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WHO POLICY IN TUBERCULOSIS CONTROL

A review of the Ninth Report of the WHO Expert Committee on Tuberculosis

by

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Pulmonary tuberculosis is still widespread in the developing countries, with an annual incidence of 200-350 cases per 100 000 inhabitants in some parts of Africa, Asia, and Oceania. Even in many technically advanced countries, where it is considered rare, tuberculosis often causes more deaths than all other notifiable diseases combined. In December 1973 the WHO Expert Committee on Tuberculosis under the Chairmanship of Professor A. Abdel-Aziz Sami, of Egypt[1] met in Geneva to review the validity of the recommendations in its eighth report[2] in the light of scientific evidence that had subsequently become available, and to make recommendations concerning advice and assistance to country health programming, the preparation of physicians and other health workers, and the establishment of priorities for research in the field of tuberculosis.

Despite the numerous problems encountered - shortage of financial, material, and human resources, and sometimes a strong reluctance to change traditional and outmoded orientations - the concept of a national tuberculosis control programme, first proposed by the WHO Expert Committee on Tuberculosis in its eighth report,[2] has been successfully implemented in several countries, which have thereby changed the status of tuberculosis as a clinical specialty and made its control a widely applied community health activity. This concept - in many ways a challenge to the

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[1] WHO Technical Report Series, No. 552, 1974 (Ninth Report of the WHO Expert Committee on Tuberculosis) refers.

[2] WHO Technical Report Series, No. 290, 1964

medical profession - has been proved valid: national tuberculosis programmes formulated on sound principles remain vital to worldwide elimination of the disease as a public health problem.

The national tuberculosis programme

For a national tuberculosis programme to be effective the following principles must be observed.

- The programme must be country-wide. Where the population is largely rural, as in most developing countries, the tuberculosis services are almost always centred in the cities and are thus out of touch with the bulk of the tuberculosis problem, which in these countries is found in the rural areas.
- The programme must be permanent. Since the majority of the world's adult population has been infected by tubercle bacilli, new cases of tuberculosis will continue to develop for several decades to come. Hence, no crash programme or one-time endeavour can replace a permanent programme.
- The programme must be adapted to the expressed demands of the population.
- The programme must be integrated in the community health structure. It is irrational either to establish specialized tuberculosis services in developing countries, where they would absorb a disproportionate share of the limited trained manpower and financial resources, or to maintain such services in countries where the problem has been greatly reduced. Instead, a network of permanent health services - including private practitioners, hospital outpatient departments, health centres, dispensaries, and health posts - is required to which people can go if they feel ill. With the simplified and standardized technology available today, tuberculosis prevention measures and diagnosis and treatment can be carried out by any health institution, and control measures can even be carried out by health auxiliaries, if they are properly trained and supervised. In most national programmes there are three

levels with clearly defined responsibilities: the central level (policy making, planning, programming, coordination, programme training, direction, and evaluation); the intermediate level (supervision and evaluation of the peripheral and referral services, and in-service training); and the peripheral level (the actual delivery of the services).

Planning and programming

Systematic planning is essential; it should use data on demography (including ethnic and other important groups and their behaviour patterns regarding health and illness), on communications and administration, school attendance, community and health development programmes, the structure of the health services and their coverage of the population, and the availability of professional,auxiliary, and voluntary manpower and other resources at all levels. A limited baseline survey may be needed to provide the necessary epidemiological and operational data. This information is then organized into a schedule for the development of preventive and curative anti-tuberculosis activities within the basic health services to cover the population for a reasonable period of time. Based on this schedule, a programme specifies the approach to be followed, the resources to be allocated, the personnel to be trained, and the area to be covered by each health agency.

Selection of technical policies

Case-finding and treatment, as well as BCG vaccination, should be initiated in almost all situations, the emphasis given to each depending on the epidemiological situation and available resources.

