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Drug resistance monitoring: combined rates may be the best indicator of programme performance

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SUMMARY

SETTING: Greater Mymensingh District, Bangladesh.

OBJECTIVES: To determine changes in prevalence of drug resistance of *Mycobacterium tuberculosis* under DOTS.

DESIGN: Drug susceptibility testing of systematic samples of *M. tuberculosis* isolated from all sputum smear-positive cases newly registered in sentinel centres during 1995 and 2001. Continuous monitoring of retreatment registrations and resistance of strains from relapse and failure cases.

RESULTS: Of 942 strains from the new cases in 2001, 10.8% showed resistance to any drug, 6.2% to isoniazid, 0.4% to rifampicin (all of them multidrug-resistant, MDR), 7.1% to streptomycin, and 1.0% to ethambutol. Corresponding rates for 99 strains from previously treated cases were 32%, 20%, 3%, 20% and 2%, respectively. Although most rates of resistance had decreased since 1995, increased streptomycin resistance was the only significant change when new and previously treated cases were considered separately. However, combined resistance for any drug, isoniazid, rifampicin and MDR had decreased significantly.

CONCLUSION: As suggested by monitoring of resistance in failure and relapse cases and by routine programme reports, drug resistance had decreased. Combined resistance demonstrated changes between periodic surveys better than its subgroups, and may be a more reliable and comprehensive indicator. However, continuous monitoring of the pool of resistant retreatment cases is a more efficient strategy.

KEY WORDS: *Mycobacterium tuberculosis*; drug susceptibility; surveillance; Bangladesh

NATIONAL Tuberculosis Programmes (NTP) have been advised to follow the evolution of drug resistance with periodic surveys about every 5 years.[1] Surveys should target a random, representative sample of new cases of sufficient size to obtain fairly accurate estimates. Little importance is given to previously treated cases. The guidelines fail to give indications concerning those methods and sample size calculation most appropriate to distinguish trends.

Damien Foundation (DF), a non-governmental organisation, has attempted to follow drug resistance in its Bangladesh project. Details concerning DF, the Bangladesh NTP and its treatment policies were published in an earlier report of the first drug resistance survey.[2] Briefly, the first survey was done at the start of the DOTS programme, and covered all five clinics existing at the time. Expansion continued, culminating in 49 clinics covering the Greater Mymensingh District in 1998. Treatment regimens used for smear-positive cases are those recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD)/World Health Organization (WHO).[3] The 8-month regimen, with ethambutol (E), isoniazid (H), rifampicin (R) and pyrazinamide in the intensive phase and isoniazid/thioacetazone in the continuation phase, is used for new patients (Category 1). In addition to the above four intensive-phase drugs, the retreatment regimen also has streptomycin (S) in the first 2 months of a 3-month intensive phase, and thrice weekly EHR for 5 months in the continuation phase (Category 2). Since 1997, about 25 cases of proven multidrug-resistant tuberculosis (MDR-TB, defined as resistance to at least H and R) have been treated and rendered non-infectious annually, with few exceptions. The quality of control work was good from the start, and has been improving ever since. Case detection is higher in this district than anywhere else in Bangladesh, and treatment results now approach 90% cure rate for new and 85% for retreatment cases.

The present study aimed to document the effect of the NTP on TB drug resistance rates in the project

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area by means of a repeat survey 6 years after the start of these activities. In parallel, resistance of strains isolated from failures and relapses after the NTP regimens was monitored continuously from the first survey. The results of this monitoring have been partially reported elsewhere.[4]

MATERIALS AND METHODS

The same five diagnostic centres that had served for patient intake in the previous survey were used. Patient enrolment was systematic, and one sputum sample from every newly registered smear-positive case (SM+, threshold 10 acid-fast bacilli per 100 high power fields) was cultured. New and retreatment (or previously treated) patients had to be included. Classification followed standard WHO/IUATLD definitions.[3] Patients were classified as new or retreatment by history-taking, scrutinising of old prescriptions and showing samples of the drugs. All patients with strains resistant to any drug tested, and an equal number of randomly chosen patients with pan-susceptible strains, were re-interviewed upon receipt of results, and reclassified whenever indicated. An attempt was made to subdivide retreatments into relapses, failures and defaulters/irregulars.

Because of changed relative caseloads (due to decentralisation), sampling periods were adjusted to reach almost equal contributions per centre, as in 1995. Thus, while intake was in principle defined as a systematic sample of patients registered over a 12-month period, it was extended to 18 months in one of the centres. No patient was sampled twice for the same treatment episode.

