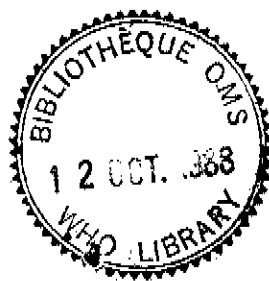




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THE ROLE OF SHORT-COURSE CHEMOTHERAPY IN
NATIONAL TUBERCULOSIS CONTROL PROGRAMMES IN DEVELOPING COUNTRIES¹

by

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¹Paper presented at the Meeting of the Working Group on Short-course Chemotherapy for Tuberculosis, WHO Regional Office for the Western Pacific, 22-26 August 1988.

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NATIONAL TUBERCULOSIS CONTROL PROGRAMMES IN DEVELOPING COUNTRIES¹

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1. Introduction

Forty years ago one of the first tasks of the emerging World Health Organization was to lay down the essentials of a comprehensive tuberculosis control policy. Tuberculosis at that time was one of the major public health problems worldwide, was considered an incurable social disease and was feared just as much as would be, a few years later, cancer and now AIDS. Although effective chemotherapeutic agents against tuberculosis started to appear, it took more than a decade for the drugs to become available more widely. Most patients until the 1950s, who were lucky enough to have had the disease diagnosed and who could afford it, were, as in the past decades, offered isolation in sanatoria, with emphasis on better nutrition, fresh air and rest.

Tuberculosis control became, in fact, a priority problem for WHO before its formal birth in 1948. Out of the nine expert committees on tuberculosis that have been convened so far, for the purpose of elaborating recommendations on technical policy concerning control of the disease, the first two were held prior to the formal establishment of the Expert Committee on Tuberculosis by the First World Health Assembly in June 1948. The first two expert committees were held in July 1947 and February 1948 respectively (1).

The importance and the urgency attached to the tuberculosis problem by WHO can also be seen from the fact that it was during the first fifteen years of the Organization's existence that eight out of nine expert committees on tuberculosis held so far, were convened and the policy on tuberculosis control established. The concept of a comprehensive tuberculosis control programme on a countrywide scale, integrated into existing health infrastructure, i.e. a population-based approach with drug treatment at home instead of traditional clinical, hospital-oriented approach, was formulated. During the last 25 years this policy has only been reviewed critically by the ninth expert committee and several study or scientific groups, has been enlarged upon, but in general reaffirmed as valid. The case-finding and chemotherapy, considered as an entity, has from the beginning been recognized as the most powerful weapon in tuberculosis control. In more recent years short-course chemotherapy regimens of 6 to 9 months duration are gradually being introduced as standard treatment in some control programmes.

2. The tuberculosis problem

In the 1980s, according to official morbidity statistics, in any one year well over a million new cases of tuberculosis are reported. Although this figure represents a considerable case-load for the health services, it is only a fraction of the estimated true number of new cases. Only for Europe, North America and Oceania (where tuberculosis incidence is already rather low) can officially reported morbidity figures be considered reasonably reliable. For Africa, Asia and Latin America, which contain about 75% of the world's population, the reported figures are, with a few exceptions, incomplete and unreliable. In such situations the best single indicator for evaluating the magnitude of tuberculosis and its trend is the annual risk of infection.

The annual risk of infection expresses the attacking force of tuberculosis within the community and, unlike morbidity and mortality notifications, has the advantage of being objective and reliable, since data for its calculation are collected independently of the routine reporting procedures. They are derived from tuberculin surveys of representative population samples, and indicate the proportion of the population which has been infected (or reinfected) with tubercle bacilli in the course of one year.

There appears to be a relatively constant ratio between the annual risk of tuberculosis infection and the annual incidence of smear-positive tuberculosis in developing countries: every 1% of the risk of infection seems to correspond to about 50-60 new smear-positive cases of pulmonary tuberculosis per 100 000 general population (2).

At the end of the 1970s, and in the early 1980s, in Europe, the incidence of smear-positive tuberculosis is calculated to have been around 20 per 100 000; in the United States of America and Canada, 7 per 100 000; and in Oceania, 12 per 100 000. For Africa, an annual risk of infection of between 2% and 3% corresponds to a smear-positive incidence of around 100-150 per 100 000; for Asia (including China), a 2% annual risk of infection on average (possibly too low) corresponds to about 100 per 100 000.

