SEMINAR ON
RECENT TRENDS IN TUBERCULOSIS CONTROL
Karachi, 23 - 30 October 1975

REPORT
The views expressed in this Report do not necessarily reflect the official policy of the World Health Organization.

This document has been prepared by the WHO Regional Office for the Eastern Mediterranean for Governments of Member States in the Region and for those who participated in the Seminar.
Group of Participants and Observers who attended the Seminar on Recent Trends in Tuberculosis Control, which was held in Karachi, Pakistan, from 23 to 30 October 1975, photographed with H. E. Mr. Hafeezullah Cheema, Minister of Labour, Health, Social Welfare and Population Planning, Government of Pakistan, Lt. Gen. A. N. Ansari, Secretary, Health and Social Welfare, Government of Pakistan, Dr. H. Mkhler, Director - General of WHO and Dr. A. H. Taba, Director, WHO Eastern Mediterranean Region.
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INTRODUCTION

The Regional Seminar on Recent Trends in Tuberculosis Control was held in Karachi, Pakistan, from 23 to 30 October 1975.

Objectives

1. To acquaint the national participants in charge of tuberculosis control programmes in the countries of the Region with the recent trends in tuberculosis control and the recommendations made in the Ninth Report of the WHO Expert Committee on Tuberculosis.

2. To review the progress made by and the problems of the national tuberculosis control programmes in the Region.

3. To recommend new approaches to planning, implementation and assessment of national programmes that could constitute realistic guidelines for the better direction of control activities under the various epidemiological and socio-economic conditions in the Region.

Participants

Twenty countries were represented. The list of participants, observers and secretariat is given in Annex III.

Opening Session

The opening session was held at the Inter-Continental Hotel on 23 October. The participants were welcomed by Dr M. Haeeen, Director, Tuberculosis Control, Government of Pakistan. Messages were read from H.E. Mr Fazal Elahi Chaudhry, President of Pakistan, H.E. Mr Zulficar Ali Bhutto, Prime Minister, Lt. General A.N. Ansari, Secretary, Ministry of Health, Population Planning and Social Welfare and Prof. Nasir Ahmed B. Shaikh, Director-General, Health. The inaugural address was given by H.E. Mr Hateezullah Cheema, Minister of Labour, Health, Social Welfare and Population Planning. Addresses were also given by Dr H. Mahler, Director-General, World Health Organization and Dr A.H. Tabs, Regional Director, World Health Organization, Eastern Mediterranean Region (Annex II).

Plenary Sessions

The plenary sessions were held in the Banquet Hall of the National Bank of Pakistan.

The topics were introduced by selected speakers, their papers being followed by general discussion.

Field visit

On 28 October the participants visited the District Tuberculosis Centre at Thatta and a Rural Health Centre at Mirpur Sakhro. The subject of "The Role of Basic Health Services in Tuberculosis Control" was presented and discussed during this visit.

Documents

Selected documents were distributed to the participants and observers during the Seminar (Annex I).
The following were elected:

**Chairman** Dr M. Hasan (Pakistan)

**Vice-Chairman** Dr H.S. Dabbagh (Saudi Arabia)

**Reporter** Professor Abdul Aziz (Pakistan)

**Secretary** Dr J. Kaleta (WHO)

**SESSION 1**

I WHO POLICY IN TUBERCULOSIS CONTROL: A REVIEW OF RECOMMENDATIONS OF THE WHO EXPERT COMMITTEE ON TUBERCULOSIS

PRESENTED BY DR K.L. HITZE, CHIEF MEDICAL OFFICER, TUBERCULOSIS UNIT, WHO/HQ8

The programme of work which the World Health Organization is carrying out in the various fields of health, including tuberculosis control, is not only monitored by the Executive Board of the Organization and the World Health Assembly (the two directing bodies of WHO) but also critically reviewed with regard to its technical policy content by independent experts. These experts, forming the WHO Expert Committees, are drawn from the Expert Advisory Panels which the Organization maintains.

After the concept of the National Tuberculosis Control Programme had been formulated, the WHO Expert Committee, in 1964, recommended it as the technical policy of choice. In this context, a number of traditional contentions and notions regarding tuberculosis were challenged on scientific grounds. At its ninth meeting in 1973, the Committee had to review the recommendations made in its eighth report, in the light of the scientific evidence and practical experience that had subsequently become available.

To ensure that the actual needs and demands of the different parts of the world were duly taken into account, the Committee comprised experts from the various WHO Regions, representing widely varying professional backgrounds and experiences as regards tuberculosis and its control, as well as health-care practice and administration in general. Most of the Committee members were also serving on the scientific committees of the International Union against Tuberculosis, or had important functions in the Union's directing Committees.

Reviewing the available control measures - preventive and curative - the Committee not only confirmed its previous technical and policy recommendations but provided further evidence to support them and gave details to facilitate their application under actual service conditions.

It was emphasized that the greatest attention must be paid to the use of high quality BCG vaccine that complied with the requirements established by WHO; that the intradermal vaccination technique by needle and syringe remains the most precise way of administering the desired vaccine dose; that it is essential to achieve a high coverage of the age groups eligible for vaccination; that direct vaccination, i.e. without previous tuberculin testing, was to be favoured under almost all circumstances owing to its operational advantages and because it facilitated simultaneous immunization against smallpox, measles, yellow fever, diphtheria, pertussis and tetanus.

It was stressed that an appropriate balance must be kept with the treatment services, and that case-finding and treatment programmes should be developed as an entity. For diagnosis, only the demonstration of tubercle bacilli is conclusive. Moreover, patients who can be diagnosed by direct sputum smear examination constitute the first priority group.

1A copy of the Ninth Report had been sent to each participant well in advance to ensure that its contents were known.
in a tuberculosis control programme since they are responsible for the transmission of infection in the community. To render them non-infectious, adequate chemotherapy should be given to each patient with infectious tuberculosis. Benefits of prolonging chemotherapy beyond one year are small but the regularity of drug-taking is crucial and all-important. Since regularity could be expected to improve with shortening the duration of chemotherapy, the Committee had emphasized the importance of research into short-course chemotherapy.

If every effort were made to ensure the highest level of success in original treatment, the need for retreatment would be reduced. Also, when patients successfully complete the prescribed course of chemotherapy subsequent relapse should be very rare and, in consequence, much less emphasis is necessary than in the past on the follow-up of patients. With a few exceptions, it is more rewarding to concentrate on organizing case-finding programmes and improving the supervision of original chemotherapy.

Since reliable diagnosis tools and efficacious preventive and curative methods are available and because they can be both simple and inexpensive, an effective tuberculosis control programme can be delivered under almost any situation, provided planning and application are guided by a clear understanding of the epidemiological, technical, operational and economic aspects. To this effect, relevant, programme-oriented training of all categories of personnel, including programme planners and supervisors, is of crucial importance. The present Seminar was held to promote the understanding of the principles as well as the requirements of the national tuberculosis control programme contained, and reiterated, in the Ninth Report of the WHO Expert Committee on Tuberculosis.

Discussion

After the presentation, a number of comments were made by participants but the discussion of specific technical points was deferred until later sessions, when each topic would be considered in detail.

SESSION 2

II THE PRESENT SITUATION OF TUBERCULOSIS CONTROL
IN THE EASTERN MEDITERRANEAN REGION
PRESENTED BY DR. J. KALETA, REGIONAL ADVISER
ON TUBERCULOSIS, WHO/EMR

There is adequate evidence that tuberculosis continues to be one of the major health problems in the majority of countries in the Region. Moderate estimates indicate that there are at least half a million open, infectious cases. More than 50 per cent of the population is infected with tubercle bacilli; and this constantly produces new cases. Despite continuous improvement and a steady decline of the disease in many member countries, in some of which annual infection rates dropped below one per cent (Cyprus, Lebanon), there are other countries with unusually high prevalence ratios where such trends have not yet been observed (Ethiopia, Somalia, Sudan and Yemen).

The great majority of countries in the Region plan and implement their national tuberculosis control programmes based on the concept recommended by WHO. Governments have adopted feasible approaches reflecting the various local epidemiological, economic and social situations.

Integration of tuberculosis activities into the general health facilities, although not uniformly adopted, is progressively gaining ground even in countries with specialized services; and collaboration with the developing basic health services is being recognized as the chief means of implementing simple tuberculosis control measures in rural areas.
In the field of prevention, BCG immunization occupies a dominant place in the countries' tuberculosis control programmes. Their strategy is continuously shifting from the sporadic and irregular mass campaigns towards integrated vaccination programmes or to combined BCG/smallpox immunization. Direct vaccination without prior tuberculin testing is being applied in almost all countries of the Region, using imported freeze-dried vaccine of high quality. Yet the quality control of vaccines (samples from the field before use, after storage and distribution) in WHO reference laboratories, which has been offered, is being rarely used. A major problem which still has to be overcome is the proper coverage of the eligible child population. In some countries it does not reach 5 per cent of pre-school children, and less than 50 per cent of school-age children.

Indiscriminate mass X-ray screening for the purpose of detecting infectious cases is definitely a method of the past. Bacteriological procedures are considered conclusive for diagnosis. Special emphasis is being placed on intensifying and improving sputum examination of coughing patients reporting themselves to the general health services, and on the strengthening of laboratories in these services. Individual X-ray examination may be useful only for screening out persons with lung abnormalities for bacteriological examination.

Hospital treatment of tuberculosis patients is giving way to ambulatory chemotherapy. However, the high rate of default among patients and irregularities in drug intake, resulting from the paucity of health centres and clinics, the long wait for attention that is often necessary and deficiencies in all aspects of the organization, remain major problems of ambulatory treatment.

Despite gradual improvement, several serious problems can be readily indentified:

1. The large number of undetected cases still causing high levels of public exposure to infection.
2. Low coverage of the target population by BCG.
4. Underdeveloped or non-utilized capacities for case-finding.

There are very rich countries and less economically fortunate countries in this Region but in none of the countries is the Tuberculosis Control Programme well-developed or its objectives achieved. Even rich countries lack the required strength of manpower.

(The tables relating to various aspects of tuberculosis in the Region are in Annex V).

Discussion

In general, the problems identified by the participants included:

1. Shortage of manpower, especially doctors and technicians, in most of the countries of the Region.
2. Insufficient number of basic health centres so that integration programmes cannot be carried out satisfactorily.
3. Lack of communications and roads and also lack of transport facilities.
4. Low BCG coverage.
5. Defaulter rates in treatment are often very high.
6. Incomplete data on all the activities of the programme.
7. Shortage of drugs. A plea was made that UNICEF/WHO should provide drugs in the form of a "drug bank". Anti-tuberculosis drugs should be available at reasonably inexpensive prices or supplied to countries under tripartite agreements.

In relation to the last item, information was given that the problem had already been brought to light by WHO and that UNICEF is prepared to assist.

Attention was drawn to the fact that in the National Tuberculosis Control Programmes, the respective countries should ensure that the programme can be maintained by their own services. This is because UNICEF assistance is inevitably time-limited and is meant only to accelerate the programme.

Attention was drawn to the World Health Assembly resolution WHA27.34 regarding assistance to the twenty-five least economically fortunate and developed countries of the world, of which five are in this Region.

It was suggested that a programme of mutual assistance should be developed within the Region so as to make available material and manpower resources to countries in need of them.

SESSION 3

III PREVENTION

1. The Strategy of BCG Vaccination Programmes: Epidemiological, Technical and Administrative Considerations

Presented by Dr M. Hasan, Director, Tuberculosis Control, Pakistan

The objective is to protect non-infected persons from tuberculous infection by increasing their resistance; and BCG vaccination is still the best available tool for the purpose. The protective efficacy of BCG vaccination has been shown to be a maximum of 80 per cent.

The world community is divided into low prevalence and high prevalence countries. More benefit from BCG can be derived in the high prevalence countries; but there is also some benefit in the low prevalence countries.

BCG vaccine should be obtained from a highly reliable source. The quality of the vaccine should be constantly assessed by an independent organization in order to maintain its maximum efficacy in the field.

Freeze-dried vaccine is the vaccine of choice. It lasts for one year provided it is stored under proper optimum conditions. Intradermal administration is the best as the dose is accurately measurable and the local reactions are within tolerable limits.

For mass work, direct vaccination up to school leaving age should be the method of choice. Simultaneous BCG and smallpox vaccination should be undertaken. Other immunization programmes can be combined with this. For the success of BCG programmes, it is imperative to vaccinate at least 80 per cent of susceptible children.

The problem of the developing countries is not the lack of technical ability but the application of the technical knowledge through an efficient administrative organization.

Vaccination programmes should be integrated with the basic health services of the country, adopting the multiple immunization programme. Newborn babies may be vaccinated at the maternity centres as well as at their homes. School health services should increase the BCG vaccination programme to its maximum coverage. A central organization is recommended for planning, co-ordination and the ultimate success of the programme.
2. **Assessment of BCG Vaccination in the Libyan Arab Republic**  
Presented by Dr M. Ashraf, Chief, Endemic Diseases Section, Ministry of Health, Libyan Arab Republic

In the Libyan Arab Republic, BCG vaccination is compulsory during the first month of life. The policy of BCG vaccination is to achieve the maximum coverage of population. Vaccination is available at maternity and child health centres, school health centres, during mass miniature radiography (MMR) surveys, and special mass vaccination campaigns. It is also given to contacts of tuberculosis cases, persons attending Tuberculosis Control Centres and found to be tuberculin negative, to contacts of patients with leprosy and to staff working in tuberculosis institutions. Training of BCG workers is carried out at Tripoli and Benghazi. Training manuals have been prepared in Arabic and English. There are 192 BCG vaccination centres in the country. The vaccine is procured every four months to assure that it is fresh from a WHO-approved source.

Continuous assessment of the activity of the vaccination campaign is necessary. Various operational and technical components can be used as indicators of efficiency, such as: (i) The convenience, accessibility and continuity of the services. (ii) Health education of the public. (iii) Technical quality of the service. (iv) Vaccine storage. (v) Technique of injection. (vi) Recording and reporting. (vii) Vaccination of newborns and school children. (viii) Incidence of tuberculous meningitis. (ix) Vaccination scar surveys. (x) Limited tuberculin surveys for special purposes. The average vaccination coverage in the age-group up to fifteen years in Libya was 80 per cent, the range being 44.3 per cent to 94.9 per cent. A brief description was given of the methods and results of a BCG scar survey carried out in school children during 1974; 90.7 per cent of the children were found to have scars.

3. **Discussion**

It was emphasized that the vaccine used should be of good quality. The World Health Assembly passed a resolution (WHA27.54) to this effect in which member countries importing BCG vaccine on a bilateral basis, or producing vaccine, are recommended to avail themselves of the international system of assaying the quality of BCG vaccine set up by WHO, until these countries have established a competent national control service of their own.

With the use of quality-controlled, freeze-dried BCG vaccine, the main objective of evaluating the BCG vaccination programme is to see that it is being conducted in an effective manner, and hence to provide a basis for corrective action. For this purpose, the effectiveness of a programme is sufficiently expressed in terms of vaccination coverage, estimated by means of sample surveys of vaccination scars.

Some information on the quality of the vaccination can be collected with little extra effort. In the first place this concerns the size of the lesion or scar. Measuring scars, rather than counting them only, not only ensures greater accuracy on the part of the evaluation team but provides information on the proportions of excessively large and conspicuously small scars, both indicating a poor technique. Such data can be supplemented with data on subcutaneous abscesses, reported lymphadenitis, hypertrophic scars, keloid formation, etc.

Separate information on the quality of the vaccine just before its application (i.e. the effect of transport and storage) may be obtained by occasionally collecting samples from the field and having them examined for viability. The handling of the vaccine during storage, transportation, and at the working site must be investigated by field visits to the respective vaccination teams, an activity which is an indispensable part of programme supervision and has to be carried out continuously.

Tuberculin surveys are required to measure the prevalence of infection and to follow the trend of the risk of infection. In view of the widespread use of BCG vaccination, it
may be thought no longer possible to undertake these surveys. However, in most countries in the Region there is a low BCG coverage in pre-school children. Therefore, it will still be possible for some time to come to conduct sample tuberculin surveys, for instance at school entrance age.

The results of vaccine calibration and operational trials of vaccination with the bifurcated needle technique were described. It was pointed out that the results with the bifurcated needle have been inferior in terms of post-vaccination allergy. As there is a dose-response relationship, this indicates that too little of the vaccine has been introduced into the skin. Thus, the objective of giving the largest tolerable amount of vaccine has so far not been obtained by the bifurcated needle technique.

However, percutaneous vaccination with a concentrated vaccine could play a role in the vaccination of newborns and small infants.

IV CASE-FINDING

1. The Relative Merits of Various Diagnostic Methods in Tuberculosis Control Programmes

Presented by Dr S.S. Badr, Head of Chest Unit, Ministry of Health, Democratic Yemen, and Dr G. Sabapathy, Medical Officer, WHO Tuberculosis Control Project, Aden

The standard diagnostic methods used in tuberculosis control programmes are sputum microscopy for tubercle bacilli and chest radiography.

Various studies have been undertaken to investigate the relative merits of the two methods. They have shown that X-ray diagnosis is not reliable in the diagnosis of tuberculosis; there is greater likelihood of error than with efficient sputum examination. Moreover, this method, when employed as a screening procedure for case-finding, is costly and is not practicable in peripheral areas of the developing countries.

Sputum smear examination is the definitive method for discovering infectious cases and it is comparatively inexpensive. Sputum culture adds more cases but these are far less infectious and the procedure adds to the cost. Therefore it was stressed that for any effective tuberculosis control programme, sputum examination should be given a high priority.

Discussion

It was made clear that it is not only the examination of the slide under the microscope which is important, but the whole procedure from the collection of sputum from the patient, selection of the best material for making a smear, fixation and staining of the slide, and finally the thorough search of the slide under the microscope by a properly trained person. All are necessary steps of equal importance in improving the diagnosis of tuberculosis by sputum microscopy.

The advantage of fluorescence microscopy was also discussed. It was stated that wherever a large number of sputum specimens had to be examined and electricity was available, the method has some advantages.

As regards sending sputum specimens or smears prepared in peripheral centres to centrally located laboratories, it was considered that, if the transport facilities were adequate, it may be worthwhile adopting this procedure.
Emphasis in the discussion was laid on the need not to extend case-finding activities beyond the capacity of the treatment services in the particular region to ensure a high proportion of cures among the cases discovered.

The use of radiography in case-finding was also discussed. It was considered that the value of indiscriminate mass X-ray surveys was small in comparison to their cost. Where X-ray facilities were already available they should be used in asymptomatic patients to select those from whom sputum should be examined. It was, however, re-emphasized that the definitive diagnosis of pulmonary tuberculosis was the finding of tubercle bacilli in the sputum.

SESSION 4

V EPIDEMIOLOGY: RECENT ADVANCES IN EPIDEMIOLOGICAL RESEARCH IN TUBERCULOSIS
PRESENTED BY DR K. STYBLO, WHO CONSULTANT

Tuberculosis epidemiology deals with the "natural" relationship between the tubercle bacilli and a given population, without any man-made interference.

The main task of tuberculosis epidemiology is to discover the values of all important parameters (a parameter is defined as a constant indicating the numerical value which links two variables). Examples of parameters are: a "contagious" parameter (an average number of persons infected with virulent tubercle bacilli during one year by one source of infection); the disease ratio (the proportion of cases in which infection with virulent tubercle bacilli will lead to the development of a source of infection); etc.

Three distinct events should be studied separately:

(a) The transmission of infection

Annual tuberculosis infection rate indicates the proportion of the population under study which will be primarily infected, or reinfected (in those who have been previously infected) with virulent tubercle bacilli in the course of one year.

Reference was made to the Tuberculosis Surveillance Research Unit (TRSU) Report No. 1 (1969) in which a technique for converting information on prevalence of infection into a smooth series of annual rates of infection is described. Several examples were given of how the annual tuberculosis infection rates could be estimated easily. It was observed that in a few countries of the Region the risk of infection had been decreasing rapidly during the last few years; however, in most of them the decrease in the risk of infection might be only 5 per cent or less; and in some of the countries of the Region no decrease in the risk of infection might have occurred. It is desirable to obtain reliable information about the level of the risk of infection and its trend in all countries of the Region. A sample of children aged about six years (at school entry) may be examined (the proportion of pre-school children vaccinated with BCG is relatively low in the Region).