Sputum samples were sent in 5 ml 1% cetylpyridinium chloride to the Institute of Tropical Medicine, Antwerp, Belgium, and processed according to standard methods: decontamination with NaOH according to Petroff,[5] with a contact time shortened to 10 min, and culture and drug susceptibility testing (DST) on Löwenstein-Jensen according to the proportion method of Canetti et al.[6] Antimicrobials tested were H, R, E, S and para-amino salicylic acid. Strains resistant to the latter drug and those with unusual features were subjected to biochemical identification tests. Tests were done directly from concentrated sputum specimens, and were repeated from the control tubes whenever DST showed too few or too many colonies on the control slopes.

From 1995 through 2002, all DF centres were requested to send sputum samples from relapse and failure cases after they had completed NTP treatment. These were processed in the Antwerp laboratory using the same methods, but with indirect DST on primary isolates.

Data were entered and analysed in Epi Info. Fisher's exact test was used for comparison of proportions, Student's *t*-test for comparison of the means, and χ^2 to test for trends.

RESULTS

Enrolment for the repeat survey was almost complete. Only 18 (1.5%) eligible patients were lacking. Except for one clinic, the proportional contribution by participating clinics was very close to that of the 1995 survey (Table 1).

A total of 1199 sputum samples were cultured. Of these, 129 (11%) remained culture-negative, 20 (1.7%) were contaminated, three (0.3%) grew *Mycobacterium avium-intracellulare* complex and 1047 (87%) *M. tuberculosis*. Six *M. tuberculosis* strains had to be excluded due to contamination of the DST, leaving 1041 DST results. These belonged to 764 (73.3%) male and 277 female patients, 942 (90.5%) of them new cases. Of 99 previously treated patients, 51 had not been treated under the NTP (48 defaulters/irregularly treated and three relapses), and 48 were NTP retreatments (30 relapses, 12 defaulters and six failures).

Table 2 shows DST results by patient and resistance type. Among strains from new patients, 840 (89.2%) were susceptible to all four drugs, while 58 (6.2%) showed overall resistance to H, four (0.4%) to R, nine (1.0%) to E and 67 (7.1%) to S. There were also four MDR strains (0.4%). Half of the non-MDR H-resistant strains were mono-resistant, while all but one of the other strains in this group showed resistance to S as well. Rates among strains from previously treated cases were 68.7% pan-susceptible, overall resistance to H 20.2%, to R 3.0%, to E 2.0%, and to S 20.2%. All R-resistant strains were MDR. Of non-NTP retreatment strains, 76% were pan-susceptible and four (8%) were resistant to H. Sixty per cent of isolates from cases previously treated under the NTP were pan-susceptible, 16 (33%) were resistant to H, and three (6%) were MDR (data not shown).

An analysis of the age distribution of new study patients revealed a shift towards higher ages, from a median/mean of 35/37 years in 1995 to 37/40 years in 2001 (data not shown). However, a more pronounced shift occurred in cases harbouring resistant strains,

Table 1 Frequency distribution of drug susceptibility tests by diagnostic centre; comparison between the 1995 and 2001 surveys

Centre	1995 *n* (%)	2001 *n* (%)
A	98 (15.2)	155 (14.9)
B	140 (21.7)	208 (20.0)
C	91 (14.1)	195 (18.7)
D	205 (31.8)	301 (28.9)
E	111 (17.2)	182 (17.5)
Total	645	1041

Table 2 Drug susceptibility profiles of the 2001 survey strains, by patient classification or combined for all study strains

Resistance pattern	Previously untreated cases *n* (%)	Previously treated cases *n* (%)	Combined resistance *n* (%)
Total cases	942	99	1041
Sensitive to all drugs	840 (89.2)	68 (68.7)	908 (87.2)
Any resistance	102 (10.8)	31 (31.3)	133 (12.8)
Monoresistance	73 (7.7)	20 (20.2)	93 (8.9)
H	29 (3.1)	9 (9.1)	38 (3.7)
R	0	0	0
E	3 (0.3)	1 (1.0)	4 (0.4)
S	41 (4.4)	10 (10.1)	51 (4.9)
H+R resistance (MDR)	4 (0.4)	3 (3.0)	7 (0.7)
HR	0	1 (1.0)	1 (0.1)
HRS	0	1 (1.0)	1 (0.1)
HRE	2 (0.2)	0	2 (0.2)
HRES	2 (0.2)	1 (1.0)	3 (0.3)
H + other resistance	25 (2.7)	8 (8.1)	33 (3.2)
HS	23 (2.4)	8 (8.1)	31 (3.0)
HE	1 (0.1)	0	1 (0.1)
HES	1 (0.1)	0	1 (0.1)
R + other resistance	0	0	0
RS	0	0	0
RE	0	0	0
RES	0	0	0
Other resistance	0	0	0
ES	0	0	0
Total resistant to			
H	58 (6.2)	20 (20.2)	78 (7.5)
R	4 (0.4)	3 (3.0)	7 (0.7)
E	9 (1.0)	2 (2.0)	11 (1.1)
S	67 (7.1)	20 (20.2)	87 (8.4)

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug-resistant.