With the total world population at present of 5 000 million and taking into account rather lower values of estimated incidence of tuberculosis related to the annual risk of infection, one can assume that the number of smear-positive cases of pulmonary tuberculosis that develops each year is in the range of 3.5 million to 4.4 million, as presented in Table 1. It is well known, however, that there are countries and areas, particularly in Africa and Asia with the annual risk of infection well above 3% and the number of 4-5 million cases of smear-positive pulmonary tuberculosis developing each year worldwide may not be an overestimate.

The number of new smear-negative cases (especially among children) and of extrapulmonary cases may be of the same order, i.e. another four to five million. The prevalence of cases is at least two times the incidence. It is estimated that between two and three million persons die from tuberculosis each year in the world.

3. The WHO Policy on Tuberculosis Control

The objectives of tuberculosis control can be stated in social and epidemiological terms:

- social: to relieve human suffering by reducing morbidity and mortality caused by tuberculosis;
- epidemiological: to progressively reduce the tuberculosis problem in the community by breaking the chain of transmission of infection.

The current WHO policy on tuberculosis control is based on the concept of a comprehensive national tuberculosis programme (NTP) implemented on a country-wide scale through the network of existing general health service institutions and primary health care. This concept was formulated for the first time in the Eighth Report of the Expert Committee on Tuberculosis in 1964 (3) and after critical review ten years later, reaffirmed and enlarged, by giving more technical and operational details, in the Ninth Report of the Expert Committee on Tuberculosis (4).

It was stated that the control of tuberculosis deserves a high priority on the list of rewarding health programmes, since reliable diagnostic tools and efficacious preventive and curative methods are available and they can be both simple and inexpensive. An effective NTP can be delivered under any situation, provided planning and application are guided by a clear understanding of the epidemiological, technical, operational, economic and social aspects.

TABLE 1 - NUMBER OF SMEAR-POSITIVE PULMONARY TUBERCULOSIS CASES DEVELOPING EACH YEAR - GLOBAL ESTIMATES

Region area	Level of risk of infection	Population at risk in millions	Estimated incidence per 100,000 (average)	Estimated number of cases per year
1. Developed countries - Europe, Australia, USA, Canada, etc.	<0.5%	1 200	10-15	120 000 - 180 000
2. Latin America Eastern Mediterranean selected African countries	0.5-1.5%	850	50-80	425 000 - 680 000
3. Most of Asian countries	1 - 3%	2 500	100-120	2 500 000 - 3 000 000
4. African countries	>2%	450	100-120	450 000 - 540 000
WORLD TOTAL		5 000		3 495 000 - 4 400 000

Four detailed recommendations were included, namely:

- (i) that the programme must be country-wide, i.e. tuberculosis services must be available to rural as well as urban populations;
- (ii) the programme must be permanent, as for many decades to come new cases of tuberculosis will develop from the pool of the world's adult population, whose majority has been infected by tubercle bacilli in the past;
- (iii) the programme must be adapted to the expressed demands of the population, as only accessible and effective services will gain public confidence;
- (iv) the programme must be integrated into the community health structure in order to meet the above-mentioned requirements;

4. The evolution of the WHO policy on treatment

4.1 Case-finding/treatment as an entity

It has always been stressed that the most powerful weapon in tuberculosis control is the combination of case-finding and chemotherapy, considered as an entity, as case-finding is a prerequisite to diagnosis and cure. At both the first referral and primary health care levels, priority should be given to the examination of patients presenting with relevant symptoms to a health facility. As appropriate in varying programme situations, case-finding can be expanded by measures such as increasing community awareness of the importance of persistent respiratory symptoms (especially cough), questioning of household heads and community leaders to identify suspects, and examination of high-risk groups such as contacts of diagnosed patients. Expansion of case-finding should not exceed the capability of the health systems to deliver effective treatment to cure the cases found.

Bacteriology plays a key role in diagnosis. Examination of direct smears is of first importance, as it is simple, inexpensive and detects those cases of pulmonary tuberculosis that are the most infectious. A target in developing countries is to provide microscopic examination of sputum on a large enough scale to permit the accurate bacteriological diagnosis of every smear-positive case. Sputum microscopy for patients with respiratory symptoms is, in fact, the method of choice in developing countries. Implementation of this policy has progressed slowly. In many countries diagnosis is still carried out mainly in specialized facilities and radiological diagnosis is still used, to varying extents, all over the world.