It was shown that the most important transmitters of infection were patients in whose sputum tubercle bacilli could be demonstrated by direct smear examination.

The "contagious" parameter, i.e. the number of persons infected with tubercle bacilli, seems to be about fourteen for the Netherlands (for the period 1921 - 1939 and 1951 - 1968) and about ten for Lesotho and Uganda (based on the surveys carried out by WHO in the late 1950s).

(b) Development of tuberculosis following infection

The disease following primary infection is usually called "primary" tuberculosis. (For the purpose of epidemiological studies, any tuberculosis developing during the first five
years following primary infection is classified as "primary" tuberculosis. Any pulmonary tuberculosis diagnosed more than five years after primary infection is classified as "secondary" tuberculosis.

It was shown that "primary" tuberculosis has a limited impact on the transmission of tuberculous infection because:

(i) Smear-positive tuberculosis cases following primary infection in children are infrequent both in low and high prevalence countries;

(ii) Smear-positive tuberculosis cases following primary infection acquired during adolescence or in adult life are relatively frequent (about 25 per cent of all cases in the age-group 15 - 19 years) but their contribution to all smear-positive cases discovered in the entire adult population is numerically small;

(iii) Primary infections among middle-aged, elderly and old people are uncommon both in low and high prevalence countries.

"Secondary" tuberculosis raises the problems of endogenous exacerbation and exogenous superinfection. The controversy between the two theories was discussed at some length. Reference was made to the TSRU studies presented at the International Tuberculosis Conferences in Moscow and Tokyo (Sutherland and Svandova), as well as to the observations made among Eskimos, and finally to the observation of the relationship between tuberculous infection and mortality and morbidity in the Netherlands, Lesotho and Uganda.

It seems that exogenous superinfection does play an important role in the pathogenesis of tuberculosis among adults, if the risk of infection is high.

(c) From development of smear-positive tuberculosis to recovery or death

Observations in Denmark (in the pre-chemotherapy period) and from the longitudinal study in India indicate that after about five to eight years one-half of the patients with smear-positive tuberculosis, if not given effective treatment, will have died from their disease and that the other half will have recovered, in the sense that they will have stopped discharging tubercle bacilli.

It was also shown that with effective treatment it is possible to cut the total prevalence of sources of infection to about a half of what it would be without such treatment. With effective treatment measures we could expect to halve the annual infection rate.

On the basis of these observations, it was concluded that:

(i) The most important epidemiological index relevant to measurement of the tuberculosis problem is the annual tuberculosis infection rate and its trend.

(ii) An important epidemiological index is the incidence and prevalence of tuberculous patients excreting bacilli demonstrable by direct smear examination.

(iii) The most important transmitters of infection are patients in whose sputum tubercle bacilli can be demonstrated by direct smear examination.

(iv) The epidemiological situation could be improved most rapidly by case-finding and effective treatment of smear-positive patients.

Discussion

Various technical questions were asked by participants and answered by the speaker.
VI TREATMENT

1. Recent Controlled Clinical Trials of Chemotherapy in Tuberculosis
   Presented by Dr. J.R. Bignall, WHO Consultant

   The greatest handicap to successful treatment has been the need to continue chemotherapy for long periods. This imposes an often insurmountable strain on the patients and the treatment services. Treatment must be made easier for the patients.

   Much can be done by efficient organization of the treatment services to avoid long distances to travel and long waits at clinics, by more sympathetic attitudes of the clinic staffs and by general health education. The administration of drugs can be monitored by urine examinations and "pill counts" during surprise visits to the homes. All treatment can be supervised. Supervision of each dose administered does not ensure regular treatment, but it does ensure that action can be taken to remedy irregularity of attendance.

   Recent controlled trials have been concerned with further exploring intermittent regimens that can be supervised and with shortening the duration of treatment.

   The essential for a successful short regimen is a powerful "initial kill" of tubercle bacilli by bactericidal drugs. These are isoniazid, rifampicin and the combination of streptomycin and pyrazinamide. Isoniazid, rifampicin and pyrazinamide are more effective when given at intervals of longer than one day. It is these three drugs, therefore, that appear most suitable for both intermittent and short course regimens.

   Among the intermittent regimens tested, attention was drawn to the regimen studied in East Africa - streptomycin, isoniazid and thiacetazone daily for eight weeks, followed by isoniazid and thiacetazone twice-weekly for a year. This had given good results and the regimen is relatively inexpensive.

   Increasing the interval between doses to a week in intermittent regimens of isoniazid and streptomycin has not been successful. It was adequate in slow inactivators of isoniazid but not in rapid inactivators. A slow-release form of isoniazid has been tried, but so far not proved successful owing to unexpected side-effects.

   It was emphasized that no trials had shown that a supervised intermittent regimen gave better results than a daily unsupervised one in co-operative patients. Supervised regimens could be valuable in certain circumstances and in certain patients, but should not be adopted as standard regimens for all patients in all circumstances.

   Intermittency and supervision will not solve the problem of obtaining full co-operation in all cases. The treatment must be shortened.

   A British/East African Medical Research Council trial of a six-month regimen of rifampicin, isoniazid and streptomycin given daily gave as favourable results as the standard regimen in that area of isoniazid and thiacetazone daily for eighteen months with streptomycin supplement the first eight weeks. The relapse rate was only 3 per cent during the thirty months after the end of treatment. The cultures from the relapsed patients were still sensitive to the drugs, so that they could be re-treated with the same regimen. Moreover, almost all relapses occurred during the first six months after treatment ceased; so that long-continued observation after such a regimen is unnecessary.

   A similar regimen with isoniazid, streptomycin and pyrazinamide was only a little less favourable, with 8 per cent relapses.

   These two six-month regimens are, of course, not practically useful for developing countries as they require daily injections and are expensive.
Further trials in East Africa have shown that the streptomycin is unnecessary if isoniazid and rifampicin are given daily for six months. Following an initial intensive phase of streptomycin, isoniazid, rifampicin and pyrazinamide for eight weeks, good results were obtained with either isoniazid and thiazetazone daily or streptomycin and isoniazid twice a week up to six months. Thus the cost of the regimens and the difficulty of applying them can be reduced.

Trials in Hong Kong have shown that streptomycin, isoniazid and pyrazinamide three times a week for nine months give good results, with a low relapse rate. The results in patients with initially resistant cultures were, as expected, less good. However it was estimated that, even with 20 per cent of initial resistance, 85 per cent of all patients treated with this regimen would achieve lasting non-infectiousness if they co-operated throughout the nine months of treatment.

No short course regimen of less than nine months' duration can at present be recommended for general use. However, it is very probable that within the next few years practicable and economical regimens of six months' duration or less will become available.

The success of such regimens will depend both on their initial efficacy and on the relapse rates. A 10 per cent relapse rate might at first sight be considered unacceptably high. However, with such a regimen there could be an important epidemiological advantage. With the existing prolonged regimens, as they are applied in the Region, a high proportion of patients remain infectious - some of them with resistant tubercle bacilli - through irregular drug ingestion and premature cessation of treatment. The number of infectious sources would be considerably reduced if a short, say two months, efficient, well-tolerated regimen were used: almost all the patients would complete treatment and become non-infectious and the few who relapsed could be quickly re-treated and made non-infectious again. Indeed, a regimen with a relapse rate of even more than 10 per cent might prove epidemiologically advantageous. And it is by the epidemiological effect within the community that any chemotherapy regimen should be judged.

The drugs and the ways in which to use them are already available to control tuberculosis. What is lacking is the social organization to put into practice the discoveries of laboratory investigations and controlled clinical trials - and the will to succeed.

2. Application of Chemotherapy in the Integrated Tuberculosis Control Programme in Ethiopia

Presented by Dr J. Susteric, Medical Officer, WHO Tuberculosis Control Project, Addis Ababa

Ethiopia is a developing country with a population of twenty-five million, poor communications and very low national income. The prevalence of infectious cases is 1 per cent. The general and basic health services have more or less successfully collaborated with tuberculosis centres especially in case-finding and treatment programmes.

Extensive tuberculosis control training of Ethiopian health workers at all levels has raised the interest in tuberculosis control in basic and general health services. Drugs and BCG vaccine have been supplied by UNICEF on the basis of the reported work performance of centres. Health education has been carried out extensively.

The Ministry of Public Health in 1971 gave official approval to programmes for hospitals, health centres and larger clinics and health stations and small clinics. Each of the fourteen provincial health departments assigned an integration health officer to supervise integrated programmes in their provinces. A referral system has been established and documentation and reporting systems introduced.
In 1973, 1,419,618 patients were examined in general hospitals and 43,048 sputum specimens examined, with 7,115 positive results. A total of 14,308 patients were diagnosed as tuberculous and treatment started.

Patients are diagnosed on the basis of sputum microscopy. But in general hospitals, by chest X-ray appearances only. No wonder many such patients fail to respond well, for they are not suffering from tuberculosis.

For advanced cases in poor condition, tuberculous patients with other diseases requiring treatment, and patients living in remote areas, short initial combined chemotherapy has been given as in-patients in hospital. By a rapid turn-over of patients it has been possible to secure adequate initial chemotherapy for 5,409 patients during one year although there are only 700 tuberculosis beds.

A survey of the results of ambulatory treatment at Addis Ababa Tuberculosis Centre showed that, in spite of all difficulties (great distances, poor communications and poverty) 67 per cent of pulmonary tuberculosis cases are known to have achieved sputum negativity on microscopy, when treated initially for an average of forty-five days in hospital, followed by domiciliary treatment. But only 33 per cent did so when treated on a domiciliary basis from the start. Such initial short intensive supervised treatment is essential for later regularity in ambulatory treatment.

Various drug regimens are used incorporating streptomycin, isoniazid and thiacetazone. The twice-weekly supervised regimen is a recognized treatment method in Ethiopia but is not often used. After the first three months with any regimen, about half the patients become irregular in collecting drugs.

Patients receive drug supplies for two or three months in the plastic containers designed for collecting sputum. This is necessary to avoid deterioration of the drugs from moisture, especially during the rainy season.

Ambulatory chemotherapy of tuberculosis has become, in spite of limited resources, a mass enterprise in all provincial health institutions.

In spite of all the shortcomings of an integrated tuberculosis control programme in a developing country, it is the only way to organize a national programme with present-day resources.

With further development, strengthening and improvement of basic and general health services, and more discipline among health workers, the integrated tuberculosis control programme will succeed.

Discussion

It can be accepted that admission to hospital is seldom necessary for effective treatment, providing that domiciliary services are adequate and well-organized. However, there appears to be a need in some circumstances for the provision of "hostels" for certain patients, particularly those living in remote areas and those without homes. The "hostels" can be merely simple, inexpensive structures designed to give shelter and feeding facilities to patients while they are given, under supervision, the important initial phase of chemotherapy.

There appeared to be considerable differences between the countries of the Region in the control of anti-tuberculosis drugs. In one country the drugs are completely controlled by the tuberculosis service. But in about half the countries the drugs can be purchased from pharmacies by the public without a doctor's prescription. Some of these countries are receiving drugs from UNICEF.
There is a great need for more operational research into the methods used to obtain full
cooperation and ensure regular drug administration. Lack of regular drug-taking is the
major factor limiting the success of treatment.

Sensitivity tests are not necessary for effective initial treatment. Although they may
be of slight value in re-treatment, they are not essential for success. Moreover, few
laboratories are able to carry out accurate sensitivity tests; inaccurate tests may mislead
the clinician and cause unnecessary changes of drug regimen or unnecessary use of expensive
drugs.

Since cost is decisive in choosing standard regimens for widespread use, those regimens
should be selected that ensure the maximum epidemiological effect for the given funds. The
following example was given:

Given a budget of $15,000 for drugs only, 1,000 bacteriologically confirmed cases of
tuberculosis could be treated with a regimen of daily streptomycin, PAS and isoniazid for
two months followed by ten months of either twice-weekly supervised administration of strep-
tomycin and isoniazid or by daily self-administered isoniazid and PAS. This regimen is
known to have a therapeutic efficacy in the order of 95 per cent. It costs about $15 per
patient per year (at UNICEF prices). Assuming that only 50 per cent of patients co-operate
and this is a not unreasonable estimate in many countries - the actual effectiveness of the
treatment would be to reduce infectiousness by about 47 per cent.

With a short-course chemotherapy regimen using rifampicin and isoniazid administered
daily for a total duration of six months, only 135 infectious patients could be treated with
the same amount of money (estimating the cost of one capsule containing 150 mg rifampicin
at $0.15). Even if 100 per cent therapeutic efficacy and 100 per cent co-operation is
assumed for this short regimen, the reduction of the tuberculosis problem in terms of
decrease of number of infectious sources will be in the order of only 13.5 per cent. After
one year, with the same budget for drugs, the original pool of 1,000 sources of infection
would be reduced to 525 by the former programme, while in the second there would remain
865 sources of infection.

Hence the need for careful programme planning and evaluation.
been rapid during the last six years, progress in the National Tuberculosis Programme was limited.

Well-developed malaria and smallpox programmes existed in 1969 in the country but were not included in the integrated programme, except to the extent that malaria field workers did help in motivating patients to co-operate fully. Now that smallpox eradication and BCG vaccination programmes have been integrated, the results achieved are satisfactory and encouraging.

The problems experienced were described: non-existence of basic health services, initially non-integration of existing vertical programmes of smallpox and malaria, lack of training in and understanding of integrated programmes by the workers, frequent transfer of staff and the problem of supplies and transportation. Without close supervision and assistance in the field and proper evaluation, it is not possible to sustain the integrated programmes efficiently.

It was recommended that development of basic health services should precede an integrated health programme. The health workers must understand and accept the benefit of integration. They must receive training to carry out such programmes efficiently and willingly. When the jobs of such workers are unattractive and suitable people do not apply for them, financial incentives have to be given.

It also seems clear that the future of an integrated tuberculosis programme depends directly on supervision, assistance and constant evaluation from the central and regional management.

Discussion

As the microscope is a multi-purpose instrument, technicians/microscopists should be trained to perform more than one of the basic microscopy examinations. Co-operation with other continuing disease control programmes, for example malaria, leprosy and smallpox, should be considered. The value of this may, however, be doubtful except in circumstances where the "vertical" programme has to be integrated with the basic health services. Co-operation of general practitioners, where they exist, may be sought.

There is great need for appropriate programme training of all categories of health personnel, their continuous supervision, and for continual evaluation of the programme activities.

Health education is also extremely important; awareness and motivation has to be developed among the people; they should have confidence in the availability and efficiency of the health services.

For better working of the programme, transfers of trained personnel should be kept to the minimum. Generous financial allowances are the only incentive to induce workers to go to and remain in unattractive and remote areas.

Instruction manuals should be provided to health workers to enable them to know what they are required to do. The training imparted must be in line with the programme and cover each step of the various activities.

Continued support by a WHO adviser to help the developing countries in the implementation of their control programmes was strongly emphasized.

In this field, as in others, there is great need for further operational research on the role of basic health services.
SESSION 6

VIII PROGRAMME EVALUATION - EVALUATION METHODOLOGIES OF TUBERCULOSIS CONTROL PROGRAMMES

PRESENTED BY DR. S. FAHMY, DIRECTOR, CHEST DISEASES DEPARTMENT, MINISTRY OF PUBLIC HEALTH, EGYPT

Evaluation can be defined as a comparison between the aim of a programme and the results achieved. The aim of a tuberculosis control programme is to reduce the tuberculosis problem within the shortest possible time. The effect of the programme can be assessed by epidemiological studies.

Epidemiological indices

1. Mortality rate: mortality is not well recorded in high prevalence countries. Moreover, it is closely related to the efficiency of chemotherapy and therefore does not give meaningful information on the total extent of the tuberculosis problem.

2. Incidence of newly-registered cases.

3. Prevalence surveys: such surveys are expensive but helpful for studying the extent of the problem and could be periodically repeated.

4. Annual tuberculosis infection rates: these can be estimated by repeated tuberculin surveys.

   (Difficulties arise in the case of a previously BCG-vaccinated population. Tuberculin surveys, however, can be done in a sample child population not previously vaccinated and can be repeated yearly).

5. Recording the incidence of tuberculous meningitis is also helpful.

   If there is a pronounced change in the trend of tuberculosis indices it may be ascribed to the activities of the tuberculosis control programme.

Operational evaluation

This evaluation concerns the operational efficiency of the existing tuberculosis services. The distribution of institutions which actually participate in the programme and their performance can be studied: are these institutions enough for diagnosis, treatment and BCG vaccination or are more institutions needed?

Evaluation activities

1. Number of persons examined.

2. Number of cases actually diagnosed in an area, compared with the number of cases expected to be diagnosed on the basis of previous prevalence surveys.

3. Treatment coverage, proportion of patients who completed treatment, percentage of defaulters, percentage of cases rendered sputum-negative and percentage of relapses which occurred within two years.

4. BCG evaluation quantitatively by percentage of coverage and qualitatively by measuring post-vaccinal tuberculin sensitivity.
Evaluation of resources

1. Health manpower: number of trained personnel as compared with the number required. Level of utilization.

2. Number of institutions and equipment utilized in the tuberculosis control programme as compared with the number required.

3. Are diagnostic material, drugs and vaccines supplied regularly in the quantities required?

4. Expenditure per capita and percentage of the health budget allocated for the tuberculosis control programme.

Efficiency should be evaluated in terms of cost in proportion to the results achieved (cost/benefit); for example, cost of the reduction of the infection rate by 1 per cent, cost of detecting one tuberculosis case, cost of making one sputum-positive case non-infectious and the cost of BCG vaccination.

The evaluation of a tuberculosis programme should not be sporadic, but should be within the framework of the tuberculosis programme and regularly performed by the health authorities concerned. Appropriate corrective action should be taken whenever deviation of performance is detected.

Discussion

It was repeatedly emphasized that evaluation of the results of treatment was important and that it should be a continuous process.

Of seventeen countries where a tuberculosis control programme is being carried out, evaluation is being done only in five. This is not a good situation, for it is of no use merely compiling reports without evaluating their meaning. Uniformity of criteria for reporting is necessary for comparison within countries and between countries.

When the risk of infection is high almost everyone becomes infected. However, the transition from infection to disease is influenced to some extent by socio-economic conditions.

Even when a good tuberculosis control programme is implemented, the curve of incidence of new cases may be horizontal for some years before it shows a downward trend. This is because more cases are being diagnosed under the improved conditions.

Attention was drawn to the fact that in the planning and implementation of a national tuberculosis control programme other sectors of health development have to be considered. Reference was made to the process of Country Health Programming (CHP). This is a national process designed to identify priority health problems of prime concern to governments in the context of their development plan, to specify objectives in these problem areas, to define strategies, to translate these strategies into health development programmes and to implement the programmes. Throughout the procedures, strong emphasis is placed on the interaction between the health sector and other sectors in the socio-economic field.

CHP is a continuous process of the health administration which is undertaken by a small group of high-level government officials with experts from various fields. The group review the situation in the health and health-related sectors before identifying the country's major health problems as well as the current activities undertaken to overcome these problems. It can then define targets for reducing the problems over the planning period, estimate the magnitude of additional health activities and resources required, and elaborate strategies for reaching these targets.
On the information and recommendations given by the group, the Minister of Health can select those development programmes for implementation to which he attaches the highest priority.

The Country Health Programming process should allow the government to present to external organizations providing assistance in the health field a coherent development programme showing clearly the intentions and needs of the government and the expected results of the national and international investments. This permits a harmonious and co-ordinated programme for external assistance.

IX TRAINING AND PERSONNEL REQUIREMENTS
PRESENTED BY DR R. RASHDAN, DIRECTOR, CHEST DISEASES DIVISION,
MINISTRY OF HEALTH, JORDAN

The National Tuberculosis Control Programme must be on a country-wide and permanent basis. It should form an integrated part of the community health services satisfying the existing needs as far as possible and remaining within the available resources. The planning of such a programme must be based on accurate data concerning epidemiological, operational, geographic and social information. The programme must include and maintain the basic measures for assessing BCG vaccination, provide services for case-finding and treatment programmes. There should be provision for standardized recording and reporting systems, supervision and evaluation. The programme must undertake health education, training and research.

Personnel requirements at central level

At the central level, attached to the Ministry of Health, there should be qualified personnel consisting of a physician, an epidemiologist, a bacteriologist and other staff, including the assessment team. This central unit should be responsible for:

(a) Planning, co-ordination and evaluation of the programme.
(b) The formulation of policies, standards, operational and technical procedures.