Case-finding and treatment. Case-finding and treatment should be developed as a single entity. Treatment should be free of charge and primarily ambulatory, the first priority logically being to provide facilities for direct smear examination of sputum, with adequate treatment for persons who are found to excrete tubercle bacilli. Specific antituberculosis chemotherapy should be given only if the diagnosis

can be confirmed bacteriologically; patients with persistent symptoms whose sputum does not contain bacilli should be followed up. Effective standard regimens should be made available for daily and for supervised intermittent chemotherapy, if possible with an initial intensive phase.

The programme should first aim at covering the entire country with conveniently situated facilities where patients can go for sputum examination and for treatment. The programme should not be expanded, however, to the detriment of the quality of the therapy. Once sufficient facilities have been provided, an active expansion of case-finding should be initiated, backed by a health education programme to increase the public's awareness of symptoms. Culture facilities for the bacteriological examination of sputum should next be introduced, bearing in mind that cases detected in this way are less infectious than smear-positive cases. Smear examination and, later, culture can be used to assess the results of treatment and to determine whether patients require retreatment. Sensitivity testing, especially to isoniazid, may provide guidance in the choice of an appropriate treatment regimen. A programme of retreatment should not be instituted until a high level of success has been achieved in the original treatment of newly diagnosed patients. The examination of high-risk groups should not be carried out at the expense of the development of adequate diagnostic and treatment services for the whole country.

BCG vaccination. A feasible target in an initial intensive mass campaign of BCG vaccination is the rapid coverage of 70-90% of the eligible population (usually all persons up to 15 or 20 years of age). Thereafter, a programme integrated with the general health services is more likely to achieve and maintain a high coverage; the same staff should undertake preventive measures against several diseases, practising simultaneous immunization whenever justified and expedient. Where infant tuberculosis is a problem, the widest possible BCG coverage should be ensured as early in life as feasible. Young adults are more likely than children of school age to develop the

disease soon after infection; and, unlike infants and young children, they develop the infectious type of tuberculosis. Hence, the maintenance of immunity by vaccination at school-leaving age.

Vaccination at school-entrance age may be justified both where the risk of infection is high and where it is known to be rapidly declining; in the first case most infection will occur during the first few years in school; in the second, a large proportion of the total infection during the lifetime of each cohort will occur before the school-leaving age is reached. Vaccination at school age should be undertaken irrespective of vaccination at birth, since it has never been demonstrated that the reduced dose of BCG usually given to the newborn will induce a lasting significant level of protection. Revaccination is also indicated in groups of persons known to have been vaccinated inadequately, i.e. with a product later demonstrated to have been of low potency.

Since tuberculin testing before vaccination always reduces the coverage and more than doubles the cost, direct BCG vaccination is preferable under almost all circumstances, and especially at revaccination. The age-specific prevalence of infection, as determined by standard tuberculin testing for the purpose of epidemiological surveillance, should be taken into account when deciding on the age-limit for direct vaccination.

Implementation

A national tuberculosis programme should have a strong directing unit with a central authority under the ministry of health. It should begin in a single area affording opportunities for practical field experience and training, with evaluation carried out from the beginning to provide the information needed to readjust the programme and extend it to other areas. Programme implementation is the main responsibility of the managerial teams who will spend most of their time in the field and at the peripheral level, carrying out in-service training of staff, the distribution of equipment and supplies, and technical evaluation of the programme.

A reliable and continuous supply line and simple but effective recording and reporting systems are necessary for programme monitoring and evaluation and for further planning.

Prior to or early during implementation, a national seminar should be held for all cadres of programme personnel, with the participation of representatives of other health sectors (e.g., maternal and child health, other communicable diseases, health laboratory services, manpower development, and health education), teachers of tuberculosis and preventive and social medicine in medical and nursing schools, and representatives of certain voluntary associations in view of their complementary role in community-oriented health programmes. The achievements of the programme and the difficulties encountered during its implementation should regularly be discussed at "workshops".