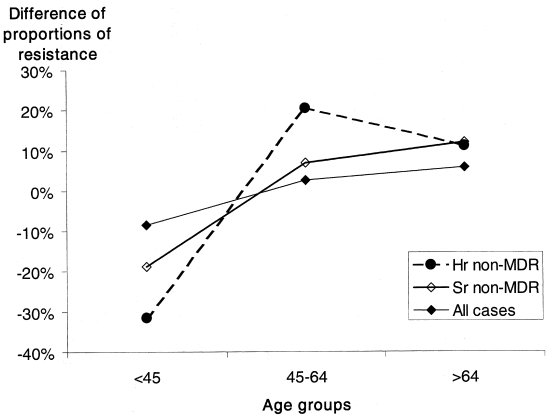

Figure 1 Difference of age distribution between 2001 and 1995 surveys, for total new cases versus such cases harbouring strains with any resistance to isoniazid (H) or to streptomycin (S), MDR excluded. Percentages shown represent the age distribution differences obtained by subtracting the 1995 from 2001 distribution. Hr non-MDR = all resistance to isoniazid except MDR; Sr non-MDR = all resistance to streptomycin except MDR. MDR = multidrug resistance.

from a median/mean of 35/34 years in 1995 to 40/43 years in 2001. Figure 1 shows this shift towards higher age for the main resistance groups (any resistance to H or S, MDR excluded), compared to the overall age-shift. The differences of the means between 1995 and 2001 were significant ($P < 0.01$) for both total and drug-resistant new patients.

Table 3 and Figure 2 show the evolution of selected resistance patterns between 1995 and 2001. Because of subsequent corrections, some of the 1995 figures differ slightly from those in our earlier report.[2] Among strains from new cases, total drug resistance increased from 8.8% to 10.8%, while H resistance decreased from 6.6% to 6.2%, resistance to R from 1.1% to 0.4% and MDR from 0.7% to 0.4%. S resistance increased from 3.3% to 7.1%. Considering previously treated cases, the total proportion of strains with any resistance did not change (31.6% vs. 31.3%), but H resistance decreased from 28.9% to 20.2%, R resistance from 7.9% to 3.0% and MDR from 6.8% to 3.0%. S resistance increased from 8.4% to 20.2%. For both groups of patients, only the S resistance changes attained statistical significance ($P < 0.01$). However, combined resistance significantly decreased for resistance to H (from 13.2% to 7.5%, $P < 0.001$), resistance to R (3.1% to 0.7%, $P < 0.001$) and MDR (2.5% to 0.7%, $P = 0.002$).

The evolution of resistance from 1995/1996 to 2002 among relapse and failure cases of NTP treatments from the whole project area is shown in Figure 3 (Category 1) and Figure 4 (Category 2). From 1997 onwards, samples from 80–90% of all registered failures and relapses were collected (details not shown), yielding 100–200 Category 1 and 50–80 Category 2 DST results annually. Among such retreatment cases after Category 1, the proportion with susceptible *M. tuberculosis* increased steadily from 14% to 62%, while non-MDR H resistance decreased from 62% to 28% and MDR from 21% to 5% (χ^2 for trend of MDR <0.001, and for susceptible and non-MDR H-resistant strains <0.000001). The evolution was fast in the first years, but has recently levelled off. After Category 2, susceptible isolates increased from 7% to 16%, non-MDR H resistance fluctuated around 10%, while MDR decreased from 80–90% in the first years to a constant level of around 70%.

DISCUSSION

Few experiences of monitoring resistance trends in NTPs have been reported, most from middle-income countries.[7–10] Periodic surveys have shown trends linked to programme performance mainly after prolonged periods, and more clearly for retreatment cases. In Hong Kong, continuous systematic enrolment of all cases enabled the demonstration of a significant decline of resistance in new and retreatment cases, thanks to the large numbers enrolled. For low-income countries, it has usually not been possible to demonstrate significant trends.[11–14] Moreover, some

Table 3 Evolution of drug susceptibility from 1995 to 2001, by patient classification or combined for all study strains