At the intermediate level, in each region or district (varying from country to country according to population) there should be a chest centre with complete case-finding and treatment facilities, BCG vaccination programme and a few beds attached to a local hospital. Headed by a Regional Director, this clinic should have medical officers, laboratory, X-ray and BCG technicians, health visitors and other necessary staff for record-keeping and administrative purposes.

The Regional/District Officer should be responsible for the execution of the entire tuberculosis control programme in his area.

At the peripheral level

At the peripheral level the tuberculosis services should be integrated into the basic health unit and BCG vaccination as well as case-finding and treatment will form a part of the work of the health unit. The District Medical Officer should make frequent visits to this peripheral health centre for supervision and guidance.

As far as laboratory facilities are concerned, sputum microscopy is all that is required; this is essential at the peripheral health centres. Cultures and sensitivity tests may be arranged at larger centrally placed clinics, but only if the country's resources permit it.
Training

The guiding principles of tuberculosis control should be included in all the teaching curricula of medical and nursing schools. Emphasis should be placed on epidemiology, preventive and community aspects of tuberculosis control. Post-graduate training should be given at the specialized institutions in the form of short diploma courses. Refresher courses should also be held frequently.

A large number of auxiliary staff is necessary to operate the programme. The object of training should be to produce efficient staff able to do preventive work as well as case-finding and treatment. Therefore, their training programme should be comprehensive and practically orientated.

Team training is an important feature of the training of tuberculosis workers and the trainees should receive adequate practice in co-ordination, supervision and assessment of the programme.

Seminar and exchange visits are recommended. Training courses must be made sufficiently attractive by giving diplomas or extra allowances. Those who are engaged in the tuberculosis programme should have much higher salaries than those engaged in clinical work. Work in the tuberculosis control programme is at present considered unattractive. Tuberculosis control officers should start with a minimum of double the salary of any clinical medical officer.

The official health authorities as well as voluntary health associations must participate in this community health programme in an organized manner.

Discussion

There is a need for mobile managerial teams to visit the peripheral clinics to find out the various difficulties and their possible solutions. The team would also try to motivate the population. The size of the area to be covered will depend upon population and number of clinics. Training should be carried out as close to the site of work as possible.

It was agreed that, as jobs in tuberculosis work are not considered attractive, allowances should be given on a generous scale.

There is an increasing shortage of medical personnel to staff the tuberculosis control programme in the Region. This is partly due to a "drain" of physicians to other countries or to more profitable professional work, and, in certain countries, to an insufficient number of physicians being trained in the available medical schools.

In view of this constraint of medical manpower prevailing in many countries of the Region, it was re-emphasized that it was essential that the control measures and technologies applied in a national tuberculosis programme should be simplified and standardized, without loss of effectiveness. Only then can much of the work be handed over to the non-medical health personnel who will have to operate the control programme throughout the country. In the field of tuberculosis, this objective of simplification and standardization has been largely achieved. Thus it should be possible for effective control programmes to be implemented and successfully operated on a truly country-wide, national scale.
X COMMUNITY PARTICIPATION

1. Obstacles to Change in Antituberculosis Work in the Middle East
   Presented by Dr A.A. Sami, Representative of the Middle East Region of the International Union against Tuberculosis

   It has been said that today there is enough knowledge and experience about tuberculosis control to lead to success under almost any existing social or economic conditions. The application of this knowledge has been outlined in the Ninth Report of the WHO Expert Committee on Tuberculosis (1974). But the application of this "enough knowledge" needs wide dissemination and adequate motivation.

   **Obstacles**

   Erroneous ideas about tuberculosis treatment held by the public vary from extreme pessimism to extreme optimism. The government authorities want to acquire as much as possible of the paraphernalia of developed countries such as more beds, more X-ray machines and more tuberculosis specialists. The medical profession has its own bias. General practitioners and the specialists believe that the treatment of tuberculosis should still lie in the hands of specialists only. The old idea of diagnosis solely with a chest X-ray still prevails in the minds of specialists and non-specialists.

   The voluntary organizations are prone to be attracted by projects which are spectacular and impressive, e.g. clinics and rehabilitation centres. Their activities are limited to cities or large towns - a natural result of the fact that the members usually live there and that the work there is more readily demonstrable.

   Some other obstacles are:

   1. Absence of a national programme or a programme guided by personal bias.
   2. A sound programme with deficient implementation. The central directing authority may not be strong enough, and management techniques may be unsound.
   3. Equipment and supplies may be lacking.
   4. Insufficient education and training for tuberculosis workers.
   5. Absence of a proper evaluation programme.

   **Conclusions**

   To succeed, there must be clear objectives and knowledge of the methods to be used or alternatives in case of obstacles.

   Dissemination of knowledge and proper orientation of the general public, the authorities, medical profession and voluntary organizations is absolutely necessary. Education of all these categories is essential and national tuberculosis associations are the proper agencies to perform this important function. A wide-based propaganda campaign and dissemination of knowledge through all possible means, e.g. seminars, radio, television, articles, pamphlets, etc., should be carried out through national tuberculosis associations.
2. Promotion of Community Participation: The Role of Non-Governmental Agencies

Presented by (a) Mr V. Mahmoud, Pakistan Tuberculosis Association

The aim of voluntary tuberculosis associations is to educate, mobilize and stir up public opinion and create consciousness among the community concerning the danger of tuberculosis. Health education is closely associated with publicity. Tuberculosis associations should form two separate committees; one for health education and the other for publicity. These committees should keep in touch with the available means of spreading information – press, radio, television, films and pamphlets. They should produce and exhibit films on tuberculosis.

The ground should be prepared for public acceptance of BCG vaccination by tuberculosis associations sending voluntary workers in advance into the field. Tuberculosis associations can also play an important role in helping the treatment programme by checking and following-up patients defaulting in treatment.

Tuberculosis associations should organize conferences and seminars for imparting information on the latest research and on socio-medical aspects of tuberculosis, and should arrange short courses for workers in their associations.

Governmental authorities of each country should closely examine the feasibility of introducing such legislative measures as may be necessary for their control programme, particularly with regard to the raising of funds.

Presented by (b) Dr A. Selvaratnam, Representative of the International Union against Tuberculosis in South East Asia

Even if a government has provided the necessary services for vaccination, case-finding and treatment, the programme will not be effective unless there is sufficient cooperation from the public. Past experience has shown that a health education programme undertaken by the government alone is not sufficient.

In any programme, the government, the medical personnel and the people - the consumers - are the three partners. The people are the most important of the three. Their cooperation must be obtained through an organized effort by the community itself, through voluntary associations.

The International Union against Tuberculosis (IUAT) is a non-governmental agency, a confederation of the national voluntary tuberculosis association of eighty-nine countries. Its aim is to improve the delivery of tuberculosis and other health services by supplementing governmental efforts, through dissemination of information, applied research, mutual aid programmes and collaboration with other agencies.

The voluntary association in a country must be organized from the national to the community level. In each community there should be a health committee organized by the provincial association, with trained volunteers as well as ordinary fee-paying members.

The volunteers are responsible citizens in the community who are prepared to give a few hours of practical work each week without any remuneration for the benefit of their fellows. They can be trained to do specific tasks in the programme. Experience in other regions has shown that the community can be mobilized to take an active part in all tuberculosis control measures - BCG vaccination, case-finding, the supervision of patients and health education.

If national and provincial health committees are to be really effective they must have some full-time employees to implement the programme.
There is a great need to develop the voluntary arm to support the government control programmes in the Eastern Mediterranean Region. The IUAT is prepared to assist if requested.

XI RECOMMENDATIONS

(a) Considerations

Being aware that tuberculosis remains a major health problem in the Region and that scientific knowledge for the effective control of tuberculosis is available, the participants consider that:

1. Tuberculosis control in the member countries should be conducted on the basis of a modern national tuberculosis control programme, adapted to each country’s epidemiological and socio-economic conditions. The recommendations contained in the Ninth Report of the WHO Expert Committee on Tuberculosis (1974) constitute a basis for the formulation of national tuberculosis control programmes in the Region.

2. The national tuberculosis control programme should contain the following main activities:
   
   (a) BCG vaccination to protect the population not yet infected, particularly the social and age groups at special risk, e.g. 0 - 15 years.
   
   (b) Effective detection and correct treatment of bacteriologically confirmed cases, especially by sputum smear. This not only reduces the reservoir of tubercle bacilli in the community but also reduces individual suffering.
   
   (c) Evaluation of the above components should constitute an integral part of the programme and should be continuously maintained.
   
   (d) Health education, programme training of health personnel and dissemination of knowledge on tuberculosis and its control measures.

3. Since resources in most of the countries of the Region are limited and the priority health problems too numerous, the Seminar considers that tuberculosis control activities in these countries must be integrated into the existing basic health services and evolve concurrently with their development. However, in the fast developing countries of the Region such full integration may not always be advantageous.

(b) Recommendations

Considering the above, the Seminar recommends:

1. **BCG vaccination** deserves high priority in the national tuberculosis control programme. All efforts should be made to improve the coverage, which is still low.

   A feasible target in an initial intensive mass BCG campaign is the rapid coverage of 70 - 90 per cent of the eligible pre-school and schoolchildren. Thereafter BCG vaccination should be integrated into the general health services, school health services, MCH centres and maternity wards where they exist.

   Direct vaccination, possibly as part of an expanded vaccination programme, using only high quality freeze-dried vaccine, should be practised under almost all circumstances.

   Early evaluation of the programme by scar survey is necessary to provide the basis for corrective action.
2. For **case-finding**, it is of greatest importance to set up an effective network capable of detecting the majority of existing sources of infection. This can be done initially by routine microscopy of sputum from patients with respiratory symptoms when they present themselves to the health services.

   The case-finding programme should not progress beyond the capability of the services to treat effectively all cases discovered.

3. **Treatment** of cases should be organized mainly on an ambulatory basis by building up a network of treatment centres within the general health services capable of making non-infectious all identified sources of infection.

   Administration of effective and inexpensive regimens should be available free of charge to the patients. All efforts must be made to increase the co-operation of patients in taking the drugs regularly and for long enough. Efforts must be made to make the treatment easier for patients.

   Consideration should be given to the provision of simple "hostels" where patients, particularly those living a long way from a health centre, can stay while receiving an initial, intensive phase of supervised chemotherapy.

   It is essential for the success of the programme that the bacteriological results of treatment should be under continuous review.

4. In order to **evaluate** the total results of the control programme it is necessary to discover by repeated tuberculin surveys (say every five years) in a randomly selected sample, the prevalence of infected children (e.g. at six years of age), to calculate the present risk of infection and to follow its trend. In addition, bacteriologically confirmed cases of tuberculosis should be centrally reported.

   The results of the evaluation should be made known to all working in the programme.

5. There should be adequate **training** of various categories of health workers responsible for implementing the programme (physicians, nurses, auxiliaries, clerical staff, voluntary workers and even private practitioners). Simple technical manuals should be prepared for all categories of workers and national seminars organized.

   Basic information on national tuberculosis programmes should be added to the curricula of medical and nursing schools; and much more emphasis should be put on the community aspects of tuberculosis and not as at present predominantly on the clinical aspects.

6. To ensure necessary **community participation**, health education of the entire population should be conducted by all available means, particularly by mobilizing volunteers from the national associations. Voluntary tuberculosis associations should be established in those countries where they do not at present exist. These associations are an essential part of the national programme.

7. There is still a great need for **international co-operation** and assistance. Recognizing that such assistance inevitably is time-limited and basically meant to accelerate and facilitate the implementation of tuberculosis programmes, it is recommended that such technical and material assistance should be available, especially to those countries of the Region most in need.

8. A programme of mutual assistance should be developed within the Region so as to make material and manpower available to countries that need them.
ANNEX I

SELECTED WORKING DOCUMENTS
## ANNEX I

**SELECTED WORKING DOCUMENTS**

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TUBERCULOSIS CONTROL

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 Egypt1 met in Geneva to review the validity of the recommendations in its eighth report2 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 report2, 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 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.

1. 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 out-patient 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, co-ordination, 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).

2. 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.

3. 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 anti-tuberculosis 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 per cent 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, practicing 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.

4. 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 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 deficiencies. 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) 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); (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 for anti-tuberculosis 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; (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 co-operative 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.

1WHO Technical Report Series, No. 491, 1972 (Fifth report of the WHO Expert Committee on Health Laboratory Services)
2These laboratories were considered to be of key importance.
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 anti-tuberculous 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 co-ordination.

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.

II METHODS AND TECHNOLOGY

1. 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.

2. 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.
3. **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.

4. **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.

5. **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.

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 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" was passed by the Assembly and this document has been sent for information and guidance, to the Governments of all Member States of WHO.

6. 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 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.

1 Resolution WHA27/54
7. **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, blood-stained 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 out-patient therapy, especially if provided free of charge, is likely to attract symptomatic cases from a wide surrounding area.

8. **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.

9. **Tuberculin Testing**

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

10. **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.

11. 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 outmoded 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 particularly 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.
Review of the present situation

by

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THE EASTERN MEDITERRANEAN REGION

The Eastern Mediterranean Region (EMR), stretching over an area exceeding 14 million square kilometres, consists of twenty-four Member States from Tunisia in the west, Cyprus and Syria in the north, Somalia in the south to Pakistan in the east. The population of some 250 million, owing to vast deserts, extensive wasteland and high mountain ranges, are unevenly distributed along rivers, coastal belts and in defined fertile or semi-fertile areas. Hence the overall density of population varies from 1 (Libyan Arab Republic) to 373 (Bahrain) per square kilometre. Though this is one of the most homogeneous regions as far as religion and language are concerned - the vast majority being Moslems and Arabic-speaking, sharing similar cultural and social habits and traditions - yet it is an area of the highest diversity and contrasts of demographic, geographic and socio-economic features. Only in the recent past an astonishingly rapid change has been witnessed in the economic and social structure of some of the countries in the Region, whose rich natural resources in oil have placed them among the richest in the world. On the other hand, there are also five of the twenty-five economically least fortunate countries of the world in this Region, with a national income of barely fifty to a hundred dollars yearly per capita. Likewise, there is one of the highest physician/population ratio in the world (1 to 300), as well as the lowest (1 to 73 000).

Despite the recent unparallelled economic upsurge, almost all the countries are equally confronted with some handicaps common to all developing countries: most of them lack skilled manpower and have a large proportion of illiterates (80 - 95 per cent), though the health problems are rapidly changing in some of them. New health hazards have crept in as a consequence of rapid industrial development, such as environmental pollution, heart disease and mental health problems. But there is still malnutrition, and widespread communicable diseases are rampant, while in certain areas there is absolutely no health care of any sort.

The estimates of birth rates (46 per thousand) and death rates (17 per thousand) are among the highest in the world, and infant mortality still records extremely high figures reaching up to almost 200 per thousand. Many of the member countries show the highest natural population increase (3.5 per cent yearly), and some countries have an average annual rate of net increase as high as 12.5 per cent.

EXTENT OF THE TUBERCULOSIS PROBLEM

The magnitude of the tuberculosis problem in a country is usually measured by two most relevant indices:

*Now six
(a) The proportion of infected population in a given age group - age-specific prevalence of tuberculosis infection as demonstrated by tuberculin testing.

(b) The proportion of persons excreting tubercle bacilli among the population, obtained by bacteriological examination.

Other indices, such as rates of X-ray positive findings indicating active tuberculosis, specific mortality rates, etc., are of less importance.

It would be extremely difficult to give a reliable picture of the present extent of the tuberculosis problem in the Region, for generally reliable statistics are not available. Even in countries where notification of tuberculosis is compulsory and a well-established reporting system is supplying relevant health statistics, the data collected reflect only the capacities and capabilities of health services to detect tuberculosis cases and suspects rather than the existing epidemiological situation.

However, the data obtained from epidemiological surveys, carried out with WHO assistance or by national teams as well as during tuberculin testing of selected population groups at different points of time, do furnish a certain insight into the distribution of tuberculosis in the Region. They reveal considerable contrasts and identify three distinct groups:

(a) Low prevalence countries comprising Cyprus, Israel, Lebanon and Syria, with an annual infection rate below 1 per cent and sputum positive rates below 0.1 per cent. Even during the ITC campaign carried out in 1949-51, these countries showed the lowest prevalence rates of infection not only in the Eastern Mediterranean Region but also as compared with some European countries.

(b) Moderate or relatively high prevalence countries, viz. Egypt, Iraq, Jordan, Oman, Pakistan, Tunisia and a few others, with 0.1 per cent - 0.3 per cent bacteriological positive rates and 5 to 20 per cent infection rates among children of 5-9 years of age, showing a constant though moderate decrease of tuberculosis.

(c) High prevalence countries including Ethiopia, Somalia, Sudan and Yemen, with unusually high bacteriological positive rates of 0.4 per cent or more and extremely high proportion of infected children of 5-9 years of age amounting to 20-30 per cent without indication that their tuberculosis problems are diminishing.

There are also countries such as Kuwait, Libyan Arab Republic, Qatar, etc., with an originally high prevalence of tuberculosis but their epidemiological situation is rapidly improving owing to an unusual intensification of health services in the recent past.

1. Tuberculosis infection

Among the various epidemiological indices, the most sensitive, simple to establish and easy to compare, is the prevalence of infection among children. Infected children in fact mirror the existing open cases in the community, provided that no BCG vaccination has been widely applied.

During the WHO/UNICEF-assisted vaccination campaigns, carried out in 1949-55, valuable data were collected from most of the countries in the Region. Later on surveys were carried out by national services in areas not included in BCG vaccination campaigns (see Table 1). Some partial results clearly point out the fact that the risk of infection is decreasing, as may be seen from the following table.
The Eastern Mediterranean Region (EMR), stretching over an area exceeding 14 million square kilometres, consists of twenty-four Member States from Tunisia in the west, Cyprus and Syria in the north, Somalia in the south to Pakistan in the east. The population of some 260 million, owing to vast deserts, extensive wasteland and high mountain ranges, are unevenly distributed along rivers, coastal belts and in defined fertile or semi-fertile areas. Hence the overall density of population varies from 1 (Libyan Arab Republic) to 373 (Bahrain) per square kilometre. Though this is one of the most homogeneous regions as far as religion and language are concerned - the vast majority being Moslems and Arabic-speaking, sharing similar cultural and social habits and traditions - yet it is an area of the highest diversity and contrasts of demographic, geographic and socio-economic features. Only in the recent past an astonishingly rapid change has been witnessed in the economic and social structure of some of the countries in the Region, whose rich natural resources in oil have placed them among the richest in the world. On the other hand, there are also five of the twenty-five economically least fortunate countries of the world in this Region, with a national income of barely fifty to a hundred dollars yearly per capita. Likewise, there is one of the highest physician/population ratio in the world (1 to 360), as well as the lowest (1 to 73 000).

Despite the recent unparallelled economic upsurge, almost all the countries are equally confronted with some handicaps common to all developing countries: most of them lack skilled manpower and have a large proportion of illiterates (80 - 95 per cent), though the health problems are rapidly changing in some of them. New health hazards have crept in as a consequence of rapid industrial development, such as environmental pollution, heart disease and mental health problems. But there is still malnutrition, and widespread communicable diseases are rampant, while in certain areas there is absolutely no health care of any sort.

The estimates of birth rates (46 per thousand) and death rates (17 per thousand) are among the highest in the world, and infant mortality still records extremely high figures reaching up to almost 200 per thousand. Many of the member countries show the highest natural population increase (3.5 per cent yearly), and some countries have an average annual rate of net increase as high as 12.5 per cent.

**II EXTENT OF THE TUBERCULOSIS PROBLEM**

The magnitude of the tuberculosis problem in a country is usually measured by two most relevant indices:

*Now six*
(a) The proportion of infected population in a given age group - age-specific prevalence of tuberculosis infection as demonstrated by tuberculin testing.

(b) The proportion of persons excreting tubercle bacilli among the population, obtained by bacteriological examination.

Other indices, such as rates of X-ray positive findings indicating active tuberculosis, specific mortality rates, etc., are of less importance.

It would be extremely difficult to give a reliable picture of the present extent of the tuberculosis problem in the Region, for generally reliable statistics are not available. Even in countries where notification of tuberculosis is compulsory and a well-established reporting system is supplying relevant health statistics, the data collected reflect only the capacities and capabilities of health services to detect tuberculosis cases and suspects rather than the existing epidemiological situation.