4.2 The role of standard ambulatory chemotherapy

As early as 1948, The Third Expert Committee on Tuberculosis (5) considered streptomycin a valuable drug and recommended research on its best use. Isoniazid became available in 1951, but on the whole the treatment of tuberculosis up to the 1960s was a clinical speciality and was synonymous with hospitalization. Gradually a sound scientific evidence from research carried out all over the world, and particularly by the Tuberculosis Chemotherapy Centre in Madras, India (an institution set up jointly by the Government of India, the Indian Council of Medical Research, the British Medical Research Council and WHO), provided the basis for a completely new approach to tuberculosis control. New far reaching recommendations, including those concerning the role of standard ambulatory chemotherapy were formulated in 1964 by the Expert Committee on Tuberculosis in its Eighth Report (3).

The Committee emphasized the fundamental epidemiological importance of giving adequate chemotherapy to every "case" of infectious pulmonary tuberculosis, and considered that, in view of the public health implications of the tuberculosis problem, treatment should be available, free of cost, to every known sufferer from the disease. Such universal availability of treatment services can be provided only if careful attention is paid to the funds and health personnel available in the country. It is neither possible nor necessary for developing countries to model their treatment services on those currently existing in the technically advanced countries.

Having reviewed results from developing countries of controlled comparisons of bed rest and ambulation and of domiciliary and institutional treatment of pulmonary tuberculosis, the Committee concluded that, in terms of the immediate response to treatment, of subsequent relapse, and of the risk to contacts, there was no evidence in those studies of special benefits resulting from hospitalization. It recommended, therefore, that all financial resources and manpower available for tuberculosis control in the developing countries be confined to organizing efficient ambulatory services and not to constructing new beds. Tuberculosis beds, where they already exist, should be integrated into the ambulatory and domiciliary services so as to ensure their most rational use (e.g. for emergencies).

The Committee noted that similar controlled comparisons of bed rest and ambulation and of domiciliary and institutional treatment carried out in technically advanced countries also did not indicate any superiority of institutional over ambulatory treatment. It emphasized that the application of these results could lead to impressive economic savings in national tuberculosis programmes. In this situation, the Committee felt that it was incumbent on those advocating the superiority of institutional treatment to conduct studies to determine whether their contention is substantiated by objective evidence.

The Committee stressed that the first priority goes to giving one year of chemotherapy to every newly diagnosed "case" of infectious pulmonary tuberculosis. The "first-line" drugs that came into consideration at that time in national tuberculosis programmes were isoniazid, streptomycin, para-aminosalicylic acid (PAS) and thioacetazone.

In reviewing experience gained upto early 1960s in the treatment of initially drug-sensitive cases, the Committee underlined three important trends in the application of chemotherapy in developing countries:

- (i) The importance of especially intensive chemotherapy at the beginning of treatment.
- (ii) The efficacy of thioacetazone as a cheap oral companion drug to isoniazid.
- (iii) The efficacy of directly supervised intermittent chemotherapy.

The Committee stressed the necessity of reviewing the current practice of chemotherapy constantly so that, as both resources and knowledge improve, they will be applied to the best effect. It was also stressed that routine assessment of the administrative organization for treatment and of the treatment results themselves is essential in a tuberculosis programme. The cohort-analysis of drug administration records, covering complete groups of patients who began treatment within a given period, constitutes the basic method of operational assessment.

In the 1960s two new drugs were introduced, i.e. ethambutol and rifampicin. For about one decade, however, their use was restricted to clinical trials and to few developed countries that could afford the cost.

The WHO Expert Committee on Tuberculosis in its Ninth Report in 1973, reiterated all the previous recommendations concerning treatment, and noted the introduction of rifampicin and ethambutol, but observed that cost is often decisive in choosing standard regimens for widespread use.

4.3 The introduction of short-duration regimens

In the early 1970s, the available scientific evidence on the use of short-course chemotherapy was still insufficient for the Expert Committee to include it in the recommendations of its Ninth Report. The Committee, however, noted all advances in this field stating: "... the use of short-course regimens of chemotherapy, some lasting only 6 months, is still at an experimental stage". The Committee noted also the promising research in the use of once-weekly continuation regimens, and discussed the need for full oral regimens.

