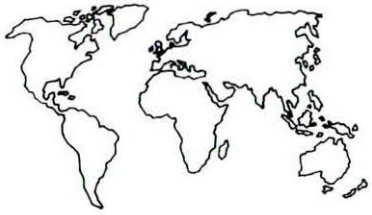

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Tubercle and Lung Disease

Editorial

Chemotherapy of tuberculosis under program conditions

With special relevance to India

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Tuberculosis, once a life-threatening disease, is now a curable one, thanks to powerful drugs and, more importantly, the development of highly useful regimens. Many of these contributions, aptly called 'landmarks'[1] have provided sufficient armamentarium in our hands to achieve complete (100%) success in controlling this disease. Equally important is the National Tuberculosis Program (NTP), which has demonstrated practical utility in many developing countries. Many classical clinical investigations and the NTP have their origin in India, a country to which the world owes a great deal in this domain, as Grzybowski has suggested.[2]

A series of epidemiological studies have indicated that there has been a slight reduction in the prevalence of tuberculosis in India as a consequence of chemotherapy and NTP activities.[3,4] The reduction is, however, only gradual and limited, and is perhaps influenced by local situations. The incidence of primary drug resistance (PDR), the 'epidemiological yard stick' indicated by Canetti,[5] also shows a reduction. For instance in Madras, a study by Krishnaswami & Rahim[6] showed PDR rates to be slightly lower than the figures obtained 10 years before by the author[7] from that center using the same techniques and source of patient populations. More recent studies[8] conducted in other regions have also indicated reductions in PDR rates.

However, some authorities suggest that if a certain amount of failure is to be anticipated and only marginal effort is to be expected, as has been seen in India, the use of costly regimens should be questioned.[4,9] While such a philosophy may have some realistic basis, one may wonder whether such a defeatist attitude is justified with today's therapeutic armamentarium provided by the short course chemotherapy (SCC) regimen, which could achieve nearly 100% clinical outcome. With the use of SCC and drugs like rifampin, no one need suffer from tuberculosis, much less die of it. Delivery of about 50 doses of drugs under a well-organized SCC program should yield the expected maximum results. Several studies completed, even under program conditions in developing countries, have in fact proved this.[10–15] Some of these[14,15] were done in India with the guidance and collaboration of the Tuberculosis Research Center (TRC). Thus the belief that one should get poorer results in program (field) conditions in comparison to the ideal control clinical study settings, may not be so with powerful SCC regimens. This may be valid with less effective regimens, as was shown extensively by Frimodt-Moller and by the studies done by the National Tuberculosis Institute (NTI).

In just such a situation, delivering a blow to the hope of achieving success with SCC regimens and in support of suggestions made by Chakraborty,[4,9] a recent study[16] from India by the TRC demonstrated utter failure of SCC in a District Tuberculosis Program. An SCC regimen consisting of rifampin 450 mg, isoniazid 600 mg and pyrazinamide 2 gm given twice weekly *under supervision* for 2 months, followed by rifampin 450 mg and isoniazid 600 mg twice a week for the next 4 months, *all doses given under supervision*, gave an outcome of high mortality, persistent sputum positivity and a high degree of acquired drug resistance. As Grzybowski[2] indicated, 'the way this study was conducted and the results obtained, constitute an unmitigated disaster'. Only about 40% of patients took more than 80% of their treatment, and a slightly larger proportion took less than 50%. More than a quarter of patients died and another quarter were persistently positive bacteriologically, with a high degree of resistance to isoniazid (60–80%) and rifampin (12%). Overall, the outcome of this study gave results which are much lower than the most pessimistic estimates anywhere in the world and are very similar to those seen in the pre-chemotherapy era.

In discussing their results, the authors[16] mention that

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no special measures beyond letter posting, a routine defaulter action recommended by the NTP, were adopted. It is not clear how efficiently this letter posting was done and what its outcome was; nor was it discussed what alternative measures were adopted besides verification of the addresses.[17] Blaming non-compliance as the chief reason for the appalling results in their study, they hoped that they could have achieved much better results in comparison to several other field studies from developing countries reported in the literature.[10–15]

Non-compliance on the part of the patient in taking the prescribed drugs for the prescribed period is a classic problem and has received extensive attention in the literature (see the excellent reviews by Fox).[18,19] The TRC authors[16] also followed suit and were ready to blame patients' non-compliance as the main reason for the failure of their study. On the other hand, it is difficult to appreciate the role of compliance in a situation where all drugs were administered 'under supervision'. In fact the only recourse of 'supervision' in this study was the treatment card!