Education and training. In the education and training of programme personnel, the community aspects of tuberculosis (and not, as at present, the clinical aspects) should receive most emphasis. Some basic information on national tuberculosis programmes should be added to the curricula of medical and nursing schools. Key medical staff should receive multidisciplinary training, including training in the social sciences and educational and management technology, at national or international centres. The managerial team responsible for implementation should be trained at a national centre; their training should include educational and management technology not necessarily limited to tuberculosis.

In the training of the general health centre staff, each task should be clearly specified in detail: what is to be done, how, by whom, and when. Periodic visits by the members of the mobile managerial team to the peripheral workers constitute a form of supervision combined with on-the-job training and retraining, as well as providing an opportunity to check performance and correct any deficiences. National seminars and refresher and orientation courses, particularly for physicians, have

proved to be valuable educationally and as a means of stimulating active support for the national programmes.

If the programme-oriented training of all categories of health workers engaged in tuberculosis control needs to be intensified priority should be given also to teacher training. A set of prototype manuals might be produced to explain the simplified and standardized basic techniques and procedures to be applied in national tuberculosis control programmes. Such material, adapted to local conditions, could be used for all kinds of training at the national level; it could form the basis of manuals and work instructions providing all categories of health workers engaged in tuberculosis control with necessary details on their day-to-day activities; it would also guide supervisors during their routine checks of health institutions and of the performance of peripheral health workers.

Organization of laboratory services. The first priority in tuberculosis laboratory services is the examination of direct smears of sputum. Three types of laboratory have been recognized:[1] (1) peripheral, employing 2 or 3 persons capable of using simple diagnostic methods under supervision - especially microscopy - for several diseases; (2) intermediate (multidisciplinary but without sections specializing in specific diseases);[2] (3) central laboratories. As a rule the majority of smear examinations are done at the peripheral and intermediate level. Cultures, simple identification tests for M. tuberculosis, and tests antituberculosis drugs in urine are carried out by the intermediate and central laboratories, while sensitivity testing should be done only at the central laboratory, where the following functions will mainly be performed (though some may be delegated to the intermediate level): (a) assistance to the programme directorate in planning the national programme; (b) surveillance and epidemiological studies, such as surveys of the prevalence of drug resistance and of results obtained in the treatment service;

[1] WHO Technical Report Series, No. 491, 1972 (Fifth report of the WHO Expert Committee on Health Laboratory Services).

[2] These laboratories were considered to be of key importance

(c) training of technicians and maintenance of their skills by regular personal contact through a service section; (d) assisting in the choice and maintenance of laboratory equipment; (e) quality control for technical procedures in the more peripheral laboratories; (f) research, often on practical problems within the country.

Organization of ambulatory chemotherapy. The major problem of chemotherapy is to ensure that patients follow their regimen regularly throughout the prescribed period of treatment. Repeated explanation to the patient and his family of the nature and duration of chemotherapy may help to ensure that patients become more cooperative in this respect. The patient's address should be obtained, as well as the addresses of other family members, the patient's employer, close friends, and his children's schools, and a staff member at each treatment centre should be nominated to trace those patients who fail to attend; postal reminders are much slower and lack urgency. Community leaders and welfare organizations should be involved in the programme.

Patients on self-administered regimens should be seen to take every dose by a family member or a responsible neighbour. Regularity can also be monitored by surprise visits to the patient's home, by counting his stock of tablets, and/or by collecting a urine specimen to test for antituberculosis drugs or their metabolites.

The administration of fully supervised intermittent chemotherapy should be decentralized (e.g.,to health centres, rural health units, dispensaries, welfare clinics, hospitals, factory clinics, general practitioners, lay supervisors) so that patients do not have too far to travel, and organized so that patients in employment do not lose time at work. The patient's progress should be periodically reviewed by the best qualified local staff.

Evaluation

Continual evaluation should be built into the programme at the very beginning.