In the late 1970s the efficacy of short-course chemotherapy for tuberculosis was established (6,7) and a joint IUAT/WHO Study Group that met in 1981 (8), stated that there are now a number of short-course regimens of 6-9 months' duration that are very highly effective, of low toxicity, and well tolerated. Some are daily regimens, others intermittent after an initial intensive daily phase, and some intermittent throughout. They are nearly as effective in patients whose strains are initially resistant to isoniazid, to streptomycin, or even to both drugs, as in patients with fully sensitive strains. Moreover a high proportion of patients are cured even within the first 3 months of treatment, so that these regimens offer an important degree of protection against failure due to premature default from treatment. These potent regimens are based on an initial intensive phase of isoniazid, rifampicin, and pyrazinamide supplemented by a fourth drug (streptomycin or ethambutol), and isoniazid plus rifampicin in the continuation phase. There is a choice between 6-month regimens with rifampicin throughout, which are expensive, or cheaper regimens of 8-9 months' duration with the expensive drugs given in an initial intensive phase that is followed by a much less costly continuation phase. It was noted that a number of technically advanced countries have recommended the use of short-course chemotherapy and that some developing countries are already basing their national programmes on short-course regimens.

In the Ninth Report of the WHO Expert Committee on Tuberculosis, two regimens were recommended for use in programme conditions in developing countries: (a) isoniazid plus thioacetazone, a combination often supplemented by streptomycin in the initial intensive phase; (b) a twice-weekly, fully supervised regimen of streptomycin plus isoniazid, preceded, whenever possible, by an initial intensive daily phase. The recommended duration of both is 12 months. The Joint IUAT/WHO Study Group affirmed that these still remain basic regimens for use under programme conditions in many developing countries. Nevertheless, the aim should be to make available effective short-course regimens for all countries, whether technically advanced or developing. The Group stressed, however, that "the efficiency of both standard and short-duration regimens in programme conditions will depend on the quality of the organizational framework of the programme." This is the key issue for all national programmes and its importance cannot be overemphasized.

5. The basic principles of chemotherapy of tuberculosis

According to a WHO model list of essential drugs (9), the following antituberculosis drugs are included in the "Main List" (in alphabetical order): ethambutol, isoniazid, pyrazinamide, rifampicin, streptomycin and thioacetazone. These drugs allow us to compose regimens of 6 to 12 months' duration, which potential efficacy varies between 90 and almost 100%, as demonstrated in different clinical and field trials and whose cost (drugs only) may vary almost tenfold. The most commonly used regimens are presented in Table 2.

TABLE 2 - TREATMENT REGIMENS COMMONLY USED IN NATIONAL TUBERCULOSIS CONTROL PROGRAMMES - main differences in duration and cost

Treatment regimen	Duration (months)	Number of doses	Risk of failures/relapses as observed in controlled clinical trials per cent	Cost of drugs approximate (in bulk procurement) in US \$ as in 1988
1SH/11TH	12	365	5 - 10	10
1SH/11EH	12	365	5 - 10	20
1SH/11S ₂ H ₂	12	126	5 - 10	15
2 HRZ/6TH	8	244	2 - 5	45
2 HRZ/4HR	6	180	0 - 3	90
2 HRZ/4H ₂ R ₂	6	92	0 - 3	50
2 H ₂ R ₂ Z ₂ /4H ₂ R ₂	6	52	0 - 3	30

The basic principles of good chemotherapy have been described in detail by Pierre Chaulet in a WHO offset series document entitled "Treatment of tuberculosis: case-holding until cure" (10). The main points are:

- (a) The patient must receive an effective drug regimen, i.e. one which has been shown in a controlled trial to be effective, is acceptable by the patient, and does not interfere with his family and social life.
- (b) The patient must know and accept to consume the exact dosages of each drug as prescribed.
- (c) Treatment must be uninterrupted, and the drugs must be taken very regularly, every day or three times or twice per week as the case may be.
- (d) Treatment must be taken for the full prescribed duration, one year, eight or six months as the case may be, even if the symptoms disappear within a few weeks.

