

## Tuberculosis elimination in the countries of Europe and other industrialized countries

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under the joint auspices of the IUATLD (Europe region) and WHO

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*Tuberculosis elimination in the countries of Europe and other industrialized countries. L. Clancy, H.L. Rieder, D.A. Enarson, S. Spinaci.*

**ABSTRACT:** The working group summarized the conclusions of the workshop with the intention of providing a guide for the preparation of national plans for tuberculosis elimination. The basic strategies that appear consistently effective are:

1. Direct government responsibility for diagnosis, treatment and prevention of tuberculosis (the government is responsible by law for assuring that tuberculosis is identified early, and that cure of the patients is achieved).
2. Maintenance (or development) of properly designed disease surveillance and a programme monitoring system.
3. Availability of specialized tuberculosis personnel at regional and provincial level, responsible for close monitoring of the diagnostic skills and patient prioritization in general health institutions.

Regarding research it was felt that no immediate practical applications of new techniques in the diagnosis of mycobacterial diseases, in treatment, or in vaccination can be recommended, but that further basic research in the field of mycobacteria should be pursued and supported.

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The workshop was organized jointly by the International Union Against Tuberculosis and Lung Disease (IUATLD) Europe Region and the World Health Organization (WHO). It was designed to assess the current tuberculosis situation in industrialized countries and to provide data that would help in devising strategies to eliminate tuberculosis from these countries. The role of existing technologies and those under development, particularly in the areas of diagnosis, treatment, prevention and evaluation methods were assessed. The participants took into account the global dimension of tuberculosis and emphasized the need for individual countries to address the impact of international migration on tuberculosis control. The need to disseminate current knowledge on tuberculosis control in low incidence countries was recognized. The elimination of tuberculosis will demand the industrious work of decades to come, particularly in the light of the pandemic with the human immunodeficiency virus (HIV). It can only be achieved with the maintenance of a high standard of knowledge and skill amongst tuberculosis workers. Modern and sophisticated technology must play its part but needs careful assessment and its likely contribution must continuously be evaluated.

### Operational definitions

To base the discussion on a common language, a few operational definitions were proposed:

1. "Infection with *M. tuberculosis*" was defined as the subclinical, latent infection with tubercle bacilli (by common understanding also including infection with *M. bovis* and *M. africanum*).
2. "Tuberculosis" refers to clinically, bacteriologically and/or radiologically active disease.
3. "Low incidence countries", a term used when the incidence of all forms of active tuberculosis is below 10 per 100,000 population.
4. "Elimination phase" is said to have been achieved when the incidence of all forms of active tuberculosis has fallen below the level of 1 per 100,000 population.
5. "Elimination" is said to have been reached when the incidence of sputum smear-positive tuberculosis is 0.1 per 100,000 population (1 per million). Alternatively, "elimination" may be said to have been achieved when the prevalence of infection with *M. tuberculosis* in the general population has fallen below 1% and continues to decrease.
6. "High risk groups" are groups with an incidence 100 per 100,000 population or more. This level is

selected because it represents a level at which active case finding may be cost-effective and because the majority of cases in low incidence countries arise from these groups.

7. "Preventive therapy" is a term used to denote treatment of subclinical infection with *M. tuberculosis* to prevent progression to tuberculosis. The term "chemoprophylaxis" (which, in its strict sense, applies to prophylactic treatment of persons exposed to infectious cases, but not yet infected with *M. tuberculosis*) is used here interchangeably.

### Epidemiology

There is still a wide range in the incidence of notified tuberculosis cases among European and other industrialized countries. The incidence varies, however, not only between, but also within, countries by area or population segments.

