

default early in regimens based on studies that have shown a 25% relapse rate at a treatment stopping point after six months. It must be assumed that default at three months has a high relapse rate.

Control Programmes

The effect of intermittent defaulting is difficult to assess since it is so variable. In addition, it is difficult to determine if patients who do not take correctly the drugs they do take are more likely to be compliant. If patients fail to take drugs only two or three times a month, this is unlikely to have a significant effect. However, if a situation arises of, say, a patient defaulting for six months, the result is likely to be a relapse. The patients probably not M+ after treatment, and there would be little effect on population prevalence of persistent, chronic infection.

One of the most serious situations is when poor compliance result in the patients on M+ treatment. If an M+ patient obtains isoniazid-resistant bacteria resistant to isoniazid due to development of drug resistance that is not controlled with totally uncertain drug compliance, the result is at all.

This also applies to poor compliance in patients who do not collect their drugs. There may be a significant initial period of good compliance, but after initial good compliance after initial good compliance.

In any programme it is essential to ensure good compliance. Defaulting can easily be avoided. Chapter 12 shows how the programme can be designed. Compliance is less easy to assess. The patient has to

Dr. Paul Shears measure blood levels, but urine

TUBERCULOSIS CONTROL PROGRAMMES IN DEVELOPING COUNTRIES

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Oxfam Practical Health Guide No. 4

First published 1985

Revised Second Edition November 1988

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British Library Cataloguing in Publication Data
Shears, Paul

Tuberculosis control programmes in developing countries. — 2nd ed

1. Developing countries. Man. Tuberculosis, Public health measures

I. Title

614.5'42'091724

ISBN 0-85598-096-6

Published by Oxfam, 274 Banbury Road, Oxford OX2 7DZ, UK

Typeset by Typo Graphics, Oxford

Printed by Oxfam Print Unit

OX3/MP/89

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ACKNOWLEDGEMENTS

The draft of this booklet was sent to a wide range of reviewers both in the United Kingdom and overseas, and the contents are a synthesis of their ideas and some data from them has been incorporated directly into the text. The Oxfam Health Unit gratefully acknowledges all this assistance, and takes responsibility for any errors in the final copy.

CHAPTER 1. INTRODUCTION

The control of tuberculosis continues to be one of the major health needs in much of the developing world. Although an effective vaccine and effective anti-tuberculosis drugs have been available for many years, a review of most tuberculosis control programmes in developing countries shows that we are currently achieving less than fifty percent success in treating patients with tuberculosis, and are even less successful in reducing the overall prevalence of the disease.

Most developing countries now have national tuberculosis control programmes responsible for the planning and implementation of TB control services, following policy laid down by WHO and the International Union Against Tuberculosis (IUAT). The relatively low success rate of TB control programmes is primarily due to difficulties in implementation at the district and village level, where the already limited health resources become overstretched. The object of this manual is to assist health workers and project leaders at this level, working in conjunction with a national TB control programme.

Much of the failure of TB programmes is related to the emphasis that is given to the dispensing of anti-TB drugs, which is only one component of TB control. The manual looks initially at the problem of TB transmission in the community, based on an understanding of the pathology and epidemiology of TB. The central role of the sputum positive (M+) patient as the source of transmission and the target of control, is emphasised throughout.

The role of BCG is considered in the light of the debate surrounding its effectiveness and emphasis is given to its value in reducing TB in childhood, but not in reducing the sputum positive reservoir.

The chapters on drug treatment consider the merits of different treatment regimens, and look in detail at the problems of defaulting and poor drug compliance. The manual also emphasises the importance of the monitoring and evaluation of TB programmes if some progress is to be made in increasing programme effectiveness. Technical details of sputum examination, drug regimens, side effects, etc. are given in the appendices.

There is little original work in this manual, but it does attempt to combine the most recent developments in the scientific understanding of TB with the realities of working at the level of a primary health centre.

It is currently estimated that there will be 10 million new cases of TB per year during the next decade. If the hope of 'Health For All by 2000' is to be approached, effective TB control must be a priority for all involved in health care.

In areas where AIDS (Acquired Immunodeficiency Syndrome) is endemic the outlook for TB control may be particularly serious. Reduced immunity in AIDS patients whether symptomatic or asymptomatic may lead to activation of quiescent TB lesions, greatly increasing the potential reservoir of TB infection. In this second edition of the manual the effects of the AIDS epidemic on TB and TB programmes are discussed in Chapter 17, and in other chapters where relevant.

CHAPTER 2.

THE DIFFICULTIES OF TB CONTROL: SOME EXAMPLES FROM THE FIELD

To understand how programme effectiveness can be improved, it is important to begin by understanding the difficulties that exist in implementing TB control in the field.

Very few TB programmes can be fully evaluated to establish how each component of the control programme has affected the aim of reducing TB in the community. Each of the following examples suffers from this limitation, but they do give a useful introduction to the components of the TB programme.

a. Refugees in Somalia

TB became a significant health problem in the crowded refugee camps in Somalia in the early 1980s. Control programmes were initiated treating self-referred cases who had been complaining of persistent cough, diagnosis being made initially on symptomatic grounds only but, later on, using sputum microscopy when facilities became available. The treatment regimen was a three-month intensive phase of streptomycin, isoniazid, and thiacetazone, followed by a nine-month maintenance phase of isoniazid and thiacetazone.

Twelve months after the programme started, a basic evaluation of progress was undertaken.

Table 2.1.

Review of Somali Refugee (Saba'ad Camp) TB Programme (August 1981)

	No.	%
Total number of patients started on treatment since July 1980	600	100
Number known to have completed twelve months' treatment	55	9
Number completely lost to follow-up during treatment	301	50
Number attending at 31.8.81 including those defaulting a few weeks	244	41
Number defaulting a few weeks at 31.8.81 (of 244)	70	28
Number of defaulters in intensive phase (of 70)	14	20

Table 2.2.**Reasons given by patients for defaulting in Somali programme**

	No.	%
Total defaulters interviewed	60	100
Left camp, returned to Ethiopia	5	8
Left camp, still in Somalia	8	13
Lost interest in treatment — feeling well	22	37
Too ill to attend	5	8
Social reasons — marriage, festival etc.	16	26
Adverse reactions to treatment	4	8

Table 2.3.**Drug compliance in apparent non-defaulters in maintenance phase in Somali programme**

Residue of drugs at home	Adults	Children
Correct within 2 days error	80%	49%
3 to 6 days error	14%	24%
More than 6 days error	6%	27%

Table 2.1 summarises the initial information collected in the evaluation using only data that was already available in the register. The main findings of this simple evaluation were:

- i. 50% of the patients started on treatment were lost to follow-up during the first year of the programme. It is immediately apparent that the programme could have no more than 50% success. Also because some of these patients were diagnosed only on history and clinical findings (before microscopy facilities were available in the camp), it is probable that not all of those started on treatment actually had TB. Later studies suggested that a significant proportion of these would have been M+. Clearly, several hundred M+ cases at large in a crowded refugee camp would present a major public health hazard.
- ii. Of the 244 patients still under treatment, 70 were intermittently defaulting. Defaulting was defined as 3 days' absence in the intensive phase and one week's absence in the maintenance phase.

Most defaulting occurred after the intensive phase of treatment.

A survey was undertaken of 60 of those current defaulters to determine the reasons for defaulting. The results are shown in Table 2.2. It is important to note that few patients were defaulting because they had left the area or because of adverse reactions to the drugs. The majority were defaulting either because they had lost interest or because of social reasons.

As we shall see in Chapter 11, it is important to distinguish between known defaulting and hidden defaulting, i.e. patients who collect their weekly or monthly drug supply but do not consume it.

A study was undertaken to check the compliance of patients in the maintenance phase by pill-counting at home visits (using the technique described in Appendix 6). Table 2.3 shows the results obtained; they indicate a major problem of drug compliance in children. If the findings of each of the components of the evaluation are combined (using the formula in Chapter 12) the overall effectiveness of the programme can be calculated thus:

Regimen efficiency \times Attendance efficiency \times Compliance efficiency
= Treatment efficiency (%).

For example: $95\% \times 40\% \times 70\% = 27\%$ of those starting treatment are efficiently treated. If only 60% of cases are found, then programme efficiency is $27\% \times 60\% = 17\%$.

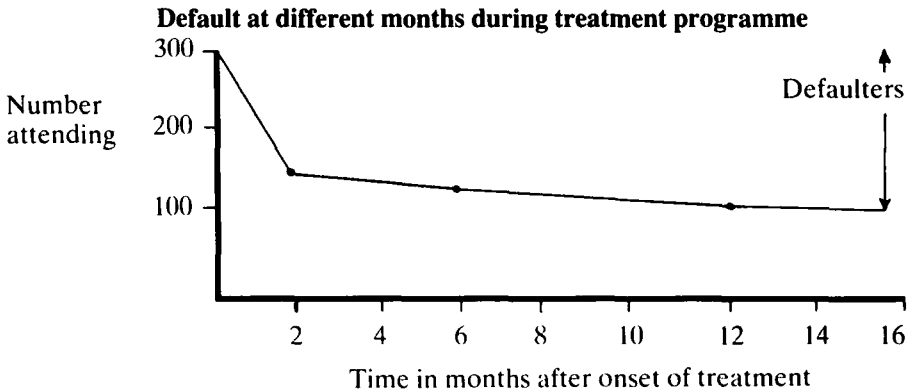
Many field programmes show a similarly low success rate when evaluated in this way.

b. **Pakistan**

A useful study on the problems of defaulting and compliance has been undertaken in the Sind area of Pakistan. The regimen used was a three-month intensive phase of isoniazid, thiacetazone and para-aminosalicylic acid (PAS) followed by a fifteen-month maintenance phase of isoniazid and thiacetazone, the drugs being collected on a weekly basis throughout both periods. Defaulting was defined as failure to attend the weekly clinic for a period of one month, and compliance was determined using urine tests for isoniazid and PAS as described in Appendix 6.

The results showed that one year after the commencement of treatment only 33% of patients had not defaulted. Fig. 2.1 shows the time at which patients began defaulting, and it can be seen that nearly 50% of all patients started on treatment had defaulted within two months. Of the patients who were regularly attending, urine tests showed that only 60% were actually taking the tablets collected. Thus the overall success rate of the programme was $95\% \times 33\% \times 60\% = 19\%$ of those *actually presenting for treatment*; there may be many more cases of TB not actually included in the treatment programme.

Fig. 2.1



The loss of 50% of the patients by two months after starting treatment is a most important finding; consequently even with short course programmes (e.g. six months) significant defaulting is likely.

c. Zaire

In Zaire an interesting study was carried out comparing the relative usefulness in TB control programmes of a district hospital and a health centre. The effectiveness in BCG coverage, case-finding, treatment compliance, and cure rate was compared between the services supplied by (i) a hospital serving an urban population of 30,000 and a rural population of 150,000, and (ii) health centres, both urban and rural, each serving populations of approximately 10,000.

The results they obtained are shown in Table 2.4.

Table 2.4.

	BCG coverage		Cases found	Default % at 12 mths	Sputum negative 1 year	Lost to treatment
	rural	urban				
Hospital	2%	20%	14/100,000	70%	28%	50%
Health Centre	95%	60%	28/100,000	30%	50%	28%

The data clearly indicates that the health centre, serving a smaller population and being closer to it, is more effective in all aspects of TB control than using a district hospital as the first point of referral.

This example shows that the success of a TB control programme depends not only on the community's attitude to TB, but also to the physical structure of the health programme.

d. **Kenya**

The final example — a study of TB in nomads in northern Kenya — looks at a situation where standardised health structures do not fit into the way of life of the community. Nomadic communities clearly present a major problem both in case-finding and in treatment compliance. For the latter, two approaches may be taken: either mobile health workers (providing drug administration) can travel with the nomadic communities, or M+ cases may be encouraged to stay in one place for the period of treatment. Although the latter may not seem practical, the programme in northern Kenya shows that it can be achieved. A six-month regimen (2SHRE/4RHE) — 2 months streptomycin, isoniazid, rifampicin, ethambutol, + 4 months rifampicin, isoniazid, ethambutol — was used, thus reducing the time the nomads had to remain. A special treatment camp was set up adjacent to one of the principal 'towns' in the nomadic area, and in a one-year period 143 M+ patients were admitted. Eight patients died during treatment; of the remainder none defaulted, and all patients were culture negative after five months' treatment.