Although a comprehensive evaluation system is long and complicated to establish, valuable results at the operational level can be obtained by the mobile managerial teams early in the programme (see above). Evaluation should provide quantified information on the health benefits derived from, and the resources used in, the different programme components; but it should not be limited to certain specific procedures. Organization and methods should be investigated as a whole so as to detect any deficiencies in coordination.

The health benefit derived from any programme activity may be meaningfully measured by relating it to a relevant, epidemiologically well defined denominator, e.g., the result of case-finding and treatment may be expressed as the number of new patients cured in relation to the number of new cases estimated to have occurred during the same period. Cost-benefit data can be used directly to compare alternatives producing the same type of health benefit (e.g., different treatment regimens or different approaches to BCG vaccination). The utilization of resources (e.g. manpower) that sometimes cannot be adequately expressed as a cost may be studied by other techniques, such as activity sampling.

BCG vaccination. The efficacy of certain vaccines can be estimated fairly accurately from controlled trials, and quality control and checks on the vaccination technique will indicate how far the field programmes are efficacious.

For precise estimates of coverage it is advisable to conduct a careful sample survey of the presence of vaccination scars. Indicators relevant to the quality of vaccination are the distribution of scar sizes, the proportions of cases of suppurative lymphadenitis (especially in the newborn), of abscesses, and of unsightly scars. For an accurate field assessment of the quality of the vaccinations it is necessary to undertake post-vaccination tuberculin testing, on a sample basis. However, such tuberculin testing requires special skill. The incidence of tuberculous meningitis in children is a general indicator of the quality and coverage of BCG vaccination in the lower age groups, its value obviously depending on the availability and accuracy of the diagnostic services and on the completeness of reporting.

Case-finding and treatment. The benefit of case-finding and therapy cannot be expressed simply as a function of the number of cases found and cured, since some individuals are incorrectly diagnosed as having tuberculosis and treated unnecessarily. Only after measuring the accuracy of diagnostic test procedures can the number of patients who actually benefit from case-finding and treatment be estimated.

Regularity of drug collection can be estimated from records, while drug ingestion can be measured directly by testing urine specimens from a sample of the patients. The inspection of records in peripheral centres will indicate whether the recommended standard regimens were prescribed, whether recommended action was taken with respect to defaulters, and whether, for how long, and why patients have been hospitalized. The proportions of failures, of relapses, of patients with primary, initial, and acquired drug resistance, as well as the case-fatality rate, may also lead to the detection of deficiencies in the chain of activities that make up the case-finding and treatment programme.

METHODS AND TECHNOLOGY

Epidemiology

In order to establish clear priorities for national programmes, it is necessary to understand and take into consideration the dynamics and interactions of epidemiological events, as well as the impact of tuberculosis control measures. Sound epidemiological and operational information is essential. However, effective chemotherapy has made mortality data of little value in estimating the magnitude of the tuberculosis problem, and notification data may reflect the intensity of sporadic case-finding efforts rather than actual trends; such data rarely indicate whether patients are smear-positive and/or culture-positive, or even whether bacteriological examinations have been performed. So-called "radiological prevalence and incidence rates" also have no definite epidemiological significance, since bacteriological confirmation is necessary to establish whether the lung shadows are of tuberculous origin.

The fundamental importance of the bacteriological confirmation of the diagnosis "tuberculosis" was discussed also at the meeting of the WHO Expert Committee on Statistics, in June 1974, in respect of the international classification of diseases (e.g. for the ninth revision of the ICD) and when meaningful reporting by countries for programme planning and evaluation, and for the purpose of epidemiological surveillance, is the goal.

The two most relevant epidemiological indices at present are (a) the prevalence of tuberculous patients excreting bacilli demonstrable by direct smear examination - such patients being the main infectious source of the disease - and (b) the age-specific prevalence of tuberculous infection as demonstrated by tuberculin testing. In most countries age-specific prevalence surveys based on a well calibrated, low-dose tuberculin test can more easily be undertaken using much smaller study populations than are needed for surveys of infectious sources (surveys of a representative sample of unvaccinated children at, for example, school entrance age are therefore the method of choice). However, for information about variations in the risk of infection, either with calendar time or with age, at least two tuberculin surveys of the same age group are required at different times in the same community.