	Previously untreated cases		Previously treated cases		Combined resistance	
Resistance pattern	1995 *n* (%)	2001 *n* (%)	1995 *n* (%)	2001 *n* (%)	1995 *n* (%)	2001 *n* (%)
Total cases	455	942	190	99	645	1041
Any resistance	40 (8.8)	102 (10.8)	60 (31.6)	31 (31.3)	100 (15.5)	133 (12.8)
Mono-resistance	30 (7)	73 (7.7)	36 (19.0)	20 (20.2)	66 (10.0)	93 (8.9)
H	20 (4.4)	29 (3.1)	32 (16.8)	9 (9.1)	52 (8.1)	38 (3.7)
R	2 (0.4)	0	1 (0.5)	0	3 (0.5)	0
E	0	3 (0.3)	1 (0.5)	1 (1.0)	1 (0.2)	4 (0.4)
S	8 (1.8)	41 (4.4)	2 (1.1)	10 (10.1)	10 (1.6)	51 (4.9)
H+R resistance (MDR)	3 (0.7)	4 (0.4)	13 (6.8)	3 (3.0)	16 (2.5)	7 (0.7)
HR	3 (0.7)	0	6 (3.2)	1 (1.0)	9 (1.4)	1 (0.1)
H + other resistance	7 (1.5)	25 (2.7)	10 (5.3)	8 (8.1)	17 (2.6)	33 (3.2)
HS	6 (1.3)	23 (2.4)	8 (4.2)	8 (8.1)	14 (2.2)	31 (3.0)
Total resistant to						
H	30 (6.6)	58 (6.2)	55 (28.9)	20 (20.2)	85 (13.2)	78 (7.5)
R	5 (1.1)	4 (0.4)	15 (7.9)	3 (3.0)	20 (3.1)	7 (0.7)
E	1 (0.2)	9 (1.0)	7 (3.7)	2 (2.0)	8 (1.2)	11 (1.1)
S	15 (3.3)	67 (7.1)	16 (8.4)	20 (20.2)	31 (4.8)	87 (8.4)

H = isoniazid; R = rifampicin; E = ethambutol; S = streptomycin; MDR = multidrug-resistant.

of the trends have been confusing: the last global report for Peru showed a significant increase in drug resistance among new cases, but a significant decrease in previously treated cases.[14]

Several frequent sources of error have been described.[15] These tend to conceal trends, especially in new cases, because of their generally low rates and slowly occurring changes. Errors of patient classification tend to add previously treated resistant cases to the non-treated, which may lead to gross over-estimation of resistance rates. Serious bias may also result from non-random sampling, or from cluster sampling if resistance is unevenly spread. In particular, urban areas or referral centres may contribute differing proportions of cases in subsequent surveys. Finally, DST has its margin of error, varying from laboratory to laboratory and over time, so that results obtained by different laboratories or in different years will vary slightly. DST quality assurance has been organised globally by the WHO and the IUATLD, starting from a top level of Supra-National Reference Laboratories (SRL).[16]

Our objective was to demonstrate significant trends as proof of the apparent efficiency of the control

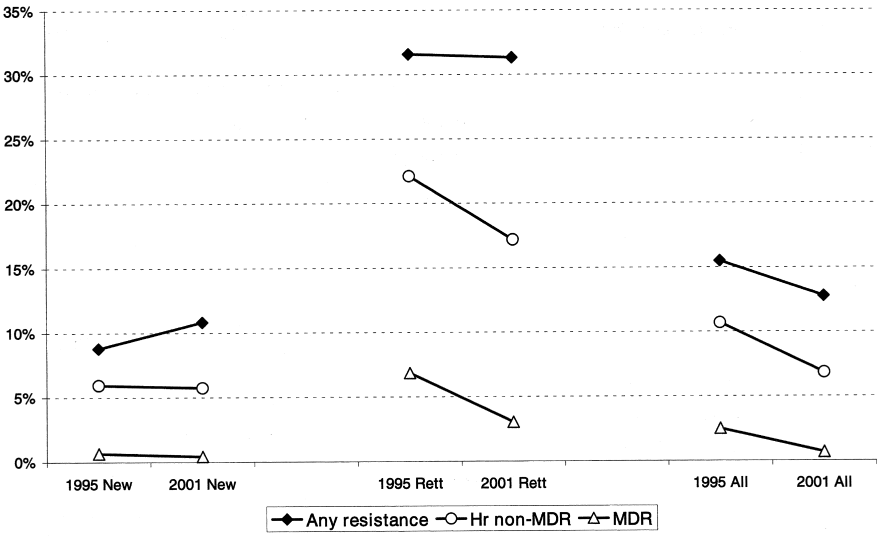

Figure 2 Evolution of drug resistance between 1995 and 2001, comparing new, previously treated and all survey cases together. Hr non-MDR = all resistance to isoniazid (H) except MDR; 1995 New, 2001 New = resistance levels for new cases of 1995 and 2001; 1995 Rett, 2001 Rett = resistance levels for previously treated cases of 1995 and 2001; 1995 All, 2001 All = combined resistance levels for both new and previously treated cases of 1995 and 2001.