The incidence of tuberculosis has been decreasing in all industrialized countries. The rate of decline in the United States has been halted and this has raised concern in other industrialized countries. This failure of tuberculosis to decline in the United States appears, in part at least, to be attributable to HIV infection, to tuberculosis among immigrants, and to microepidemics. Because of the decrease of tuberculosis among the majority of the indigenous population, the incidence of tuberculosis cases among minorities, including immigrants and refugees, will become a relatively more important problem in the future. An adaptation of available intervention strategies to an ever changing situation is thus required if elimination is to be achieved.

### Surveillance

To achieve elimination of tuberculosis, low incidence countries should establish, maintain and evaluate, focused surveillance systems that identify socio-demographic groups or geographic areas with high rates of disease or infection. Specific programmes can then be designed to reduce the emergence of disease and the spread of infection through early case detection and treatment, identification of infected individuals and intervention with preventive chemotherapy. Such surveillance and intervention programmes can only be effected through the maintenance of efficient tuberculosis control services in each country.

New parameters for monitoring tuberculosis need to be established, e.g. monitoring of recent infection in young people might be developed as a means of monitoring hidden transmission of tuberculosis especially where bacille Calmette-Guérin (BCG) is not widely applied. The criteria and methods used for recording new cases should be standardized. Death from tuberculosis has become a relatively rare event in most low incidence countries but continues to

occur. Diagnosis of tuberculosis at autopsy is unfortunately not rare and may be a useful monitoring tool but only where the frequency of autopsies is high. A major factor contributing to fatality appears to be the failure of diagnosis or misdiagnosis.

The annual risk of infection with *M. tuberculosis* is regarded as a very useful index, but its derivation from infection prevalence data is fraught with problems where BCG has been widely used. In low incidence countries an increasingly larger number of individuals need to be tested to obtain a reliable estimate. Furthermore, the predictive value of the test declines with decreasing prevalence of infection.

The evaluation of the efficiency of tuberculosis control measures is often poorly performed and needs to be strengthened. The role of BCG vaccination programmes in low incidence countries is decreasing with decreasing incidence of tuberculosis. The emphasis in tuberculosis control should shift to the increased use of other tools of intervention in order to interrupt the transition from exposure to disease. The efficacy of modern treatment regimens under controlled trial conditions is well established, but there are very few data available on treatment effectiveness and efficiency under routine programme conditions in low incidence countries. The high frequency of abandonment of treatment even in some industrialized nations must urgently be addressed. A more frequent utilization of directly administered regimens is needed to deal with this problem. Local conditions and the needs of the individual patient will usually dictate the form of treatment supervision that is necessary. It may vary from daily supervised treatment, to intermittent supervised treatment, to in-patient care for any individual patient. The use of treatment regimens other than those recognized as the shortest possible and most effective continues to be common, especially where patients are cared for in the private sector. Resistance of *M. tuberculosis* to the most potent anti-tuberculosis drugs is at present uncommon and unlikely to have a large impact on the control of tuberculosis in industrialized countries. However, emergence of drug-resistant strains, and even outbreaks of drug-resistant tuberculosis, continue to be reported and pose challenges to containment and control.

### Reference centres

Inevitably, the number of health care workers fully trained in tuberculosis is declining in low incidence countries. It is therefore essential that centres of expertise be maintained or established where they do not (or no longer) exist. These centres should play a leading role in developing programmes to improve surveillance and in the evaluation of established programmes. They should also act as a resource offering service guidance, training and support for all health care workers dealing with tuberculosis.

### Intervention strategies

The community of public health workers and clinicians has three major tasks to accomplish with respect to tuberculosis:

1. those who have tuberculosis must be cured;
2. those who are infected with *M. tuberculosis* must be prevented from developing the disease;
3. those who are not infected with *M. tuberculosis* must be protected from acquiring the infection;

To accomplish these tasks three intervention tools are available:

1. short-course chemotherapy of disease;
2. preventive chemotherapy (chemoprophylaxis) of those already infected but not considered to have disease;
3. vaccination with BCG of new born among those segments of the population that have a high potential of exposure to sources of infection, and in which the feasibility of delivering other control measures, such as contact tracing, chemoprophylaxis and ensuring follow-up is uncertain.