Special-risk groups

Since equal case-finding coverage for all segments of the population is neither economically nor operationally feasible, the epidemiology of special-risk groups is of particular interest. Older adolescents and adults seeking medical advice because of respiratory symptoms - especially when these persist for more than four weeks - constitute the highest priority group for case-finding. Other special-risk groups include: persons who have been in close contact with a smear-positive index case; health staff who are exposed to infection in wards and laboratories; former tuberculous patients who have had inadequate chemotherapy or none at all; persons with so-called "fibrotic lesions" in the lung, especially if these are large and recently detected; elderly persons living alone; migrant groups; patients with certain

concomitant diseases (e.g., diabetes, pulmonary dust disease, gastro-intestinal malabsorption syndromes); alcoholics; and patients on steroids.

Primary drug resistance

Although the level of primary drug resistance has been shown to be usually higher in developing countries than in technically advanced countries, it has not increased appreciably during the past decade; in fact, with improved standards of chemotherapy it appears to become stabilized. Furthermore, primary drug resistance occurs mainly to a single drug and the response of the patients to standard triple-drug chemotherapy is usually good.

Predictive epidemiology and epidemiological surveillance

Mathematical models describing the epidemiological course of tuberculosis make it possible to predict the effects of such activities as BCG vaccination and case-finding plus treatment. These models have paved the way for cost-effectiveness analysis and, together with resource allocation models, for cost-health-benefit calculations.

Whereas evaluation is concerned with the current events of the programme, epidemiological surveillance is concerned with the measurement of the trends of the rates of infection, disease and deaths and can guide the epidemiologist and public health planner by indicating whether the tuberculosis problem is increasing, static, or declining, for example, by measuring, as mentioned above, the annual infection rates. Another example is the measurement of the incidence of tuberculous meningitis in children, which may help to decide at what age to give BCG. Whether continuous or periodic, surveillance requires the orderly collection, consolidation, and analysis of pertinent data and their dissemination to those in a position to take the necessary action. The application of surveillance in tuberculosis control programmes should be improved and extended.

BCG vaccination

During the past decade BCG coverage has been improved by increased use of direct

vaccination (i.e., without a prior tuberculin test) and the simultaneous administration of BCG and smallpox vaccination. In addition better vaccines have become more widely available.

The vaccine

A BCG strain used in the production of vaccine should have properties resembling those of vaccines that have proved effective in controlled trials. Since delayed hypersensitivity and acquired resistance to tuberculosis are concomitant cell-mediated immune responses that are perhaps expressions of the same process, it is advisable to avoid strains of low allergenicity. Today, viable and reasonably stable vaccines can be prepared even from strains that are difficult to handle in production, thus making it possible to give priority to immunological criteria. Changes arising through mutation and selection during the maintenance of the strain by serial subculturing can now be prevented by using the seed-lot system, i.e., by keeping dried BCG for use as seed for the preparation of the cultures from which the vaccine is harvested.

A BCG vaccine should contain the highest possible proportion of live bacilli: the dead organisms contribute more to the size of the lesion at the site of inoculation than to the degree of induced tuberculin sensitivity. Several laboratories have now achieved a high and uniform viability in their liquid vaccines and, in some instances,in their freeze-dried vaccines as well. Freeze-dried vaccines, when reconstituted, have a lower viability than the liquid vaccines from which they were prepared; however, they are almost always preferable because of their far superior keeping qualities (including, in some cases, substantial heat stability) which simplify shipment, considerably reduce waste, and make it possible to complete quality control before releasing a batch for use.

Since the manufacture of dried BCG in a small laboratory to meet a limited demand usually results in a poor and expensive product, it is desirable to limit international technical support to those laboratories capable of covering the needs of large populations. Reducing the number of laboratories would also facilitate

both national and international control.