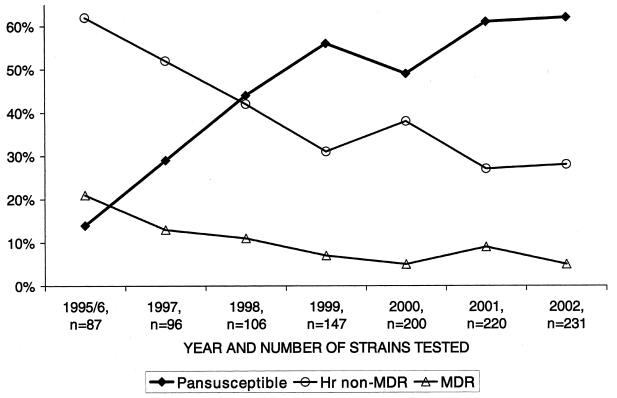

Figure 3 Evolution of percentage drug-resistant strains isolated from failure and relapse cases after Category 1 treatment, 1995 to 2002. Hr non-MDR = all resistance to isoniazid (H) except MDR.

project, but not primarily to obtain information representative for the area or for Bangladesh. We therefore deliberately opted for a sentinel population, systematically sampling a full year's cohort from exactly the same five centres as during the previous survey, and adjusting the sampling period to the changed proportional enrolment from these centres. All new registrations were enrolled, including previously treated cases, as we wanted to study the evolution of drug resistance in both groups. Moreover, it was felt that this is operationally the best system. Enrolment criteria can be kept very simple, and, more importantly, comparison of rates between both groups of patients allows the reliability of history-taking and classification to be estimated. This was attempted by re-interviewing all new cases found to have resistant strains, which resulted in only one change of classification from untreated to treated. Finally, the same SRL performed DST as in 1995, using essentially the same methods.

Despite all these precautions and the intake of a high number of new cases, changes in drug resistance rates in this group were non-significant, with the exception of the increase in streptomycin resistance. The latter was so high compared to the decline of resistance to R, MDR and possibly H, that it resulted in a (non-significant) increase of resistance to any drug. In the previously treated group, overall resistance remained at the same level and the decrease of resistance to H and R was pronounced, but because of the low number of cases only the increase in S resistance was significant. However, combined rates of resistance for previously treated and untreated cases together did indeed confirm what had been deduced from case detection and treatment outcome data, i.e., rates of resistance to any drug, to H, R and MDR had declined significantly.

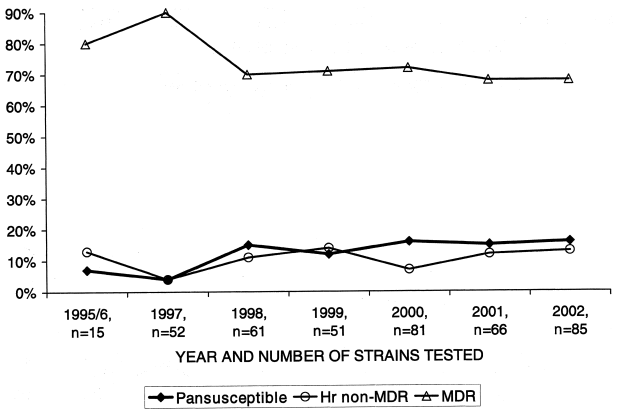

Figure 4 Evolution of percentage drug-resistant strains isolated from failure and relapse cases after Category 2 treatment, 1995 to 2002. Hr non-MDR = all resistance to isoniazid (H) except MDR.

To show significant trends, combined resistance may thus be the preferred indicator for drug resistance surveillance. Provided that proportionate sampling of both types of cases is achieved, combined rates eliminate one important source of bias, i.e. erroneous classification. Finally, the proportion of retreatment cases registered reflects not only the effectiveness of the NTP treatments, but overall NTP coverage or efficiency as well. A possible negative effect of other services, such as the private sector, will cause an afflux of partially treated cases to the public services.

Proportional sampling of new and previously treated cases does not present a problem with any of the recommended sampling schemes, be it systematic, random or cluster-based. But a mixture of systematic sampling of previously treated patients with another sampling method for new cases, as proposed in the drug resistance surveillance guidelines,[1] obviously does. If sampling of previously treated cases is extended beyond that of new cases, combined resistance must be evaluated on the part of the sample obtained during the period when all cases were included. A separate analysis of the total sample of previously treated cases will then serve to obtain more precise rates within this group, or to establish trends from continuous sampling of NTP retreatment cases.[4]