Undoubtedly, the most efficient method of prevention of new infections is case-finding and cure of infectious cases.

### Chemotherapy

Short-course chemotherapy is the treatment of choice in all low incidence countries for all forms of tuberculosis. In most instances, a two month initial phase of treatment with rifampicin, isoniazid and pyrazinamide, followed by a four month continuation phase with rifampicin and isoniazid is the standard regimen, but a fourth drug, such as ethambutol or streptomycin, should be added to the initial phase of the regimen in individuals suspected of harbouring drug-resistant organisms (such as in persons born in countries with a high prevalence of drug resistance). If resistance is confirmed, the continuation phase will also have to be modified. The necessary duration of treatment and the need of an additional drug for tuberculosis in HIV infected individuals is still uncertain. In some countries, the same regimen, but for a minimum of nine months and for at least six months beyond documented culture conversion, has been recommended. The role of supervised chemotherapy in achieving compliance was strongly endorsed.

A review of new drugs for the treatment of tuberculosis and *M. avium* complex disease was disappointing. None of the new drugs has definitively been shown to be superior to available drugs. However, some developments among fluoroquinolones, macrolides, the new rifamycin derivatives, and phenazines are promising.

Hospitalization for isolation purposes is usually unnecessary. The main indications for hospitalization are treatment of patients who are seriously ill because of extensive disease, miliary disease or tuberculous

meningitis. Toxic reactions to drugs or multiple drug resistance may sometimes warrant in-patient management and investigation. Admission for diagnosis of suspected tuberculosis may be needed and is commonly used. Admission because of social and/or other medical conditions may be necessary. Patients with pulmonary tuberculosis who are in hospital and who are bacteriologically positive, or are suspected of being so, should be separated from patients without tuberculosis.

Most patients with pulmonary tuberculosis quickly become non-infectious once they are diagnosed and placed on an effective treatment regimen. This greatly facilitates the use of domiciliary treatment. Some patients continue to excrete viable bacilli for a prolonged period of time and may also continue to be infectious for susceptible humans especially for those who are particularly vulnerable. This is an important consideration before deciding to discontinue isolation of hospitalized patients with bacteriologically positive pulmonary tuberculosis. It should also be considered when deciding to allow patients with tuberculosis to return to regular work, especially should such work involve potential exposure of susceptible individuals (as may arise when the patient's occupation involves working with immunosuppressed individuals or young children).

### Preventive chemotherapy (chemoprophylaxis)

Preventive chemotherapy in tuberculosis, that is the treatment of persons with latent, subclinical infection with *M. tuberculosis*, has proved to be very efficacious in preventing progression to tuberculosis. It is however, an inefficient tool, if used indiscriminately, i.e. a large number of infected individuals has to be treated to prevent the occurrence of a single case. It is thus necessary to clearly define groups at particularly high risk of developing tuberculosis in whom preventive chemotherapy provides individual and public health benefit. Such individuals include in particular persons with *M. tuberculosis* infection who are also infected with HIV, persons with fibrotic lesions on chest radiography in the absence of active disease), and persons with recently acquired infection. In order to achieve the goal of elimination of tuberculosis in low incidence countries, preventive therapy must play a major role in tuberculosis control.

### BCG vaccination

The role of BCG vaccination in prevention of tuberculosis deserves continued consideration. The efficacy of BCG vaccines is well accepted in European countries, the degree of confirmed protection being up to 80%. Nevertheless, the impact of BCG vaccination should continue to be carefully assessed in order to measure its cost-effectiveness in the light of the continuing decrease in the incidence of tuberculosis.