Since the findings of this study,[16] monitored by the TRC which has an extensive 'track-record of clinical trials', might influence the thinking and implementation of tuberculosis programs in India and perhaps in other developing countries, a closer scrutiny of the findings and projections is warranted.

In this analysis, besides the patient, whom the authors first blame for his non-compliance, other key factors should be considered. Certainly the patient plays an important role. A non-compliant patient is a danger not only to himself but also to the community because of the spread of drug-resistant bacilli. While earlier literature[18,19] has given some common reasons, chief among them being indolence, more recent experience gives slightly different perspectives. The reasons for non-compliance are vastly different between patients from developed and developing countries. In the developed countries, the most common reasons are drug abuse, alcoholism, homelessness and lack of civic responsibility.[20] Even though the TRC group[16] has suggested following the US experience,[20,21] the problems that are faced in India will be very different.

In developing countries, although indolence may play a role, the most common reasons are economic, and prioritization of the patients' own needs. Most patients are poor and many are daily wage earners and cannot forego a day's wages, nor afford to travel with their meager financial resources to the clinic to get their treatment.[22] On the other hand, given that a good proportion of the patients are conscious of their disease and would like to be cured, and that the treatment can be taken to places convenient to them (residence or work), it should not be difficult to achieve success.

With SCC one needs to give about 50 doses twice a week. If the health authorities deliver the pills to the patients, most will swallow them in their presence. Such treatment achieved success in a well organized system in Bohemia.[23] In this study, intermittent chemotherapy was delivered to the patient either in his place of residence, place of work or other convenient place at scheduled intervals and maximum efficiency was reached. Such a system can be organized in any part of the world. Some authorities[24] have questioned that such an approach could only be feasible in urban or semi-urban communities but not in rural areas, mainly due to transport and access problems. Now such fears need not be deterring factors because of the enormous global improvement in communications; in many developing countries, particularly India, even the remotest villages have been connected by road and by other communications including television. In such situations, it should not be impossible for a committed health worker to visit patients twice a week by manual or motorized bicycle or scooter, distribute the drugs and see that the patients swallow the pills in his presence. As a practice, the patient should be asked to talk a few words (like the 'name, number and rank' expression used in the army, to make sure that the pills are swallowed), lest they spit them out, as has been shown in field experience in Assam.[25]

Even the most remote villages in any part of the country could be covered, although there may be some areas which are difficult to reach; such places will be very small in number and with very few patients to cater to. Several years ago, Bignal[26] expressed such optimism: 'To control tuberculosis in, for instance, the vastness of deserts, the depths of Amazonian jungle or the remote foot-hills of the Himalayas is a formidable task. But those who live in such places are only a tiny fraction of the total world population.' Even then, attempts can be made to get the patients to the nearest major village or township where the treatment can be administered twice weekly. Again, one need not be tired of stressing that with a system with fool-proof, honest, conscientious effort, success can be achieved.

The second important point to be considered in the analysis of the recent study[16] is the quality, stability and proper and timely supply of the drugs. Many of these aspects are poorly respected in the mass application of chemotherapy in many countries, and particularly in India. Quite often, the purchasing authorities bid for the cheapest source and not all drugs are procured at the same time. If they are imported, a prolonged stay in a hot and humid environment before clearance by customs, due to bureaucratic red tape, will influence the stability of the drugs. Many of these points have been reported in tuberculosis conferences in India and have been discussed by Fox,[27] Chaulet[28] and myself.[29]

By far the most important point in the success of chemotherapy of tuberculosis is the implementation of supervision, which is not necessarily confined to the patient, but to the whole hierarchy of the health distribution personnel, from the directors, doctors, nurses and pharmacists to the field workers. If each person is doing his or her duty properly and conscientiously, success is inevitable. In other words, supervision is not only to see that the patients take the drugs, which is the ultimate purpose, but the quality control of everybody's responsibility by the proper authorities, strictly implemented and enforced at every stage. While many reports show idealistic regimens in operation, in actual practice they can fail to achieve good results unless properly and honestly conducted.

