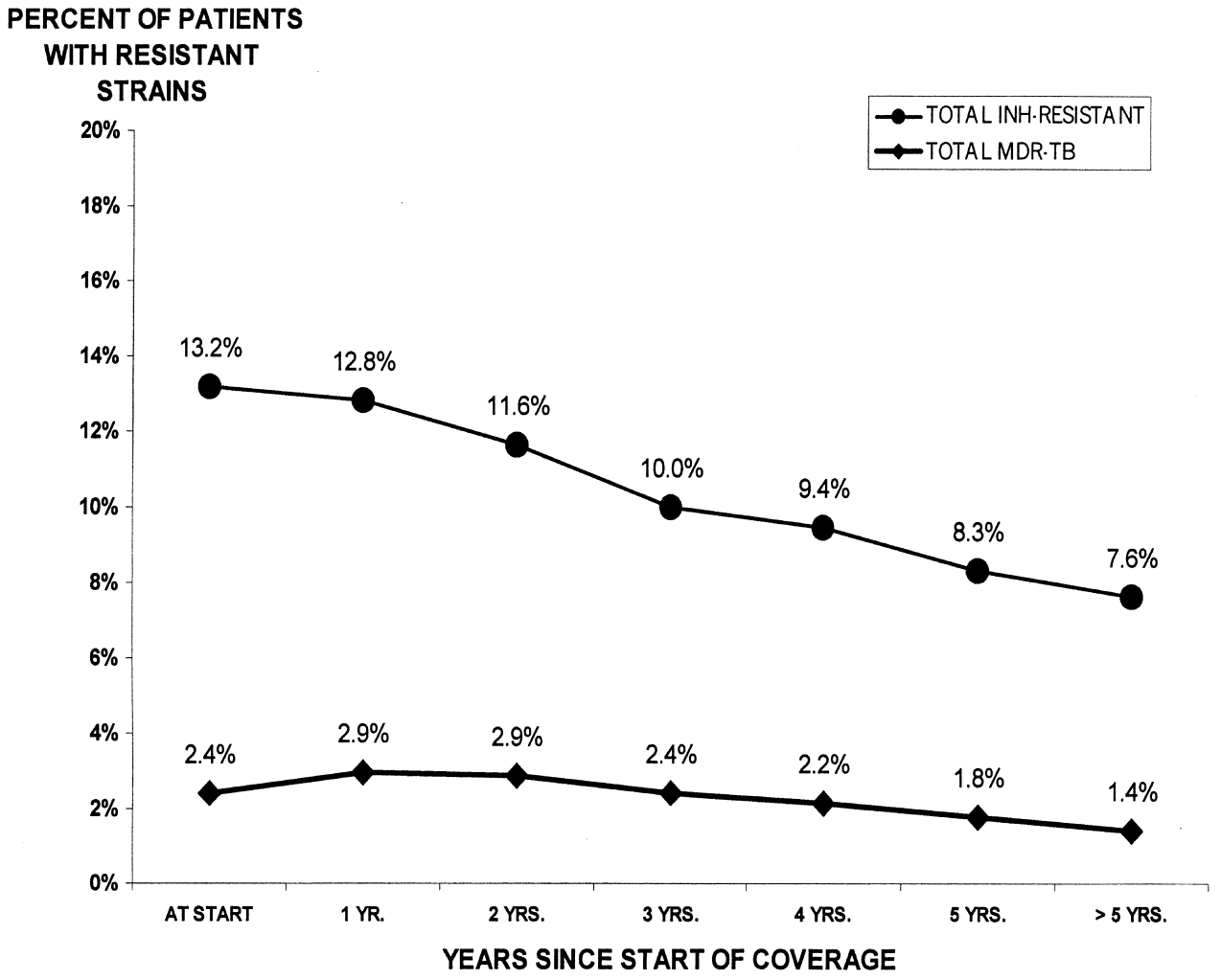

Figure 2 Evolution of combined drug resistance in cases presenting for treatment, by year of coverage under the NTP. 'Patients with resistant strains' refers to all patients, new as well as previously treated cases. Registrations have been regrouped according to the number of years since the NTP started in a particular thana (diagnostic and treatment centre). INH = isoniazid; MDR-TB = multidrug-resistant TB; NTP = National Tuberculosis Programme.

came very close to justifying the drug resistance rates observed (Table 1, last column, upper and lower part).