Streptomycin was not used in Category 1 treatments. The doubling to tripling rates of resistance to S could thus not be acquired, but were partly explained by changes in laboratory performance. Whereas the results of the SRL DST quality assurance rounds had shown a somewhat reduced sensitivity for S resistance around the time of the first survey, this changed to a slight lack of specificity later on. Considerably more resistance to S would thus be declared during the second survey. Both parameters reached 100% for H and R during both survey periods. Repeat indirect tests have shown that the direct tests were not responsible for this difference (data not shown), but other factors, such as a change of culture tubes and caps, may have played a role. As in many poor countries, streptomycin is widely used in Bangladesh for a range

of diseases other than TB, but this may be an unlikely alternative explanation for the pronounced rise in S resistance. A similar increase in S resistance with simultaneous reductions in rates for H and R, despite the fact that S was no longer in use for primary treatment, has been reported in South Africa.[8] Considering the widespread use of S in weak regimens in the past, one might wonder if increasing resistance to S, together with decreasing resistance to H and to R, represents a pattern accompanying disappearing drug resistance together with reduced transmission. Support for this hypothesis was found from the age-specific analysis of our cases. While the average and median age increased slightly between the two surveys, possibly indicating the effect of TB control activities on transmission, the increase was much more marked among resistant cases. While the age-shift with H resistance was most pronounced from the young to the middle-aged, the shift was towards old age with S resistance.

We reported earlier that continuous DST of failures and relapses after a first course of NTP treatment may be the most efficient method of monitoring drug resistance.[4] The spread of the workload is better, records for classification of cases are available, and the sample represents a concentration of primary drug resistance at high levels that show significant changes more readily. Moreover, a deterioration of the situation due to added true acquired resistance must by definition become apparent earlier than among new cases. The evolution of resistance determined in our two surveys was found to correlate well with what had been extrapolated from continuous monitoring of failures and relapses. The initial rapid decrease among the latter was followed by a slower decrease or levelling off. However, resistance among previously treated cases should be evaluated as the pool it represents in the population, which may become smaller while rates remain stable or may even rise. This is also why combined resistance in our surveys showed a significant favourable evolution, although each group considered separately did not. On top of the decrease in most rates, the proportion of retreatments among new registrations dropped from almost 30% (virtually all from outside the NTP) to less than 10% (of whom only half were from outside). Others have shown that more refined monitoring of drug resistance requires insight into the pool of cases remaining, sometimes from a long time previously.[17] The favourable overall evolution provides support for our hypothesis, meant to explain the far higher drug resistance rates among isolates from cases previously treated by the NTP compared to those from cases coming from outside the NTP.[3] This is consistent with a mechanism of selection of pre-existing drug resistance through adequate treatment, not with resistance acquired during treatment.

Figure 5 shows the evolution of selected key indicators from registration and treatment outcome reports in our resistance surveillance sentinel centres, compared to the results from all other DF centres covered for at least 3 years (own data, not shown).

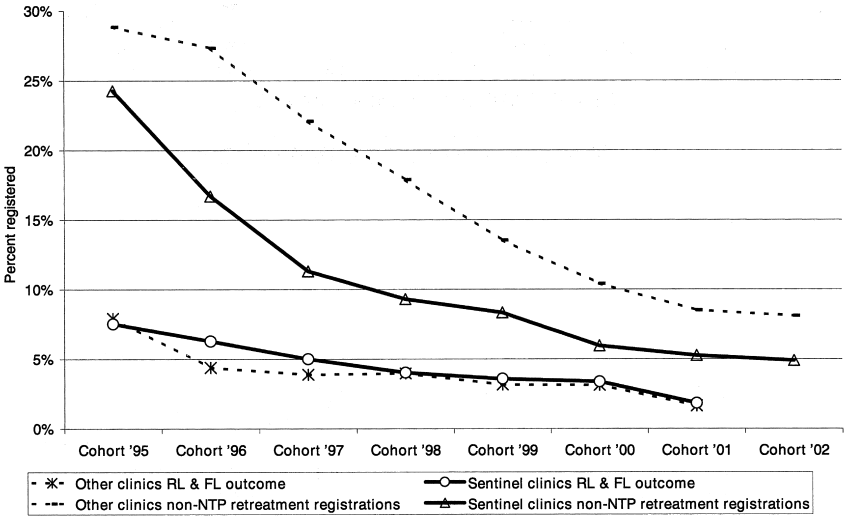

Figure 5 Smear-positive cases registered and treated by Category 1 or 2. Evolution of selected registration and treatment outcome indicators of cohorts registered from 1995 to 2002, comparing drug resistance surveillance sentinel centres to all other centres. RL & FL outcome = per cent of relapses (RL) registered within up to 3 years out of total cases cured, plus per cent failure (FL) outcome on total cohort treated; Non-NTP retreatment registrations = all cases registered as previously treated, but not under the NTP regimen; Sentinel clinics = the five clinics used for sampling during the drug resistance surveys of 1995 and 2001; Other clinics = all other Damien Foundation clinics started before 1999. NTP = National Tuberculosis Programme.