While this approach differs from the policy of ambulatory treatment, it emphasises that for special situations an adaptable approach must be taken.

CHAPTER 3.

BASIC PATHOLOGY AND EPIDEMIOLOGY OF TB

Most tuberculosis in humans is caused by one of two bacteria: mycobacterium bovis and mycobacterium tuberculosis. The tuberculosis of *M. bovis* is caused by drinking infected cow's milk; while it is a significant problem in some areas, it is rapidly being brought under control and is a minor problem when compared to *M. tuberculosis*, with which most of this manual is concerned.

Because of its staining properties, the bacteria *M. tuberculosis* is called the acid fast bacillus (AFB). *M. tuberculosis* has no other host than man, and it is transmitted only by a person with TB infection in the lung coughing *infected* sputum: droplets from this infected sputum are inhaled by other person. From the lung, *M. tuberculosis* can lead to infection in many parts of the body — bone, joints, kidney, abdomen, lymph glands etc. — but it is only *active infection in the lung that transmits infection*. TB in the lung is called pulmonary tuberculosis (PTB) and all our work on control is aimed at this component.

Unfortunately infection by *M. tuberculosis* is not a simple case of the bacteria being inhaled and causing an active infection, as occurs in more 'simple' chest infections. When the bacteria is inhaled and rests in the lung, a complex lesion is formed by the migration of different types of cells from the body's defence mechanisms. In a small number of cases — particularly in children — this primary focus may rapidly spread to active disease in the lung, or to more widespread disease such as tuberculous meningitis. However, in most cases the primary focus becomes quiescent and so, although the person has an *infection*, they do not have active *disease*. This is a most important distinction.

A special test, called the tuberculin sensitivity test, can be used to discover people who have a quiescent or active infection. The principle of the test is that the person is given an intradermal injection of a small amount of purified protein derivative (PPD), which is a protein derived from the bacterium; if the person already has a primary infection, their defence cells give a hypersensitive reaction to the PPD at the injection site — PPD positive (PPD +ve). Appendix 1 gives practical details of using PPD.

The hypersensitive reaction to the PPD also means that the body can give a hypersensitive reaction if further *M. tuberculosis* bacteria are inhaled, and thus the primary focus gives some resistance to further TB infections.

Fig. 3.1.

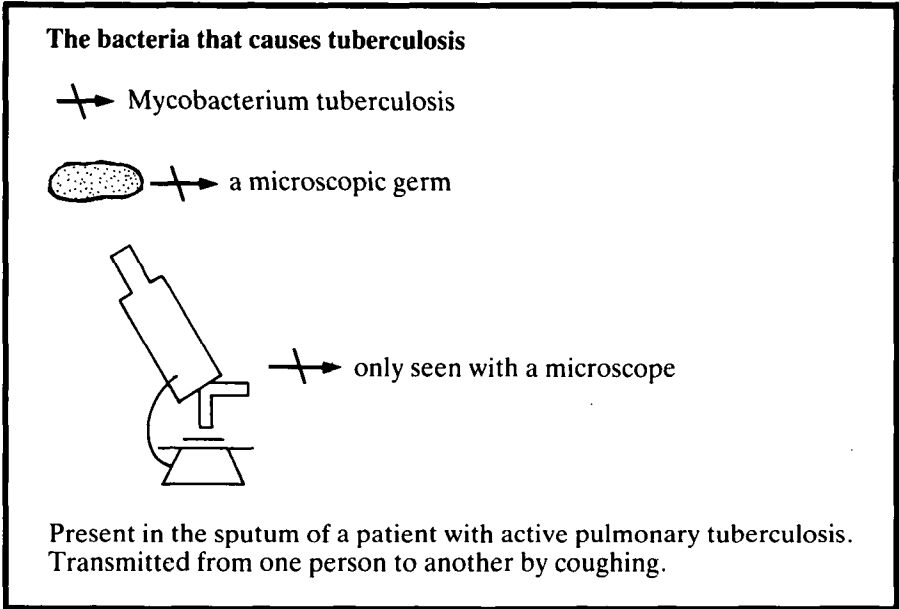
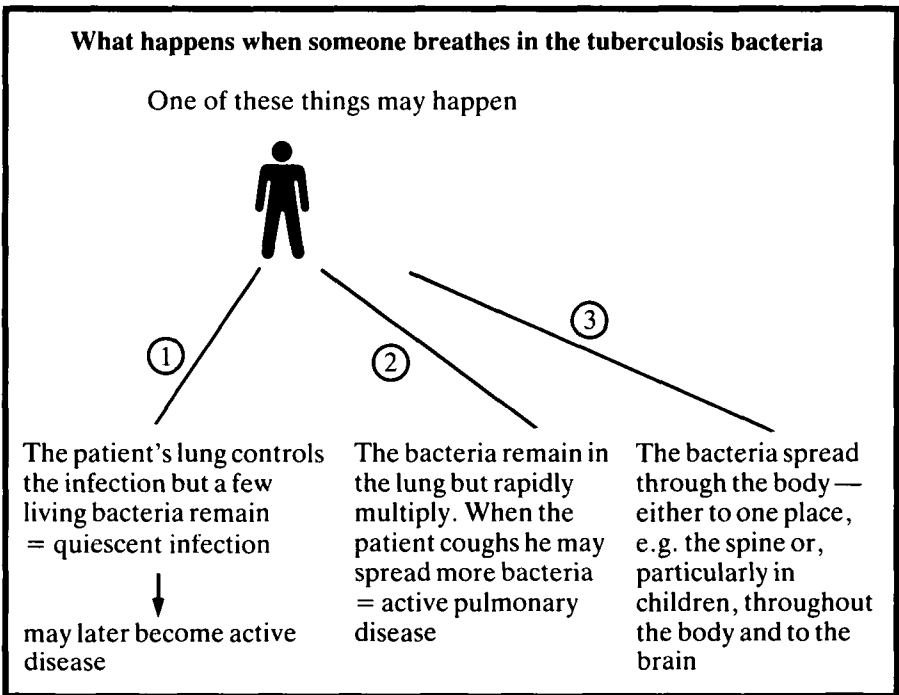


Fig. 3.2.



A small proportion of people with a primary focus will at a later stage develop active pulmonary tuberculosis, i.e. they will develop tuberculosis *disease*. This may arise from a reactivation of the primary focus (endogenous infection), or from infection by newly inhaled *M. tuberculosis* (exogenous infection).

Although the reasons why a primary focus becomes reactivated are not clear, it may be due to poor nutrition, intercurrent illness, etc.

In countries where there is a high level of active PTB it is felt that exogenous (i.e. 'new') infections are of major importance.

In active PTB disease the bacteria multiply rapidly, causing extensive damage to the lung tissue. The ability of the body's defence mechanisms to reduce the effect of the infection varies, resulting in different pictures of infection. In those with the most severe infection, when they cough their sputum will be loaded with bacteria — easily seen using simple microscopy (as described in Appendix 2) — and these patients are termed sputum positive (M+).

In those with less severe infection, there will be very few bacteria in the sputum; none will be seen by microscopy, but if special techniques are used to culture the sputum the bacteria can be found. These patients are termed culture positive (C+). Some patients will have limited active disease, and will show no bacteria either on microscopy or culture. Such patients are termed M-, C-.

As we shall see in the section on epidemiology, it is primarily the M+ patients who are responsible for disease transmission.

Each of the three groups would show abnormal chest X-rays. However, as we are primarily concerned with TB *control* — i.e. the M+ patients who can be easily diagnosed using simple microscopy — and as X-ray facilities are expensive, difficult to maintain, and do not distinguish between M+ and other patients, they have little role to play in control programmes in areas with limited resources.

For the individual, active pulmonary TB is a serious matter. Without treatment, 50% of M+ patients will die within two years of diagnosis. A smaller proportion of C+ and M- C- patients will die, but most will become increasingly incapacitated; some will eventually recover, and some will become M+.

Effective treatment is now available that, theoretically, can lead to cure in most cases. However, as later chapters demonstrate and as the examples from Chapter 2 have suggested, this ideal is rarely achieved.

While TB disease in the *individual* is of great concern, it is its chronic and unrelenting spread through poor *communities* that is the reason why such a major effort is required in TB control. The following part of this chapter looks at the *epidemiology* of TB: how we proceed from an understanding of the pathology in the individual to the disease in the community.

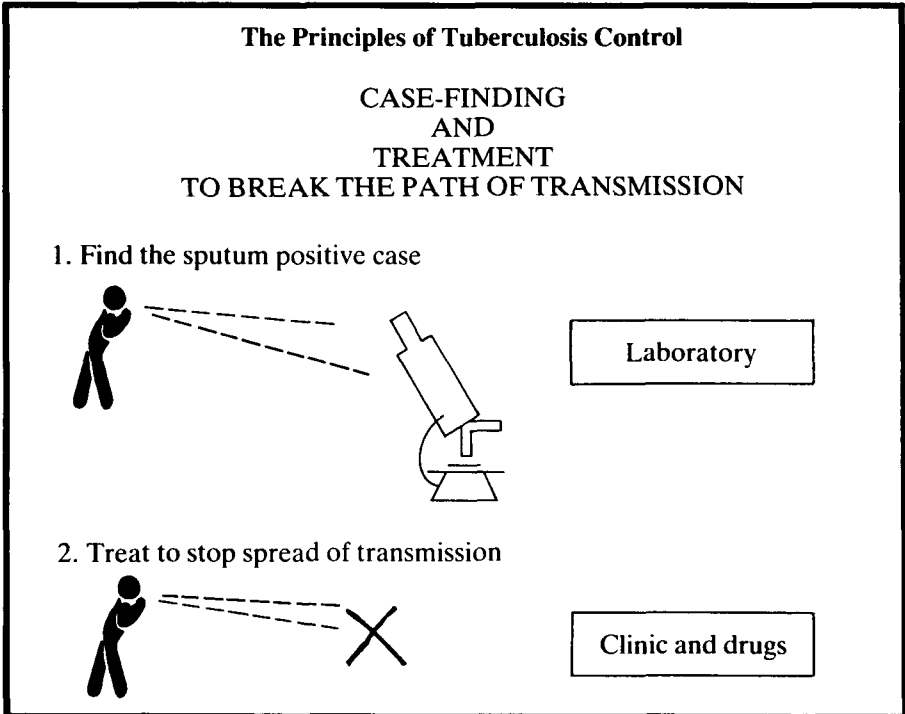
Epidemiology

Epidemiology is concerned with *measuring* the amount of a disease in the community. It is useful initially to describe the situation in general terms, based on an understanding of the pathology of TB described in the previous section. Many people may have TB *infection*, but relatively few will have active TB *disease*; of those who have TB *disease* some will have non-pulmonary disease (described in Chapter 14) and some will have pulmonary disease. Patients with active pulmonary disease may be divided into three groups:

- a. Those whose sputum shows many AFB easily seen on microscopy (M+).
- b. Those whose sputum shows no AFB on microscopy, but when the sputum is cultured AFB are shown to be present (C+).
- c. Those whose sputum has no AFB on microscopy or culture, (M–, C–) but in whom chest X-ray would suggest an active lesion.

Many studies have shown that patients in groups (b) and (c) are hardly infectious, if at all, but that patients in group (a) are highly infectious and are responsible for most TB transmission. Therefore, if we are principally concerned with *control* of tuberculosis in the community, our priority must be to break the chain of transmission by *finding* and *treating* the sputum positive cases.

Fig. 3.3.



The second component of control is to protect individuals from infection. Because TB is a disease of complex pathology, protection of the individual is not as simple as in other infectious diseases such as measles and polio.

The most direct way to protect individuals against a disease is by immunisation to develop the body's own defence mechanisms. There has been much debate and some controversy about the role of BCG immunisation; it will be discussed fully in later chapters, but here we must consider how the use of BCG affects the epidemiology of TB and its role in TB control.