In addition to the above technical principles of good chemotherapy, there are several operational ones which must also be observed in national tuberculosis programmes:

- (i) Only the standard drug regimens with proven efficacy must be prescribed. There is no place for tailoring the drug regimen to the needs of a particular patient or for haphazard modifications to regimens made on the spot by the personnel and not in line with the technical recommendations. Standardization of regimens is the first requisite to permanent availability of drugs in a programme.
- (ii) Prescribed regimens must be supplied free of charge to every patient, to ensure that treatment is not interrupted because of the inability of the patient to pay for the drugs.
- (iii) Patients' convenience, and not that of staff in the health unit, is what matters most in ensuring good chemotherapy. Thus treatment organization must make sure that the chemotherapy is made available near to the patient's home; that his treatment is readily transferred to another convenient health centre when he moves home; that he is precisely informed about the new place where he should call or the name of the person whom he should contact to continue his chemotherapy.
- (iv) Health education of the patient and his family should not be limited in time, and independent from treatment activities. It must be systematic, repeated and integrated with other activities. Welcoming, clean and accessible health clinics together with punctual, conscientious and kind health staff are very powerful factors of health education.

Recently published "Recommendations from the Committee on Treatment of the International Union Against Tuberculosis and Lung Diseases" also provide detailed information on treatment regimens and stress the importance of patients compliance and of appropriate supervision of treatment. The recommendations indicate clearly that "it is wrong to assume that standards of supervision are necessarily better in hospital than in outpatients" (11). Hospitalisation or short duration of treatment is certainly not synonymous with compliance.

6. The effectiveness of chemotherapy in national programmes of developing countries

It is a well-known fact that the overall success of any national tuberculosis control programme depends on efficient implementation of all programme components, i.e. case-finding, case-holding and chemotherapy (12). Most often, however, the success, or lack of it, is presented in terms of the level of efficiency of chemotherapy alone, with cure rates achieved as the main indicator and it is claimed that regimens of long duration are to be blamed for the poor results of treatment in most developing countries. Table 3 presents the fate of smear-positive cases as observed under different programme conditions in developing countries at present.

TABLE 3 - EFFECTIVENESS OF CHEMOTHERAPY UNDER DIFFERENT PROGRAMME CONDITIONS - FATE OF SMEAR-POSITIVE CASES

Programme Conditions	Per cent of patients not completing treatment (absconded, transferred out, etc.)	Per cent of patients remaining positive after treatment (chronics relapses, failures	Died	Per cent of patients cured
A	30 - 40	10 - 20	10	30 - 50
B	15 - 25	10 - 15	5 - 10	50 - 70
C	10 - 15	< 5	5 - 10	70 - 80
No Chemotherapy*		18	50	32

A: results observed in most developing countries, usually with 12-months treatment regimens of SHT and poor quality of case-holding

B: results observed in countries with a reasonably good case-holding with treatment regimens mostly of 12-months duration

C: results of short-course regimens in Tanzania, as applied to 10,690 patients (about 30% of the total of newly detected smear-positive cases) in the years 1982-1986 (14).

* These figures represent the results of a longitudinal study in Bangalore, India, and may be considered as representing the fate of cases of tuberculosis in the pre-chemotherapy era (15).

There is no doubt that short-course chemotherapy regimens offer several advantages: the total quantity of drugs used is less, resulting in less toxicity; because of the potency of these regimens patients who default are less likely to relapse than those on SHT regimens; results are nearly as good in patients with initially resistant strains as in those with fully susceptible strains; and, what is most important, more effort can be concentrated on ensuring regularity of patient attendance and drug administration for a shorter period of time. However, it is not necessarily the regimens or the composition of drugs themselves that brings about a substantial improvement in the cure rate, it is the correct application of a regimen and the organizational set up, that makes the difference. Short-course regimens should not, therefore, be considered as a short-cut for all the developing countries with weak programmes. They may lessen the workload in well-organized programmes which perform adequate supervision and may in fact be more efficient in spite of higher drug costs, if used in ambulatory treatment (16). In general, therefore, the regimens of one year's duration will remain the basic chemotherapy for the tuberculosis programme of most developing countries with a high prevalence of tuberculosis (see Table 1), unless both substantial improvements in the programme's management at all levels (particularly case-holding) and substantial reductions in the cost of drugs for short-course chemotherapy (particularly rifampicin and pyrazinamide) are made.