Considering all smear-positive cases treated by Category 1 or 2, cohort-wise failures plus early relapses (passively registered within up to 3 years) have been at almost exactly the same level since 1998. As to extent of coverage, over the last years the proportion of registrations of retreatment after (partial) treatment outside the NTP runs a closely parallel course in sentinel and other centres. The larger differences in earlier years were caused by gradual expansion of coverage. The closely similar favourable evolution of both registration and treatment outcome parameters suggests that drug resistance in the whole DF-covered population is declining rapidly.

Considering the workload and expense of the surveys, it will be difficult to justify repeating the exercise after another 5 years, if routine indicators continue to be favourable. This includes high cure rates, but also a low proportion of retreatment cases registered, indicating the dwindling influence of the private sector as well as more effective NTP treatment. However, we intend to continue systematic DST of recurrences after NTP treatments as a more efficient monitoring system, especially because this also yields clinically useful information for ongoing MDR-TB treatment.

CONCLUSIONS

Six years after the start of an efficient DOTS programme, with free treatment and high cure rates attracting patients from the private sector, the pool of drug resistance in the DF-covered area in Bangladesh had decreased significantly. For periodic survey data, trends of drug resistance prevalence are best evaluated by considering levels for new and previously treated cases combined, on a sample obtained simultaneously for both. However, continuous monitoring of drug resistance among NTP retreatment cases may be a more efficient surveillance strategy, especially if treatment for MDR-TB can be offered.

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References

1 World Health Organization, International Union Against Tuberculosis and Lung Disease. Guidelines for surveillance of drug resistance in tuberculosis. WHO/TB/96.216: 1–35. Geneva, Switzerland: WHO, 1996.
2 Van Deun A, Aung K J M, Chowdhury S, et al. Drug susceptibility of *Mycobacterium tuberculosis* in a rural area of Bangladesh and its relevance to the national treatment regimens. Int J Tuberc Lung Dis 1999; 3: 143–148.
3 WHO, IUATLD, KNCV. Revised international definitions in tuberculosis control: comments from the Aral Sea Area tuberculosis programme. In reply (Correspondence). Int J Tuberc Lung Dis 2001; 5: 1072.
4 Van Deun A, Hamid Salim A, Rigouts L, Rahman M, Fissette K, Portaels F. Evaluation of tuberculosis control by periodic or routine susceptibility testing in previously treated cases. Int J Tuberc Lung Dis 2001; 5: 329–338.
5 Petroff S A. A new and rapid method for the isolation and cultivation of tubercle bacilli directly from the sputum and feces. J Exp Med 1915; 21: 38–42.
6 Canetti G, Fox W, Khomenko A, Mitchison D A, Rist N, Smelev N A. Advances in techniques of testing mycobacterial drug sensitivity, and the use of sensitivity tests in tuberculosis control programmes. Bull World Health Organ 1969; 41: 21–43.
7 Boulahbal F, Khaled S, Tazir M. The interest of follow-up of resistance of the tubercle bacillus in the evaluation of a programme. Bull Int Union Tuberc Lung Dis 1989; 64(3): 23–25.
8 Weyer K, Kleeberg H H. Primary and acquired drug resistance in adult black patients with tuberculosis in South Africa: results of a continuous national drug surveillance programme involvement. Tubercle Lung Dis 1992; 73: 106–112.
9 Kim S J, Bai G H, Hong Y P. Drug-resistant tuberculosis in Korea, 1994. Int J Tuberc Lung Dis 1997; 1: 302–308.
10 Kam K M, Yip C W. Surveillance of *Mycobacterium tuberculosis* drug resistance in Hong Kong, 1986–1999, after the implementation of directly observed treatment. Int J Tuberc Lung Dis 2001; 5: 815–823.
11 Warndorff D K, Yates M, Ngwira B, et al. Trends in antituberculosis drug resistance in Karonga District, Malawi, 1986–1998. Int J Tuberc Lung Dis 2000; 4: 752–757.
12 Paramasivan C N, Venkataraman P, Chandrasekaran V, Bhat S, Narayanan P R. Surveillance of drug resistance in tuberculosis in two districts of South India. Int J Tuberc Lung Dis 2002; 6: 479–484.
13 Zhang L X, Kan G Q, Tu D H, Li J S, Liu X X. Trend of initial drug resistance of tubercle bacilli isolated from new patients with pulmonary tuberculosis and its correlation with the tuberculosis programme in Beijing. Tubercle Lung Dis 1995; 76: 100–103.
14 Espinal M A, Laszlo A, Simonsen L, et al. Global trends in resistance to antituberculosis drugs. N Engl J Med 2001; 344: 1294–1303.
15 Chaulet P, Boulahbal F, Grosset J. Surveillance of drug resistance for tuberculosis control: why and how? (Leading article). Tubercle Lung Dis 1995; 76: 487–492.
16 Laszlo A, Rahman M, Espinal M, Raviglione M. Quality assurance programme for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Reference Laboratory Network: five rounds of proficiency testing, 1994–1998. Int J Tuberc Lung Dis 2002; 6: 748–756.
17 Hong Y P, Kim S J, Bai J Y, Lew W J, Lee E G. Twenty-year trend of chronic excretors of tubercle bacilli based on the nationwide tuberculosis prevalence surveys in Korea, 1975–1995. Int J Tuberc Lung Dis 2000; 4: 911–919.