As one example, a urine test which was found to be useful[30] was reported to be giving many false-positive results and therefore branded as utterly useless under field conditions.[31] When the basic data of the study were analyzed, it was recognized that about 50% of the participating centers did not even collect any urine specimen, and in others the collected specimens were not tested.[32] The technicians were bold enough to mark the results in the work book without even looking at the samples! Such examples, many of which might not be seen in technical literature or aired in conferences, will perhaps explain that even the best method of treatment or procedure will not give the expected results unless properly conducted and supervised.

The necessity of thorough supervision and motivation on the part of all health personnel in carrying out their duties according to the protocol was underlined several years ago by Rouillon,[33] who stated that: 'the default of the patient was a minor matter in comparison with that of the people responsible for the public relations aspect and delivery of the services'. More recently, Chaulet,[34] in attempting to identify those responsible for non-compliance in developing countries, stated: 'non-compliance with antituberculosis chemotherapy is less often due to the patient's failure to comply with treatment than to other factors. These factors are not abstract entities or forced and uncontrollable situations; these are people, men and women, who are not doing the jobs to which they have been assigned and for which they are paid'. Most of these important aspects of non-compliance on the part of the health delivery system officials have been totally ignored or concealed in many cases due to bureaucratic and governmental controls. In connection with this, it is worth referring to an example given by philosophers in India: 'While we point our forefinger of complaint at somebody, let us realize that three fingers point towards us!' In the present context, when we blame the patient, let us realize that we, the health delivery personnel, are to be blamed to a greater extent. As Sbarbaro[35] said in a brilliant editorial, instead of blaming the patients, 'physicians and health professionals heal and correct themselves'.

Besides the irresponsibility on the part of the health delivery machinery, other serious reasons which contribute to the failure of treatment in many developing countries are the dishonest and illegal practices in drug distribution at various levels. Even though the drugs are supposed to be delivered to the patients, in many cases they may not reach them, but will only find their way via the black market or to selfish profit-making individuals. It would not be an exaggeration to suspect that in some cases, similar to the unfortunate experience with the urine tests cited earlier, the drugs might not have been procured; only the records will log entries of purchase and distribution to the patient. For instance, in the study from the TRC,[16] the only evidence of drug consumption was the treatment card. Several years ago, Bignal[26] and Chaulet[34] expressed similar concerns, but these have not been seriously considered by tuberculosis treatment officials. Such malpractice is more likely to occur with SCC regimens involving costly drugs such as rifampin and pyrazinamide, rather than the inexpensive drugs such as isoniazid and thiacetazone. On these grounds, one can add further support to Chakraborty's[4,9] claim that in a potentially ineffectent system of drug distribution and drug consumption, a cheaper regimen will be less tempting to those involved in malpractice. Maybe some of the depot-type drug delivery systems[36,37] involving only one or two administrations may offer some hope in the future.

To sum up, one can easily hope that with a committed team, we can take the treatment to the patient, even in the remotest part of the country, and see that they swallow the pills in our presence. What we need are sincerity, commitment and a good supply of drugs. After all, making this work for 50 doses on twice weekly administration is not an impossible task. By doing so, we can prove that tuberculosis is really a curable disease. On the other hand, if these problems are not solved we cannot achieve success, even if some super drugs are introduced tomorrow.

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4-, 5- and 6-month regimens containing isoniazid, rifampicin, pyrazinamide and streptomycin for treatment of pulmonary tuberculosis under program conditions in Hong Kong

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SUMMARY. ***Setting:*** **Ten full time urban government chest clinics in Hong Kong.**
Objective: **To assess the effectiveness of 4-, 5- and 6-month fully supervised thrice-weekly regimens containing 4 months of isoniazid, rifampicin, pyrazinamide and streptomycin followed by nil, 1 or 2 months of isoniazid and rifampicin for the treatment of smear-negative culture-negative, smear-negative culture-positive and smear-positive pulmonary tuberculosis.**
Design: **Retrospective study of the 3 antituberculosis treatment regimens given under program conditions during a 6-month period in 1983.**
Results: **Of the 1616 patients assessed, 953 (59%) completed their treatment strictly as planned, 443 (27%) had their treatment prolonged, 107 (7%) had their treatment modified and 113 (7%) defaulted or did not complete their treatment as planned. There were 2 treatment failures at the end of chemotherapy. At 60 months of follow-up, 67 patients died, 2 from the sequelae of tuberculosis. Of 1287 patients assessable up to 60 months, a total of 47 (3.7%) patients relapsed and were eventually treated successfully. 11 (20%) relapses occurred among the 55 patients who had defaulted and did not complete treatment as planned.**
Conclusion: **The effectiveness of the 3 treatment regimens depended very much on the patient's adherence to treatment. The necessity of prolongation of treatment is not known and requires further assessment.**