BCG does not prevent *infection*, but acts by preventing the *spread* of an infection within the lung and to other parts of the body. It offers no more protection than does a primary focus; thus, once people are PPD+ve it is useless to give BCG. The protective role of BCG only lasts 10–15 years. In areas of high TB prevalence, most adults will be PPD+ve, so there is no point in giving BCG to adult populations; it is thus usually given to infants to protect them in the first 10–15 years of life. Very few children ever develop M+ PTB. TB *disease* in children usually involves sites other than the lungs; thus, protecting *children* by using BCG has virtually no effect on reducing the number of M+ cases in a community, and therefore *no effect in reducing disease transmission*. The main value of BCG is in preventing the serious forms of TB in children, particularly TB meningitis.

The prevalence of TB will also be reduced by improvements in nutrition and housing, i.e. the reduction of poverty. Improved nutrition will increase individual resistance to disease, and improved housing will reduce crowding and disease transmission. While all programmes should work towards reducing poverty in the long-term fight against TB, case-finding, treatment and BCG immunisation of children are our first lines of attack.

So far, we have considered the epidemiology of TB in descriptive terms. To estimate the size of the TB problem in an area and to plan a programme it is useful to have some quantitative epidemiological indicators. Considerable work has been done by the IUAT to provide a quantitative basis to TB control, which is summarised below.

The terms are defined as follows:

- a. **Total prevalence of TB infection:** the proportion of the population who have either a quiescent focus, or active disease. This is determined by PPD surveys.

$$\text{Total prevalence of TB infection (\%)} = \frac{\text{No. of people with PPD+ve}}{\text{Total no. in sample}} \times 100$$

For example, if in a sample of 500 people 40 are PPD positive, the total prevalence of infection is $\frac{40}{500} \times 100 = 8\%$.

In many developing countries, more than 50% of the population may have TB infection. The percentage found will depend on the age group of the sample being studied, as older people will have had more chance to get the infection. The prevalence in many countries (from WHO surveys) is 100–400 per 100,000 population.

b. The average annual TB infection rate

$$= \frac{\% \text{ of PPD positive children aged 10 years}}{10}$$

Thus, if the % of PPD positive children aged 10 years is 30%, assuming an equal chance of infection in each year of their life, the average annual infection rate is 3%.

c. Prevalence of M+ patients (%)

$$= \frac{\text{No. of M+ patients in a sample of the population} \times 100}{\text{Total size of sample}}$$

Thus, if in a sample of 1000 people five M+ cases are found, the prevalence is 0.5% so, in a population of 100,000, 500 M+ cases could be expected.

A large number of studies have been undertaken to relate the amount of active *disease* to the prevalence of infection, enabling us to estimate the parameters without having to carry out surveys. One new term needs to be introduced: *incidence* of M+ cases = the number of *new* M+ cases that occur in one year.

The relationships that have been derived can be summarised as follows:

If annual TB infection rate	= 1% (derived from a survey of 10-year-olds)
Incidence of M+ cases	= 55/100,000 population
Prevalence of M+ cases	= 110/100,000 population
Prevalence of C+ and M– C– cases	= 220/100,000 population
Mortality of M+ cases	= 30/100,000 population
Incidence of TB Meningitis in 0–4-year-olds	= 5/100,000 population

In addition, on average one M+ case infects 15 more people per annum — but clearly this can be very much greater in crowded communities.

Because the risk of infection increases with age, there is *not* a simple relationship between the annual TB infection rate derived from a sample of 10-year-olds and the *prevalence* of TB infection in different age groups. However, the following figures are a general guide:

Annual risk of infection	% of population aged 30 yrs infected (PPD+ve)
1.5%	36%
3%	60%
6%	80%

The basic parameter is thus the average annual TB infection rate, derived from PPD surveys (see Appendix 1). Such surveys can only be done on children who have not received BCG, as BCG also gives a PPD+ve. In an area without previous BCG, it would therefore be possible to determine the annual infection rate directly. In areas of relatively high transmission, the average annual infection rates range from 3% to 6%.

Chapter 6 shows how to use these indicators in the planning of a TB control programme.

Fig. 3.4.

Indicators of the size of the TB problem	
Prevalence of TB infection	= % with positive PPD
Annual TB infection rate	= $\frac{\% \text{ PPD positive children aged 10}}{10}$
If annual TB infection	= 1%
Incidence of M+ cases	= 55/100,000/year
Prevalence of M+ cases	= 110/100,000

CHAPTER 4.

THE PRINCIPLES OF CONTROL

An understanding of the basic pathology and epidemiology of TB described in Chapter 3, and the lessons learned from field programmes such as those described in Chapter 2, will help in making a rational approach to TB control.

As explained, while there may be a high level of TB *infection* in the community, it is only those who are M+ who are responsible for transmitting the disease. Thus the basis of a control programme must be:

- a. To locate as many M+ cases as possible.
- b. To provide effective chemotherapy to the M+ cases.

Isolation of M+ cases probably has no useful role in most developing countries. When an M+ case is located, he is likely to have been M+ for more than a month, giving ample time to expose family and other contacts to infection. Once chemotherapy is started infectiousness is reduced rapidly, and usually within 2–3 weeks the case is virtually non-infectious even if he remains M+ for several more weeks. So long as the patient is careful with coughing and avoids contact, particularly with new groups of children, he is most unlikely significantly to infect more people during the short time he remains infectious after the beginning of treatment.

Chemo-prophylaxis of M+ contacts also has little role to play in developing countries, since programmes are fully stretched attempting to maintain drug compliance with M+ cases.

In summary, the principles of control are simple: case-finding and treatment, to break the chain of transmission. The following chapters attempt to relate this ideal to the realities in the field.

CHAPTER 5.

INVOLVING THE COMMUNITY

Many health programmes assume that the introduction of a TB control programme into an area is the first time the community has heard about TB. Health workers start to teach the community about a disease that causes ‘sputum with blood’, weight loss, etc. as though it is something unknown; if it were unknown, it would not be a problem. Clearly, the community will recognise the disease even if they do not know it as ‘tuberculosis’; in the era before the discovery by Koch of the TB bacteria (in 1882), ‘consumption’ — as TB was called in Europe — was already known to be a major cause of morbidity and mortality.

If the community is going to participate fully in the TB control programme (and such participation is essential for programme effectiveness) it must begin with what the community already understands about TB, i.e. *they* must teach the health workers rather than vice versa. When the health team understands the community’s traditional view on TB (e.g. how do they think it is caused, do they think it is transmitted from person to person, etc.), a bridge must be built between this understanding and the possibly quite alien ideas of sputum microscopy, prolonged drug treatment and BCG vaccination.

It is not appropriate here to go into methods of health communication, except to emphasise that the traditional pattern of a young urban-educated teacher instructing village elders — who have seen more TB than the young teacher is ever likely to see — needs to be reconsidered. Also, the *medium* of communication must be appropriate: standard packages of health education visual materials are of little value in communities who have never seen pictures and who use stories and poems as their means of communication.

So the first part of a new TB programme, or when revitalising an existing programme, must be community meetings so that all are aware of what the programme involves. The next stage is to discuss with community leaders — both traditional such as chiefs, sheiks etc., and modern such as teachers and administrators — the help that will be needed from them in finding suspected cases of TB, in doing everything possible to reduce treatment defaulting and improve drug compliance, and in assisting with BCG programmes.

Achieving this participation will require more than discussion. Specific programmes will need to be drawn up, where specific members of the community have the responsibility to ensure attendance at clinics, taking of treatment, etc. It should form part of the community’s existing involvement in health programmes. In fact TB control can often provide a useful focus for such involvement.

Fig. 5.1.

Involving the Community

TB is a community disease and needs community action to fight it

1. Find out what the community already knows about TB.
2. Help them to understand how it is transmitted and how drugs treat it.
3. Ask them to help you find the cases, and to ensure that people take regular treatment.
4. Ask them to help look after those very sick with TB.
5. Help them to find ways of improving their nutrition and housing.
6. Help them to understand why all children should be protected with BCG.

CHAPTER 6.

ESTABLISHING THE SIZE OF THE TB PROBLEM IN YOUR COMMUNITY

It is important to make some assessment of the size of the TB problem in the programme area, both to help in planning the programme and to assist later evaluation. There are a number of basic epidemiological indices that can be used (see Chapter 3).

Some estimate of the total population of the programme area is important, and also the subdivision of the population into age groups, e.g. 0–5 years, 6–15 years, 16–30 years, over 30 years.

If the population is known, and there is some idea of the average annual infection rate, it is possible to estimate the likely prevalence of active TB and therefore the expected number of M+ cases. The latter is most important, as it can then be determined whether a high proportion of the M+ cases are being identified by the case-finding programme (Chapter 9).

It is useful to consider an example of determining the size of the TB problem in a typical community:

- a. Population of Project Area (from Government statistics): 200,000 living in approximately 100 villages of an average population of 2,000.
- b. Annual average rate of infection: 5%.
- c. Using the formula from Chapter 3, the following can be determined:
 - i. Percentage of population aged 30 years infected: 70%.
 - ii. Prevalence of active PTB: $1650/100,000 = 3300$ in this population.
 - iii. Prevalence of M+ cases: 1100.
 - iv. Incidence of new M+ cases/1 year: 550.
- d. Estimated 0–5 years population for planning BCG programme: 20% of 200,000 = 40,000.

The most important aim of the programme is to attack c.iv., i.e. the risk of 550 new M+ cases per year unless an effective programme is set up. This can only be achieved if as many as possible of the estimated 1100 M+ cases can be *found* and *effective* treatment instituted. The following chapters consider how this may be achieved.

CHAPTER 7.

PLANNING AN APPROPRIATE TB CONTROL PROGRAMME

While TB services consisting of institutions and isolation mainly evolved from the pre-antibiotic era of the West, there is abundant evidence that the most effective programmes are community-based, involving the various components of case-finding, chemotherapy, follow-up and BCG. It is the recommendation of the IUAT/WHO study group (WHO Technical Report 671) that TB services should be integrated into the existing health structure, and the emphasis of the programme should be 'non-institutional'.

In such a system the primary health centre — serving a population of 10,000 to 50,000 — and the village-based community health worker become the cornerstones of the organisation of TB services.

Most developing countries now have a National TB Programme with the responsibility of planning (with WHO co-operation) the policy of TB control for the country, and implementing the programme through the existing health structure. The following paragraphs are taken from the WHO recommendations for National TB Programmes.