However, the data obtained from epidemiological surveys, carried out with WHO assistance or by national teams as well as during tuberculin testing of selected population groups at different points of time, do furnish a certain insight into the distribution of tuberculosis in the Region. They reveal considerable contrasts and identify three distinct groups:

(a) Low prevalence countries comprising Cyprus, Israel, Lebanon and Syria, with an annual infection rate below 1 per cent and sputum positive rates below 0.1 per cent. Even during the ITC campaign carried out in 1949-51, these countries showed the lowest prevalence rates of infection not only in the Eastern Mediterranean Region but also as compared with some European countries.

(b) Moderate or relatively high prevalence countries, viz. Egypt, Iraq, Jordan, Oman, Pakistan, Tunisia and a few others, with 0.1 per cent - 0.3 per cent bacteriological positive rates and 5 to 20 per cent infection rates among children of 5-9 years of age, showing a constant though moderate decrease of tuberculosis.

(c) High prevalence countries including Ethiopia, Somalia, Sudan and Yemen, with unusually high bacteriological positive rates of 0.4 per cent or more and extremely high proportion of infected children of 5-9 years of age amounting to 20-30 per cent without indication that their tuberculosis problems are diminishing.

There are also countries such as Kuwait, Libyan Arab Republic, Qatar, etc. with an originally high prevalence of tuberculosis but their epidemiological situation is rapidly improving owing to an unusual intensification of health services in the recent past.

1. **Tuberculosis infection**

Among the various epidemiological indices, the most sensitive, simple to establish and easy to compare, is the prevalence of infection among children. Infected children in fact mirror the existing open cases in the community, provided that no BCG vaccination has been widely applied.

During the WHO/UNICEF-assisted vaccination campaigns, carried out in 1949-55, valuable data were collected from most of the countries in the Region. Later on surveys were carried out by national services in areas not included in BCG vaccination campaigns (see Table 1). Some partial results clearly point out the fact that the risk of infection is decreasing, as may be seen from the following table.
However, this trend has not been observed in some other countries like Somalia, Sudan and Yemen.

Tuberculin survey carried out by national teams among selected, non-vaccinated groups of children of 5-9 years of age during the past ten years (1965-1975) revealed the following percentage of infection:

<table>
<thead>
<tr>
<th>Country</th>
<th>%</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Lebanon</td>
<td>2.7</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Syria</td>
<td>4.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bahrain</td>
<td>7.0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Libya</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Saudi Arabia</td>
<td>7.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>9.4</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jordan</td>
<td>10.5</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Iraq</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Afghanistan</td>
<td>11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pakistan</td>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ethiopia</td>
<td>16</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sudan</td>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yemen</td>
<td>28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Somalia</td>
<td>35</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
2. Prevalence and incidence of tuberculosis

Since comprehensive tuberculosis prevalence surveys, including X-ray and bacteriological examinations, have not been carried out in the Region for the last ten - fifteen years, no reliable data are available on the prevalence of bacteriological positive cases nor on X-ray suspects.

Estimates indicate that prevalence of bacteriological positive cases ranges from 0.05 per cent (Cyprus) to almost 1 per cent (Somalia) and those radiologically positive, from 0.4 per cent (Kuwait) to 6 per cent (Somalia).

Incidence trends in some countries also indicate an obvious decrease in the disease:

<table>
<thead>
<tr>
<th>Year</th>
<th>Kuwait new cases rate per 100 000</th>
<th>Libya new cases rate per 100 000</th>
</tr>
</thead>
<tbody>
<tr>
<td>1965</td>
<td>257</td>
<td>-</td>
</tr>
<tr>
<td>1966</td>
<td>251</td>
<td>210</td>
</tr>
<tr>
<td>1967</td>
<td>208</td>
<td>230</td>
</tr>
<tr>
<td>1968</td>
<td>174</td>
<td>180</td>
</tr>
<tr>
<td>1969</td>
<td>140</td>
<td>100</td>
</tr>
<tr>
<td>1970</td>
<td>127</td>
<td>130</td>
</tr>
<tr>
<td>1971</td>
<td>-</td>
<td>60</td>
</tr>
<tr>
<td>1972</td>
<td>-</td>
<td>60</td>
</tr>
</tbody>
</table>

The need for further epidemiological surveys is felt in almost all countries. Such surveys would not only spotlight the present tuberculosis problems and the progress achieved, but also provide useful data for current programme policies in the frame of a broader and a more systematic analytical approach.

III NATIONAL TUBERCULOSIS CONTROL SERVICES

In the absence of reliable data, a questionnaire was sent to responsible tuberculosis officers in twenty-two member countries of the Region in order to form an idea of the present situation in tuberculosis control in the Region. Twenty countries so far responded to the enquiry. After consolidation and evaluation of compiled information (see tables 3 - 7) the most important findings were summed up as follows:

1. National Tuberculosis Control Programme

The basic concept of a national tuberculosis control programme has been adopted in almost all member countries and is being increasingly applied under widely varying and, in some countries, rapidly changing socio-economic conditions through specialized or general health services. Only a few countries remain which have yet not developed their strategy in tuberculosis control.
7. Integration

Although a more or less developed network of basic health services is operating at various levels of efficiency in all of the twenty-two interrogated countries, only nine of them claim to have integrated tuberculosis activities into the routine work of these services. In ten others tuberculosis control measures are being executed through specialized tuberculosis services while in three smaller ones the type of the programme has yet to be properly established. Countries such as Afghanistan, Democratic Yemen, Ethiopia, Iran, Jordan, Pakistan, Somalia and Sudan recorded moderate to substantial achievements in integration of tuberculosis activities into the Basic Health Services; though some of them have not yet succeeded in establishing fully-flung programmes they have at least started to apply the basic principle underlying integration.

In Ethiopia, 67 per cent of the general hospitals, 83 per cent of the existing rural health centres and 27 per cent of the dispensaries are participating in integrated tuberculosis activities and thereby contribute with 55 per cent to the present extent of tuberculosis control. In Somalia, 75 per cent of districts have developed tuberculosis control activities, and although the overall output is still modest, 70 per cent of new cases are being detected just in the integrated Basic Health Services.

<table>
<thead>
<tr>
<th>Year</th>
<th>% in TB centres</th>
<th>% in BHS</th>
</tr>
</thead>
<tbody>
<tr>
<td>1972</td>
<td>69</td>
<td>31</td>
</tr>
<tr>
<td>1973</td>
<td>48</td>
<td>52</td>
</tr>
<tr>
<td>1974</td>
<td>30</td>
<td>70</td>
</tr>
</tbody>
</table>

In Afghanistan, forty-one out of the 105 Basic Health Centres were involved in tuberculosis activities in 1974. In Pakistan, nuclei of integrated activities or even fairly developed rural programmes have been established in thirty out of the sixty-two existing districts.

However, the scope and intensity of such endeavours depend largely on the state of development of the basic health services and their ability to undertake additional responsibilities as well as on the attitude and orientation of those responsible for implementation of this policy.

It is obvious that the task of integration, uphill as it is, demands continued strenuous efforts on the part of all concerned in order to ensure it a permanent place in the national tuberculosis programme.

3. Administration and supervision

Administration of tuberculosis control is mostly with central tuberculosis offices attached to ministries of health (fourteen countries) or less frequently with public health departments (eight countries). Their responsibility involves organization, planning of programmes and their implementation, management, co-ordination, follow-up and evaluation and training of health workers.
Supervision, which has been established in seventeen countries through central public health departments, tuberculosis institutions, or other authorities, remains, however, one of the weakest points of programme implementation. The "managerial team" techniques of supervision has, so far, not materialized for various reasons.

4. Specialized institutions and personnel

Attempts to establish national tuberculosis institutes responsible for implementing tuberculosis programmes did not generally succeed due to various constraints, except in Iran, Iraq and recently in Afghanistan. Instead, directorates of tuberculosis control were set up and attached to Ministries of Health or leading tuberculosis centres. On the other hand, training and demonstration centres were established and are operating in the majority of countries. The number of specialized tuberculosis/chest centres or clinics varies considerably from country to country, one centre covering an average of 600,000 inhabitants, in the Region, ranging from 140,000 inhabitants in the Libyan Arab Republic to 1 per 5.7 million inhabitants in Ethiopia. Similarly the number of tuberculosis beds, though not an essential item for tuberculosis control, is relatively the highest in Kuwait (1 per 1,500 inhabitants) and Somalia (1 per 1,600 inhabitants) whereas it is the lowest in Afghanistan (1 per 275,000 inhabitants). The most favourable physician/population rate in tuberculosis services has been noted in the Libyan Arab Republic (1 per 33,000 population) and the worst in Ethiopia (1 per 4 million population).

It should be noted that some of the developing countries are vexed with the problem of permanent exodus of skilled personnel (doctors and para-medicals) who are migrating to other countries for better jobs and thus jeopardizing tuberculosis control and the functioning of health services, particularly in rural areas of their own country.

5. Legislation

Compulsory notification of tuberculosis cases has been introduced only in nine countries, representing 22 per cent of the whole population. Paid sick-leave is permitted to workers and other health insured persons in eleven countries while financial assistance is provided to the non-insured in five countries. (See Table 4).

BCG vaccination is free of charge in all countries, as are diagnostic and treatment services in government tuberculosis clinics. Ambulatory treatment is charged only in one country while hospitalization has to be paid by tuberculosis patients in three countries and partly in several others.

6. Recording, reporting and assessment

A recording and reporting system is in operation in eighteen countries. In some of them, however, it is working on a limited scale, i.e. collecting selected information pertaining to certain activities only, such as bacteriological work in Iraq, BCG vaccination and MMR investigation, as in Kuwait, etc. Efforts are being made to improve national recording and reporting systems in specialized services and to incorporate simple elements of tuberculosis activities in the overall system of general health services, particularly in Afghanistan, Ethiopia, Jordan, Pakistan and Somalia. A uniform quarterly reporting form on tuberculosis activities has been finalized at WHO/EMRO and recommended for use in the national tuberculosis programmes throughout the Region. These would ensure better uniform monitoring and assessment of tuberculosis activities.
IV TUBERCULOSIS CONTROL ACTIVITIES

1. BCG vaccination

It is gratifying to note that BCG vaccination occupies a dominant place in tuberculosis control in all countries of the Region, with the exception of one. The strategy of vaccination programmes is constantly shifting from the sporadic and irregularly conducted mass campaigns towards integrated vaccination programmes, presently operating at different levels of development in eighteen of the twenty integrated countries, often in addition to mass campaigns. Also combined BCG/smallpox vaccination programmes have been introduced in eight countries for their operational and economical advantages, and are being applied on an increasing scale, particularly in Afghanistan, Ethiopia, Somalia and Sudan. Apart from the tuberculosis services, other health institutions are also participating in BCG vaccination programmes in almost all countries - maternity wards and MCH centres (14), school services (14), basic health services (11) and others.

The methodology being used is direct vaccination without prior tuberculin test. Only four countries in the Region (Iran, Kuwait, Saudi Arabia and Cyprus) practise tuberculin testing before vaccination.

There has been a manifest desire on the part of all those responsible for tuberculosis control to use only high quality vaccine. Since liquid vaccines are unstable, difficult to transport and highly susceptible to light as well as heat, thus giving poor protection under field conditions, freeze-dried vaccines have been generally introduced. Three countries are, however, producing and applying their own liquid BCG vaccine.

The production of freeze-dried BCG vaccine in the Region is still at the experimental stage under WHO assistance in Cairo and Teheran. Because of the difficulties involved in producing BCG vaccine of high quality, the initiative by some member countries to establish "their own" BCG production centres has been strongly discouraged. Emphasis has been laid on regular checking of the quality of BCG vaccine applied in BCG mass vaccination programmes by the International Reference Centre for BCG Quality Control in Copenhagen. But only a few countries have responded positively.

As for the target groups, new-borns and pre-school children are included in vaccination programmes of fourteen countries, while school-going children are being vaccinated in almost all countries. The strategy of vaccination varies from country to country. After having conducted an intensive mass campaign, some countries are now concentrating the maintenance phase on school-entering children, while others are trying to cover unvaccinated children and the new generation through integrated services. However, a factor which still remains to be overcome is the proper BCG coverage of the eligible population, particularly the youngest lot. In a good number of countries this coverage does not exceed 2 - 5 per cent of new-borns and 10 - 15 per cent of pre-school children. However, the coverage of school-going children is usually satisfactory, reaching 50 - 90 per cent.

2. Case-finding

Systematic mass X-ray screening for the purpose of detection of infectious sources is definitely a method of the past. Only two countries are conducting mass mobile (MMP) screening for case-finding purposes on a very limited scale.
Bacteriological procedures are unanimously considered to be the priority in case-finding. Special emphasis is being placed on direct microscopy examination as an efficient, cheap, simple and diagnosis-proving method to identify the most important sources of infection among coughing patients reporting themselves to various health institutions.

To meet this need, an efficient and reliable network of laboratory services at all levels is indispensable, and should be established in consonance with the strengthening of rural services and overall development of health facilities. Where such services already exist and are involved in tuberculosis control, it has been observed that their output could be increased manifold by systematic selection of patients for sputum examination. This requires first, collaboration of doctors in general health services, frequently missing, second, training and orientation of microscopists to overcome doctors' distrust of these methods, and third, regular supervision of peripheral laboratories by highly skilled technicians. Microscopy examination of sputum is still not available to the majority of people in many countries as evident from the fact that only eleven countries have introduced this method in the basic health services, and that on a limited scale.

Examination of sputum by culture - important for improving diagnosis and follow-up of treatment - as well as drug sensibility testing of tubercle bacilli, is currently beyond the reach of several countries of the Region (Democratic Yemen, Qatar, sensibility testing is not available in Jordan and Somalia). Improvement in the quality of work in most of the central laboratories is needed, demonstrated by the often surprisingly low yield of positive cultures (5 - 10 per cent) in addition to positive microscopy findings, as compared with European or other countries, where 50 - 70 per cent contribution from cultures could be expected. Another noteworthy problem is that peripheral health institutions have not been able to take full advantage of the services of central bacteriological laboratories owing to considerable difficulties in forwarding sputum.

To sum up, further efforts in strengthening the laboratory network at all stages are necessary to bring case-finding to a satisfactory level.

It should be kept in mind that even the best case-finding programme is useless, unless an efficient treatment programme is organized to neutralize the discovered sources of infection.

3. Treatment

The spectacular technical progress made in the past twenty years has made it possible to cure nearly all tuberculosis patients, i.e. to neutralize them as spreaders of infection. Therefore treatment is at the same time a most effective preventive method too.

Proper organization of ambulatory treatment in many countries has still a long way to go to minimize the existing rates of defaulters and irregularities in drug intake, which lead to treatment failures and drug resistance.

Efforts are being made in a number of countries to improve ambulatory treatment and regularity of drug intake by systematic motivation of patients (motivation rooms in tuberculosis clinics). At present, there is practically no treatment supervision due to lack of manpower.

As for treatment regimens applied, the standard combination of STM + INH + PAS, followed by INH + PAS is predominant in most countries (17), while combination of INH with Thiacetazone is much rarer (7 countries). On the other hand, an increasing number of countries apply the so-called "second line" drugs in primary ambulatory treatment, using combinations with Myambutol or Rifampicin.
The fully-supervised intermittent, twice-weekly chemotherapy regime tried under programme conditions in a few countries of the Region proved disappointing and extremely difficult to organize.

The new realistic wish to shorten treatment to nine or even six months with INH/RIF/STR/PZ might not be economically feasible in the majority of the countries in the Region, although the more fortunate may take advantage of it.

There was no tendency in the Region to increase the number of hospital beds for tuberculosis control. The allotment varies from as high as 1 bed per 1,500 inhabitants (Kuwait) to 1 bed per 273,000 inhabitants (Afghanistan). Recommendations that hospital treatment should not be expanded even in countries experiencing a considerable shortage of beds are being attended to promptly but no co-ordinated efforts have been made to extend and organize ambulatory treatment. On the other hand, the excess of tuberculosis beds in some countries due to the decreasing tuberculosis problem (Lebanon, Libyan Arab Republic) is compensated up to 50 per cent by treatment of chronic lung-disease patients. Although the average hospital treatment of tuberculosis patients has been shortened to one to two months in four countries, it is still unnecessarily long in the majority of countries, averaging three to six months in eleven countries and seven to eighteen months in four.

It is also obvious that priorities of treatment are not being adhered to. Only two member countries are strictly pursuing treatment of bacteriological proven cases, though sputum negative suspects are being treated in all other countries too. Taking into account that the proportion of cases/suspects is often 1:4 or 1:6, an unnecessary lot of additionally treated suspects lays considerable burden on the scarce services and meagre resources in many countries.

Although not quite strictly relevant to the scope of this paper, it would be worthwhile mentioning some additional important problems for consideration:

- Staff in specialized or general health services is decreasing in some countries owing to the great drain on manpower. There is also a rapidly decreasing interest among doctors in specialization in tuberculosis.

- Training is insufficient and inadequate and the situation is aggravated by the frequent transfer of trained personnel to non-tuberculosis activities.

- Programme implementation often suffers owing to total absence of supervision at all levels or because of managerial difficulties in programme implementation. Managerial teams have yet to be established.

- Investment policy. Many governments have stopped investment into construction and consolidation of tuberculosis clinic networks without undertaking proper compensation on the side of development of integrated rural programmes.

- International assistance is critically decreasing (assistance in drugs, equipment, technical advice, etc.) to some countries still needing such assistance.
<table>
<thead>
<tr>
<th>Country</th>
<th>Age (years)</th>
<th>Date (year)</th>
<th>Source</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0 - 4</td>
<td>5 - 9</td>
<td>10 - 14</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>8</td>
<td>20</td>
<td>42</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>19</td>
<td>39</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>21</td>
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</tr>
<tr>
<td></td>
<td>5</td>
<td>11</td>
<td>21</td>
</tr>
<tr>
<td>Bahrain</td>
<td>2</td>
<td>7</td>
<td>16</td>
</tr>
<tr>
<td>Cyprus</td>
<td>-</td>
<td>4.3</td>
<td>12</td>
</tr>
<tr>
<td>Democratic</td>
<td>-</td>
<td>36</td>
<td>52</td>
</tr>
<tr>
<td>Yemen</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Egypt</td>
<td>9</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td></td>
<td>2.6</td>
<td>9.4</td>
<td>20.5</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>11</td>
<td>26</td>
<td>45</td>
</tr>
<tr>
<td></td>
<td>12</td>
<td>26</td>
<td>61</td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>16</td>
<td>33</td>
</tr>
<tr>
<td>Iraq</td>
<td>18.5</td>
<td>-</td>
<td>42.2</td>
</tr>
<tr>
<td></td>
<td>2.7</td>
<td>12.5</td>
<td>24.3</td>
</tr>
<tr>
<td></td>
<td>2.0</td>
<td>11</td>
<td>-</td>
</tr>
<tr>
<td>Iran</td>
<td>13.5</td>
<td>29</td>
<td>35</td>
</tr>
<tr>
<td>Jordan</td>
<td>5</td>
<td>13</td>
<td>21</td>
</tr>
<tr>
<td></td>
<td>8</td>
<td>10.5</td>
<td>16</td>
</tr>
<tr>
<td>Kuwait</td>
<td>1.6</td>
<td>10.7</td>
<td>24</td>
</tr>
<tr>
<td>Lebanon</td>
<td>2.5</td>
<td>4.0</td>
<td>12</td>
</tr>
<tr>
<td></td>
<td>1.8</td>
<td>3.7</td>
<td>9.7</td>
</tr>
</tbody>
</table>

**TABLE 1**

RESULTS OF TUBERCULIN TESTING, EMR

PERCENTAGE OF TUBERCULIN POSITIVES AMONG NON-VACCINATED CHILDREN ACCORDING TO AGE
### TABLE 2

**BCG VACCINATION**

*(in 1974 or latest available data)*

<table>
<thead>
<tr>
<th>Country</th>
<th>No. vaccinated</th>
<th>% covered in age groups</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>0</td>
<td>1-4</td>
</tr>
<tr>
<td>Afghanistan</td>
<td>276,985 (+ 364,600)</td>
<td>6.6</td>
<td>3.1</td>
</tr>
<tr>
<td>Democratic Yemen</td>
<td>6,758</td>
<td>6.7</td>
<td>0.4</td>
</tr>
<tr>
<td>Egypt</td>
<td>2,172,479</td>
<td>79.3</td>
<td>1.9</td>
</tr>
<tr>
<td>Ethiopia</td>
<td>316,212</td>
<td>5.4</td>
<td>2.8</td>
</tr>
<tr>
<td>Iraq</td>
<td>121,292</td>
<td>10.8</td>
<td>1.2</td>
</tr>
<tr>
<td>Jordan (East)</td>
<td>611,419</td>
<td>38.0</td>
<td>67.0</td>
</tr>
<tr>
<td>Kuwait</td>
<td>43,578</td>
<td>2.7</td>
<td>6.9</td>
</tr>
<tr>
<td>Libya</td>
<td>1,033,477</td>
<td>26.0</td>
<td>33.6</td>
</tr>
<tr>
<td>Pakistan</td>
<td>1,234,288</td>
<td>1.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Somalia</td>
<td>570,079</td>
<td>22.3</td>
<td>47.0</td>
</tr>
<tr>
<td>Syria</td>
<td>225,094</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

* indications to be evaluated with regard to different vaccination policies

.. not evaluated
Estimated proportion of infected children tuberculin surveys 1965 - 1975.