RÉSUMÉ. ***Cadre:*** **Dix dispensaires thoraciques urbains gouvernementaux, à plein temps, à Hong Kong.**
Objet: **Evaluer l'efficacité de régimes hautement surveillés, administrés trois fois par semaine pendant une durée de 4, 5 et 6 mois respectivement, consistant en 4 mois de isoniazide, rifampicine, pyrazinamide et streptomycine, suivis d'arret, 1 ou 2 mois de isoniazide et rifampicine, pour le traitement d'une tuberculose pulmonaire frottis négatif et culture négative, frottis négatif et culture positive, ou frottis positif.**
Schéma: **Etude rétrospective des trois régimes antituberculeux appliqués dans les conditions du programme pendant une période de 6 mois en 1983.**
Résultats: **Des 1616 patients évalués, 953 (59%) ont terminé leur traitement exactement comme prévu, pour 443 (27%) leur traitement a été prolongé, pour 107 (7%) leur traitement a été modifié, et 113 (7%) ont abandonné ou n'ont pas terminé le traitement prévu. Il y a eu deux échecs de traitement à la fin de la chimiothérapie. Après 60 mois de suivi, 67 patients étaient décédés, 2 de séquelles de la tuberculose. Des 1287 patients qu'il a été possible d'évaluer après 60 mois, au total 47 (3,7%) patients ont rechuté et ont été soignés avec succès par la suite. 11 (20%) rechutes sont survenues chez les 55 patients qui avaient abandonné et qui n'avaient donc pas terminé le traitement prévu.**
Conclusion: **L'efficacité des trois régimes de traitement dépendait en effet de l'adhérence des patients à leur traitement. La nécessité de prolonger le traitement n'est pas prouvée et demande une évaluation supplémentaire.**

RESUMEN. ***Marco de referencia:*** **Diez dispensarios urbanos y gubernamentales que trabajan a tiempo completo en enfermedades respiratorias en Hong-Kong.**

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ANTITUBERCULOSIS DRUG RESISTANCE: CAUSES

What is generally understood by drug resistance is that a patient infected with resistant strains of *Mycobacterium tuberculosis* will fail to respond to treatment with the drug concerned. There are more precise and complex laboratory definitions,[1,2] but they are less suitable for the purposes of this paper. Resistance to antituberculosis drugs is the inevitable result of poor management of tuberculosis control.[3] Poor management takes many forms: most commonly, poor supervision of the patient's drug-taking, as well as the prescription of regimens with an insufficient number of drugs to which the patient's organisms are likely to be susceptible, inadequate dose or duration of therapy, and poor drug supplies, such that drugs are taken irregularly. In the past, patients have taken much of the blame for poor compliance,[4] but it is now recognised that tuberculosis services and their staff are not entirely innocent.[5,6] Drug resistance is thought by some to be a measure of medical malpractice. Either way, such deficiencies lead to patients acquiring resistance. If they then transmit the resistant organisms to their contacts, and if those contacts later develop tuberculosis also, then these latter cases are said to have primary resistance.

THE IMPACT OF ANTITUBERCULOSIS DRUG RESISTANCE

Whatever tuberculosis programmes might do to cause drug resistance it is clear that drug resistance can do considerable harm to tuberculosis treatment. Failure of treatment, which is commonly defined as the persistence of positive cultures for *M. tuberculosis* at the end of the treatment period, is more likely to occur if the initial organisms were resistant. Moreover, the more potent the drug, and the more drugs to which an organism is resistant, the greater the chances of treatment failure. Probably the best of the very few studies in this area was conducted by the British Medical Research Council (BMRC) trials in Africa, Hong Kong and Singapore.[7] Of 11 patients with isolates resistant to rifampicin, 9 of whom also had organisms resistant to another drug or drugs, 5 (45%) patients failed on treatment and a further 3 (27%) had a subsequent relapse. On the other hand, resistance to just isoniazid and/or streptomycin led to chemotherapy failure in only 12% of 264 patients.