The overall epidemiological impact of BCG is negligible, as its main role is in the prevention of non-infectious tuberculosis in children. Data from Sweden and Czechoslovakia suggest that discontinuation is acceptable even if it results in (albeit comparatively small) increases in the incidence of tuberculosis in non-vaccinated cohorts. Although used in many countries, there is little evidence to support a programme of revaccination of tuberculin-negative BCG vaccinated persons in low incidence countries. It is felt, however, that because of the much higher incidence of tuberculosis infection and disease in some groups, BCG vaccination should be maintained or considered afresh in those identified risk groups. In countries considering discontinuing BCG vaccination it is imperative that a reliable surveillance system be in place so that comprehensive tuberculin testing in contact tracing can be undertaken.

BCG should not be given to known HIV-positive persons in low incidence countries. However, there is no indication for HIV testing before vaccination of new-borns.

### Case finding

#### *Methods*

Passive case-finding remains the principle source of new notifications of tuberculosis in low incidence countries. The identification of risk groups makes active case-finding a possibility by intensive screening, especially of contacts of tuberculosis cases. The identification of risk groups is dependent on reliable methods of surveillance which must include an appropriate notification system under the direct supervision of tuberculosis experts. Special aspects of tuberculosis control in low incidence countries, which must be anticipated, include the frequent occurrence of micro-epidemics, tuberculosis in displaced people, individuals or groups with special likelihood of infection and other high risk groups.

These problems can best be handled when the epidemiological baseline data are accurate and when suitably trained personnel are available to implement the programme.

#### *Micro-epidemics*

As the incidence of tuberculosis decreases it is likely that small epidemics will become more commonly recognized. An appropriate plan to evaluate such outbreaks must take into account whether BCG has been used in the population or not. Those persons with most exposure in terms of duration and closeness of contact with a potentially infectious case should be tested with tuberculin. If no reactions are found among these, then it is unlikely that transmission will have occurred outside this close circle. Where reactors are identified, a decision has to be made about how

widely further skin testing should be performed. If the background prevalence of infection in the general population is known, skin testing can be discontinued when the proportion of reactors approximates that which is to be expected. Where the proportion of identified reactors exceeds the expected, less close contacts in the "next circle" need to be tested. Radiographic examination of positive reactors should be carried out during such contact tracing to rule out active tuberculosis. Preventive chemotherapy should then be offered to those tuberculin positive contacts who are likely to have become infected by the index case. Finding of even small tuberculin reactions should be considered as suspicious for new infection, particularly if the contacts had not been vaccinated with BCG and the prevalence of sensitization to environmental mycobacteria is low. Where BCG has been used, the cut-off of what is considered to be a significant tuberculin reaction will need to be raised, based on local epidemiological expectations. The advantages of a gain in specificity however, have to be weighed against the errors that might be made in falsely classifying a person as uninfected who has a small reaction because of loss of sensitivity. Thus, in the evaluation of skin test results, errors are inevitable.

### Identification of high risk groups

#### *Population segments with high incidence of tuberculosis*

An appropriate surveillance system should provide epidemiological information that allows the identification, within each country, of population groups that have an incidence of tuberculosis that is greatly in excess of that in the general population. From numerous studies it is known that there are factors among individuals with pre-existing infection with *M. tuberculosis* that put them at particular risk of developing the disease. The identification of such groups and persons is important, because they may gain particular benefit from preventive interventions. Several such populations segments and persons have been identified in various countries and are discussed here to the extent that such findings appear to be generally applicable.

*Minorities, immigrants and displaced persons.* Tuberculosis in immigrants largely mirrors the prevalence of infection with *M. tuberculosis* in the country of origin. The incidence is usually slightly lower than in the country of origin but may be modified to some extent by host country factors including population density and socio-economic status. The trend of tuberculosis incidence among immigrants continues to parallel that in the country of origin, which suggests that the most important determinant of the development of disease in low incidence countries is remote infection. Fibrotic lesions in immigrants from high incidence countries seems to account for a

large proportion of the subsequent disease in this group. This suggests that properly applied preventive chemotherapy should substantially reduce the problem.