Age group 5-9 years in sample population.
RECENT ADVANCES IN EPIDEMIOLOGICAL RESEARCH IN TUBERCULOSIS

by

Dr. K. Styblo
WHO Consultant

Tuberculosis epidemiology deals with the natural trend of tuberculosis, i.e. with the natural relationship between the tubercle bacillus and a given population, without any man-made interference.

Naturally, the aim of any tuberculosis programme is to interfere in the natural relationship between tubercle bacilli and the people.

Several expressions should be clarified before discussing this topic, especially the distinction between a parameter and a variable.

A parameter is defined as a constant indicating the numerical value which links together two variables. For instance, a "contagious" parameter refers to an average number of persons infected with virulent tubercle bacilli during one year by one source of infection; or the disease ratio expresses the proportion of cases in which infection with virulent tubercle bacilli will lead to the development of a source of infection: etc. It has to be stressed, however, that the parameters are constant under natural conditions only, i.e. without man-made interference. For this reason, post-war routine statistics in developed countries cannot be used for exploring various parameters in tuberculosis epidemiology, as there has been an uninterrupted interference in the natural trend of tuberculosis, especially with chemotherapy, influencing one or more parameters. On the other hand, some estimates on how great this influence can be under ideal conditions can be determined from well conducted controlled trials.

A prevalence is the proportion of the population which, on a given day, has a well defined attribute; i.e. a proportion of subjects of a particular age-group found to have been infected with virulent tubercle bacilli on 31 December, or a proportion of persons, aged ten years or more found to have excreted tubercle bacilli demonstrable by microscopy, on the day of a survey, etc.
The most important examinations for establishing reliable prevalence data in tuberculosis are the standard tuberculin test and the microscopic (and culture) examinations of sputum for tubercle bacilli. By far the most important sources of infection are persons discharging sputum containing so many tubercle bacilli that they can be demonstrated by direct microscopy, and therefore numbers and rates for smear-positive patients should always be reported and analyzed separately.

Prevalence, being a simple proportion of the population who have, on a given day, well-defined attributes, should be referred to as a ratio, as it describes the static epidemiological situation in the population.

An incidence gives the number of persons of a given population, who, during a given period of time (usually during one year), will acquire a well-defined attribute. The interesting attributes for incidences are again the annual incidence of people infected with tubercle bacilli and the annual incidence of bacteriologically confirmed cases (separately for those positive on smear and those positive on culture only); in addition, the annual mortality from tuberculosis should be known. Incidence is referred to as a rate.

Tuberculosis epidemiology should provide the values of all important parameters. Although a considerable amount of information about various parameters has been recently collected, it is necessary to undertake more fundamental research into the way tuberculosis is behaving and maintaining itself in the community.

Three distinct events should be studied:

1. The transmission of tubercle bacilli
   The aim of the study is to discover the average chance or risk of a person in a given community inhaling tubercle bacilli.

2. Development from infection to pulmonary disease
   The overall probability of developing a "case of pulmonary tuberculosis" is different for:
   (a) those who are non-responders at the time of infection, and
   (b) those who are reactors to tuberculin at the time of (super) infection.

3. From development of a "case of pulmonary tuberculosis" to recovery or death
   The aim of the study is to discover the probability of recovery (absence of tubercle bacilli of say two years) or death from tuberculosis.

   1. "Contagious" parameter (average number of persons infected with tuberculosis during one year by one source of infection)

      This is a parameter which links together two variables: annual tuberculosis infection rate and prevalence of the sources of infection.

      (a) Annual tuberculosis infection rate: This rate indicates the proportion of the population under study which will be primarily infected, or reinfected (in those who have been previously infected) with virulent tubercle bacilli in the course of one year.
The annual tuberculosis infection rate is derived from the results of tuberculin testing. A technique for converting information on prevalence of infection into a smooth series of annual rates of tuberculous infection has been developed recently by the TSRU (Tuberculosis Surveillance Research Unit) and published in a comprehensive report in 1969 (TSRU, 1969). To obtain reliable estimates of the annual tuberculosis infection rates and their changes in a particular period, several tuberculin surveys are required at intervals, each in a representative sample of non-BCG vaccinated subjects of the same age, tested by the same technique.

The approach used by the TSRU for estimating the average annual risks of tuberculous infection in the Netherlands is complicated, partly because little was previously known about the way risk of infection was changing and this had to be assessed carefully, and partly because it was desirable, in the process, to make comprehensive use of the extensive prevalence data available in the Netherlands. However, for routine tuberculosis control a simple method of estimating the annual tuberculosis infection rate is described in the short section VIII of the same report. Appendix I shows an example of how the annual tuberculosis infection rates can be estimated easily.

The annual risk of tuberculous infection is usually expressed as a percentage. If, in a given community, the annual risk of infection is 3 per cent, 3,000 persons of each 100,000 inhabitants will be infected, during twelve months, with virulent tubercle bacilli from human sources of infection (in the absence of bovine infection). A proportion of the 3,000 infected will acquire primary infection (mostly children and young adults), the remainder (mostly middle-aged, elderly, and old people) will be superinfected. For the purpose of the study, the risk of inhaling tubercle bacilli to be of the same magnitude (for the same age-group) for those not yet infected (tuberculin-negatives) and those already infected (tuberculin-positives) has to be studied.

(b) Prevalence of sources of infection: In this context, the most important sources of infection have to be defined. Persons who have been in intimate contact with tuberculous patients represent the most suitable population group for the study of this problem. Several studies demonstrate that smear-positive patients play the greatest role in spreading infection and in doing so perpetuate the epidemic; in contrast, those patients in whom the presence of bacilli in the sputa can be demonstrated by culture only, or who are culture-negative, are relatively harmless.

Figure 1 shows the situation in Rotterdam (the Netherlands). The percentage of positive reactors, i.e., the infection prevalence, was high among intimate contacts of smear-positive index cases; 50 per cent of such contacts aged 0-14 years were found to be infected, as compared with 1 per cent in the same age-group among the general population. However, the prevalence of infection was low (about 6 per cent) in child contacts of culture-positive and culture-negative index cases (For the full report see TSRU report No.3, in press.)

An extensive study on morbidity in contacts (more than 8,000 intimate "white" and Indian contacts, and more than 11,000 casual contacts in the same two racial groups) has been recently carried out in British Columbia and Saskatchewan (TSRU report No.3, in press). Appendix Tables II and III show that tuberculosis was rare in intimate contacts of culture-negative sources, and no cases of tuberculosis were observed among casual contacts of culture-negative sources. Disease rates were also substantially lower (0.8 per cent for whites and 2.3 per cent for Indians) among intimate contacts of culture-positive cases than among intimate contacts of smear-positive sources (5.9 per cent and 8.2 per cent respectively).

These observations confirm once more that the bacillary status of the patient decides the extent to which he can transmit tubercle bacilli to other hosts. The most important transmitters are patients in whose sputa tubercle bacilli can be demonstrated by direct smear examination.
For the purpose of the study, patients with smear-positive tuberculosis will be considered as sources of infection.

(c) The "contagious" parameter is computed as:

\[
\text{Annual tuberculosis infection rate (\%)} \times 1,000 = \frac{\text{Prevalence of sources of infection (per 100,000)}}{\text{Incidence of smear-positive cases (at all ages)}
\]

Assuming no effective chemotherapy, the prevalence rate of smear-positive cases (at all ages) is twice as high as the incidence rate of smear-positive cases, and the incidence rate of smear-positive cases is twice as high as the death rate from tuberculosis.

The relationships between the annual tuberculosis infection rates and mortality and morbidity rates in the Netherlands were recently analyzed. The data refer to the infection rates published in TSNU report No.1 (TSRU, 1969, Table 5), to the official mortality rates for the period 1921-1938 (Table 1A), and to the morbidity rates for the period 1951-1968 (Table 1B).

In order to obtain estimates for the "contagious" parameter concerning prevalence (and not mortality, or incidence), estimates related to mortality rates (column 3, Table 1A) were divided by four as the prevalence of smear-positive cases was assumed to be four times as high as mortality from tuberculosis; and estimates related to the incidence (column 3, Table 1B) were divided by two, as the prevalence of smear-positive cases was assumed to be twice as high as the incidence of smear-positive cases. The estimates derived from both mortality (Table 1A) and morbidity (Table 1B) indicate that, on average, about fourteen persons were infected with tuberculosis during one year by one source of infection in the Dutch community in the periods 1921-1938 and 1951-1968.

The "contagious" parameter may depend, to some extent, on various socio-economic conditions; one should therefore attempt to obtain values for different populations. Sutherland and Fayers calculated annual tuberculosis infection rates for Lesotho and Uganda (TSRU report No.3, in press); their rates can be related to the estimates of smear-positive tuberculosis cases aged ten years and over from the original WHO surveys carried out in the late 1950s. The "contagious" parameter for these two countries is about ten, as there was a prevalence of about 100 smear-positive cases per 100,000 population for each one per cent of infection.

2. Development of tuberculosis following infection

It is evident that the risk resulting from tuberculous infection is greater for persons not yet infected than for those who have been already infected with virulent tubercle bacilli. The disease following primary infection is usually called "primary" tuberculosis. The disease which occurs in those previously infected with virulent tubercle bacilli should be called "secondary" tuberculosis. For the purpose of epidemiological studies, it is necessary to adopt a precise (working) distinction between "primary" and "secondary" pulmonary tuberculosis. Dr Holm suggested the following definitions:

(a) Any pulmonary tuberculosis developing (and being diagnosed) during the first five years following primary infection is classified as "primary" tuberculosis.

(b) Any pulmonary tuberculosis diagnosed more than five years after primary infection is classified as "secondary" tuberculosis.
(a) Primary tuberculosis

If the risk of tuberculous infection is high, as it was in developed countries before World War II and still is in many developing countries at present, primary tuberculosis occurs mostly among children. If the risk of infection is low, primary tuberculosis occurs (at a low rate), in addition, among young persons.

Extensive information on the bacteriological status in children suffering from primary tuberculosis is available in many developed countries where BCG vaccination has not been practised. All the statistics show that few children with primary tuberculosis develop bacillary tuberculosis (in Norway 2.6 per cent; in Denmark 4.9 per cent; in the Netherlands 0.9 per cent - based on reported cases during the period 1951-1968); and very few children develop smear-positive tuberculosis which is considered to be the most important source of infection.

However, much less is known about the development of the disease, and especially its bacteriological status, if the primary infection occurs during adolescence or adult age.

Extensive information on this subject is available from the MRC Vaccines Trial in which 13,000 children aged 14 3/4 years, chosen at random, were left unvaccinated, and were followed by means of tuberculin tests and X-rays of the chest for a period of about 10 years. Out of 1,261 persons with indurations 10 mm or more, 7.5 per cent developed clinical tuberculosis during the ten years following primary infection. Unfortunately, there is no complete information on bacteriological status in persons who developed clinical tuberculosis.

This problem has been studied among the general population of the province of Saskatchewan (Canada), where extensive tuberculin and MMF surveys of the entire population have been carried out since 1955. During the period 1960-1973, a total of 529 smear-positive cases of pulmonary tuberculosis were reported in the Province (just below 1 million inhabitants). Seven cases occurred among children aged 0-14 years, 113 cases among those aged 15-29 years and the remaining 409 patients were older than twenty years at the time of the diagnosis of their disease. About one-third of smear-positive pulmonary tuberculosis in the age-group 15-29 years originated from the "previously tuberculin-negative" group. If all cases (smear-positive and smear-negative) from the latter group aged 15-29 years are considered (97 cases), smear-positive pulmonary tuberculosis form nearly 25 per cent of all primary tuberculosis cases.

It is felt that "primary" tuberculosis has a limited impact on the transmission of tuberculous infection: (i) Sources of infection among children are infrequent both in low and high prevalence countries; (ii) sources of infection following primary infection acquired during adolescence or adult age are relatively frequent if the risk of tuberculous infection is low (about 25 per cent of all cases in the age-group 15-29 years) but their contribution to all smear-positive cases discovered in the entire adult population is numerically small; (iii) sources of infection among middle-aged, elderly and old people are uncommon both in low and high prevalence countries.

(b) Secondary tuberculosis

As it is not possible to detect superinfection by means of tuberculin testing among those who have been previously infected with virulent tubercle bacilli, it cannot be directly discovered whether or not exogenous superinfection is important in the development of secondary tuberculosis.
The problem of the endogenous or exogenous origin of secondary tuberculosis has long been at the centre of the arguments about phthisiogenesis, and opposing opinions have been put forward on this subject.

The proponents of the endogenous theory maintain that the tubercle bacilli resulting from primary infection can remain alive within their human host for his life-time, and that they can at any time, for reasons mostly unknown, start multiplying and produce such pathology in the lungs that a discharge of tubercle bacilli through the respiratory tract will result. They also maintain that such endogenous flare-up of an old infection is the most common cause of secondary pulmonary tuberculosis, or in other words, that exogenous infection (inhalation of tubercle bacilli by already infected persons) plays an unimportant role. The basis for this theory must be that primary tuberculosis infection induces a high degree of immunity and that this protection lasts for a very long period and usually for life.

The proponents of the exogenous theory maintain that exogenous re-infection plays an important role in the development of secondary pulmonary tuberculosis. In other words, the inhalation of tubercle bacilli by persons who had a tuberculosis infection more than five years ago represents a considerable risk of development of pulmonary tuberculosis relatively shortly after this re-infection.

The controversy between the two theories is not only interesting from the academic point of view but is of vital importance in the planning of rational tuberculosis control programmes in high prevalence countries. If the unitary concept of tuberculosis in man is the answer to the problem, efforts should be primarily directed towards the prevention of primary infection. If exogenous infection in high prevalence countries often leads to secondary tuberculosis, the programme should be primarily focused on the decrease in sources of infection.

The TSRU has been dealing with this problem for a number of years. Sutherland and Svandova presented their mathematical model (limited to the age-group 40-59 years) to the International Tuberculosis Conference in Moscow in 1971. Two years later, the proponents of the endogenous theory had an opportunity to explain their arguments at the International Tuberculosis Conference in Tokyo. A more comprehensive model of the TSRU covering a larger proportion of the population than that referred to in Moscow will be presented, by the same authors, at the coming Conference in Mexico. Reference is made to the first two series of the reports published in the Proceedings of the Conference in Moscow and Tokyo.

Two observations showing the impact of the high levels of tuberculosis infection rates on the magnitude of the tuberculosis problem in the respective populations, and the close relationship between these two variables, should be noted.

The first observation concerns Eskimos in Alaska, Greenland and North-west Territories of Canada. The annual incidence rates of tuberculosis among the native population were extremely high in all three circumpolar areas in the early 1950s, in the order of 2.5 per cent of new (mostly bacteriologically confirmed) cases of tuberculosis each year (Fig.2). The annual tuberculosis infection rate in Alaska estimated by Comstock and Philip was, at that time, as high as 25 per cent (1). In twenty years tuberculosis incidence rates decreased dramatically, in Greenland from about 2,500 per 100,000 in 1950-1954 to about 60 per 100,000 in the early 1970s, and in Alaska from a similar rate in the early 1950s to less than 200 in 1967, or by more than 90 per cent in about fifteen years.

Naturally, decrease in the tuberculosis problem can also be seen in mortality rates (Fig.3). They fell from about 750 per 100,000 in 1950 to less than 5 per 100,000 during the last few years - a reduction of some 90 per cent each year.
The dramatic decreases in mortality and morbidity rates have been preceded, naturally, by a sharp decrease in the tuberculous infection rates. Whereas more than 95 per cent of Eskimo children were reported to have been infected with tubercle bacilli at the age of 6-7 years in 1950, the tuberculin surveys from 1970 discovered practically no infections at that age (Fig.4).

The further two graphs (Fig.5 and 6) illustrate the decreases in the incidence rates not only among children and young adults but at all ages, i.e. also in persons previously infected. Thus the same number of infected subjects aged say 35 years or more in the N.W.T. of Canada produced 0.9 per cent bacillary cases each year during 1967-1969, whereas the incidence was "only" 0.3 per cent each year in 1973-1975 (Fig.5). In Greenland, the rates in the same age-group fell from nearly 3.0 per cent in 1955-1957 to less than 1.0 per cent in 1963-1965 (Fig.6).

The second observation refers to the relationship between tuberculosis infection rates, and mortality and morbidity rates. The data for the Netherlands have been already presented in Tables 1A and 1B; this time, the above-mentioned relationship is studied. The results are presented below:

(a) Relationship between the mortality from tuberculosis (all forms) and the tuberculosis infection rates, The Netherlands, 1921-1938

<table>
<thead>
<tr>
<th>Year</th>
<th>Death rate from tuberculosis per 100 000</th>
<th>Risk of tuberculous infection (%)</th>
<th>Ratio of death to risk ( x )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1922</td>
<td>115.1</td>
<td>6.02</td>
<td>19</td>
</tr>
<tr>
<td>1925</td>
<td>100.3</td>
<td>5.13</td>
<td>20</td>
</tr>
<tr>
<td>1928</td>
<td>87.9</td>
<td>4.37</td>
<td>20</td>
</tr>
<tr>
<td>1931</td>
<td>70.5</td>
<td>3.72</td>
<td>19</td>
</tr>
<tr>
<td>1934</td>
<td>55.5</td>
<td>3.16</td>
<td>18</td>
</tr>
<tr>
<td>1937</td>
<td>47.7</td>
<td>2.69</td>
<td>18</td>
</tr>
<tr>
<td>1921 - 1938</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>1921 - 1938</td>
<td>-</td>
<td>-</td>
<td>19</td>
</tr>
</tbody>
</table>

(b) Relationship between the incidence of smear-positive tuberculosis and the risk of tuberculous infection, The Netherlands, 1951-1968

<table>
<thead>
<tr>
<th>Year</th>
<th>Incidence rate of smear-positive tuberculosis per 100 000</th>
<th>Risk of tuberculous infection (%)</th>
<th>Ratio of incidence to risk ( x )</th>
</tr>
</thead>
<tbody>
<tr>
<td>1952</td>
<td>12.9</td>
<td>0.400</td>
<td>35</td>
</tr>
<tr>
<td>1955</td>
<td>7.8</td>
<td>0.265</td>
<td>29</td>
</tr>
<tr>
<td>1958</td>
<td>5.7</td>
<td>0.176</td>
<td>32</td>
</tr>
<tr>
<td>1961</td>
<td>4.6</td>
<td>0.116</td>
<td>40</td>
</tr>
<tr>
<td>1964</td>
<td>3.2</td>
<td>0.077</td>
<td>42</td>
</tr>
<tr>
<td>1967</td>
<td>2.4</td>
<td>0.051</td>
<td>47</td>
</tr>
<tr>
<td>1951 - 1968</td>
<td>-</td>
<td>-</td>
<td>38</td>
</tr>
</tbody>
</table>

\( x \) Expressed as mortality from tuberculosis and incidence of smear-positive cases respectively per 100 000 general population for each 1 per cent of the tuberculosis infection rate.
The above table under (a) shows the relationship between the estimated risk of tuberculosis infection for the years 1921-1938, and observed death rates from tuberculosis. Assuming no effective chemotherapy, death rates correspond, as already mentioned, to one-half of the incidence rates of smear-positive cases of tuberculosis. The same table shows that in the Netherlands the ratio between the estimated risk of tuberculous infection and observed death rates during the period under study, was 1 per cent risk of infection for nineteen deaths from tuberculosis per 100,000 general population.