MULTIDRUG-RESISTANCE

In recent years attention has focused on multidrug-resistant (MDR) strains of *M. tuberculosis*. MDR strains are usually defined as those that are resistant to at least rifampicin and isoniazid, and often to other drugs as well. While occasional MDR strains have been isolated from time to time over the past few decades, it is outbreaks of MDR tuberculosis in the United States which have brought it into the limelight.[8–15] These outbreaks have been characterised by an association with the human immunodeficiency virus (HIV) and by an alarmingly high mortality, often over 80%, despite the availability of a full range of reserve drugs. Widespread occurrence of MDR, especially primary MDR, would constitute a major threat to tuberculosis control, particularly to resource-poor countries, since effective treatment would become impossibly expensive.[16]

However, there are grounds for some optimism. Rates of resistance do not rise inexorably. In Styblo's classic study in Kolin, in the former Czechoslovakia,[17] for example, the introduction of stronger control measures, especially supervision of all patients in hospital, ensured that almost all patients completed their therapy. The prevalence and incidence of resistance declined. Nevertheless, the single most important measure against resistance is to ensure that it does not happen. This is achieved by making certain that all patients complete a full course of adequate treatment.

THE ROLE OF HIV

The impact of HIV on drug resistance is not yet fully understood. The MDR outbreaks in the US suggest that HIV might be associated with antituberculosis drug resistance. HIV-associated tuberculosis in some societies, such as parts of the US[11] and Zaire,[18] is associated with poorer adherence to therapy than in the case of patients with tuberculosis alone, and this could lead to the acquisition of resistance. HIV-infected tuberculosis patients are up to 20 times more likely than HIV-negative patients to have household contacts who are themselves HIV infected[19] and these contacts are particularly susceptible to contracting tuberculosis,[20,21] which would likely be resistant if the source case also had resistant disease. On the other hand, the few studies, in the US,[12,22] Haiti[23] and Africa,[24,25] that have so far measured resistance levels in more representative groups of patients have not found an excess of resistance in the HIV-positive groups.

One can intuitively see that the impact of resistance will depend on the number and efficacy of the drugs available to treat tuberculosis. There are, in current use in the developing world, 6 main drugs for the treatment of tuberculosis: isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S) and thiacetazone (T). The first 3 are the most essential. Streptomycin is given parenterally, and therefore constitutes a risk for HIV and hepatitis B virus transmission in those areas where sterilization of injection equipment cannot be guaranteed. The World Health Organisation (WHO) does not therefore recommend it for use in areas with a high prevalence of HIV infection.[26] However, the risk has never been quantified for tuberculosis control programmes with sufficient supplies and equipment. Furthermore, though, the cost of streptomycin has also increased considerably over the past few years. In addition, HIV infection has been shown greatly to increase the risk of severe, and potentially fatal, cutaneous hypersensitivity reactions in patients treated with thiacetazone.[26–29] It is therefore advised not to use this drug either in individual patients known or suspected to be infected with HIV. The armamentarium available for treating tuberculosis is thus somewhat reduced in high HIV prevalence areas.

Further, there is a possibility that withdrawal of thiacetazone might actually create resistance to more powerful drugs. If the commonly used regimen of 2SHRZ/6TH (an initial phase of 2 months of daily SHRZ, followed by 6 months of a continuation phase of T and H) is altered to 2EHRZ/6EH in some areas, then a proportion (unknown) of those patients with isoniazid resistance will, in effect, receive monotherapy in the continuation phase. Ethambutol resistance is therefore probable in a percentage (unknown) of patients so treated. Since the retreatment regimen recommended by the International Union Against Tuberculosis and Lung Disease (IUATLD)[30] and WHO consists of 2SHRZE/HRZE/5HRE, the continuation phase will again, in effect, be monotherapy, this time with rifampicin. Rifampicin resistance in a proportion (again, unknown) is the likely result. This is the domino theory of resistance. Surveillance will at least help to determine the present unknowns in this scenario.

It is already clear that new, effective, low-cost antituberculosis drugs are urgently needed in the fight against tuberculosis in both developing and industrialized worlds.