*The elderly.* In many low incidence countries, tuberculosis in the indigenous, non-minority population has become a disease of the elderly. It is common that the incidence rates are highest in the oldest segments of the population. In several low incidence countries also a significant proportion of the cases are found in the population segment aged 65 yrs and older. This can be explained by a high prevalence of infection in this population segment that has lived through periods when the risk of infection was much higher than today. Most cases in this age group are attributable to reactivation of subclinical infection with *M. tuberculosis* acquired in the remote past. Given infection, the elderly may also be more susceptible to reactivation because of a downgrading of the functioning of cellular immunity in old age. Because symptoms and signs of tuberculosis in the elderly may mimic those of other commonly encountered ailments and conditions in this age groups, particularly malignancies, the necessity of including tuberculosis in the differential diagnosis of conditions encountered in the elderly patient cannot be overemphasized. This should help to reduce unnecessary and premature death from tuberculosis and hidden transmission to those who are in contact with this group.

#### *Individuals infected with M. tuberculosis at increased risk of tuberculosis*

Numerous factors that increase the risk of progression to tuberculosis from latent, subclinical infection with *M. tuberculosis* have been identified. Some of these factors bear a very high risk and are also fairly prevalent, others bear a high relative risk, but are rarely encountered, while others are associated with a low (but still increased) relative risk, but are fairly common. Such considerations need to be addressed when designing preventive intervention strategies.

*Persons with HIV infection.* Infection with HIV has emerged as the strongest yet identified factor to increase the risk of progression to tuberculosis among those infected with tubercle bacilli. Subjects infected with *M. tuberculosis* among persons with HIV infection should be identified, in order to provide them with preventive therapy (after exclusion of current tuberculosis). Tuberculosis is the major disease in HIV infected persons that is transmissible to non-HIV infected persons and which is both preventable and treatable. Because the spread of HIV infection is likely to continue for some time to come, tuberculosis control programmes must urgently address the problem and formulate guidelines that help clinicians and public health workers to deal with the problem.

In low incidence countries the contribution of HIV infection to the spread of tuberculosis in the

general population is likely to be small. This contribution will critically depend on the underlying prevalence of infection with *M. tuberculosis* in the community, especially in the 15–50 yr old age group. In population segments with a high prevalence of infection with *M. tuberculosis*, the impact of HIV will become increasingly relevant. In low incidence countries this is likely to be significant in special groups, such as intravenous drug users, in whom the risk of tuberculosis and of HIV infection is relatively high.

*Recent infection.* Recent infection with *M. tuberculosis* has been identified as a strong risk factor for tuberculosis. The risk of tuberculosis following infection is highest in the years immediately following infection. Contact investigation among newly discovered cases must thus have priority next to treatment of new cases, because the yield in discovering new transmission is likely to be high. Thus, preventive therapy in such cases will be particularly efficient.

*Persons with fibrotic lesions.* Persons who have had an episode of tuberculosis in the past that has spontaneously regressed without specific treatment and healed with residual fibrotic lesions in the lungs are at high risk of recurrence of tuberculosis. Whenever a chest radiograph is taken for whatever reason and fibrotic lesions are seen and active tuberculosis has been excluded, preventive therapy should be considered for those in whom it is not contraindicated for other reasons.

*Persons with other risk factors.* Numerous other factors have been identified that increase the risk of progression to tuberculosis among persons infected with *M. tuberculosis*. Notably these include silicosis, haemodialysis, diabetes mellitus, carcinomas (particularly of the head and neck), immunosuppressive treatment, gastrectomy, underweight, and jejunoileal bypass. Some of these are important, because they might be common (such as diabetes or underweight), others have only anecdotal relevance (such as jejunoileal bypass for obesity).