The above table under (b) shows the relationship between the estimated risk of tuberculous infection for the years 1951-1968, and observed incidence rates of smear-positive cases of pulmonary tuberculosis during the same period. The ratio for the whole period is 1 per cent risk of infection for thirty-eight smear-positive cases per 100,000 general population.

The relationship between the incidence of smear-positive tuberculosis and the risk of tuberculous infection has also been studied for Lesotho and Uganda. For these countries there are estimates of the prevalence of smear-positive tuberculosis at ages ten years and over (and for Uganda an estimate of all bacillary tuberculosis) in the late 1950s from the original WHO surveys, and these may be compared with estimated risk of infection in the same year derived from tuberculin surveys made at the same time and later (calculated from the figures given by Sutherland and Fayers, TSRU report No.3, in press); see Appendix IV.

Considering smear-positive tuberculosis only, the ratios of prevalence to risk agree closely in the two countries (Appendix IV); the all-ages prevalence of smear-positive tuberculosis per 100,000 population is about 100 for every 1 per cent in the risk of infection in the same calendar year. Assuming that the prevalence of smear-positive cases in a general population is twice the incidence of smear-positive cases, the incidence may be taken as fifty cases per 100,000 general population for each 1 per cent in the risk of infection.

It is felt, there is reliable evidence that exogenous superinfection plays a predominant role in the pathogenesis of pulmonary tuberculosis in the adults, if the risk of tuberculous infection is high. And there is ample evidence that the risk of tuberculous infection is high, at present, in most developing countries.

(See for the evidence that exogenous superinfection is important in the development of secondary tuberculosis based on various anatomical and bacteriological studies see Dr. Canetti's report "Endogenous reactivation and exogenous reinfection. Their relative importance with regard to the development of non-primary tuberculosis" read at the International Tuberculosis Conference in Moscow; Bull. Int. Un. Tub., 1972 47, 116.)

3. From development of smear-positive tuberculosis to recovery or death

Two sources of information concerning this problem are known. The first refers to extensive Holm's studies based on the Danish material for the period between the two World Wars (Fig.7). His estimates of recovery and death from smear-positive tuberculosis, assuming no interference by effective treatment (the upper part of Fig.7), are compared with those where interference by chemotherapy did occur (the lower part of Fig.7). This material is taken from Dr. Holm's contributions to various meetings of the TSRU.

The upper part of Fig.7 indicates what the situation will be for one hundred persons, diagnosed as smear-positive pulmonary tuberculosis at a year "0", and followed yearly for eight years without interference by effective treatment. After eight years half of them will have died from their disease and the other half will have recovered in the sense that they have stopped discharging tubercle bacilli. After two years about half of those who
are to die, will have died, and half of those who are to recover, will have recovered. The dotted area represents the prevalence of known sources of infection, and it has been found that this area is about double the area corresponding to one year. The area to the left of year "0" represents the undiagnosed sources of infection; it consists mainly of sources of infection before they are diagnosed. If this area corresponds to the area of one year, one-third of the real prevalence of sources of infection is represented by undiagnosed cases.

The lower part of Fig.7 indicates theoretically what may be obtained by adequate chemotherapy given immediately after diagnosis to all the 100 persons with smear-positive tuberculosis. The sputum can be converted in about 95 per cent of all of them within a short time, and with very little chance of relapse. The 5 per cent treated but not converted will live longer than if they were not treated, and act as sources of infection, but a certain proportion of them will recover spontaneously as if no treatment had been given. The prevalence of smear-positive cases after diagnosis may be cut down to less than one quarter but, by the treatment, the prevalence of undiagnosed cases has of course not been influenced. The end result of such an almost ideal treatment measure would be that the total prevalence of sources of infection would be cut to about half of what it would be without interference with treatment. With such a treatment measure it would be expected to cut the annual infection rate to half of what it would be without treatment. It should, however, be noted that even with a 100 per cent effective treatment giving immediate sputum conversion, by treatment only the prevalence of sources of infection could be cut to one-third.

The second source of information from the late 1970s is the longitudinal study which was carried out by the Indian Health Authorities in co-operation with WHO in Bangaloro. It will be interesting to study the results of this extremely important experience after its publication.
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Table 1A

**RELATIONSHIP BETWEEN THE ANNUAL TUBERCULOSIS INFECTION RATES AND THE MORTALITY FROM TUBERCULOSIS (all forms)**

The Netherlands, 1921-1938

| Year    | The annual tuberculosis infection rate (%) | Death rate from TB (all forms) per 100,000 x) | (1) x 1000 | (3) |
|---------|-------------------------------------------|-----------------------------------------------|------------|
| 1922    | 6.02                                      | 115.1                                         | 52.3       |
| 1925    | 5.13                                      | 100.3                                         | 51.1       |
| 1928    | 4.37                                      | 87.9                                          | 49.7       |
| 1931    | 3.72                                      | 70.5                                          | 52.8       |
| 1934    | 3.16                                      | 55.5                                          | 56.9       |
| 1937    | 2.69                                      | 47.7                                          | 56.4       |

1921-1938 -- -- 53.2 13.3

x) Averages for 1921-1923, 1924-1926, ...... 1936-1938
xx) Ratio Mortality: Prevalence = 1 : 4 (see text)

Table 1B

**RELATIONSHIP BETWEEN THE ANNUAL TUBERCULOSIS INFECTION RATES AND THE INCIDENCE OF SMEAR-POSITIVE TUBERCULOSIS**

The Netherlands, 1951-1968

| Year | The annual tuberculosis infection rate (%) | Incidence rate of smear-positive tuberculosis (per 100,000 x) | (1) x 1000 | (3) |
|------|-------------------------------------------|-------------------------------------------------------------|------------|
| 1952 | 0.400                                     | 13.9                                                        | 28.8       |
| 1955 | 0.265                                     | 7.8                                                         | 34.0       |
| 1958 | 0.176                                     | 5.7                                                         | 30.9       |
| 1961 | 0.116                                     | 4.6                                                         | 25.2       |
| 1964 | 0.077                                     | 3.2                                                         | 24.1       |
| 1967 | 0.051                                     | 2.4                                                         | 21.2       |

1951-1968 -- -- 27.4 13.7

xx) Ratio Incidence: Prevalence = 1 : 2 (see text)
PERCENTAGE OF POSITIVE REACTORS AMONG CONTACTS AGED 0-14 YEARS, Rotterdam, 1967-69

Contacts of Index cases
- Smear positive
- Culture positive
- Culture negative
FIGURE 2

TUBERCULOSIS INCIDENCE RATES IN GREENLAND, ALASKA, NWT OF CANADA, AND CANADA AS A WHOLE (NATIVE POPULATION), 1950-1972
FIGURE 3
TUBERCULOSIS DEATH RATES IN THE NATIVES OF ARCTIC
1950 - 1972

RATE PER 10,000


NWT OF CANADA
ALASKA
GREENLAND
FIGURE 4

PREVALENCE OF TUBERCULIN SENSITIVITY AMONG ESKIMO CHILDREN
TESTED IN FIVE SUCCESSIVE SURVEYS, BY AGE

YUKON, KUSKOKWIM DELTA, ALASKA
1949-51 TO 1969-70

POSITIVE (%)
FIGURE 5

THE AVERAGE ANNUAL RATES (per 10,000) BY SEX AND AGE, N.W.T.

A. NEW CASES

Rate per 10,000

Males

Rate per 10,000

Females

B. RELAPSES

0-14 15-24 25-34 35+

Age (years)

0-14 15-24 25-34 35+
FIGURE 6

INCIDENCE OF RESPIRATORY TUBERCULOSIS BY SEX AND AGE


Stein et al., Arch Environ Health—Vol 17, Oct 1966
FIGURE 7

ESTIMATES OF RECOVERY AND DEATH FROM SMEAR-POSITIVE PULMONARY TB

a. assuming no interference by effective treatment

b. assuming interference by effective treatment

Source of information: Dr. Holm, internal report to the TSKH, 1971
**APPENDIX I**

**HOW TO ESTIMATE THE ANNUAL TUBERCULOSIS INFECTION RATES?**

There are:

Two steps in assessing the annual tuberculosis infection rates:

a) Estimation of the percentage decrease in the annual risk of infection using Appendix Table C of TSRI report no.1.

Table 1 shows a part of this table. The percentage decrease in the annual tuberculosis infection rates can be estimated if two or more prevalence figures are available for subjects of the same age. If the prevalence of infection in children aged, say 10 years was, for instance, 5.5% in 1966, and 2.5% in 1972, entry 80 in the table is divided by 6 years (from 1966 to 1972) to give the approximate annual percentage decrease, which is about 13%. The approximate annual percentage decrease is needed for use in Appendix Table B.

### Table 1

<table>
<thead>
<tr>
<th>PERCENTAGE ALREADY INFECTED AT THE TIME OF</th>
<th>THE LATER SURVEY</th>
</tr>
</thead>
<tbody>
<tr>
<td>0.2</td>
<td>0.4</td>
</tr>
<tr>
<td>0.4</td>
<td>69</td>
</tr>
<tr>
<td>0.8</td>
<td>161</td>
</tr>
<tr>
<td>1.0</td>
<td>202</td>
</tr>
<tr>
<td>1.5</td>
<td>231</td>
</tr>
<tr>
<td>2.0</td>
<td>254</td>
</tr>
<tr>
<td>2.5</td>
<td>277</td>
</tr>
<tr>
<td>3.0</td>
<td>288</td>
</tr>
<tr>
<td>3.5</td>
<td>302</td>
</tr>
<tr>
<td>4.0</td>
<td>314</td>
</tr>
<tr>
<td>4.5</td>
<td>326</td>
</tr>
<tr>
<td>5.0</td>
<td>338</td>
</tr>
<tr>
<td>5.5</td>
<td>348</td>
</tr>
<tr>
<td>etc.</td>
<td></td>
</tr>
</tbody>
</table>

Divide the entry in the table by the number of years between the surveys to obtain the approximate annual percentage decrease for use in Appendix Table B.

b) Using the estimate of the percentage decrease, Appendix Table B of the same report provides direct assessments of the risk of tuberculous infection in two calendar years, namely the year in which the prevalence of tuberculous infection was determined, and a few years earlier (Table 2). In the above mentioned case one consults Appendix Table B for children aged 10 years, last column (13% annual...
decrease in risk of infection each year). The table indicates the following annual tuberculosis infection rates:

1966: 0.25% (and in 1956: 0.92%)
1972: 0.11% (and in 1962: 0.43%)

Table 2

<table>
<thead>
<tr>
<th>PERCENTAGE ALREADY INFELECTED</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
<th>8</th>
<th>9</th>
<th>10</th>
<th>11</th>
<th>12</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.0</td>
<td>0.09</td>
<td>0.10</td>
<td>0.08</td>
<td>0.11</td>
<td>etc.</td>
<td>0.06</td>
<td>0.10</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2.0</td>
<td>0.14</td>
<td>0.13</td>
<td>0.12</td>
<td>0.16</td>
<td>etc.</td>
<td>0.07</td>
<td>0.15</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.0</td>
<td>0.18</td>
<td>0.20</td>
<td>0.16</td>
<td>0.22</td>
<td>etc.</td>
<td>0.09</td>
<td>0.33</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3.5</td>
<td>etc.</td>
<td>0.20</td>
<td>0.16</td>
<td>0.22</td>
<td>etc.</td>
<td>0.11</td>
<td>0.41</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.0</td>
<td>0.16</td>
<td>0.15</td>
<td>0.13</td>
<td>0.16</td>
<td>etc.</td>
<td>0.16</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>4.5</td>
<td>0.16</td>
<td>0.15</td>
<td>0.13</td>
<td>0.16</td>
<td>etc.</td>
<td>0.16</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.0</td>
<td>0.16</td>
<td>0.15</td>
<td>0.13</td>
<td>0.16</td>
<td>etc.</td>
<td>0.16</td>
<td>0.30</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5.2</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>0.20</td>
<td>etc.</td>
<td>0.25</td>
<td>0.25</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

### APPENDIX II

#### Table 5

ACTIVE TUBERCULOSIS AMONG INTIMATE CONTACTS ACCORDING TO BACTERIOLOGICAL STATUS OF SOURCES

British Columbia and Saskatchewan, 1966 - 1971

#### Table 5A - Whites

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>a. No. of contacts</th>
<th>Bacteriological status of source</th>
<th>% active tuberculosis in general population in 1966-1971</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. No. of active cases</td>
<td>c. % with active tb</td>
<td>Smear positive</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>1088</td>
</tr>
<tr>
<td>0 - 14</td>
<td>11.3(3.3)</td>
<td></td>
<td>123(36)***</td>
</tr>
<tr>
<td>15 - 29</td>
<td>721</td>
<td>31(13)</td>
<td>394</td>
</tr>
<tr>
<td>30+</td>
<td>1276</td>
<td>27(22)</td>
<td>721</td>
</tr>
<tr>
<td>Total</td>
<td>3085</td>
<td>181(71)</td>
<td>1693</td>
</tr>
</tbody>
</table>

*Population figures do not include Registered Indians in Saskatchewan

**Figures in brackets represent bacteriologically confirmed cases

#### Table 5B - Indians

<table>
<thead>
<tr>
<th>Age-group (years)</th>
<th>a. No. of contacts</th>
<th>Bacteriological status of source</th>
<th>% active tuberculosis in general population in 1966-1971</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>b. No. of active cases</td>
<td>c. % with active tb</td>
<td>707</td>
</tr>
<tr>
<td>0 - 14</td>
<td>12.0(5.0)</td>
<td></td>
<td>85(35)*</td>
</tr>
<tr>
<td>15 - 29</td>
<td>262</td>
<td>13(6)</td>
<td>154</td>
</tr>
<tr>
<td>30+</td>
<td>301</td>
<td>6(5)</td>
<td>157</td>
</tr>
<tr>
<td>Total</td>
<td>1270</td>
<td>104(46)</td>
<td>707</td>
</tr>
</tbody>
</table>

* Figures in brackets represent bacteriologically confirmed cases
### APPENDIX III

#### Table 6

**ACTIVE TUBERCULOSIS AMONG CASUAL CONTACTS ACCORDING TO BACTERIOLOGICAL STATUS OF SOURCES**

**British Columbia and Saskatchewan, 1966 - 1971**

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No. of Contacts</th>
<th>Smear positive</th>
<th>Culture positive</th>
<th>Culture negative</th>
<th>Total</th>
<th>Active tuberculosis in general population in 1966-1971</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bacteriological status of source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a.</td>
<td>b.</td>
<td>c.</td>
<td>a.</td>
<td>b.</td>
<td>c.</td>
</tr>
<tr>
<td>0 - 14</td>
<td>1927</td>
<td>46(12)</td>
<td>2.3(0.6)</td>
<td>870</td>
<td>4(-)</td>
<td>0.5(-)</td>
</tr>
<tr>
<td>15 - 29</td>
<td>1871</td>
<td>28(18)</td>
<td>1.5(1.0)</td>
<td>607</td>
<td>3(1)</td>
<td>0.5(0.2)</td>
</tr>
<tr>
<td>30+</td>
<td>2408</td>
<td>10(13)</td>
<td>0.7(0.5)</td>
<td>1011</td>
<td>7(5)</td>
<td>0.7(0.5)</td>
</tr>
<tr>
<td>Total</td>
<td>6206</td>
<td>91(43)</td>
<td>1.5(0.7)</td>
<td>2480</td>
<td>14(6)</td>
<td>0.6(0.2)</td>
</tr>
</tbody>
</table>

*Population figures do not include registered Indians in Saskatchewan

*Figures in brackets represent bacteriologically confirmed cases.

### Table 6B - Indians

<table>
<thead>
<tr>
<th>Age Group (years)</th>
<th>No. of Contacts</th>
<th>Smear positive</th>
<th>Culture positive</th>
<th>Culture negative</th>
<th>Total</th>
<th>Active tuberculosis in general population in 1966-1971</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Bacteriological status of source</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>a.</td>
<td>b.</td>
<td>c.</td>
<td>a.</td>
<td>b.</td>
<td>c.</td>
</tr>
<tr>
<td>0 - 14</td>
<td>453</td>
<td>35(11)*</td>
<td>7.7(2.4)</td>
<td>239</td>
<td>5(1)</td>
<td>2.1(0.4)</td>
</tr>
<tr>
<td>15 - 29</td>
<td>197</td>
<td>7(1)</td>
<td>3.6(0.5)</td>
<td>150</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>30+</td>
<td>224</td>
<td>3(2)</td>
<td>1.3(0.9)</td>
<td>155</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>Total</td>
<td>874</td>
<td>45(14)</td>
<td>5.1(1.6)</td>
<td>544</td>
<td>5(1)</td>
<td>0.9(0.2)</td>
</tr>
</tbody>
</table>

*Figures in brackets represent bacteriologically confirmed cases
## APPENDIX IV

### RELATIONSHIP BETWEEN THE PREVALENCE OF SMEAR-POSITIVE TUBERCULOSIS AND THE RISK OF TUBERCLOUS INFECTION

Lesotho (1957) and Uganda (1958)

<table>
<thead>
<tr>
<th>Country</th>
<th>Year</th>
<th>Bact. positivity</th>
<th>Prevalence (excreting acid-fast bacilli) per 1000 aged 10+ (with 95% Poisson range)</th>
<th>Percent of population aged 10+</th>
<th>Prevalence at all ages per 1000 ( \times )</th>
<th>Estimated risk of infection at age 10 per cent</th>
<th>Ratio of prevalence to risk xx</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lesotho</td>
<td>1957</td>
<td>Direct</td>
<td>5 (3-9)</td>
<td>70.8</td>
<td>3.54</td>
<td>3.89</td>
<td>91</td>
</tr>
<tr>
<td>(Basutoland)</td>
<td></td>
<td>Direct (Direct + Culture)</td>
<td>7.5(2.5-19.7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Uganda</td>
<td>1958</td>
<td>(Direct + Culture)</td>
<td>3.2(1.7-5.5)</td>
<td>69.3</td>
<td>(2.22)</td>
<td>2.24</td>
<td>(232)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Direct + Culture</td>
<td>5.20</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

x  Assuming there is no bacteriologically positive tuberculosis under age 10

xx  Expressed as a prevalence per 100,000 population for each 1 per cent in the risk of infection.
RECENT CONTROLLED CLINICAL TRIALS IN PULMONARY TUBERCULOSIS

by

Dr J.R. Bignall
WHO Consultant

During the past five years controlled clinical trials in pulmonary tuberculosis have been largely directed towards solving one major problem - making effective treatment easier for the patients.

Two factors limit the efficacy of treatment: the need to co-operate in drug administration and the need to continue co-operation for long periods. The effects of these limiting factors can be reduced in several ways.

First, the co-operation of patients can be improved by explanation and exhortation, by general health education, by better trained staff and by eliminating all unnecessary work in clinics so that the staff can give more time to each patient. The easier the treatment is for the patient the better he will co-operate. Long journeys to clinics, long waits in queues, inefficient and unsympathetic service and large numbers of tablets to be swallowed each day will not help patients to maintain regular treatment.

Secondly, co-operation can be monitored. By this is meant detecting irregularity of drug administration so that the necessary action can be taken to achieve regularity. This has been attempted in the case of self-administration of drugs by urine tests and surprise visits to the patients' homes to check that the correct numbers of tablets have been taken. This is of only small value. If the drugs are not administered by the patients but by some other person there is a complete check on regularity. Regularity will not necessarily be improved; but irregularities will be known and action can be taken.

Hence the concept of supervision of chemotherapy regimens.

If it is necessary to give drugs daily, a supervised regimen becomes difficult for the patient; this may lead to even more irregularity or complete cessation of treatment. A practical supervised regimen requires, in most instances, a non-daily regimen - an intermittent regimen. The two concepts - supervision and intermittency - are quite separate. A daily regimen can be supervised and an intermittent regimen can be self-administered. The regimens that have been explored by controlled clinical trials have been both supervised and intermittent.