These calculations were made without taking into account the confidence intervals of the rates, but repeat DST before and after 2EHRZ/6HT provided additional support for our residue hypothesis. Of the 17 pairs available, only one strain had changed from borderline to fully Hr, and no other evidence of acquired resistance to INH or RMP could be found.

Thus, as they are a mixture of ADR and transmitted PDR in unknown proportions, the rates of drug resistance among failures/relapses do not readily allow conclusions to be drawn on programme performance. However, tabulating drug resistance rates by year showed clear trends, with a significant increase in susceptible isolates, and a decrease in both Hr and MDR cases. We interpret this as the effect of a decreasing pool of existing resistant cases, in the absence of significant rates of true acquired resistance.

We also looked for indications of ADR by calculating expected numbers of resistant failures. The calculated estimates could justify all MDR observed among failure cases as pre-existing, but not all Hr. However, the excess was less than 1% of the cohort treated.

Pre-existing drug resistance thus seems to explain more than half of our failures/relapses during the first years of the programme, contrary to the general belief that they are mainly due to poor treatment practices.[3] Comparing the regularity of drug collection and the numbers of supervised doses among these patients with those of definitively cured cases, only small differences could be found. The average number of doses taken as DOT, as well as the proportion of high frequency DOT patients, were equal or possibly better among failures/relapses. However, in areas of quite low PDR (which contributes little to drug resistance in those who have been treated previously), and/or areas with very poor case management, a bet-

ter correlation of regularity and DOT with failures/relapses, and possibly more true ADR, might well be found.

Extrapolating rates and trends in drug resistance to our complete registration data, the proportion of total Hr patients registered has declined almost linearly (Figures 1 and 2), while the MDR rates have remained constant for most of the period, with a decrease after 5 years only. With better case-management under the NTP, the rates of cases to be retreated decline and drug resistance becomes more concentrated in the group of NTP re-treatments. However, in this model PDR cases constitute an ever-increasing proportion of the total resistant load. Deviations from the 1995 baseline PDR rates that were used throughout might have accelerated or counteracted the estimated trend.

CONCLUSIONS

The term ADR is not readily applicable to first-line treatment failures/relapses, as most of their drug resistance may be transmitted PDR. The proportion will depend on epidemiological (rates of PDR) as well as operational parameters. For instance, a first-line regimen with RMP throughout should not lead to a concentration of Hr but one mainly of MDR, while careless application might lead to more susceptible cases, but possibly also to more real ADR. Hence interpretation of a one-time value remains very difficult.

Provided average case management is reasonably good, pre-existing drug resistance may thus be the single most important cause of failure and relapse in areas where PDR rates are not low, i.e., at the beginning of a well-organised NTP. Contrary to earlier recommendations,[19] it would be imperative to prescribe a re-treatment regimen for all such cases.

The 2EHRZ/6HT regimen was found to cause almost as little true ADR under routine conditions in the field as has been shown in clinical trials. Nowadays, lack of funding is considered the only good reason for not replacing this regimen by others containing RMP throughout,[20] or replacing Th by EMB. However, avoidance of creation of drug resistance has not been sufficiently proven under field conditions. In a few published cases,[21,22] DOT regimens with intermittent RMP throughout have led to frequent acquisition of Hr and MDR, while the Ivory Coast now has a rate of 5.3% primary MDR after 10 years of 2HRZ/4HR.[23] It might be wiser not to sacrifice the sturdiness of a daily regimen in order to gain more potential, but hardly a guarantee, for the application of DOT. And the virtual absence of resistance to RMP or EMB only in our failures/relapses was felt to counterbalance the very rare Th-related deaths that occurred, by fully preserving the potential of the re-treatment regimen.

Drug resistance studies will always require a considerable additional effort. Routine follow-up of drug resistance rates in re-treatment cases may be the easiest and fastest way to evaluate the effects of a tuberculosis control programme, besides occasionally being useful for clinical purposes. The lower and more continuous workload is definitely to the advantage of the few laboratories that can perform DST. Trends of (combined) resistance can be distinguished more quickly, even with relatively small sample sizes, as rates are much higher in previously treated than in new cases. Repeat random drug resistance surveys are much more difficult to perform and are more likely to suffer from flaws, such as incorrect history-taking and poor representativeness. The occasional PDR survey may then serve to provide point-prevalence rates of drug resistance. Sampling NTP re-treatment cases does not provide direct information on many patients detected outside the NTP. However, if an important number of patients are poorly cared for, such as in the private sector, some are bound to present again to the NTP, while others will cause a rise in national PDR rates. Follow-up of drug resistance in relapse/failure cases may thus give a fair idea of the effectiveness of treatment practices as well as of coverage under the NTP.