#### **Laboratory services**

Microscopy and culture for mycobacteria, identification and differentiation of species and drug sensitivity testing remain the most important laboratory techniques in mycobacteriology at present. Mycobacterial laboratory services are faced with problems in quality assurance in low incidence countries. The maintenance of proficiency and high quality services requires that laboratories regularly receive positive specimens. A service based on the recommendations in table 1 is likely to be satisfactory in terms of availability and required standard of performance and reliability.

Table 1. — Prospective organization of laboratory services for tuberculosis (TB) in low incidence countries

Class	Expertise	Amount of work
Level I: local	Smear only (Ziehl-Neelsen)	Occasional
Level II: 1–4 million inh.	Smear (Ziehl-Neelsen or fluorescence) Culture Standard identification tests for TB only	45–50 pathological specimens daily
Level III: 5–10 million inh. or national	Elaborate identification tests Drug sensitivity tests	2–20 mycobacterial strains daily

It is particularly recommended that services such as differentiation of mycobacterial species, drug sensitivity testing, studies on drug resistance and the development and testing of new technology should be reserved for reference laboratories that serve a national population or some 5–10 million inhabitants of larger countries.

## Research

### *Treatment and prevention*

The continued investigation of drug combinations and the development of new anti-mycobacterial drugs remain absolutely essential. Non-compliant behaviour combined with the rising frequency of drug resistant organisms in less-developed countries and the growing role of opportunistic environmental mycobacteria in human disease all contribute to the urgent necessity to identify new therapeutic agents.

There is an urgent need for the evaluation of new preventive therapy regimens. It seems unlikely that isoniazid as a single agent, which has been used for some 40 yrs, will remain a practical preventive chemotherapeutic modality. Fully effective short-course regimens of 6 months for active disease make preventive therapy of one year duration unacceptable in today's circumstances. Animal studies suggest that complete elimination of dormant organisms by isoniazid alone is less effective than combinations of drugs for a shorter duration. Adequate alternatives are thus needed, particularly in light of the HIV pandemic. The investigation of alternative preventive therapy regimens is mandatory. There is also urgent need to evaluate multiple drug regimens for prevention, especially of combination pills using shortened duration and possibly on an intermittent basis.

Investigation and development of immunotherapy techniques have already created a challenging conceptual model and offer an interesting opportunity for further scientific investigation.

### *BCG*

It was noted that various BCG products have been adopted in the Expanded Programme of Immunization (EPI) and that BCG vaccines may differ in their protective efficacy and in the frequency of producing adverse reactions. Because good protection may be achieved by potent vaccines with few adverse reactions, it is recommended that the most suitable vaccines be identified and recommended.

### *Intervention strategies and HIV infection*

Standard short-course chemotherapy appears to be effective in the treatment of tuberculosis in acquired immune deficiency (AIDS) patients but the frequency of adverse reactions appears to be higher, and failure to deliver an effective programme is also a greater problem in reports available to date. There are enormous challenges in the delivery of successful preventive programmes in this group.

Environmental mycobacteria that usually only cause disease in the immunocompetent, frequently cause disease in HIV infected patients and contributes to the urgent necessity to identify more effective therapeutic agents against these organisms.

The development of standardization of antigens from opportunistic environmental mycobacteria, so that epidemiologists may be provided with a reliable surveillance tool for these mycobacteria, is also a major challenge.

### *Basic research*

Research is being carried out in the field of genetic engineering which could play an important role for the development of new techniques in the diagnosis of mycobacterial disease. No immediate practical applications for diagnosis or monitoring of treatment have so far been developed. However, one of the exciting benefits of such research has been the formation of