Although intermittent regimens were first used in order to make supervision easier, there, is, in fact, good experimental evidence to support them in the case of some of the antituberculosis drugs. Indeed, in the case of three of them - isoniazid, rifampicin and pyrazinamide - there is evidence that in certain doses they are more effective given at intervals longer than one day².

The second limiting factor is the length of treatment. The minimum duration with the old regimens has been at least one year. This is far too long for many patients to continue co-operating either in taking drugs at home or in attending a clinic for supervised drug administration. The duration of treatment must be considerably reduced.

*Consultant Physician, Brompton Hospital, London
Successful treatment has two phases. In the first, the initial 'kill', the drugs kill tubercle bacilli that are dividing. But some are not; they are in a dormant state. The long period of treatment has in the past been necessary in order to suppress bacterial multiplication and to kill those bacilli that escape the suppression. To reduce the duration of the suppression phase it is necessary to kill as many as possible of the bacilli during the 'killing' phase. To do this requires highly bactericidal drugs. Those with the greatest killing power are rifampicin, isoniazid and the combination of streptomycin and pyrazinamide. Thus, these are the drugs most likely to be of value in reducing the period of treatment by increasing the efficacy of the 'killing' phase.

The objectives are reduction of the frequency of drug administration - to make supervision easier - and shortening of the total duration of treatment. Rifampicin, isoniazid and streptomycin with pyrazinamide are likely to succeed in both.

Controlled clinical trials have, therefore, been mainly concerned during the past five years with exploring the possibilities of regimens including some or all of these drugs.

Supervised intermittent regimens

The high efficacy of streptomycin and high-dose isoniazid was reported in 1964. It is well-known. At one year 91 per cent of patients with initially sensitive cultures had quiescent disease. Trials reported during the past five years have confirmed its efficacy and explored the value of an initial intensive phase.

In 1970, the International Union against Tuberculosis reported a trial of this regimen with a four-week initial daily phase of streptomycin, isoniazid and thiacetazone. After a year's treatment 93 per cent had quiescent disease. In Czechoslovakia a trial with a three-month's daily phase of streptomycin, isoniazid and PAS produced 100 per cent quiescence, and the results were similar when the daily phase was reduced to six weeks. With the same regimen in Singapore 98 per cent quiescence was reported. In Great Britain a controlled trial was reported in 1973: the three-drug regimen for the first three months followed by twice-weekly streptomycin and isoniazid produced 95 per cent quiescence.

The figures of quiescence reported in these trials should not be compared with each other. There were differences, among other factors, in the definition of quiesence used. It is not known whether the initial phase with three drugs does, in fact, improve results in patients with sensitive cultures; for no direct comparison of regimens with and without a daily phase has been made.

The results in patients with initially resistant cultures have, as expected, been less good; and in these an initial three-drug phase is probably important. Adding a third drug - PAS or thiacetazone - in both the initial daily phase and the intermittent phase does not improve the results in patients with sensitive cultures; but there is a suggestion that it may do so in those with resistant cultures, but at the cost of increased toxicity and unacceptability of the regimen.

As the twice-weekly regimen has been so satisfactory it was reasonable to increase the interval further, to once a week. Using the same doses of streptomycin and isoniazid as in the twice-weekly regimen, the results were much worse. Only 66 per cent had a favourable response. The response was greatly influenced by the rate of inactivation of isoniazid. With slow inactivators 76 per cent had a favourable response, but only 56 per cent of rapid inactivators. Adding pyrazinamide made no difference. When the streptomycin and isoniazid were given daily at the start the response was improved in both groups, to 95 per cent in slow inactivators but to only 76 per cent in rapid inactivators. Neither increasing the dose of isoniazid nor adding PAS improved the results.10
A slow-release form of isoniazid may make the once-weekly regimen efficient in rapid inactivators. It can bring the serum concentrations and durations of coverage up to those found with ordinary isoniazid in slow inactivators. But trials of its therapeutic efficacy have not been completed.

Other drug regimens have been tried in supervised intermittent regimens. Ethambutol and isoniazid once or twice a week after an initial two weeks supplement of streptomycin is not highly effective - especially in rapid inactivators. But a similar regimen with PAS instead of ethambutol twice weekly gave results similar, though probably slightly less good, to those obtained with isoniazid and PAS daily. The twice weekly regimen was much more acceptable, only 6 per cent complaining of side-effects compared with 21 per cent on the daily regimen. Thiacetazone and isoniazid after eight weeks supplement with streptomycin have also given good results. An orally administered twice-weekly regimen has some practical advantages in certain circumstances.

Rifampicin is another drug that experimentally appears suitable for intermittent regimens. In Hong Kong, a trial was done in patients with cultures resistant to isoniazid. They received either rifampicin and ethambutol daily, rifampicin and ethambutol twice or once weekly, and a fourth group had the weekly continuation phase supplemented by a daily phase for two months. The results were less good in the twice-weekly (80 per cent favourable) and once-weekly (82 per cent favourable) than in the daily group (89 per cent favourable). But the once-weekly regimen produced 91 per cent favourable results when the drugs were given daily for the first two months.

The disadvantage of intermittent rifampicin is the frequency of unpleasant side-effects. Febrile episodes ('flu-like) occurred in 54 per cent of those given weekly doses from the start. These are mediated by an immune mechanism and rifampicin-dependent antibodies can be detected in the serum. An attempt to overcome them by giving small doses of rifampicin daily in addition to the large weekly doses has not been entirely successful.

In Poland, good results were also reported with ethambutol and rifampicin either once or twice weekly after an initial period of three months daily treatment. Twice weekly gave no better results than once weekly. Toxicity was much less than in the Hong Kong trial - only 18 per cent of 'flu episodes compared with 35 per cent. A once-weekly regimen has also been reported on favourably from the German Democratic Republic and from Singapore. In Singapore a lower dose of rifampicin - 600mg - was found to be as effective as 900mg in the twice-weekly regimen.

It should be noted that none of the trials has shown that a supervised intermittent regimen gives better results than giving the same drugs in a daily unsupervised daily regimen in co-operative patients. There is nothing magical about supervision or intermittency. Both are merely ways of trying to obtain regular drug administration. A supervised intermittent regimen is valuable in certain types of patients and in certain environments. With other patients and other environments supervision and intermittency are unnecessary or unobtainable. One regimen should not be used to the exclusion of all others.

Shortened regimens

The British and East African Medical Research Councils carried out a trial of a six-month regimen of rifampicin, isoniazid and streptomycin given daily. The patients were followed up for two years after the end of treatment. The results were compared with those of the standard regimen of isoniazid and thiacetazone for eighteen months with daily streptomycin for the first eight weeks. Of those with a favourable status at the end of treatment in both regimens - almost all those who completed treatment - only 3 per cent had relapsed after thirty months of observation from the start of treatment. Thus the six-month
rifampicin regimen had produced as good, and as lastingly good, results as the eighteen-month regimen. Moreover, almost all who relapsed did so within the first six months after stopping treatment and had sensitive cultures, so that they could be retreated with the same drugs.

This particular six-month regimen is, of course, not a practically useful one for many countries, requiring daily injections and costing much money, as rifampicin is a very expensive drug. The next step, therefore, was to investigate whether streptomycin was necessary, whether the duration of rifampicin treatment could be reduced, and whether the second phase of treatment could be given with cheaper drugs or with a twice-weekly regimen which could be adequately supervised.

In the first trial a third regimen had been used: isoniazid with streptomycin and pyrazinamide. These latter two drugs together form a bactericidal combination. The results were less good than the rifampicin regimen - 8 per cent relapses - but they were still quite encouraging. In the second trial, therefore, pyrazinamide was added to strengthen the bactericidal effect.

The regimens were: SHR daily, HR daily, SHRZ for eight weeks followed by TH or S2H2. The relapse rates six months after treatment stopped were: SHR - 2 per cent; HR - 5 per cent; SHRZ/TH - 6 per cent; SHRZ/S2H2 - 4 per cent. The differences were not significant. Further observation is, of course, necessary. But we can tentatively conclude that, in patients with initially sensitive cultures 1) streptomycin is unnecessary if rifampicin and isoniazid are given daily for six months; 2) rifampicin need be given for only eight weeks with streptomycin and pyrazinamide if 3) for the remaining four months isoniazid and thiacetazone are given daily or streptomycin and isoniazid are given twice a week.

Similar rifampicin regimens have been investigated in France, United Kingdom and Brazil. In France, only one certain bacteriological relapse was observed during the eighteen-month follow-up of fifty-nine patients treated for six months with rifampicin and isoniazid with either streptomycin or ethambutol for the first three months. With the period of treatment extended to nine months no relapses were observed. In the United Kingdom, only three per cent relapses were reported at eighteen months after a similar regimen given for six months; and no relapses had been observed after nine months treatment. In Brazil, 3 per cent relapses were observed after two years follow-up after six months treatment with rifampicin, isoniazid and ethambutol.

As the degree of supervision of drug administration and the criteria for assessing relapses were different in these trials the results should not be uncritically compared.

All that can be stated at present is that rifampicin-containing regimens of six or nine months' duration can be highly effective in producing lasting non-infectiousness of even far-advanced pulmonary tuberculosis.

But rifampicin is expensive. Need it be used at all? In Hong Kong, a trial was carried out to explore the possibilities of streptomycin plus pyrazinamide as one bactericidal agent and isoniazid as the other.

Three regimens were given for either six or nine months. In one, all three drugs were given daily. In another, they were given three times a week, and in the third twice a week. Observation has so far extended to only six months after the end of treatment - the period during which most relapses are likely to occur. When given for only six months the relapse rates were high (13 - 18 per cent). But with nine months treatment the relapse rates were low (3 - 4 per cent). The three times weekly regimen for nine months was as good as the daily regimen. But the twice-weekly regimen appeared less good; for, although the relapse rate was low, the proportion with unsatisfactory results at the end of treatment was slightly, though not significantly, higher than the proportions in the daily and thrice-weekly regimens.
These results all refer to patients with initially sensitive cultures. But, because of bad treatment and inefficient medical organization many patients coming to health centres already have resistant cultures. From the Hong Kong results it was possible to estimate the total effect of applying the streptomycin, isoniazid, pyrazinamide regimen in all patients, both those with sensitive and those with resistant cultures. In Hong Kong, 21 per cent of patients coming for treatment have resistant cultures. In such a population daily streptomycin, isoniazid and pyrazinamide for nine months would produce lasting non-infectiousness in about 90 per cent of all patients who co-operated for the whole period of treatment. With a thrice-weekly regimen the proportion would be about 85 per cent. This is an impressive demonstration of the potency of short regimens of bactericidal drugs.

Prospects for more efficient treatment

It is highly likely that even shorter and less exacting regimens will be discovered within the next ten years. The duration of treatment may be reduced to less than six months, with part of it being given once weekly.

The drugs and the ways in which to use them are already available to control tuberculosis in the world. All that is lacking is the social organization to put into practice the discoveries of laboratory investigations and controlled clinical trials. The scientists have provided the tools: the politicians, the administrators and the people themselves must use them efficiently.

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### Doses of drugs used in clinical trials of intermittent regimens

<table>
<thead>
<tr>
<th>Drug</th>
<th>Twice weekly</th>
<th>Once weekly</th>
</tr>
</thead>
<tbody>
<tr>
<td>Streptomycin</td>
<td>19</td>
<td>19</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>15 mg/kg</td>
<td>15 mg/kg</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>17-25 mg/kg</td>
<td>25 mg/kg</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>45 mg/kg</td>
<td>90 mg/kg</td>
</tr>
<tr>
<td>Pyrazinamide</td>
<td>3-3.5 g.</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(2-2.5 g. three times weekly)</td>
<td></td>
</tr>
<tr>
<td>Thiacetazone</td>
<td>300-450 mg.</td>
<td></td>
</tr>
<tr>
<td>PAS</td>
<td>7.5-12 g.</td>
<td></td>
</tr>
</tbody>
</table>
### APPENDIX II

**Regimens and doses of drugs used in clinical trials of short regimens**

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Regimen</th>
<th>Doses of drugs</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>S</td>
</tr>
<tr>
<td>24</td>
<td>SHR or SHZ 6/12</td>
<td>1g.</td>
</tr>
<tr>
<td>25</td>
<td>SHR or HR 6/12</td>
<td>1g.</td>
</tr>
<tr>
<td></td>
<td>SHRZ 2/12 - S2H2Z2 or TH 4/12</td>
<td></td>
</tr>
<tr>
<td>26</td>
<td>S(E)HR 3/12 - HR 3 or 6/12</td>
<td>1g.</td>
</tr>
<tr>
<td>27</td>
<td>S(E)HR 2/12 - HR 4 or 7/12</td>
<td>0.75 g.</td>
</tr>
<tr>
<td>28</td>
<td>EHR 6/12</td>
<td></td>
</tr>
<tr>
<td>29</td>
<td>SHZ 6 or 9/12</td>
<td>0.75-1 g.</td>
</tr>
<tr>
<td></td>
<td>S3H3Z3</td>
<td>0.75-1 g.</td>
</tr>
<tr>
<td></td>
<td>S2H2Z2</td>
<td>0.75-1 g.</td>
</tr>
<tr>
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</tbody>
</table>
ANNEX II

INAUGURAL SESSION

The inaugural session was held in the Hotel Inter-Continental, Karachi, on 23 October 1975 and was attended by 500 guests.

The programme of the inaugural session started by the recitation from the Holy Koran. Dr M. Hassan, Director of Tuberculosis Control, Government of Pakistan and Chairman of the National Organizing Committee, then welcomed the participants and read the messages of H.E. Mr Chaudhry Fazal Elahi, President of Pakistan, as well as of H.E. Mr Zulficar Ali Bhutto, Prime Minister of Pakistan.

The Seminar was attended by medical officers, tuberculosis and public health specialists in charge of tuberculosis control programmes designated by their Governments at the invitation of the World Health Organization, Regional Office for the Eastern Mediterranean, observers from Pakistan, the United Nations Development Programme, the United Nations Children's Fund and the International Union against Tuberculosis.
Message from
H.E. Mr Chaudhry Fazal Elahi
President of Pakistan

I am very pleased to know that a Seminar on Recent Trends in Tuberculosis Control is being held in our country in the last week of October this year under the auspices of WHO.

Tuberculosis, in the past, caused untold miseries to innumerable families all over the world. Many great men including politicians, poets, public leaders and even physicians have been victims of the white scourge and met premature death. Recent advances in medical science and technology offer us hope. Technically advanced countries have successfully demonstrated that tuberculosis is preventable and can be controlled. I feel confident that the experts and specialists assembling in this Seminar will suggest effective ways and means of controlling tuberculosis in developing countries where it is still a major public health problem.

I wish the Seminar every success.
Message from
H.E. Mr Zulficar Ali Bhutto
Prime Minister of Pakistan

I am very pleased that the World Health Organization is sponsoring a Regional Seminar on "Recent Trends in Tuberculosis Control" in Pakistan. Deliberations of such a seminar are always beneficial to participating countries. The World Health Organization deserves deep appreciation for undertaking such a task.

Tuberculosis is still a major public health problem in our country and other countries of the Region. Every year many precious lives are lost and many more are invalidated on account of this dreadful disease. International co-operation is, therefore, needed to bring it under control. The World Health Organization has always been active in assisting national governments in their fight against the white scourge and I hope that their assistance will continue till the problem of tuberculosis is under full control.

I am confident that the Seminar will review the progress and problems related to the National Tuberculosis Control Programme in the Region and will recommend new approaches to the effective implementation of the control programmes.

I wish the Seminar every success.
Inaugural Address

by

H.E. Mr Hafeezullah Cheema
Minister for Labour, Health
Social Welfare and Population Planning
Government of Pakistan

Dr Mahler, Dr Taba, your Excellencies, Distinguished Delegates, Ladies and Gentlemen,

1. It is my pleasure to be here on this occasion to inaugurate the WHO Seminar on Recent Trends in Tuberculosis Control. I am glad that Dr H. Mahler, Director-General and Dr A.H. Taba, Regional Director, World Health Organization, could be here. This is a sure indication of the importance they attach to this Seminar.

2. I am also pleased to see so many distinguished TB specialists and public health administrators from neighbouring countries with whom we are bound in strong ties of mutual respect and friendship. Their presence in our country is a matter of great pleasure for us. The benefit of their experience and expert knowledge of the tuberculosis problem of the Region, I am sure, will inspire our TB workers to greater efforts for its control. They have travelled far and wide to come to our country. I do welcome them on behalf of the Government of Pakistan and wish them a comfortable and pleasant stay.

3. The importance of an International Seminar on Tuberculosis cannot be over-emphasised. Tuberculosis is still a public health problem all over the world. Although varying enormously from the large under-privileged areas of the world to the highly industrialized and technically advanced countries, the prevalence of this fell disease is of serious concern to all. Even those few countries which are gradually eliminating the problem within their own frontiers, cannot be safe as long as tuberculosis is highly prevalent elsewhere. The increasing rapidity and volume of international communications as well as migration of workers across the national boundaries tends to intensify the risk of infection. Nobody is, therefore, safe from tuberculosis until everybody is safe. Tuberculosis must be wiped out from everywhere. This requires concerted international effort. WHO, by organizing this Seminar has given to all the distinguished participants of the Region an opportunity to exchange views, share experiences and recommend future line of action. WHO deserves thanks for having sponsored this very important Seminar.

4. In recent years there have been great advances in the field of prevention and treatment of tuberculosis. As to prevention, the introduction of stable and long-lasting freeze dried BCG vaccine and simplification of the vaccination method have made it more effective. The BCG vaccine is easy to apply and it is well accepted by the people. Its cost benefit ratio is also very favourable.

5. For treatment, a number of effective anti-TB drugs have been discovered, and these have revolutionised the treatment of tuberculosis. They are wonder drugs but to me they seem to be slow-acting. The patients are required to take simultaneously more than one of these
drugs continuously over a year for a cure. Patients can hardly keep patience for such a long time to take the drugs regularly. This frequently causes treatment failure. I do hope scientists will continue research to find quick-acting drugs which will cure tuberculosis in a shorter period.

b. In spite of all the recent advances, the developing countries are still facing difficulties to control this disease. The resources available to them, for this purpose, are very limited. Shortage of technical personnel, diagnostic equipment, reagents, anti-TB drugs and of specialized institutions is a serious handicap for a developing country in organizing a comprehensive National Tuberculosis Control Programme. But a popular government cannot sit back and allow their people to suffer. Whatever resources are available should be utilized to organise a country-wide control programme. In such a programme, priority is to be given to the prevention of the disease by immunising non-infected persons and by treating infectious cases. The existing basic health services may be utilized for this purpose. Such national effort should naturally attract assistance from International Organizations.

7. The World Health Organization from its very inception has recognized the international character of the problem of tuberculosis and has assisted national governments in bringing tuberculosis under control by providing expert advice and teams of specialists. It has also assisted the developing countries by providing facilities for training of technical personnel. Pakistan has, substantially, been benefited by WHO assistance. The material aids given by UNICEF for our National Tuberculosis Control Programme also need mention here. WHO and UNICEF deserve thanks for giving assistance to developing countries in tuberculosis control.

8. In this context, I should outline briefly some of Pakistan's efforts. When Pakistan was created there was literally no anti-tuberculosis service in the country, except some sanatorium beds. The resources available at that time did not permit us to start a comprehensive National Tuberculosis Control Programme in the country. Therefore, we started a mass BCG vaccination campaign to protect the susceptible children. The Government also organized tuberculosis control and training centres for training of technical personnel. With the availability of trained staff more and more tuberculosis centres and clinics were established and about 100 of them are in operation now. A random sample survey was conducted to collect information on the prevalence and epidemiological pattern of the disease. Another survey is being conducted now. In the light of the information collected in the previous survey an Integrated National Tuberculosis Control Programme was planned and put into operation. The programme has now extended over a major part of the country. For higher training of medical officers in tuberculosis, two universities are running regular courses and awarding postgraduate diplomas. The Pakistan College of Physicians and Surgeons have also introduced a diploma course in tuberculosis from this year; People's Government is fully alive to the problem and doing whatever is possible within the limit of its resources.

9. The role of voluntary organizations in the fight against tuberculosis is also commendable. In addition to organizing some tuberculosis institutions, the Pakistan National Tuberculosis Association and its component branches have been taking active part in the implementation of the National Tuberculosis Control Programme.