Organisation of the National Tuberculosis Programme

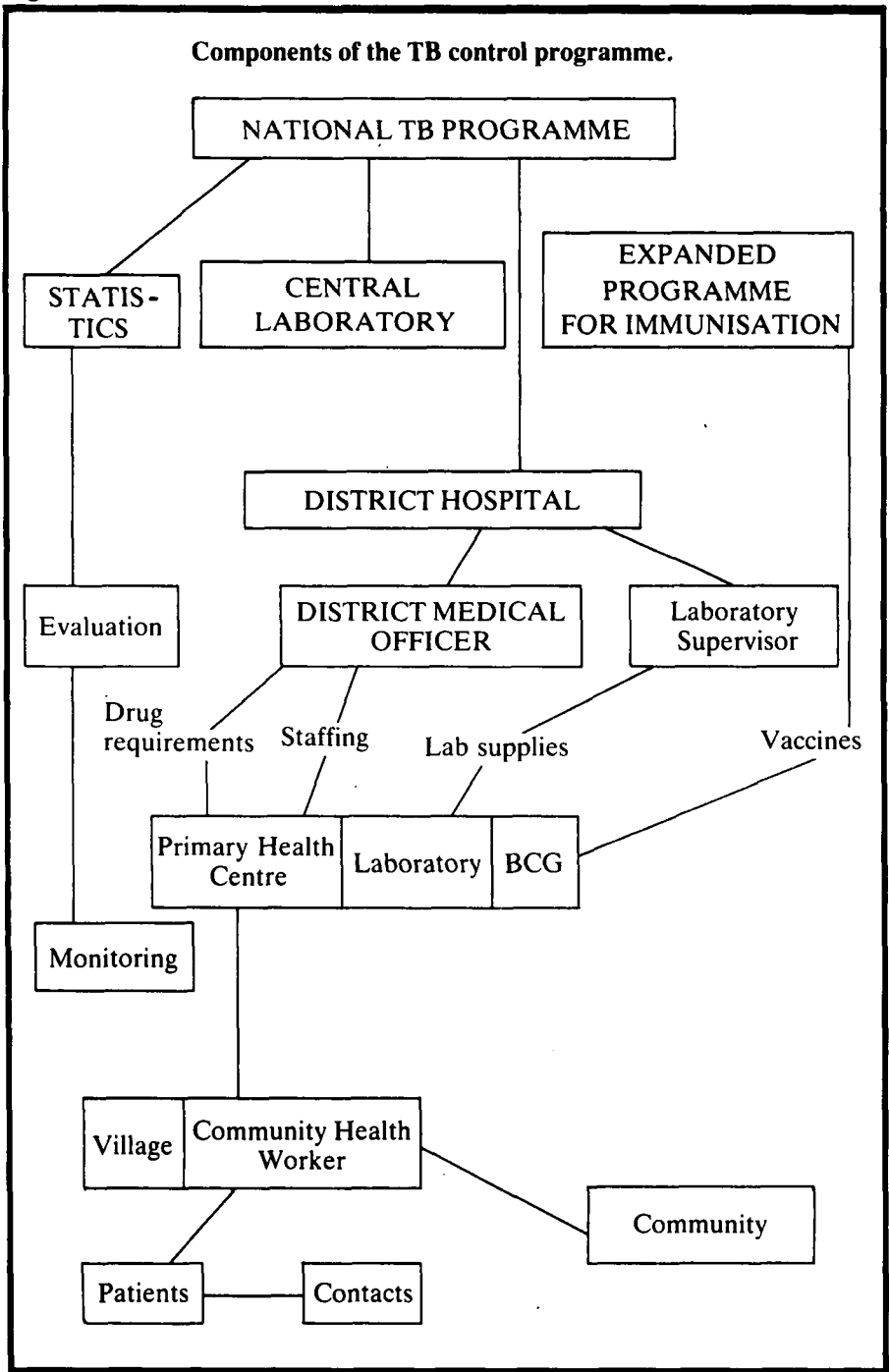
The main recommendations in the 1974 report were:

1. The programme should be permanent, organised on a country-wide basis (serving the rural and urban areas equally), be a well-balanced component of the country's health programme, integrated into the community health structure, meet the public demand, and be accessible, available and convenient for the *consumer* rather than for those providing the services.
2. The plan should clearly enumerate the main events and the actions required to achieve them in their logical sequence. There should be a systematic planning of operational steps for implementation, monitoring and evaluation of the TB programme which should be based on demographical information, the system of administration and communications, the structure and coverage of the health services, and the availability of manpower and resources at the central, intermediate and peripheral levels.
3. Diagnosis and treatment should be carried out by suitably trained staff operating from a network of permanent health services including outpatient departments of hospitals, health centres, dispensaries and health posts. These should be located so that all the people have reasonable access to a health unit of some sort.

4. For the implementation of the programme there should be a single strong directing authority at the central level under the Ministry of Health which should be responsible for policy-making, planning co-ordination, training, direction and evaluation. Managerial teams, especially trained in the technical and operational aspects of the programme, should play a key role and be responsible for the implementation of the programme; they should spend much of their time in the field supervising the activities and on-the-job training of the field workers, particularly at the peripheral level. Their other activities should include the organisation of the distribution of equipment and supplies, and the technical evaluation of the programme components based on simple, effective and meaningful recording and reporting systems which should provide information for future planning.
5. Adequate training for all categories of health personnel emphasising the community aspects of TB. Members of the managerial teams should, in principle, be trained as a group at a national centre and particular importance should be attached to management technology, not necessarily limited to TB. Basic information on National Tuberculosis Programmes should be added to the curricula of medical, para-medical and nursing schools.

Fig 7.1. summarises the many components of a National TB Programme.

Fig. 7.1.



In many situations, because of limited resources and logistic problems, national programmes do not function well below the district hospital level; yet it is below the district hospital level that the major work of the control programme must occur. This chapter will, therefore, concentrate on the organisation of the TB control programme at the level of the primary health centre, to help to fill the gap that so often exists in the field.

The organisation of the health system has to provide the following functions for TB control:

1. Educating the community about TB.
2. Case-finding and diagnosis.
3. Educating patients and their contacts.
4. Treatment and follow-up.
5. BCG vaccination programme.
6. Programme evaluation.

1. **Educating the community about TB**

Chapter 5 demonstrates the importance of community participation in the programme. The central person in education/information is the village health worker. In addition, existing information systems such as schools and radio can be used to inform the community about TB.

2. **Case-finding and diagnosis**

Chapter 9 discusses the different approaches to case-finding. A major decision that has to be taken is the location of the basic laboratory for sputum examination. (The practical details of collecting sputum and laboratory examination are given in Appendix 2.) Ideally, the sputum should be examined at the same location from which chemotherapy and follow-up are to be organised; however, because of shortages of trained staff and the need to ensure quality control of the microscopy services, regular supervision of peripheral laboratories is important and limits the number of such laboratories that can be supported.

Sputum examination should be included with other basic laboratory investigations (haemoglobin, malaria, parasites, etc.). On this basis, a laboratory serving a population of 50,000 would probably provide a balance between proximity to the community and adequate supervision. If a new laboratory is being set up in a programme area, it is essential that it is done under the overall supervision of the regional laboratory, to ensure a standardisation of techniques and quality control.

Sputum examination should be done at diagnosis, at two months, six months and twelve months during chemotherapy (assuming a twelve-month regimen) and, if possible, at six months and twelve months after the completion of treatment.

The regional laboratory will organise the examination of sputum of patients thought to have drug resistance.

Experience has shown that people with basic literacy and numeracy can be trained to do sputum investigations, so it is usually possible to train someone from within the community.

3. Educating patients and their contacts

While community participation has been emphasised, specific encouragement must also be given to the newly diagnosed patient, stressing the importance of non-defaulting and good drug compliance and, above all, making him feel not a diseased outcast but an essential member of the TB control programme. For patients who are literate, many programmes have devised simple booklets for patient information.

Ideally, the whole family should be involved in this 'education' so that they can encourage the patient to attend. It is also important that at the time of diagnosis the village health worker visits the family to look for other TB cases among the M+ contacts, as discussed in Chapter 9.

4. Treatment and follow-up

a. Treatment

Before treatment begins it is essential that there is an efficient registration system, and the most effective arrangement is to have both a register at the health centre and a card kept by the patient. The register should enable a new page for each month to be put against the list of names. It is best to have a separate page for each village. At the end of each month the defaulter list can then be made easily. The patient card should include the date of diagnosis and details of treatment.

The treatment regimen will in most cases be that laid down by the National Tuberculosis Programme. Different standard regimens are discussed in Chapter 10.

Although TB treatment will be organised through general primary health centres, there should be a separate 'clinic' (which may just mean a table in a shady location adjacent to the health centre) for the TB patients. If they are mixed in with the daily general outpatients, it will be difficult to maintain proper registration and to discuss problems of follow-up etc. The only staff requirements for the TB clinic are a clerk to keep the register and issue tablets, and a basically trained health worker to give streptomycin injections.

While patients are on daily therapy the sequence of the visit is usually:

- i. registration (e.g. a tick in the register and on the patient's card)
- ii. taking oral medication
- iii. streptomycin injection

Patients in the maintenance phase — collecting their drugs on a weekly or monthly basis — will be similarly registered and then collect their required number of drugs. Sometimes patients cannot attend the clinic, either because they are too ill or because they live too far away. In such

cases it will be the role of the village health worker (VHW), in conjunction with the primary health centre, to give the treatment; this may range from the VHW visiting the primary health centre each day to collect the required streptomycin and oral drugs, to one who, carrying a supply of drugs sufficient for a month or more, travels with nomadic groups or around remote villages. If such a VHW system can be adequately supervised and monitored, in many situations it may be an effective way to overcome defaulting and poor drug compliance. The work of the TB clinic and of the VHWs will be supervised by the medical assistant or nurse in charge of the health centre.

b. Follow-up

Defaulting and poor compliance are the major reasons for the low success rate of TB treatment. Consequently, *follow-up is as important as the issue of drugs.*

At clinic level, at the end of each week the clerk must make a list of all patients in the intensive phase who have failed to attend for more than three days, and of patients in the maintenance phase who have not collected their week's or month's supply. Similarly, the VHWs giving medications must report on any patients who have failed to receive their treatment.

The lists of all defaulting patients must then be given to the appropriate VHW who must attempt to locate the patient and re-institute treatment. Chapter 11 discusses modifications to the treatment regimen that may be necessary in cases of defaulting. Appendix 6 discusses how drug compliance can be checked to ensure that the patients who collect their weekly or monthly drugs do actually take them.

5. BCG vaccination programme

Full details of the organisation of the BCG programme are given in Chapter 8.

6. Programme evaluation

Ongoing monitoring and evaluation are essential to determine the effectiveness of the programme, and are discussed in Chapter 12.

Fig. 7.2.

Components of the TB programme	
1.	Discussions with the community
2.	Case-finding and diagnosis
3.	Educating patients and their contacts
4.	Treatment and treatment follow-up
5.	BCG programme
6.	Programme evaluation

CHAPTER 8.

BCG VACCINATION PROGRAMME

In Chapters 3 and 4 we have discussed the background of BCG immunisation. The practical considerations on which to base BCG immunisation as part of an integrated TB control programme are:

- a. BCG does not *prevent* infection, but prevents the spread of bacteria from the primary infection site.
- b. BCG offers no greater protection against *re-infection* than does a primary infection.
- c. BCG plays virtually no role in reducing the pool of infectious M+ TB.
- d. BCG does play an important role in protecting children against the development of TB meningitis and other non-pulmonary forms of TB. The efficiency of the protection is about 80% and lasts up to fifteen years.

Based on the results of many trials, the World Health Organisation recommends that for high prevalence countries — which include most developing countries — BCG should be given to all infants. In an area where no BCG immunisation has been done previously, there are two stages of immunisation:

- a. A 'mass' campaign to cover all existing children up to the age of 5 years.
 - b. An ongoing system to provide immunisation for children born after the campaign.
- a. **Organisation of the mass campaign**

Mass campaigns have the following components:

- i. Planning the programme with health workers and community leaders.
- ii. Training health workers.
- iii. Education campaign to inform the population.
- iv. Registration of the 0–5 years population.
- v. Organisation of the cold-chain.
- vi. Supply of vaccine.
- vii. Implementation of the vaccination programme.
- viii. Follow-up survey to determine vaccination coverage.

Different community structures will require very different organisational approaches: all aspects of the programme will be far more easily pursued in a crowded slum or refugee camp, where the population is accessible, than in a mountainous region where villages are remote and difficult to

reach, or in a nomadic community where there are no permanent places of habitation.

It is best to fit the planning of BCG programmes into the existing system for delivering health services to the community. Although situations will be very different one from another, planning should always be based around those eight components.

i. Planning the programme with health workers and community leaders

The support and involvement of all health workers and members of the community are essential for a successful vaccination campaign. Initially meetings should be held with all health workers to discuss the reason for giving BCG, the components of the campaign, and to learn — particularly from village-level health workers — how they feel the programme should be implemented. Health workers should then have meetings with community leaders to explain the programme to them and, if immunisation programmes have not been implemented in the area before, explain the function of vaccination. It is important to find out from the community leaders about cultural patterns and traditions which may affect the implementation of the programme; for example festivals, agricultural work such as planting and harvesting etc., or perhaps restrictions preventing babies below a certain age being exposed for immunisation.

ii. Training health workers

If an immunisation programme has not been carried out before, the health workers will need instruction on all its components. Different health workers will need to be allocated different tasks: all may be involved in the education campaign and registering children, some will be responsible for working with the cold chain, some for vaccine administration etc. At this point a clear timetable and an implementation plan (such as that in Fig. 8.1) need to be drawn up for the programme.

iii. Education campaign to inform the population

This has been fully discussed in Chapter 5. A good coverage of children will be ensured only if the community — especially the mothers — understand the value of BCG immunisation.

iv. Registration of the 0-5 years population

If all children can be registered, the size of the 0-5 years population can automatically be counted. As an initial estimate — which may be necessary for the early ordering of vaccine — the 0-5 years population constitutes approximately 20% of the total in most developing countries. If the registration of children has been done for recent previous immunisation campaigns, and the registers still exist, it may not be necessary to re-register children. However, rapid sample surveys should be done in a few locations to ensure that at least 70% of children are

registered. If less than 70% are registered it is preferable that a re-registration is done.