RÉSUMÉ

CONTEXTE : Le District du Grand Mymensingh, Bengladesh.
OBJECTIFS : Déterminer les modifications de prévalence de la résistance de *Mycobacterium tuberculosis* aux médicaments sous DOTS.
SCHÉMA : Détermination de la sensibilité aux médicaments d'échantillons systématisés de *M. tuberculosis* isolés à partir de tous les cas à bacilloscopie positive des expectorations en registrés dans des centres-sentinelle au cours de 1995 et de 2001. Suivi continue des enregistrements des retraitements et la résistance des souches provenant des rechutes et des échecs.
RÉSULTATS : Sur 942 souches provenant des nouveaux patients enrôlés en 2001, 10,8% étaient résistantes à n'importe quel médicament, 6,2% à l'isoniazide, 0,4% à la rifampicine (tous multirésistants, MR), 7,1% à la streptomycine et 1,0% à l'éthambutol. Les taux correspondants pour 99 souches provenant de cas traités antérieurement ont été respectivement de 32%, 20%, 3%, 20% et 2%. Bien que la plupart des taux de résistance aient diminué depuis 1995, les seules modifications significatives quand on considère séparément les cas neufs et ceux traités antérieurement concernent une augmentation de la résistance à la streptomycine. Toutefois, la résistance combinée a diminué de manière significative à la fois pour n'importe quel médicament, pour l'isoniazide, pour la rifampicine et pour la MR.
CONCLUSION : Comme suggéré à partir du suivi de la résistance dans les cas d'échec et de rechute ainsi qu'à partir des déclarations de routine des programmes, la résistance aux médicaments a diminué. Une résistance combinée s'est avérée démontrer les modifications entre les enquêtes périodiques de façon plus valable que ne le faisaient ses sous-groupes, et pourrait être plus fiable et plus complète. Toutefois, un suivi continu du réservoir des cas de retraitement résistants est une stratégie plus efficiente.

RESUMEN

CONTEXTO : Distrito de Greater Mymensingh, Bangladesh.
OBJETIVO : Determinar los cambios en la prevalencia de la fármaco-resistencia de *Mycobacterium tuberculosis* con DOTS.
DISEÑO : Realización de tests de sensibilidad a los medicamentos en muestras sistemáticas de *M. tuberculosis* aislado a partir de todos los casos con baciloscopia positiva recientemente registrados en centros centinelas durante 1995 y en 2001. Control de manera continuada de los registros de retratamientos y la resistencia de las cepas provenientes de casos de recaídas y fracasos.
RESULTADOS : De 942 cepas provenientes de casos nuevos enrolados en 2001, el 10,8% mostraba una resistencia a algún medicamento, el 6,2% a la isoniacida, el 0,4% a la rifampicina (todos ellos con multirresistencia, MDR), el 7,1 a la estreptomicina y el 1,0% al etambutol. Las tasas correspondientes para 99 cepas provenientes de casos previamente tratados eran 32%, 20%, 3%, 20% y 2%, respectivamente. Aunque la mayoría de las tasas habían disminuido desde 1995, el único cambio significativo, cuando se consideran separadamente los casos nuevos y los tratados previamente, se refiere a un aumento de la resistencia a la estreptomicina. Sin embargo, la resistencia para cualquier medicamento, para la isoniacida, la rifampicina y la MDR había disminuido significativamente.
CONCLUSIÓN : Como se había demostrado, a partir del seguimiento de la resistencia en los casos de fracaso y de recaída, así como de los informes rutinarios del programa, la resistencia a los medicamentos había disminuido. Se constató que el estudio de la resistencia combinada demuestra mejor los cambios entre las encuestas periódicas, comparado con los subgrupos ; además es más fiable y completo. Sin embargo, el seguimiento continuo del pool de casos resistentes de retratamiento es una estrategia más eficaz.