SURVEILLANCE FOR ANTITUBERCULOSIS DRUG RESISTANCE

Until recently, few countries in the world, rich or poor, considered it necessary to carry out systematic surveillance for antituberculosis drug resistance. The USA, for example, ceased surveillance in 1986, although it was resumed in 1993. It was generally maintained in some other countries in the industrialized world that the recommended treatment regimens were designed to succeed even in the presence of resistance to one or two of the commonly used drugs; the minority of patients who failed to respond to treatment could be investigated for resistance as the need arose; surveillance was expensive, resources were limited, and, in any case, tuberculosis was disappearing fast. The occurrence of MDR, and the rising incidence of tuberculosis in many Western countries[31–33] due to HIV, immigration and the failure to maintain adequate health services in deprived inner cities, has led to a reexamination of this position.

Likewise, in the developing world, in spite of a general failure to control tuberculosis, surveillance for drug resistance was not an issue until recently. Nevertheless, a number of countries, such as Kenya,[34] Tanzania[35] and Korea,[3] conducted nationwide surveys at 5 or 10 year intervals to assess the extent of their tuberculosis problems. Ongoing surveillance was conducted in Algeria.[36] Representative information on drug resistance was included in each of these surveys. In East Africa, it was clearly not a major problem, with resistance to one or more drugs varying from 7–10% between 1964 and 1984. In Korea, primary resistance to one or more drugs rose to 31% of isolates tested in 1960, but fell to 15% in 1990 with the introduction of improved tuberculosis control. Acquired resistance was as high as 75% in 1980, falling to 47% in 1990. Apart from these 4 studies, which also had their share of methodological problems, the majority of published work has suffered from at least one of 3 major deficiences, making interpretation difficult, if not impossible: selection bias (in favour of patients referred to major hospitals and thus more likely to have resistant disease); failure to distinguish clearly between those patients who had had previous treatment from those who had not; and the use of non-standard or unclear laboratory methods. Our current level of ignorance of the scale and nature of drug resistance in the developing world is therefore profound, although we know that HIV is plentiful, and that MDR exists there (M. Kinyanjui and W. Githui, personal communication).

For those industrialized countries with large tuberculosis burdens among immigrant populations, such as the Netherlands, Switzerland[33] and Canada, information on resistance levels in the countries of origin of their immigrants is essential for proper formulation of domestic treatment policy. The risk of drug resistance in immigrants can be 10 times that of native born patients.[37]

AIMS OF SURVEILLANCE

The potential benefits of suitable surveillance for drug resistance are many. At an international level, surveillance could determine the geographical extent and severity of resistance in given countries or regions, and thus determine the need for major, international changes in treatment policy. Such information would also determine the extent of the need for international research into new chemotherapeutic agents, or new combinations of drugs. At a national level, a surveillance system would provide a useful indicator of tuberculosis control programme performance and assessment of the need for changing current treatment policy, identify districts or health centres in need of support, and determine the risk factors for resistance.

But there are potential disadvantages. By diverting scarce resources to resistance surveillance, the essential tuberculosis control targets of curing 85% of all new smear-positive cases diagnosed and finding 70% of all cases could be jeopardised. However, it is in precisely those countries with poor programme performance that resistance could be predicted. National resources should then, perhaps, focus on achieving the targets, and donor agencies on resistance surveillance.

RECOMMENDATIONS

The Tuberculosis Programme at WHO has developed a strategy which will determine the nature and extent of antituberculosis drug resistance in regions of the developing world. Countries with viable tuberculosis control programmes will be encouraged and assisted to develop their own surveillance systems using guidelines for surveillance drawn up by the Programme, which avoid the defects, mentioned above, of many previous resistance surveys. With the collaboration of the IUATLD, it is intended to establish a network of supra-national reference laboratories to provide the quality control and standardization of susceptibility testing that will be essential for international comparison. At the same time, much needed support will be given to national reference laboratories in developing countries to develop their own capacity for work on drug resistance.

CONCLUSIONS

Antituberculosis drug resistance, and especially multidrug-resistance, constitutes a major threat to tuberculosis control programmes. This danger is amplified by the presence of HIV. Our current state of knowledge about the extent and severity of resistance, especially in the developing world, is woefully inadequate. Surveillance for drug resistance is therefore essential. WHO is taking the initiative, together with the IUATLD, to set up such a system.

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