Registration is best dealt with by village health workers together with community leaders. In each village or other sub-division of the community, the details (name, family name etc.) must be entered of all children 0-5 years old.

v. **Organisation of the cold-chain**

BCG vaccine is easily destroyed by warmth and direct sunlight, so an efficient system of protecting the vaccine — not just in regional or district stores but to the point of administration — is essential.

vi. **Supply of vaccine**

The programme should be *planned* to cover 100% of the 0-5 years population but, if over 70% coverage is achieved, this is a good result. There is always some wastage of vaccine through breakages in transport and in the actual administration. Most field experience suggests that wastage of about 30% can be expected; therefore when calculating the number of doses required an extra 30% must be ordered.

For example: Total population of sub-district: 50,000
0-5 years population: 10,000
Number of doses required;
 $10,000 \text{ plus } \frac{(30 \times 10,000)}{100} = \text{approx. } 13,000 \text{ doses}$

BCG vaccine is usually now supplied in the freeze-dried form and requires saline as diluent, so it is essential that saline is also requested.

The vaccine is normally available through the National Tuberculosis Programme, but additional support may be required to improve the cold-chain.

vii. **Implementation of the vaccination programme**

According to the organisation of the community, BCG may be given at 'mass collecting points', e.g. schools, watering points, where up to 1,000 children may be immunised in a day by one group of vaccinators; or the programme may be carried out by mobile vaccinators visiting isolated groups of people. It must be emphasised that the logistics are far easier in the former situation, where it is also easier to ensure that vaccines remain at the correct temperature. UNICEF have made available very useful BCG kits containing syringes etc. for intradermal injection.

If vaccination is being done with large groups at one time, it is essential that there is good organisation, with the vaccination area completely fenced off, the place of vaccine-mixing and administration being shaded, and mothers and children let in only at the rate at which they can be immunised. Their names must be ticked in the register as they enter the

vaccination area. When doing mass campaigns in one place, it is useful to have a practice run a few days in advance to ensure all equipment and arrangements are ready.

viii. **Follow-up survey to determine vaccination coverage**

Because BCG leaves a visible scar, it is easy to determine how many children have been vaccinated following a campaign. This can be done by choosing a few random villages, seeing all the children who should have been vaccinated (i.e. all the 0–5 year olds) and seeing what proportion have BCG scars.

$$\text{Vaccination coverage} = \frac{\text{number of children with scars} \times 100}{\text{total number of children}}$$

Coverage over 75% is excellent. Coverage below 50% suggests major improvements are needed. But it is important to determine why the coverage is low; it could be that the vaccine was of poor quality or was not kept at the correct temperature so that, although children may have received the vaccine, an immune response did not occur.

It must be emphasised that a BCG vaccination programme is not complete until a coverage survey has been undertaken.

b. **Ongoing vaccination**

BCG vaccination should be included in the standard vaccination campaigns through MCH clinics, where they exist. However, there are usually so many logistical problems in maintaining adequate vaccine supplies in outlying MCH clinics that this aspect of the programme should not be a priority in the overall control programme. Sadly, in many primary health care programmes far more time is devoted to maintaining BCG vaccination through MCH clinics than in case-finding and treatment.

c. **BCG and AIDS**

In view of the potentially sinister impact which the AIDS epidemic may have on our current attempts to control tuberculosis, the subject is dealt with in some detail in Chapter 17. With regard to BCG, it should be noted that there have been reports of abscesses in some individuals positive for HIV (Human Immunodeficiency Virus) and of disseminated *Mycobacterium bovis* of BCG strain in one case (where BCG had in fact been given as part of the treatment for AIDS). There have also been a few other cases of disseminated *M. bovis* infection in HIV-positive infants and it is clearly important to be at least aware of the possible risks. The current recommendations (WHO/SPA/INF/87.11) from the WHO Global Programme on AIDS (GPA) with regard to childhood immunisation are that children in developing countries should continue to be immunised against all six target diseases independently of their HIV status. Individuals with clinical symptomatic AIDS should not receive BCG (see Fig. 8.2).

Fig. 8.1.

- Organisation of the mass BCG Campaign**
1. Planning the programme with health workers and community leaders.
 2. Training health workers.
 3. Education campaign to inform the population.
 4. Registration of the 0–5 years population.
 5. Supply of vaccine and equipment.
 6. Implementation of the vaccination programme.
 7. Follow-up survey to determine vaccination coverage.

Fig. 8.2.

Recommendations on the use of EPI antigens in HIV-infected individuals in countries where the EPI target diseases remain important causes of morbidity

	Vaccine	Asymptomatic	Clinical AIDS
Infants	BCG	Yes	No
	DPT	Yes	Yes
	OPV	Yes	Yes
	IPV	Yes	Yes
	Measles	Yes	Yes
Women	Tetanus toxoid	Yes	Yes

CHAPTER 9.

CASE-FINDING

The basis of a TB control programme is *case-finding* and *treatment*, and it is the M+ cases which are the first priority. It must be emphasised that case-finding *must* be followed by treatment. Little is to be gained by having a massive case-finding programme but not having the resources or health structure to ensure adequate chemotherapy. Thus, although in this manual case-finding and treatment are considered in separate chapters, their mutual dependence must always be remembered.

Not all M+ cases will present themselves to clinics for diagnosis and treatment; therefore an active programme of case-finding is necessary if most M+ cases are to be identified, and it has been found that the most effective system has two components:

- a. The investigation of the sputum of all the people in the community who are complaining of a chronic cough that has not settled after standard antibiotic treatment. Not all such people will present themselves to clinics, and the participation of community leaders and community health workers will be essential to ensure that as many as possible of the potential M+ cases are seen.
- b. To investigate the contacts of M+ cases. An M+ case is a focus of infection. When a new M+ case is diagnosed, a close investigation should be made of his family contacts and those living in neighbouring parts of the village. Often an old person is found who has a cough that has been accepted by all because of its long duration; this person is diagnosed as M+ and potentially infecting many people, particularly young children who are often looked after by the elderly. Subsequently, three months and six months after the start of treatment the contacts of the M+ case should be assessed again. It has been found that such a target-orientated approach — following the trail of infection — can have a major impact on reducing the size of the TB problem.

Although the epidemiology is different, the enthusiasm demonstrated in the containment system during the last years of the smallpox control programme provides a model for the enthusiasm that should be aimed for in TB control programmes.

As well as the contacts of M+ cases, certain locations often provide a high M+ yield. Tea shops and traditional meeting places, where the old men congregate, are often a focal point where there may be ten or twenty times as many M+ cases as in the general community.

In each programme it is important to consider which locations may have a particularly high M+ level and make a special case-finding effort in such places.

The practical details of sputum collection and investigation are given in Appendix 2.

Fig. 9.1.

<p style="text-align: center;">Case-finding to discover those who spread TB — that means those with positive sputum</p> <ol style="list-style-type: none">1. All people complaining of chronic cough, including old people who may not normally come to a clinic.2. Contacts of M+ cases in each of the five or six nearest houses.3. Social centres: tea shops, village meeting places, mosques, churches.

CHAPTER 10.

THE PRINCIPLES OF DRUG TREATMENT

More than ten drugs are currently being used in the treatment of TB. The different drugs work in different ways, and they must be used in the correct combinations and for the correct periods of time. A drug regimen describes both the combination of drugs and the duration for which they are used. To make objective decisions about the type of regimen to use, it is important to have a basic understanding of how the drugs act on the TB bacteria in the body.

In an active TB lesion in the lung, there are three groups of TB bacteria:

- a. Actively multiplying bacteria in open cavities: those that cause the sputum to be positive.
- b. Slowly multiplying bacteria in the body defence cells (macrophages) close to the open cavity.
- c. Bacteria in solid lesions that divide only intermittently.

Fig. 10.1 (on facing page) shows how the different TB drugs act on these different bacterial populations.

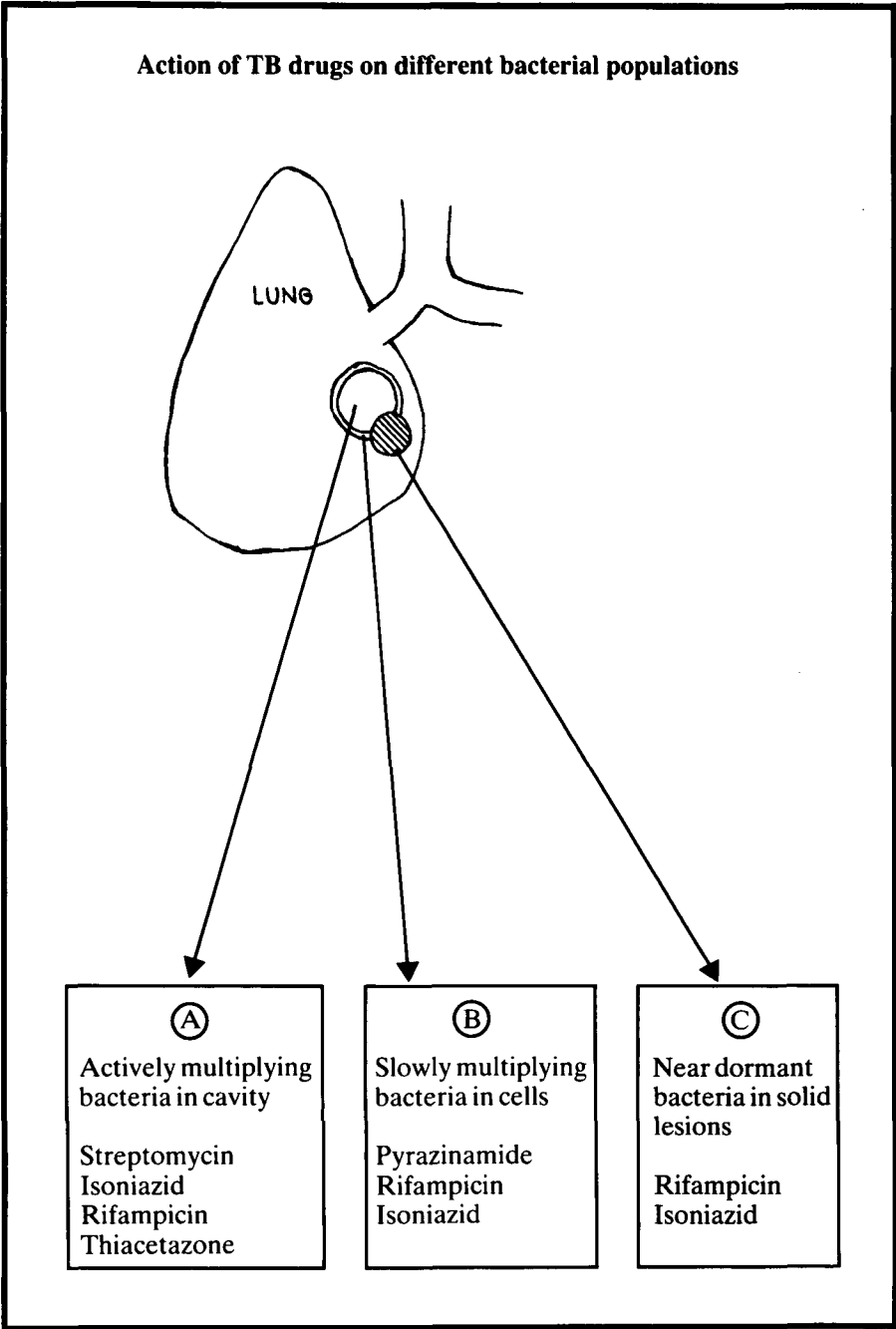
The requirements of a drug regimen are the following:

- i. To reduce rapidly the size of bacteria population (A) to stop the presence of bacteria in the sputum and hence stop disease transmission.
- ii. Ultimately to reduce or destroy all three populations of bacteria.
- iii. To prevent the development of drug resistance.
- iv. To have little adverse side-effect on the patient.