Extensive quality control is crucial at various stages in production and at both national and international levels.

The 27th World Health Assembly, in 1974, re-emphasized that the effectiveness of BCG vaccination depends largely on the quality of the vaccine used. It urged member countries importing BCG vaccine on a bilateral basis, or producing it themselves to make use, until they have established a competent national control service, of the international quality control system (which has been established) by WHO for monitoring the freeze-dried BCG vaccine that is supplied by or through UNICEF. To that effect, a Resolution on the "Quality Control of BCG Vaccines"[1] was passed by the Assembly and this document has been sent, for information and guidance, to the Government of all Member States of WHO.

The response in man

Controlled trials in man suggest that not only tuberculin sensitivity but the degree of protection against tuberculosis varies with the dose of BCG. Therefore the highest dose should be administered that produces an acceptably low rate of local and regional adverse reactions. Since the frequency of suppurative lymphadenitis in newborn and young infants increases sharply with BCG dose, it should be lower for this group than for older children and adults.

Epidemiological observations in man indicate that sensitization by atypical mycobacteria - common in tropical and subtropical populations - is associated with a certain degree of protection against tuberculosis. Laboratory experiments in animals have confirmed that such protection is weaker than that induced by a potent BCG vaccine and can be increased by BCG vaccination. A vaccine that did not increase the level of protection acquired from sensitization by atypical mycobacteria would in fact be useless.

Intradermal vaccination by syringe and needle remains the most precise way of administering the desired dose. Intradermal injection by jet injector is expensive

[1] Resolution WHA27/54

and less accurate. Percutaneous vaccination, while just as likely as intradermal techniques to require training and supervision, is even less accurate and does not permit the desired high dose of vaccine to be introduced into the skin. The bifurcated needle, which has greatly facilitated percutaneous vaccination against smallpox, appears attractive for simultaneous BCG and smallpox vaccination; but, even with the strongest percutaneous vaccines, only about one-third of the amount of BCG usually recommended for intradermal injection can be inoculated.

Prolonged experience has confirmed the safety and acceptability of direct vaccination of whole age groups without prior tuberculin testing. BCG has also been administered with immunization against smallpox, measles, yellow fever, diphtheria, pertussis, and tetanus without reducing the immune responses or increasing the rate of complications. The simultaneous administration of BCG and smallpox vaccines, now well established, has reduced cost per vaccination while increasing coverage.

Case-finding and treatment

A case-finding programme should be based on the cost per case found and should not develop faster than the ability of the health service to cure the patients by chemotherapy. The following methods are most likely to produce significant yields:

--- the examination of patients with relevant symptoms who seek medical advice,

--- alerting the tuberculosis programme staff and the community to the importance of respiratory symptoms (in particular persistent and productive cough, bloodstained sputum, and chest pain), especially when present for more than four weeks,

--- the examination of contacts, especially those with symptoms,

--- the bacteriological examination of patients in whom chest radiography has shown a possibly tuberculous lesion,

--- the examination of immigrants and foreign workers coming from high prevalence areas (the host country should assume responsibility for treatment).

In addition, well organized outpatient therapy, especially if provided free of charge, is likely to attract symptomatic cases from a wide surrounding area.

Mass radiography

Even when the prevalence of tuberculosis is high, mass miniature radiography is an expensive screening procedure with the following additional disadvantages:

(1) it contributes only a small proportion of the total number of cases found;

(2) it does not significantly affect the subsequent occurrence of rapidly developing smear-positive cases between the rounds of mass examinations (facilities for case-finding as well as treatment need to be offered constantly rather than sporadically);

(3) it requires the services of highly qualified technicians and medical staff who could be more usefully employed;

(4) the X-ray apparatus and the requisite transport vehicles are frequently out of service owing to mechanical breakdowns.

The policy of indiscriminate tuberculosis case-finding by mobile mass radiography should, therefore, be abandoned.