research links with workers outside the field of mycobacterial disease and this is considered important for the future development and support of such research. This is particularly so in the field of polymerase chain reaction (PCR) technology. The results so far suggest that gene amplification for diagnosis, deoxyribonucleic acid (DNA) probes for typing and the use of plasmids and mycobacteriophages for genetic engineering offer the most promising prospects. There is hope that molecular biology will change our understanding of the disease and expand the tools available for control programmes. The possibility to clone genes for specific antigens, offers the possibility of leading to more potent vaccines, provided that specific protective antigens can be recognized. These investigations are leading to a better understanding of the immune status in individuals infected with tubercle bacilli and offer the possibility of manipulating the immune response in vaccinated people or in patients with tuberculosis. For instance there is some evidence that the tissue damage by tuberculosis is mediated at least in part by the release of tumour necrosis factor from macrophages. These advances in our understanding offer a rational basis for the possibility of combining chemotherapy and immunotherapy with vaccines derived from killed environmental bacteria. It is felt that further basic research in this field should be encouraged and supported.

### Recommendations from the working group

#### *National tuberculosis services*

A nationwide information and data collection system should be established to facilitate the prompt and accurate reporting of cases and to quantify the incidence of tuberculosis. Ideally these data collecting systems should be computer-based and should remain under the direct supervision of epidemiologists with expertise in tuberculosis, thereby facilitating the recognition of deficiencies in control programmes and their correction. Monitoring of programme outcomes would be facilitated and the systems could also be extended to offer advice on individual patient supervision or treatment.

Each country should maintain a central (national) tuberculosis programme unit. Responsibilities of this unit should, in addition to surveillance, include:

1. development and revision of a National Tuberculosis Control Programme;
2. monitoring of programme effectiveness;
3. training and provision of an adequate number of personnel with specialized tuberculosis expertise.

There should be direct governmental responsibility for the provision of a comprehensive tuberculosis service including the implementation of the control programme.

#### *Surveillance*

A nation-wide information and data collection system should be established to facilitate the prompt and accurate reporting of cases and to quantify the incidence of tuberculosis. Ideally these data collecting systems should be computer-based and should remain under the direct supervision of tuberculosis experts, thereby facilitating the recognition of deficiencies in control programmes and their correction. Monitoring of programme outcomes would be facilitated and the systems could also be extended to offer advice on individual patient supervision or treatment.

#### *Parameters for monitoring tuberculosis in the elimination phase*

The limitations of the traditional epidemiological parameters need to be recognized and new methods formulated for low incidence countries. The basic parameters, namely incidence of active tuberculosis mortality from tuberculosis, and incidence of tuberculosis meningitis in children should continue to be monitored but must be reviewed by a tuberculosis expert who understands the inherent limitations of these indices. The incidence of active tuberculosis in young people and tuberculin conversion in contacts reflects the current transmission of tuberculosis in a more precise way and should also be useful. The annual risk of infection and its trend over time is the most sensitive parameter of the epidemiology of tuberculosis in the community but has particular limitations where BCG has been widely used and is a difficult index to derive in countries who do not have a well established data base or where the prevalence of infection with *M. tuberculosis* has become very low.

The desirability of adhering to the WHO standard tuberculin Mantoux test with 2 tuberculin units (TU) of purified protein derivative (PPD) RT23 is reaffirmed (WHO/TB/Techn. Guide/3/1963) for both clinical and epidemiological purposes.

#### *Case finding in the elimination phase of tuberculosis*

It is recommended that the national tuberculosis control programme should formulate plans based on local epidemiological conditions. Special plans are needed in industrialized countries with large numbers of displaced people. It is recognized that the best approach to preventing spread to individuals or groups with special susceptibility to tuberculosis remains the early identification of patients with bacteriologically positive disease, particularly of the respiratory tract, and appropriate chemotherapy, coupled with contact tracing and preventive therapy for infected contacts. Preventive chemotherapy must play a major role in high risk groups.

### Treatment

Short-course chemotherapy is recommended for all forms of tuberculosis in all patients. The prevalence of drug resistance especially in immigrants should always be considered. Supervised regimens are needed to overcome compliance problems.

### Preventive chemotherapy

It is recommended that the identification of high risk groups be given priority and that preventive therapy be provided to those infected with *M. tuberculosis*. Evaluation by cohort analysis and efficiency of preventive intervention must form part of any such strategy.