The above are the pharmacological requirements of a regimen. Very often these have been the only factors of a regimen that have been considered. However, unless the 'social' factors of a regimen, particularly drug compliance, are regarded as a priority, theoretical pharmacological success is of little value.

It is important to consider the question of drug resistance. In the actively multiplying population (A), the bacterial population will be more than 10 million. In such a vast number, there will be a few bacteria that will be resistant to any one of the anti-TB drugs; thus if only one drug is used, a population of bacteria resistant to this drug will develop. If more than one drug is used, then any bacteria resistant to one drug will be dealt with by the second drug. The principle of all effective regimens is to use three drugs for an intensive phase of two to three months, to reduce rapidly the large number of bacteria in population (A) without allowing the development of resistance. As the size of the bacterial population is very much smaller after the intensive phase, there is little chance of resistant organisms arising if adequate treatment is continued and a maintenance phase of two drugs is used.

Fig. 10.1.



There are therefore two reasons why *combinations* of drugs are required: the first is that different drugs are required to act on the different bacteria populations, and the second is to prevent the development of drug resistance. Drug resistance that develops because of inadequate chemotherapy is called *secondary* resistance. When a patient who has developed secondary resistance infects another person, that person will begin with resistant organisms. Patients who thus begin with resistant organisms are said to have *primary* resistance. If a patient begins with primary resistance, they must have a drug regimen different from that of the source of the resistance. Such regimens are discussed in Appendix 6.

The duration of drug treatment also needs to be considered. If all the bacteria were in population (A), relatively short courses of most drug combinations would result in effective treatment. However, it is because of populations (B) and (C) that long courses are required.

There is now much evidence to show that regimens that include rifampicin can achieve cures after a six-month treatment programme, assuming that all the prescribed drugs are taken regularly for the whole period. Regimens not using rifampicin require twelve months of therapy.

It is important to define treatment success. This is most simply considered in the case of M+ patients. An M+ patient is cured if:

- a. At the end of treatment his sputum is M- C-.
- b. He is clinically well.
- c. He remains well, and M- C- for an indefinite period after treatment is complete. Most studies assume that if a patient is M- C- two years after the completion of treatment, cure has been achieved. Very few programmes in the field are in a position to follow up patients for such a period after completion of treatment.

With the wide range of drugs available, a large number of treatment regimens have been used, some of them not based on a rational understanding of the bacteriological effects of the drugs, alone in or in combination.

The following are three well-tried regimens, each appropriate to different field situations:

- a. Twelve-month regimen based on:
 - three-month intensive phase of daily streptomycin, isoniazid, thiacetazone;
 - nine-month maintenance phase of daily isoniazid, thiacetazone.
- b. Twelve-month regimen based on:
 - two-month intensive phase of daily streptomycin, isoniazid, thiacetazone;
 - ten-month maintenance phase of twice-weekly streptomycin and isoniazid.

c. Six-month regimen based on:

- two-month intensive phase of daily rifampicin, pyrazinamide, isoniazid, streptomycin;
- four-month maintenance phase of daily rifampicin and isoniazid.

The dosages and costs of the drugs are given in Appendix 4, and the side effects of the drugs in Appendix 5.

The major problem in all chemotherapy regimens is default from treatment, when patients either fail to come to the clinic to collect drugs or do not take the drugs they collect. The advantage of regimen (b) — requiring streptomycin injections throughout — is that it can be fully supervised, as the isoniazid can be given at the same time as the streptomycin injection. The disadvantage is that in many communities it may be impractical to attend a clinic two days a week for one year. However, it may be possible to set up a system whereby village-level health workers administer the streptomycin at the patient's home.

Short-course regimens have two potential advantages. Firstly, because the treatment period is six months it is assumed that there will be less defaulting; however, many studies show that most defaulting occurs within two or three months of the start of treatment. This means that defaulting *cannot* be prevented by short-course regimens, only by increased individual and community participation in the programme, and active follow-up of defaulters by the clinic staff and village health workers.

The second advantage of short-course regimens is that, because of their very efficient four-drug intensive phase, even if people do default early a significant proportion of them may have been cured.

The following figures show what can be achieved:

Regimen	Duration	Relapse 2 years after end of treatment.
2 SHRZ/4HRZ	6 months	0
2 SHRZ/2HR	4 months	10%
2 SHRZ/2H	4 months	30%

S = streptomycin

H = isoniazid

R = rifampicin

Z = pyrazinamide

Although normally a 10% failure rate at two years' follow-up may not seem acceptable, if we compare that with the 50% failure rate that occurs in most programmes, we may have to think again. If, for instance, we could ensure in mobile groups in situations of high transmission, e.g. refugees, migrant workers, 100% compliance for four months in a four-drug regimen (rifampicin,

streptomycin, isoniazid and thiacetazone) — which could be possible — this may be a more effective way of controlling TB *transmission* than the usual intermittent compliance in a twelve-month traditional regimen. Such an approach would not be acceptable to many clinicians, but it is important to adjust our chemotherapy regimens to the realities in the field.

A common problem is deciding what regimen to use in areas where streptomycin, and more recently rifampicin, are indiscriminately used for non-tuberculous infections. Ideally, anti-tuberculosis drugs should only be available through the National Tuberculosis Programme, but in most countries it is unlikely that this could be achieved.

While it seems that no detailed studies have been done, as long as triple-drug therapy is given in the intensive phase it is unlikely that the occasional use of single anti-TB drugs in the past should prevent the use of the standard regimens detailed above.

Finally, in view of the risks of transmission of hepatitis B and AIDS (see Chapter 17), particular care should be taken in the use of syringes and needles in those regimens described above which involve the use of streptomycin by injection. Where these virus diseases are prevalent (and the regions are often precisely those where tuberculosis is also prevalent), the 'multiple' use of either syringes or needles without meticulous attention to sterilisation could be dangerous and may, under some circumstances, influence the choice of a regimen which uses only tablets or capsules.

CHAPTER 11.

PROBLEMS OF DRUG TREATMENT: RESISTANCE, DEFAULT OR POOR COMPLIANCE

Although adequate drug regimens exist such as those described in Chapter 10, in most programmes rarely more than 50% of the M+ patients started on treatment are cured, most of the failures not completing the full treatment programme. It is necessary to see the *problems* of drug treatment as an integral part of the treatment programme, so that continual attempts can be made to reduce defaulting and poor drug compliance and the possibilities of drug resistance can be investigated.

Fig. 11.1. (overleaf) illustrates the many possible reasons for treatment failure. It is useful to classify the reasons into three groups:

1. Drug dependant
2. Programme dependant
3. Patient dependant

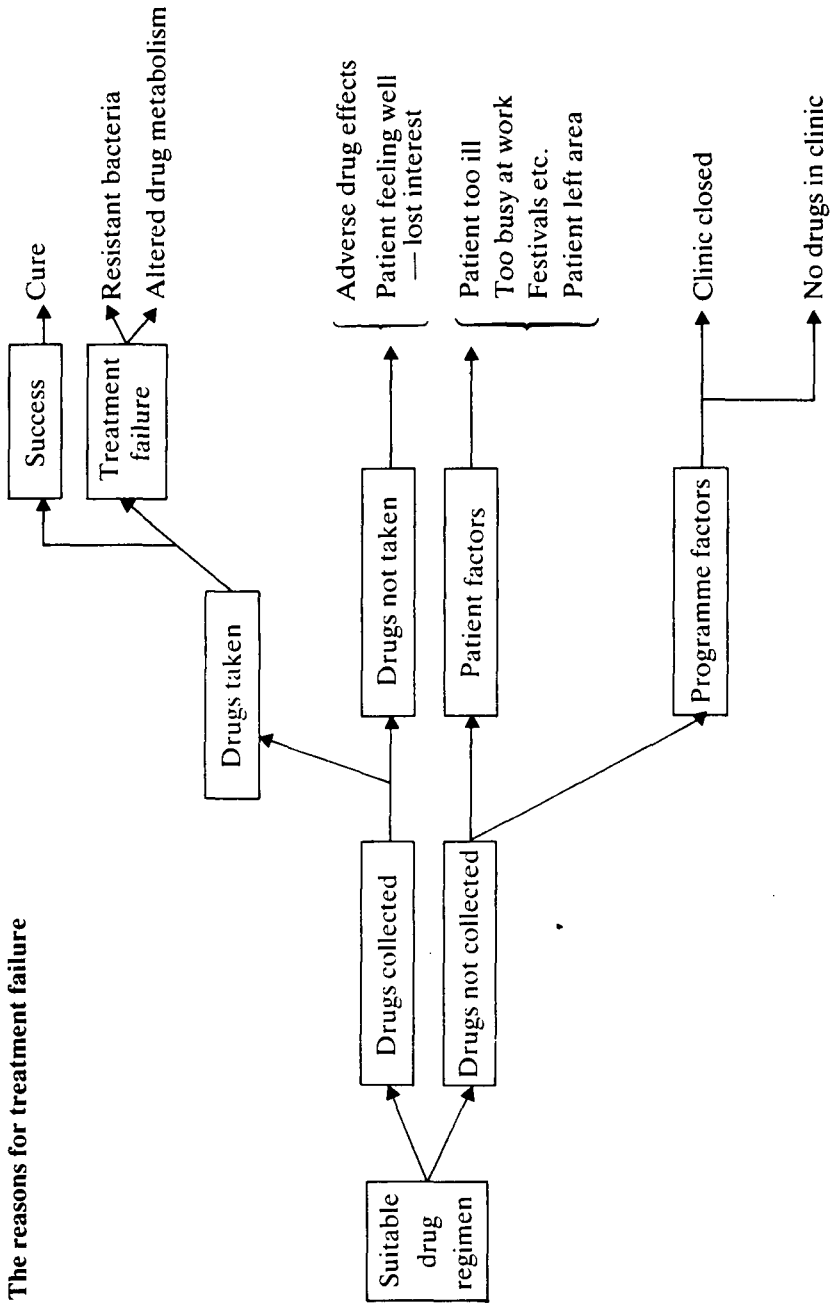
1. **Drug dependant** reasons exist if, despite correct drug intake, the patient does not improve. Either the drugs are not reaching the bacteria in an active form, because they are improperly absorbed or because of altered drug metabolism, or the bacteria are resistant to the drugs. Problems of drug absorption and metabolism are very rare, only the altered metabolism of isoniazid being significant in some areas.

Drug resistance is far less common than some programmes suggest. Indeed, many programmes blame low treatment success rates on drug resistance and introduce expensive new drugs that have potentially serious side-effects, when a more careful observation of the causes, using a systematic approach such as that in Fig. 11.1, has shown the reason to be poor drug compliance.

The possible effects of defaulting and poor drug compliance on bacterial resistance are discussed later in this chapter.

2. **Programme dependant.** Many programmes blame patients for defaulting and poor compliance when in fact the reason may lie with the organisation of the programme. Clinics may have insufficient drug supplies or only open infrequently. They may be far from the patients' villages, or village health workers may fail to distribute drugs. It is essential that such programme dependant reasons are considered before failure is blamed on the patient. Indeed, in the original planning of a programme it is essential to organise clinics and drug distribution *not* around the convenience of the health service, but in relation to how the patients can use the service with the minimum interruption in their lives and work.

The reasons for treatment failure



3. **Patient dependant.** The results of most programmes with an effective drug supply and organisation show that in most cases of treatment failure patients default from treatment of their own accord.