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RÉSUMÉ

CADRE : Un programme de lutte antituberculeuse connaissant les taux de base de résistance à l'égard des médicaments et utilisant le schéma 2EHRZ/6TH dans le traitement des nouveaux cas.

OBJECTIF : Estimer le degré de résistance médicamenteuse créé par ce programme.

SCHÉMA : On a comparé les taux de résistance dans les cas d'échec et de rechute après traitement par 2EHRZ/6TH aux valeurs de base et on a suivi les profils de résistance d'isolats répétés. Les nombres d'échecs résistants observés ont été comparés aux nombres attendus en raison d'une résistance préexistante. On a extrapolé les tendances de résistance dans les nouveaux cas et dans les retraitements combinés.

RÉSULTATS : On a observé des taux très élevés de résistance médicamenteuse, mais les modifications dans la résistance à la streptomycine, l'absence virtuelle de résistance acquise documentée et la superposition étroite des échecs observés et des échecs attendus indiquent tous que le mécanisme principal est l'accumulation des résistances primaires aux médicaments. La résistance dans les cas de rechute ou d'échec a une tendance significativement régressive et la décroissance estimée de la résistance combinée aux médicaments est rapide.

CONCLUSIONS : La résistance à l'égard des médicaments dans les cas traités antérieurement semble résulter d'une résistance primaire transmise plutôt que d'une véritable résistance acquise. Une enquête unique peut donc entraîner des confusions, mais des tests de routine permanents peuvent constituer la meilleure méthode de suivi de la résistance médicamenteuse. Les cas traités antérieurement par chimiothérapie de courte durée peuvent présenter une résistance aux médicaments beaucoup plus souvent que l'on ne le croit généralement et devraient tous bénéficier d'un régime de retraitement. Le régime 2EHRZ/6TH s'est avéré très sûr dans les conditions du terrain, n'entraînant aucune «amplification» vers une multirésistance et pratiquement aucune résistance acquise à l'égard de l'isoniazide. La mise en ouvre de ce régime en association avec un régime standardisé de retraitement a semblé réduire rapidement les niveaux de résistance à l'isoniazide et ceux de multirésistance, bienqu'il n'y ait pas eu d'application stricte d'un traitement directement observé.

RESUMEN

MARCO DE REFERENCIA : Un programa de control de la tuberculosis que dispone de datos sobre las tasas básicas de drogo-resistencia y que utiliza 2EHRZ/6TH en el tratamiento de los casos nuevos.

OBJETIVO : Estimar la extensión de la drogo-resistencia creada por el programa.

MÉTODO : Las tasas de resistencia en los casos de fracasos y recaídas con 2EHRZ/6TH se compararon con las tasas iniciales, y se controlaron los perfiles de resistencia de las cepas repetidas. Se comparó el número de fracasos con resistencia con el número esperado, de acuerdo con la resistencia pre-existente. Se extrapolaron las tendencias a la resistencia en los casos nuevos y en los retratados.

RESULTADOS : Se observaron altas tasas de drogo-resistencia. Pero los cambios en la resistencia a la estreptomicina, la ausencia virtual de resistencia adquirida documentada y una íntima coincidencia entre las resistencias observadas y esperadas en los fracasos, todo esto indicó que la acumulación de resistencia primaria fue el mecanismo principal. La resistencia en los casos de recaída/fracaso mostró una tendencia significativamente declinante, y la resistencia combinada estimada descendió rápidamente.

CONCLUSIONES : La drogo-resistencia en los casos previamente tratados parece consistir más en una resistencia primaria transmitida que en una verdadera resistencia adquirida. Un control único se presta a confusión, pero los tests rutinarios continuos constituyen el mejor método para controlar la resistencia. Los casos previamente tratados con quimioterapia de corta duración pueden presentar drogo-resistencia mucho más frecuentemente que lo que generalmente se piensa y deben recibir todos un esquema de retratamiento. El esquema 2EHRZ/6TH demostró ser muy seguro en el trabajo de terreno, no produjo 'amplificación' hacia la multi-resistencia y casi ninguna resistencia adquirida a la isoniacida. La implementación de este esquema junto con un estándar de retratamiento parece reducir rápidamente la resistencia a la isoniacida y a la multi-resistencia, a pesar de que no se haya aplicado un esquema de tratamiento directamente observado estricto.