### BCG vaccination

Low incidence countries should consider discontinuing routine universal BCG vaccination of children. Countries with an incidence greater than 10 per 100,000 active cases of tuberculosis should also consider discontinuation but may have to contend with increases in the incidence of tuberculosis in non-vaccinated cohorts, which will usually be non-infectious but may include a small number of cases of tuberculosis meningitis. Modified BCG vaccination programmes could then be focused on groups considered to be at increased risk of infection. It is felt that these decisions can only be made with safety in countries with effective national tuberculosis control programmes which provide accurate contact investigation, preventive chemotherapy, data collection and programme monitoring facilities.

It is also recommended that the most suitable type and dosage of BCG be identified and that only those should be recommended.

### HIV infection

The greatly increased risk of progression of tuberculosis from latent infection with *M. tuberculosis* is well-established. Screening of HIV infected persons for tuberculosis and infection with *M. tuberculosis* is recommended but the limitations of the tuberculin skin test among immunosuppressed persons are recognized. Preventive chemotherapy with isoniazid should be used, but there is urgent need for trials to establish the most effective regimens.

Standard short-course chemotherapy is recommended in HIV infected patients with tuberculosis. The need for a longer continuation phase or the value of using a single agent chemotherapy after completion of treatment is unknown but these measures are practised in some circumstances. Follow-up of patients after completion of treatment may be maintained by close monitoring.

### Mycobacterial laboratory services

It is recommended that mycobacterial laboratory services recognize the problems in assuring quality.

It is recommended that a Level I (local) laboratory would undertake only microscopic smear examinations for mycobacteria. Level II (1 million inhabitants) would perform smear (Ziehl-Neelsen) (ZN) or fluorescence, culture and standard identification test for *M. tuberculosis* only. Level III (5–10 million inhabitants or national) would perform Level II work plus more elaborate identification tests and drug sensitivity tests. National drug resistance should be monitored to assure confidence in treatment regimens. Inter-laboratory quality control validation is recommended.

### Research

New epidemiological parameters need to be formulated and the existing parameters need to be re-evaluated in low incidence conditions. The search for a more specific tuberculin test substance should continue as the problems of differentiating reactions to tubercle bacilli from those due to opportunistic mycobacteria will become even more important as the incidence of tuberculosis decreases.

The role of preventive therapy urgently needs further evaluation and is likely to be helped by the development of multiple-drug regimens used for short durations.

The continued investigation of drug combinations and the development of new anti-mycobacterial medication are highly recommended.

Immunotherapeutic techniques should be further investigated. Basic research in genetic engineering is exciting but has little tangible benefit at present. The possibilities are, however, enormous and therefore such research should be encouraged.

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RÉSUMÉ: Le groupe de travail a résumé les conclusions de l'atelier dans le but de définir les grandes lignes pour la préparation de plans nationaux pour l'élimination de la tuberculose.

Les stratégies fondamentales ayant prouvé leur efficacité peuvent être décrites comme suit:

1. Le service public a la responsabilité directe du diagnostic, du traitement et de la prévention de la tuberculose (l'Etat est légalement responsable de l'identification précoce de la tuberculose et de la guérison des malades).
2. Renforcement ou mise en place d'un système efficace de la surveillance de la maladie et de suivi du programme.
3. Existence au niveau régional et provincial de personnel spécialisé en tuberculose, ayant la responsabilité de maintenir la qualité du diagnostic et d'assurer que les tuberculeux reçoivent l'attention nécessaire dans les centres de santé.

En ce qui concerne la recherche, le sentiment général est qu'aucune des innovations diagnostiques, thérapeutiques ou vaccino-logiques ne peuvent pour le moment être introduites dans la pratique générale. La recherche fondamentale en mycobactériologie doit cependant être encouragée et soutenue.

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