10. Before concluding I must once again extend a most warm welcome to all the participants in the Seminar. I sincerely hope that the Seminar will be crowned with success and thus mark an important step forward in the Tuberculosis Control Programme of this Region.

11. I now declare the Seminar opened and wish it once again all success.
Address by Dr H. Mahler
Director-General of the World Health Organization

Mr Minister, distinguished guests, ladies and gentlemen,

Most health workers consider that the "best" health care is one where everything known to medicine, is applied to every individual, by the highest trained medical scientist, in the most specialized institution. This type of thinking is clearly as dangerous as it would be for me, who spends so much time flying from Member State to Member State, if I preferred the aircraft in which I was travelling to be flown by a professor of aeronautical engineering rather than an experienced pilot.

If one follows this same line of thought one understands the inevitable side effect that, as health care action moves higher and higher up the referral ladder, it becomes to be justified more and more by the actions themselves and is more and more restricted to a privileged few. It is frightening but expected that when a specialized group is created to perform certain actions it is evaluated and continues to be financially supported because of the number of such actions which it does, rather than by whether a problem is solved. The specialized disease palaces in certain developing countries catering for an insignificant proportion of the epidemiological and socio-economic problem of these diseases provide ample evidence of this danger.

Such trends towards restricted high technology might be said to be a by-product of medical research distortions and a good case might be made to direct a portion of the blame to the priorities of research workers supported for the most part from national funds. But such finger-pointing cannot explain all that is happening. The movements of interventions further up the professional ladder and the increased restriction of action to fewer and fewer people does not seem to be only related to new research findings. The implications of such a movement are not only seen as an increase in costs with few measurable health advantages in terms of either morbidity and mortality; they are also seen as a downgrading in social status of health workers at the bottom of the pyramid, changing aspirations of health workers who understandably want to be legitimized to as high a point in the pyramid as possible. The social distortion caused by this type of techno-colonialism has a lot to do with the present crisis of the medical industry. If we are to reduce this unsatisfactory state of affairs then there are four questions that in my opinion must be answered, if we are to make any headway in satisfying basic health needs without discriminating as to rich or poor, town or village.

(1) Is it possible to assign resources within a country on a basis that will solve health problems using different mixes of preventive and curative actions?

(2) What medical interventions are truly effective and specific for prevention and treatment as measured in objective terms?

(3) Can such medical interventions and the risk groups to which they should be applied be described objectively and in such a manner that the amount of skill and knowledge required for their application can be assessed?
(4) Is it possible to design a health care system to carry out the above tasks which will result in the most meaningful interventions reaching the greatest proportion of persons at risk, as early as possible, at the least cost and in an acceptable manner?

There is little doubt that it would be considered reasonable to ask this type of question if we were dealing with a non-health topic such as education or transportation, and to answer them with a positive reply. In health, persons such as ourselves within the establishment, might both disagree that the questions are the dominant ones, or relevant, or even try to make the case that health is in some way different. Non-health individuals might react differently and even express astonishment at those questions because many may fondly assume that their health services are designed to deal with problems; the interventions they pay for are known to be effective and appropriate; and the person who is responsible for the medical care they receive is the appropriate person in training and position for their needs. All of us here know that such is not the case.

As I try to answer these questions for myself I am convinced that all of the questions can be answered positively and I believe tuberculosis will go down in history as the living proof of this conviction.

The entry point in my view are my questions 2 and 3. In tuberculosis we have indeed examined medical technology and expressed in objective terms what works, does it matter and what it costs.

The studies on such subjects have been of three types. The first were cold, planned, controlled clinical trials testing whether intervention A gave a better result than intervention B. Such clinical trials are medical extensions of the scientific method; their mechanics are widely known, and both their conduct and their results give satisfactions to both the investigators and the consumers. Both the chemotherapy and the ECG trials are outstanding examples of this type of study. The second type is much more rare and has not been greeted with such universal approval. What is a case of tuberculosis? What level of disease really matters? How important is treatment or secondary prevention to persons below that level?. So much of ill-health as we now accept it is not divided from the normal by a clear division point, yet where the dividing line rests is not only of commanding attention to millions of individuals, but if it can be defined by outcomes it can save huge amounts of money and manhours of work, and false explanations to patients with complaints. Some members of the establishment looked upon such studies as a threat aimed at attacking longheld assumptions. The design and conduct of such studies were very difficult, expensive and time-consuming and did face ethical difficulties. There are even fewer examples of the third type of study. These were trials which required the results of the previous two trials as their starting point. They started from a dialogue between the national medical establishment and the national government which recommended that at this point of time, and from evidence provided by trials such as the above, that such and such a tuberculosis problem is relevant and important and that this or that intervention to a certain part of the population could be the best national strategy. From this decision a trial could be designed to see how this could best be done on the grounds of cost, efficiency and acceptability. Systems analysis and operations research in a number of countries provide promising examples and though these methodologies still lack in the stringency of controlled intervention trials they are nevertheless providing decision-makers with more relevant and more sensitive information than is usually available for strategic decisions in health care. What is more these three types of objective studies would provide a positive answer to my questions 1 and 4 viz. that it is possible to assign resources to a country on a basis that will solve health problems, and that it is possible to design a health care system that will result in the most meaningful interventions reaching the greatest proportion of persons at risk, as early as possible, at the least cost and in an acceptable manner. In some countries the findings of these three types of studies have indeed been accepted and applied. But in many other countries they have been accepted but not applied. I leave it to you to answer why not!
Address by Dr A.H. Taba
Director
WHO Eastern Mediterranean Region

Your Excellency, distinguished participants and observers, dear colleagues,

It is a great pleasure for me to welcome you all here and to address the Regional Seminar on Recent Trends in Tuberculosis Control, whose sponsorship we are honoured to share with the Government of Pakistan.

In convening the Seminar the Organization responds to the Resolution of Sub-Committee A of the Regional Committee, calling for continuous attention to tuberculosis control and, in particular, to the need that has been felt in various technical bodies, institutions and among the medical profession of the member countries to review the present situation and to consider ways and means of attacking tuberculosis more efficiently and rationally through application of technical knowledge acquired in the recent past.

Tuberculosis, once the scourge of mankind, became a curable and preventable disease some twenty-five years ago, when highly effective drugs and vaccine became available. Yet it continues to be one of the major health problems not only in the Region but also in the great majority of other countries in the world. Moderate estimates indicate that there are nearly one million open, infectious cases and three million persons with radiological findings suggesting active tuberculosis in the Region, while at least 50 per cent of the population is infected with tubercle bacilli - a formidable pool of potential patients threatening further addition of new cases for many years to come. What are the reasons for this unsatisfactory situation persisting even after a quarter century of availability of potent tools against this disease?

The WHO Expert Committee on Tuberculosis, in its Eighth Report published some ten years ago (1964) agreed that it was possible with the then available tools to execute effective anti-tuberculosis programmes under almost any socio-economic conditions, i.e. even in the poorest countries. Since then, considerable new knowledge and experience have been gained with regard to case-finding, treatment and prevention as well as in the strategy of efficient application of these measures, presented in the Ninth Report of the WHO Expert Committee (1974). It has been demonstrated beyond doubt that the majority of infectious cases could be easily detected by microscopy, a facility available in most centres; that new cases could be successfully treated and cured under domiciliary treatment at a cost not exceeding about ten dollars; and that up to 80 per cent of tuberculosis cases could be prevented by application of a potent BCG vaccine. Moreover, methods and procedures for implementation of these measures have been standardized and simplified to such an extent that they can be efficiently and safely applied by trained medical auxiliaries working in basic health services, and thus become practically accessible to the rural population, where most of the tuberculosis problem is hidden. Consequently, treatment and management of tuberculosis has ceased to be the privilege of some few institutions or specialists and shifted to the hands of general practitioners and medical auxiliaries of general health services, who, logically, have to accept it as a part of their day-to-day responsibilities.
However, despite the technical advances and existing facilities, the fact remains that in many of the member countries more than 50 per cent of children do not have the benefit of immunity that can be conferred by vaccination, that patients often have to travel long distances to be diagnosed and treated, that many unknown tuberculosis patients receive no treatment and that a good deal of sources of infection remain undetected.

I do not believe that the fight against tuberculosis today is a technological or even a financial problem in the Region - it is mainly one of organization. Tuberculosis can no longer be regarded as a separate health problem but must be conceived as part of a country's overall health problems. Consequently, its control must be vested with the general health services. Basically, what has been lacking in the pursuance of this concept is the firm resolve and imaginative effort to integrate tuberculosis activities into the basic health structure. Often the plans were adopted but the necessary changes were not produced.

I do admit that there has been a tangible progress in tuberculosis control in the Region, but at the same time there is no denying the fact that the practical results are still lagging behind what really could have been accomplished. A number of countries recorded substantial achievements in integration of tuberculosis activities into the basic health services or at least in starting to apply the basic principles underlying integration. BCG vaccination has been intensified and has become a routine activity in the overall immunization programme; case-finding programmes are being focused mainly on symptomatic groups and the expensive and low-yielding mass radiography campaigns abandoned; construction of costly tuberculosis hospitals has given way to domiciliary treatment and attempts to introduce legislation, reporting and evaluation are commendable. Besides, the spectacularly increasing capacities of oil-producing countries have generated new potentialities, creating at the same time new dimensions for programme application, thus broadening and intensifying the scope of activity. These, of course, call for considerable flexibility in approaches and strategies.

I am confident that this Seminar will provide us sufficient opportunity to critically review the problems impeding the execution of efficient national programmes and formulate recommendations that will constitute realistic guidelines for better and more concerted efforts within the framework of general health services. I wish you every success in your deliberations.

I also wish to express our sincere gratitude and appreciation to the Government of Pakistan for the valuable assistance rendered us in organizing this Seminar, and, of course, for the traditional Pakistani hospitality with which they welcomed us.
Message from
Lt. Gen. A.N. Ansari
Secretary, Health and Social Welfare
Government of Pakistan

It is gratifying that the WHO Eastern Mediterranean Region is sponsoring a Seminar on 'Recent Trends in Tuberculosis Control' in Pakistan at Karachi. The strategy of tuberculosis control underwent a revolutionary change after the Second World War due to introduction of number of effective anti-tuberculosis drugs and mass application of BCG Vaccination. Recently more effective drugs have been introduced, improvements have been made in the quality of BCG vaccine and technique of vaccination. It has, therefore, become necessary to assess the present position of Tuberculosis Control Programme and to reconsider its strategy in view of the present changed situation. This Seminar is, therefore, a very timely one and of great importance.

2. The world is passing through a critical phase and the developing countries have been badly effected by the world wide inflation. An ambitious Tuberculosis Control Programme is, so beyond their means. The socio-economic condition must be kept in mind while formulating the policy of control programme.

3. I hope that the participants specially those who are engaged in our National Tuberculosis Control Programme will immensely benefit from the deliberation of the Seminar.

I wish the Seminar a great achievement.
Message from
Dr Naareen Ahmed B. Sheikh
Director-General of Health
and Joint Secretary to Government of
Pakistan

Tuberculosis still remains the major public health problem in most developing countries including Pakistan. Most of the countries that form part of the Eastern Mediterranean Region of WHO are faced with similar problems of high prevalence rate and limited resources. It is, therefore, essential that experts from countries of the Region sit down in order to review the situation and deliberate on the means of achieving positive results in the shortest possible time.

In essence, Tuberculosis Control Programme consists of immunization of the susceptible population particularly children, case-finding and chemotherapy of the cases thus discovered. The main problem, however, lies in the organizational field.

A successful programme should be permanent, should ensure total coverage of the population and should be within the limited means available to us. As our infrastructure in the health delivery system is in the process of evolution we are forced to channelise our limited human and material resources in that direction. It is heartening to note that WHO and member countries are fully conscious of the position and are giving the necessary emphasis that this disease deserves. If we can find cheap and effective methodology without sacrificing the essential requirements, we can evolve a programme which is within our limited resources and which can offer demonstrable results and in foreseeable future can control the disease.

It is also essential that as our experience increases we should constantly review and evaluate and improve our programme. The WHO Regional Seminar on Recent Trends in Tuberculosis Control is being held at the right time and I wish this Seminar all success.
ANNEX III

LIST OF PARTICIPANTS

AFGHANISTAN

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Dr. Abdul-Ghani Arafah
Chief, Tuberculosis Control Services and Superintendent, Ibn Nafis Sanatorium
Ministry of Health
Damascus

UNITED ARAB EMIRATES
Dr. Amal Abdul Aziz Sakr
Chest Specialist
Head of the Tuberculosis Preventive Section
Chest Hospital
Sharjah

YEMEN
Dr. Ahmed Ali Ei Khedur
Under-Secretary
Ministry of Public Health
Sana'a

OBSEVERS FROM HOST COUNTRY
Dr. Pirzada Mahboob Shah
Provincial BCG and Tuberculosis Control Officer
Punjab
Lahore

Dr. Sadar-ud-Din
Section Officer (Public Health)
Punjab Health Department
Lahore
OBSERVERS FROM HOST COUNTRY (CONT'D)

Dr Shahbaz Munir
Assistant Professor of Tuberculosis
Quaid Azam Medical College
Bahawalpur

Dr Mohammad Anwar
Provincial Tuberculosis Control Officer
Tuberculosis Hospital, Baghdad
Mardan

Dr S.M. Sabihuddin
Professor of Tuberculosis and Tuberculosis Control Officer
Hyderabad

Professor S.Y. Bokhari
Professor of Tuberculosis Diseases
Nishtar Medical College
Multan

Dr Ashraf Ali
Demonstrator Tuberculosis and Chest Department
King Edward Medical College
Lahore

Dr Iqbal
Medical Officer (Tuberculosis) District Headquarters Hospital Sahiwal

Dr Rafi-ul-Qadir
Medical Superintendent Government Tuberculosis Hospital Sargodha

Dr Islamuddin Qureshi
District Tuberculosis Officer Nawabshah

Dr Alimuddin
Deputy Director Tuberculosis Health Centre Karachi

Dr Ali Gohar Laghari
Assistant Director (health) Pakistan Secretariat
Karachi
OBSEVERS FROM HOST COUNTRY (CONT'D)

Dr Qamar Ali Khan  
Senior Officer (Public Health)  
Health Department  
Karachi

Dr Janul Ahmed  
Assistant Professor, Tuberculosis  
Liaquat Medical College  
Jamshoro

Dr Mazhar Owasi  
District Tuberculosis Control Officer  
Khairpur

Dr Zafar Hyderi  
Deputy Medical Superintendent  
Ojha Institute  
Karachi

Dr Ashiq Rizvi  
Medical Officer  
Tuberculosis Clinic  
Khairpur

Dr Mohd. Shafi Qureshi  
Medical Superintendent  
Kotri Tuberculosis Sanatorium  
Kotri

Dr Mushtaq Ahmad Chaudhry  
Assistant Director-General (Public Health)  
Health and Social Welfare Division  
Islamabad

Dr Abdul Latif Minhas  
Associate Physician and Assistant Professor of Medicine  
Jinnah Post-Graduate Medical Centre  
Karachi

Dr Salman H. Siddiqui  
Officer-in-charge  
Tuberculosis Research Unit  
Institute of Tuberculosis and Chest Diseases  
Mayo Hospital  
Lahore
OBSERVERS FROM HOST COUNTRY (CONT'D)

Dr Abdul Khaliq  
Director, Health Services  
Baluchistan  
Quetta

Dr Shah Farman  
Civil Medical Officer  
Agency Hospital  
Gilgit

Dr Mohammad Rafique  
President  
Sind Provincial Tuberculosis Association  
Hyderabad

Dr Mohammad Akhtar  
Medical Officer  
Tuberculosis Association  
Gujranwala

REPRESENTATIVES FROM UNITED NATIONS BODIES

UNITED NATIONS DEVELOPMENT PROGRAMME  
Mr J. Everts  
Resident Representative  
United Nations Development Programme  
Islamabad

UNITED NATIONS CHILDREN'S FUND  
Mr M. Assadi-Baiki  
UNICEF Representative  
Islamabad

OBSERVERS FROM OTHER ORGANIZATIONS

INTERNATIONAL UNION AGAINST TUBERCULOSIS  
Dr Abdel Aziz Sami  
Representative of IUAT and its Middle East Region  
Cairo  
EGYPT

Dr A. Selvaratnam  
Representative of the Oriental Region of IUAT  
Kuala Lumpur  
MALAYSIA
WHO SECRETARIAT

Dr H. Mahler  Director-General  World Health Organization, Geneva
Dr A.H. Taba  Director  Regional Office for the Eastern Mediterranean, Alexandria
Dr K.L. Hitze  Chief Medical Officer  Tuberculosis Unit, Headquarters, Geneva
Dr J. Kaleta  Regional Adviser on Tuberculosis and Secretary of the Seminar  Regional Office for the Eastern Mediterranean, Alexandria
Dr J.R. Bignall  Consultant  Consultant Physician, Brompton Hospital, London
Dr K. Styblo  Consultant  Research Director, Tuberculosis Surveillance Research Unit, The Hague
Miss C. Cartoudis  Conference Officer  Regional Office for the Eastern Mediterranean, Alexandria
Mrs M. Soliman  Secretary  Regional Office for the Eastern Mediterranean, Alexandria

RESOURCE PERSONNEL

Dr J. Susticio  Medical Officer  WHO Tuberculosis Control Project, Addis Ababa
Dr G. Sabapathy  Medical Officer  WHO Tuberculosis Control Project, Aden
ANNEX IV

BACKGROUND MATERIAL


8. CASE-FINDING BY MICROSCOPY, by Nagpaul, D.R. et al. (WHO/TB/Techn. Inform./63)


12. TUBERCULOSIS VACCINES CLINICAL TRIALS COMMITTEE, FOURTH REPORT (1972) BCG AND VOLE BACILLUS VACCINES IN THE PREVENTION OF TUBERCULOSIS IN ADOLESCENCE AND EARLY ADULT LIFE, Bull. Wld Hlth Org., 46, 371 (Reprint No.2813)


15. RESOURCE ALLOCATION MODEL FOR PUBLIC HEALTH PLANNING - A CASE STUDY OF TUBERCULOSIS CONTROL, by Faldestein, M.S. et al. (1973), Geneva, World Health Organization

16. PRESENT KNOWLEDGE OF IMMUNIZATION AGAINST TUBERCULOSIS (document WHO/TB/73.98)


19. TECHNIQUE OF INTRADERMAL ADMINISTRATION OF BCG VACCINE, by Borges, M.V., Pan-American Health Organization/World Health Organization

20. GUIDELINES FOR THE USE OF BCG VACCINE IN COUNTRY PROGRAMMES (document WHO/TB/75.101)

21. WHO EXPANDED PROGRAMME ON IMMUNIZATION, A28/WP/5
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*According to "Basic Country Information", WHO EMRO Health Statistics Unit, circulated 10 January 1975.

aUN estimates.
### TABLE II

**SUMMARY TABLES ON COUNTRIES IN WHO EMR**

(latest available data)

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<th>COUNTRY</th>
<th>Physicians No.</th>
<th>Physicians One per No. pop.</th>
<th>Medical auxiliaries No.</th>
<th>Hospital beds No.</th>
<th>Hospital beds One per No. pop.</th>
<th>National income per cap. (US $)</th>
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* According to "Basic Country Information", WHO EMRO Health Statistics Unit, circulated 10 January 1975.
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* According to "Basic Country Information", WHO EMRO Health Statistics Unit, circulated 10 January 1975

1 Mass Campaign Dec. 1971 - June 1973

2 Mass Campaign 1970 - 1973
### Summary of Replies to Questionnaire on National Tuberculosis Control Services

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* Completed with data available in EMRO/WHO
### Table V

**Evaluation of Questionnaire on National Tuberculosis Control Services**

1. National Tuberculosis Control Programme (cont.)

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<th>Record, Reporting</th>
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* Completed with data available in WHO/EMRO
TABLE VI

EVALUATION OF QUESTIONNAIRE ON NATIONAL TUBERCULOSIS CONTROL SERVICES

2. Epidemiology and 4. Case finding

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<th>Country</th>
<th>Epidemiological information</th>
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* Completed with data available in WHO/EMRO
### TABLE VII

**EVALUATION OF QUESTIONNAIRE ON NATIONAL TUBERCULOSIS CONTROL SERVICES**

#### 3. BCG Vaccination

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*Completed with data available in WHO/EMRO
### Table 5. Treatment

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