7. Conclusions

The history of tuberculosis during the past century shows a clear correlation between the decline of the problem and the rate of socio-economic development. But development invariably included improvement of health services and it would be unwise for countries that still face tuberculosis as a health problem to passively wait for economic development to take care of it. Since tuberculosis is transmitted mainly from man to man and infection is air-borne, improvements in sanitary conditions have far less effect on the risk of infection than for instance in enteric infections. Moreover, in tuberculosis there is a tremendous infected pool, about half the population in developing countries being infected already. Because of the chronic incapacity and high case fatality it entails, tuberculosis constitutes not only a long-term epidemiological, but also an acute social problem. Effective means to alleviate this are available: BCG vaccination can, to a large extent, prevent the serious forms of childhood tuberculosis and appropriate chemotherapy will give rapid relief and prevent death as well as break the transmission of infection. To have any impact, however, tuberculosis services should be available on a country-wide scale and this can only be achieved through a well-organized national programme.

Planning a national programme implies a clear definition of objectives and targets, a statement of the means whereby the objectives and targets are to be achieved, setting a time limit for each target and selection of criteria for assessing achievements. Objectives and targets for tuberculosis control, in view of the dimensions of the problem, must be epidemiological, operational and sociological. Evaluation has to be built into the active management of the programme and has to be applied on a continuing basis, so that the programme's effectiveness and impact can be assessed to indicate a need for replanning of one or more components of the programme.

An urgent priority for developing countries is to integrate tuberculosis control programmes into the existing components of the primary health care system. Resources for tuberculosis will be very limited if they are allocated in proportion to its relative importance as a health problem and commensurately with the socio-economic possibilities of the country concerned. However, resources should be sufficient to make essential facilities for diagnosis and

treatment available directly or through a referral system to any patient who actively seeks care for tuberculosis. The cost of meeting this social target can be around US\$ 0.10 per head, assuming that diagnosis is made only by microscopy and the standard chemotherapeutic regimens of one year's duration are applied. This cost is compatible with the projected financial resources for primary health care of even the least developed countries.

A basic tuberculosis programme, providing microscopic diagnosis, ambulatory chemotherapy as affordable, and BCG vaccination as part of an expanded programme on immunization, together with other essential health care readily accessible to all people, would be within the possibilities of all health care systems if the strategy of health for all is successfully put into practice. Thus, the social target of alleviating human suffering from tuberculosis can be largely achieved by the year 2000.

So far, however, the progress has been very slow. Already in 1973, the Expert Committee on Tuberculosis, in the introduction to its ninth report, stated that "the implementation of the new approach to tuberculosis control has encountered many problems. Shortages of financial, material and physical resources and a shortage and maldistribution of trained manpower are aggravated by a lack of managerial skill. The health infrastructures of many countries have deficiencies that remain uncorrected. These often lead to an increasing feeling of dissatisfaction because of inability to apply, on an adequate scale, the potent weapons against tuberculosis. In some countries, a major constraint has been a reluctance to change traditional and outmoded orientations. Determined leadership is needed to effect the necessary changes and to apply more effectively the potent measures available for tuberculosis control" (4).

This situation did not change very substantially in the following ten years either. In 1981 the joint IUAT/WHO Study Group found the basic concepts of tuberculosis control policies as described by the WHO Expert Committee on Tuberculosis sound and valid, and stressed that the disappointing results were largely attributable to both quantitative and qualitative deficiencies in programme implementation (8).

The Thirty-sixth World Health Assembly in 1983 (13), after reviewing the tuberculosis situation in the world, noted that tuberculosis continues to be a most important health problem, especially in developing countries, where little improvement has been achieved in the last two decades and urged Member States, among others, to intensify their efforts to extend tuberculosis diagnosis, treatment and prevention services to the whole population. This can only be achieved by providing the basic tuberculosis services through primary health care which is being gradually developed throughout the world. The primary health care system makes it possible to overcome the two main obstacles in tuberculosis control in developing countries - rapid case-finding and sustained chemotherapy as affordable - both of which require a productive cooperation between the system and the population.

The analysis of the current situation indicates clearly that for only one quarter of the world's population tuberculosis is no longer a public health problem. By the year 2000, taking into account both the population increase and the continuing decline in the risk of infection and the incidence, tuberculosis will certainly still remain a major public health problem for half of the world's population. Our efforts, therefore, need to continue for several decades. The AIDS epidemic may have an adverse influence on this prognosis because of the known interaction between the two infections. In such a case we would need to review carefully the policy on tuberculosis control in order to be able to adjust the tools to the worsening global situation that the next few generations will face.

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