It is important to realise that default from *treatment* includes both failure to come to clinics to collect drugs and failure to consume the drugs that are collected. This latter is not a problem where treatment is fully supervised. Many programmes assume that if people collect drugs from the clinic they are not defaulting, but the limited studies done on drug compliance show that only 50–70% actually take their drugs correctly.

Information on patients failing to collect treatment can easily be obtained from clinic registers so that, at the end of each week or month, a check can be made on the number of patients in the intensive and maintenance phases who have not been to the clinic. There are usually two patterns in this type of defaulting: firstly those patients who attend regularly for some time and then stop attending completely, and secondly those who attend regularly for some time and then attend intermittently. In most programmes both types of defaulting occur; for example, in the Somali programme described in Chapter 2, 50% of the patients who started on treatment eventually defaulted completely, and 25% of the remainder continued to default intermittently.

Sudden defaulting

The two types of defaulting may have different effects on treatment outcome. It is easiest first to consider those patients who attend regularly for a certain period and then default completely. If such defaulting occurs in the first one or two months of any treatment regimen, while most of the bacterial population (A) (see Chapter 10, Fig. 10.1.) will have been reduced, populations (B) and (C) will have been little affected.

On cessation of treatment there will be a gradual increase in bacterial population (A), probably supplied by populations (B) and (C), and some months after cessation of treatment the patient will again be M+. Because all drugs were used correctly up to the point of default there is little chance of resistant bacteria developing, and when the patient again presents as M+ he should be sensitive to the drugs that were used previously.

If sudden default occurs later in the regimen, the effects will vary with the treatment used. Studies on regimens using rifampicin and pyrazinamide have shown that if treatment is stopped after three to four months, up to 50% of patients remain cured when studied twelve months following cessation of treatment.

There are few studies investigating the relapse rate of patients who default early in regimens based on streptomycin and isoniazid. One study has shown a 25% relapse rate at a twelve-months' follow-up in patients stopping treatment after six months of streptomycin and isoniazid, so it must be assumed that default at three or four months would lead to a very high relapse rate.

Intermittent defaulting

The effect of intermittent defaulting is far more difficult to determine, since it is so variable. In addition, in only partially supervised regimens patients who only attend intermittently are also likely to be those who do not take correctly the drugs they do collect, so there is likely to be a problem of poor drug compliance as well as collection defaulting. If patients fail to take drugs only two or three days at a time not more than twice a month, this is unlikely to have any effect on treatment outcome. However, if a situation arises of, say, two weeks' defaulting each two months, the result is likely to be a reduced bacterial population (A), with the patients probably not M+ after the first few months of treatment; but there would be little effect on populations (B) and (C), and therefore a persistent, chronic infection.

One of the most serious situations is where defaulting and poor compliance result in the patients only taking one drug instead of two or three. If an M+ patient obtains isoniazid tablets, and takes them but fails to attend for streptomycin injections, there is then a very real chance of bacteria resistant to isoniazid developing. It is this risk of the development of drug resistance that makes poorly supervised treatment, with totally uncertain drug compliance, possibly worse than no treatment at all.

This also applies to poor compliance alone in patients who regularly collect their drugs. There may be a sudden cessation of tablet-taking after an initial period of good compliance, or there may be 'chaotic' compliance after initial good compliance.

In any programme it is essential to monitor defaulting and poor compliance. Defaulting can easily be determined from the registers, and Chapter 12 shows how the programme should use this information. Compliance is less easy to assess. The only completely accurate method is to determine if the patient has taken the drugs. It is not practical to measure blood levels, but urine tests are available to determine if isoniazid has been taken regularly (see Appendix 6). Less accurate, but easier to do, are pill counts, where patients are visited on a known day of their drug cycle to determine if they have the appropriate number of drugs remaining (Appendix 6). In Pakistan, urine tests showed only 50% compliance of patients who were non-defaulters according to the registers, and in the Somali programme, pill counts showed compliance of 30% to 70%.

If defaulting is to be reduced and drug compliance improved, it is essential that the reasons for people's defaulting are understood. Table 2.2 shows the results of a survey of intermittent defaults in the Somali programme.

Surveys in other programmes have shown similar reasons for defaulting. Occasionally the reasons are that the patient is too ill to attend, or they have adverse reaction to the drugs (see Appendix 4). However, in most cases it is because the patient is feeling relatively well, and other activities — whether work or social events — divert him from treatment; therefore, to reduce defaulting the programme should concentrate on this non-technical area by improving individual and community participation (discussed in Chapter 5) and, if possible, attempting to improve the supervision of treatment. If this cannot be done at the clinic, it may be possible for village health workers to supervise tablet consumption.

An important question is the treatment regimen to be used for patients who return after defaulting: which drugs should be used must be considered, and how long treatment should continue.

If a patient has defaulted during the intensive phase, he should restart the full course of treatment, using the same regimen.

For a patient who has defaulted in the maintenance phase after previously regular treatment, if he has been absent for less than one month he should continue with the remainder of the maintenance phase. If he has defaulted for more than one month, or has been a persistent intermittent defaulter, it is essential to re-check his sputum; if it is negative, he should continue with the maintenance phase with a full maintenance duration from the time of restarting treatment.

If it is *positive*, two actions should be taken: (a) he should restart on the full treatment regimen as before, and (b) if facilities exist, a sample of the sputum should be sent to the regional or central laboratory to ensure drug resistance has not developed. If it has, a decision must be taken on an alternative regimen. Appendix 5 considers such alternative regimens; but it must be emphasised that the use of such drugs requires far closer supervision than the standard regimens.

The management of default and poor compliance have been discussed at length, because they are such an important part of treatment programmes. Chapter 12 discusses how the programme can be monitored to allow early detection of defaulting and poor compliance.

CHAPTER 12.

MONITORING AND EVALUATING THE PROGRAMME

The examples in Chapter 2 demonstrate that unless some monitoring and evaluation of a programme is undertaken, it is almost certain that overall programme effectiveness will be very low.

Appropriate monitoring and evaluation helps to identify how the programme may be improved. It is necessary to evaluate the effectiveness of:

1. Case-finding.
 2. Chemotherapy.
 3. BCG vaccination (see Chapter 8).
1. **Case-finding**

Chapter 3 shows how to estimate the probable number of new M+ cases per year from the average annual infection rate.

Efficiency of case-finding =

$$\frac{\text{Actual number of M+ cases found in last 12 months per 100,000 population} \times 100}{\text{Estimated incidence of M+ cases/100,000 population}}$$

For example, if the estimated incidence is 500/100,000 and, in a population of 50,000, 150 M+ cases have been found the efficiency of case-finding is

$$\frac{300 \times 100}{500} = 60\%$$

Even with effective case-finding programmes, not many would locate more than 70% of M+ cases.

If the efficiency is below 40%, it is important to find out why; the possible reasons include:

- some groups of people not included at all in case-finding, e.g. because too distant, etc.
- health workers not locating suspect cases in villages.
- microscopy facilities giving false results (this occurred in the programme example from Somalia where out-of-date stains caused positive sputums to be read as negative).

2. **Efficiency of chemotherapy**

Overall efficiency of chemotherapy = (efficiency of regimen if 100% compliance and no resistance) × (% of patients started on treatment who remain non-defaulting) × (compliance rate in the non-defaulters).

Most regimens assume an efficiency of 95% cure if there was no resistance and 100% drug compliance.

The percentage of patients remaining on treatment throughout can be determined from the registers.

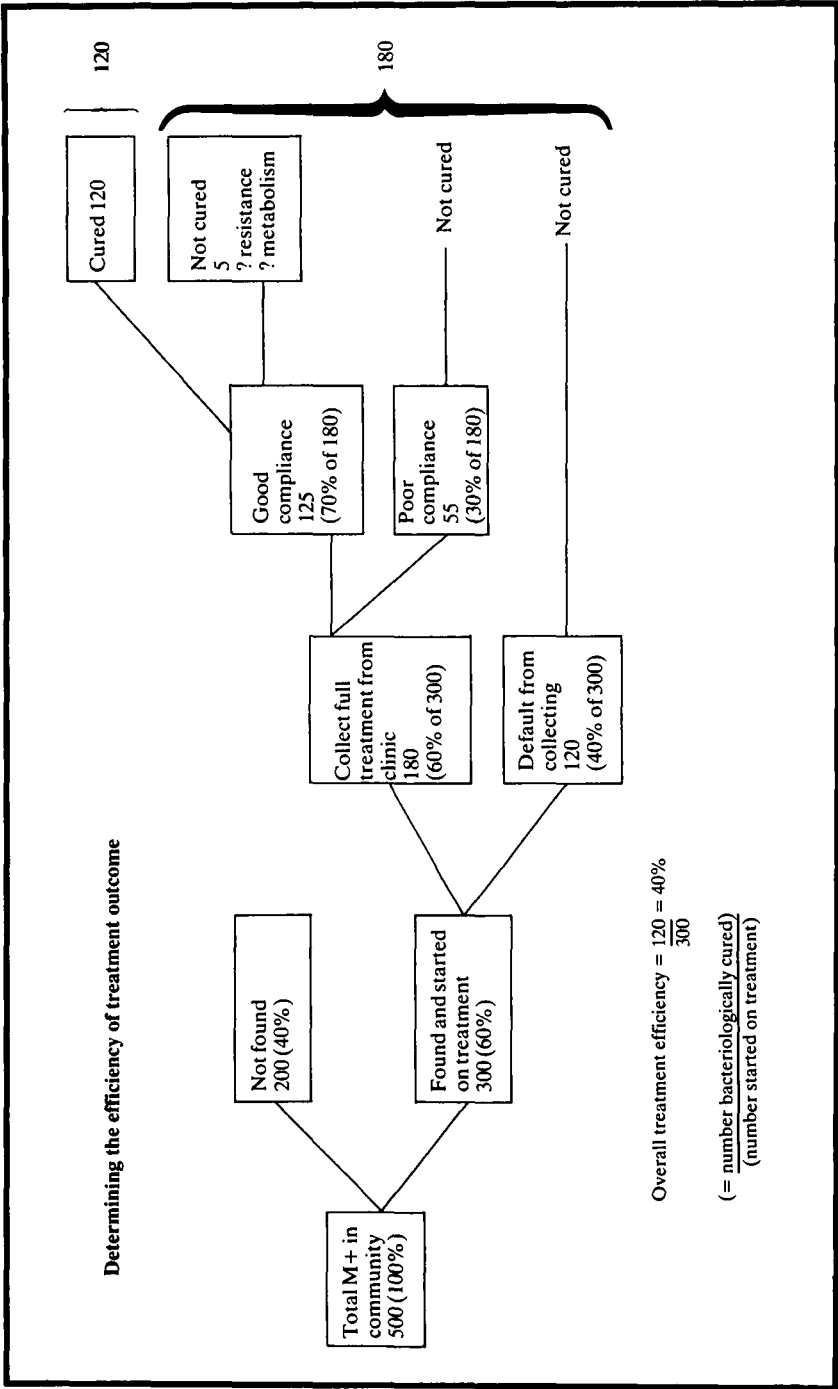
The drug compliance rate can be determined from pill counts or urine tests. Thus in a programme with theoretical treatment efficiency of 95%, attendance rate of 60% (i.e. 40% of patients defaulted) and 70% compliance rate, overall chemotherapy efficiency would be $95\% \times 60\% \times 70\% = 40\%$.

If only 60% of M+ cases had been included, then programme efficiency would be $40\% \times 60\% = 24\%$.

Fig. 12.1. (overleaf) shows how each of these components affect the programme. These figures emphasise how low programme efficiency is likely to be in most situations. Throughout the programme it is essential continually to monitor defaulting and compliance and to attempt to improve them. A basic aim of all programmes should be:

- to find 80% of all M+ cases.
- to have 80% attendance.
- to have 80% compliance.

Fig. 12.1.



CHAPTER 13.

TB PROGRAMMES FOR SPECIAL SITUATIONS

The basic structure of TB control programmes discussed in the manual has assumed a typical developing country rural environment, with a health centre serving a village population of, say, fifty villages.