Tuberculin testing

Large-scale tuberculin testing to identify the sources of infection of recent converters is of little value in a tuberculosis control programme.

Diagnosis

Wide observer variation has been repeatedly demonstrated in the interpretation of abnormalities in chest radiographs. When treatment for tuberculosis is initiated on the basis of radiographic findings alone a substantial proportion of patients are treated unnecessarily, wasting resources and needlessly exposing many patients to economic loss and social stigma. Hence the importance of making a bacteriological diagnosis, which is conclusive.

In a tuberculosis programme, bacteriological techniques may be ranked in the following order of value: examination of direct smears, culture, and sensitivity testing. The aim of a bacteriological service in a developing country should be primarily to perform enough microscopic examinations of sputum to diagnose every

smear-positive case, and then to follow the progress of chemotherapy. Patients should be carefully instructed how to collect "good" sputum specimens, which should be transported in a suitable container as rapidly as possible for examination. Bright-field microscopy (e.g., using Ziehl-Neelsen staining) is most suitable for peripheral laboratories, while fluorescence microscopy is preferable in larger laboratories because it allows more specimens to be examined in the same time. The number of cases detected depends on the number of sputum specimens examined per patient; if the prevalence of smear-positive patients is high in the patient population, the examination of smears from several specimens, especially an early morning or overnight collection, will detect a large proportion of the infectious cases in the community.

The examination of cultures will confirm the diagnosis of tuberculosis in an additional number of patients, mainly those not excreting large numbers of bacilli; however, culture services should be provided only in large laboratories, and only when a reasonably high proportion of smear -positive cases are already being discovered and treated by chemotherapy.

Sensitivity tests are mainly of value for epidemiological purposes and for selecting standard regimens for large-scale chemotherapy programmes in individual countries. In the individual patient such tests are useful when the smear and culture examinations suggest that chemotherapy has failed. However, no laboratory should embark on sensitivity testing without skilled staff, adequate equipment, and sufficient interest to sustain a high standard of work.

Risk of infection among laboratory staff is higher in laboratories undertaking culture and sensitivity testing than in those doing smear examinations only: the most effective single safety precaution is the provision of ventilated inoculation cabinets.

Chemotherapy

Adequate chemotherapy should be given free of charge to every patient detected; such treatment reduces transmission of infection and saves many lives.

Ambulatory treatment. Since the eighth meeting of the WHO Expert Committee on Tuberculosis, further studies comparing domiciliary and institutional treatment have been reported, and all have confirmed that the latter is not essential. The Committee therefore reaffirmed its support for ambulatory programmes rather than hospital treatment. Despite the dramatic progress in chemotherapy in the last 20 years some countries adhere to out-moded long-term sanatorium treatment.

Intensive chemotherapy at the beginning of treatment. The early stages of chemotherapy are crucial, especially for infectious patients. If supplies of the standard drugs are plentiful, treatment should start with a course of triple-drug chemotherapy including isoniazid) for 1-3 months, followed by a two-drug regimen (including isoniazid). Intensive chemotherapy is also more effective in minimizing the influence of initial drug resistance by the strains.

Effective regimens and regularity of chemotherapy. In selecting the regimens for national programmes, the efficacy, toxicity, acceptability, bulk, and cost of the available drug combinations must be considered. Combinations and dosages used for standard regimens in national programmes should be those established in well conducted clinical trials. The main drugs available are isoniazid, streptomycin, p.aminosalicylic acid (PAS), and thioacetazone, with which highly effective and relatively inexpensive regimens can be formed. Doses of 300 mg of isoniazid and 150 mg of thioacetazone in patients weighing 35 kg or more combine effectiveness and low toxicity; the combination is widely used in one daily dose in a single tablet. It is inexpensive, has good keeping properties even in tropical conditions, and is convenient both to dispense and to take. More recently rifampicin (which is particulary expensive) and ethambutol have been introduced in affluent countries, but even in these countries cost is often decisive in choosing standard regimens for widespread use. Modern chemotherapy should cure almost all newly diagnosed patients if an

effective regimen is provided for an adequate period and if regular ingestion of the drugs is ensured either by careful supervision of a standard self-administered regimen or by intermittent regimens under full supervision.

Intermittent regimens. Fully supervised intermittent chemotherapy overcomes any undetected irregularity in long-term self-administration of drugs; appropriate action can be taken at once when a patient fails to attend for a supervised dose. The standard intermittent regimen is 1 g or 0.75 g of streptomycin, plus isoniazid in a single dose of approximately 15 mg per kg body-weight, given together on 2 days each week, preferably with 5-10 mg of pyridoxine to prevent peripheral neuritis. There is a need also for fully oral, standard, intermittent regimens; promising results have been obtained with twice-weekly PAS plus high-dosage isoniazid. As with daily regimens, intermittent regimens should be preceded by a daily intensive phase of chemotherapy for 1-3 months. Once-weekly continuation regimens cannot yet be recommended for general use, but research on them is continuing.

Duration of chemotherapy and retreatment. In many countries chemotherapy is still prescribed for a minimum of 18 months to 2 years for bacteriologically confirmed cases. It is becoming evident that the benefits of prolonging chemotherapy beyond a year are small, and that efforts should rather be concentrated on ensuring an uninterrupted regimen of 1 year for every patient. The use of short-course regimens, some lasting only 6 months, is still at an experimental stage.

The need for retreatment should be avoided as far as possible. However, if the original treatment fails, despite every effort to ensure the highest standards, several choices of retreatment regimen are now available. When isoniazid and thioacetazone strengthened by streptomycin in the initial intensive phase constitute the usual regimen, a combination of streptomycin, PAS, and pyrazinamide is still effective in retreatment and has a relatively low toxicity. Traditional regimens containing ethionamide, pyrazinamide, and cycloserine are expensive, toxic and usually require hospitalization; they are being replaced where possible by regimens of rifampicin and ethambutol.

Initial drug resistance. Failure to respond to the standard regimens of chemotherapy because of initial drug resistance is more likely to occur in the very small proportion of patients with multiple drug-resistant strains than in those with resistance to one drug only. A few areas in Africa report thioacetazone-resistant strains (of the type Mycobacterium africanum) to be so common as to make regimens containing thioacetazone unsuitable.

Observations and follow-up. Bacteriological investigations are much more informative than radiography in following the progress of chemotherapy. The examination of sputum smears from six months onwards will detect the majority of failures, whether due to persisting bacteriological positivity or to relapse. Culture examination, used in addition, may occasionally provide earlier evidence of failure; and sensitivity tests may then be carried out to assist the planning of further chemotherapy, e.g. by determining whether failure is due to the emergence of drug resistance or to inadequate drug ingestion, in which case the organisms often remain drug-sensitive and will still respond to the original regimen, if well supervised.

With better organized administration of increasingly potent regimens, relapse in patients who have completed the prescribed course of chemotherapy should be rare. Much less emphasis is therefore necessary than in the past on the follow-up of such patients, who can simply be advised to return if the symptoms recur. Concentration on case-finding programmes and the supervision of original chemotherapy is being found more rewarding, even in the technically advanced countries.

Preventive treatment. A policy of preventive treatment (often termed chemoprophylaxis) is irrational, even for special risk groups, unless the treatment programme for patients suffering from infectious tuberculosis is widespread and well organized, with a high rate of cure. In chemoprophylaxis programmes cases of isoniazid-associated hepatitis, some of them fatal, have been reported in increasing numbers, and such side effects must be weighed against the small chance of benefits. Furthermore, the social and economic penalties to the individual labelled "high-risk" or "tuberculous", the substantial cost, and the difficulty of persuading

apparently health individuals to accept long-term treatment make preventive treatment unsuitable for mass application in a community health programme.