The spectrum of communities may range from a densely populated slum where no patient's home is more than a few kilometres from a clinic, to a mobile nomadic community, who may pass near a health centre only once a year. These extremes of community structure require different approaches to the implementation of TB control, but the same principles of *case-finding*, *treatment* and *BCG vaccination* apply.

The following are examples of community structures where modified approaches to control may be required:

1. **Inaccessible, remote villages**

Areas such as Nepal create a particular problem for TB control. People live in remote villages with few roads, and there is probably a high level of TB transmission in cold, crowded dwellings. Health care must be taken *to* the villages by mobile health workers, who may visit clinics at monthly intervals.

2. **Nomadic communities**

Chapter 2 outlines one programme that was successful in treating M+ cases by having a permanent camp for the nomads and using short-course chemotherapy. There may be many situations where such static *treatment* programmes would not be acceptable and, in addition, case-finding and BCG vaccinations would have to be taken into consideration.

The use of mobile health workers rather than static treatment services is an alternative that is successful in some locations.

BCG vaccination would be done more easily on a mass scale, particularly because of the difficulty of maintaining a cold-chain to many small, remote nomadic groups. If there are seasonal locations where large numbers congregate — such as watering places or markets — these may be places where BCG vaccination can be carried out.

3. **Refugees**

When refugees are in virtually permanent camps such as those in Somalia described in Chapter 2, TB control programmes can follow a standard pattern. A major problem exists, however, when refugees may be in camps for periods of less than six months, and subsequently move to areas where they may not be accessible to effective health services. If camps are crowded and scope for transmission is high, it may be that chemotherapy should be started, in spite of the fact that the full course may not be

collected. For the shorter duration of treatment, good compliance must be obtained. The object of such a programme is solely to render M+ cases sputum negative to stop transmission in the crowded camp, even though individual cure may not be achieved.

4. Migrant labour

This is an increasing problem as the rural poor move to the slum areas around large cities in search of work; the dilemma is similar to that presented by short-term refugees, since they live in crowded conditions with high transmission potential, but they may not stay for more than three or four months. However, if the villages to which they then return are known, it may be possible to co-ordinate continuing treatment.

5. Interruption of health services by war and insecurity

There are many areas of extensive conflict where civilian populations are not directly involved in hostilities but health services are unable to operate because of insecurity, supply problems etc. This has grave implications for TB control and can lead to a major increase in TB incidence, because case-finding and treatment facilities cease to exist. In the Somali camps, a significant number of patients previously treated for TB arrived solely to get continuing treatment, because such facilities were no longer available in the Ogaden region. The continuation of effective programmes in such areas needs a high degree of initiative and commitment.

CHAPTER 14

TB IN CHILDREN AND NON-PULMONARY TB IN ADULTS

1. TB in children

Chapter 3 has shown that children do not play an important role in the spread of TB. However, because TB in children can be a devastating disease, and because the child contacts of M+ patients located in the control programme are the most likely ones to suffer, a brief review of TB in children is important.

TB disease can affect almost every part of the body, from the skin to the brain, following the initial infection in the lung. Some forms in children are acute, and the child presents seriously ill and in a rapidly deteriorating condition. Other forms are chronic, and any child who presents with a long history of being lethargic, weight loss, being generally unwell, may be suspected of having TB, particularly if they are a contact of a known M+.

There are some excellent texts on TB in children, and this chapter will consider specifically only those types of TB that are very common and/or very serious.

a. Miliary TB

Miliary TB occurs when, following a primary infection, there is a rapid spread of bacteria through the blood stream and the development of TB lesions throughout the body. The child usually presents as unwell, pyrexial, showing recent weight loss, but with no localising signs. Prior to chemotherapy, miliary TB was invariably fatal. In the absence of X-ray facilities (a characteristic X-ray showing fine white flecks throughout the lung fields) the diagnosis should be suspected in any child with the above symptoms who is a contact of an M+ patient.

b. TB Meningitis (TBM)

With miliary TB, TBM is the most serious form of TB. Unless recognised and treated *early* it will be fatal, or lead to permanent disability. It should be suspected in any child — particularly if a known M+ contact — presenting generally unwell, lethargic, off food and irritable. While classical signs of neck stiffness etc. are mentioned as criteria of diagnosis, they are often not useful in infants.

Since early treatment is so important, it must be remembered that the patient is likely to be managed at a health post rather than a district hospital, and diagnosis and treatment must be instituted appropriately. In such situations, lumbar puncture and investigations of CSF may not be appropriate.

The principal *treatable* differential diagnosis will be TBM, other bacterial meningitis, and malaria. In the absence of any diagnostic facilities, in a severely ill child it may be best to initiate treatment for all three conditions simultaneously: (i) the local standard TB regimen, (ii) penicillin/ampicillin, (iii) chloroquine. If the illness is acute bacterial meningitis or malaria, improvement should be seen after four or five days. If so, all treatment can be stopped. If the child is still ill, TBM is more likely and the TB regimens should be continued. Such a therapeutic trial approach to treatment may not be approved by clinicians, but it is based on the reality of most primary health centres.

c. **TB of the spine**

While this is a less acute form of TB than miliary TB or TBM, the long-term physical handicap it can lead to makes it a form of TB of major concern. The child may present relatively early with pain over a localised area — usually over the lumbar or thoracic vertebrae — or when the disease has progressed considerably and a visible swelling caused by an abscess is seen in the affected area, or very late, when the spinal cord has been involved and the child presents with restricted limb movements.

Earlier treatments for TB of the spine involved prolonged bed rest and surgical intervention. Recent work has shown that with adequate chemotherapy, most cases — even with limb involvement — will improve and, unless there is evidence of sudden spinal cord compression, surgery need only be considered in those who do not begin to respond after several months of treatment.

d. **TB of the cervical lymph nodes**

TB infection of the cervical lymph nodes is included because it is relatively common. Lymph node involvement represents an extension of a primary focus, and so there is some debate on how actively it should be treated. Treatment will certainly reduce the node mass, but abscess formation — requiring local cleansing if no other suitable surgical facilities are available — is still likely to occur.

Two aspects of TB in childhood must be emphasised: firstly, that most studies show drug compliance to be worse in children than in adults, hence treatment supervision is very important; secondly, that the morbidity and mortality of TB in children, particularly the potentially fatal miliary TB and TBM, can be prevented by BCG.

2. **Non-pulmonary TB in adults**

Tuberculosis can affect many organs of the body, some of the more common being renal, bone, etc. Such patients will be diagnosed at a district hospital, and will require the same treatment as for PTB. As emphasised previously, such patients do not transmit the disease and they are not a priority in the control programme.

CHAPTER 15.

THE ROLE OF DEVELOPMENT PROGRAMMES IN REDUCING THE TB PROBLEM

In the industrialised countries, the major decrease in the incidence of TB occurred *before* the introduction of chemotherapy and was almost certainly related to the improving standards of living, with better nutrition and general health, better quality and less crowded housing, etc. While every effort must be given to effective case-finding, treatment, and BCG programmes, TB is likely to remain a major health problem as long as communities face poor housing, crowding and poor nutrition. One of the major concerns at present is that, as communities move from rural areas into crowded peri-urban areas, TB is likely to increase rather than decrease. There is little objective data at present to confirm this, but the findings in crowded refugee camps have shown a dramatic increase in TB incidence compared with the prevalence among the rural population whence the refugees came.

While little can be done in the short-term to reduce migration from rural to urban areas or to prevent the slum-like conditions that develop, it should be anticipated that TB is likely to become a major problem, and effective TB control programmes should be organised as a priority.

TB is a very useful indicator of 'development' as it is primarily a disease of poverty and overcrowding.

CHAPTER 16.

FUNDING TB CONTROL PROGRAMMES

Tuberculosis control is an added financial burden to the already overstretched health budgets of most developing countries. The expenses include the capital costs of clinics and laboratory services, the personnel costs from a regional level doctor to village health workers, and the cost of drugs. In most situations it is unlikely that the patients themselves can contribute individually, but some attempts have been made to create village health insurance schemes, where either each family contributes an amount to a scheme or a village co-operative project is created to provide for health and education.

While the capital and personnel costs are likely to be similar in different situations, it is difficult to make objective comparisons of drugs costs, but the following table gives relative prices:

Regimens	Cost of treatment for one patient (US Dollars)
1STH/TH (1)	14
1STH/S2H2 (2)	17
2SHRZ/RH (3)	161

- (1) 1 month streptomycin, thiacetazone, isoniazid, 11 months thiacetazone, isoniazid
- (2) 1 month streptomycin, thiacetazone, isoniazid, 11 months bi-weekly streptomycin, isoniazid
- (3) 2 months streptomycin, isoniazid, rifampicin, pyrazinamide, 4 months rifampicin, isoniazid

There may be many development agencies in a position to contribute to the funding of TB programmes, particularly at the district and village level. For such funding agencies it is essential that objective assessments of the TB problem are made, and a system instituted for monitoring and evaluating programme progress.

CHAPTER 17

TUBERCULOSIS AND AIDS (ACQUIRED IMMUNODEFICIENCY SYNDROME)

AIDS (Acquired Immunodeficiency Syndrome) was first recognised in 1981 and by August 1988 over 108,000 cases had been officially reported to WHO. Of these cases, nearly 80,000 were from 40 countries in the Americas, of which around 70,000 were from the USA; 13,000 were from Europe and over 14,000 from Africa. However, it should be remembered that notification systems vary from country to country and in some countries or regions there is almost certainly under-notification. In addition to patients with AIDS (many of whom have already died), WHO estimates that there are between 5 and 10 million people currently infected with HIV (Human Immunodeficiency Virus) and that by 1991 the number of cases of AIDS globally will exceed one million.

The subject of 'Interrelations of Tropical Disease and HIV Infection' was discussed at an international consultation in Kenya in December 1987 (see p.63). The report of the meeting and many others in the literature emphasise the profound effect of AIDS on the human immune system, and the consequent increased liability to infection with various mycobacteria. This is of particular importance for those countries where tuberculosis is still a major health problem.

There is some evidence of an increased risk of tuberculosis among HIV-positive individuals from the USA. Further evidence comes from several countries where infection with both organisms is prevalent. High rates of HIV infection among TB patients, which are from 3 to 20 times the rates found in the general population, have been reported from these countries. The following table summarises this information:

Fig. 17.1.

Prevalence of antibody to AIDS virus (HIV) among tuberculosis patients, 1985-87

CENTRAL AND EAST AFRICA

Burundi	(Bujumbura)	177/328	54.0%
Uganda	(National)	22/36	61.1%
	(Gulu)	14/31	45.0%
	(Kampala)	45/150	30.0%
Zaire	(Kinshasa)	43/159	27.0%

NORTH AMERICA

New York City		20/48	41.7%
Florida (Dade Co.)		22/71	31.0%
Seattle, Washington		4/22	18.2%

Source: Slutkin G, Liowski J and Mann J, "The effects of the AIDS epidemic on the TB problem and TB programmes", *Bulletin of IUATLD*, 63 (2), p. 21-25, June 1988.

In people infected with HIV there appears to be an increased rate of progression from asymptomatic to overt TB. As the number of 'active' cases increases, there is an increased risk of transmission to other people as well. Thus, the TB problem could become even more serious in countries which are already struggling with the existing TB control programmes.

TB programmes in developing countries will need to take HIV and AIDS into consideration, particularly in areas where both diseases have a high prevalence. It will be important to monitor changes in the incidence and severity of TB. Questions about the possible effects of HIV on the response to current therapy and to tuberculin skin tests need further research. Possible problems with BCG have been mentioned elsewhere (see Chapter 8, Section c on p. 28).

Appendix 1

Methods of tuberculin surveys

Tuberculin surveys can be used to estimate the prevalence of TB infection in the community, enabling some estimate of the likely number of M+ cases (as described in Chapter 3). The principle of tuberculin surveys is that a standard amount of a protein derived from the tubercle bacillus is injected intradermally: people who have had a previous exposure to TB, i.e. who have TB infection, will give a larger skin reaction than a person who has no TB infection.

For large surveys, the most simple technique of tuberculin-testing is the Heaf multiple puncture test.

There are two aspects of tuberculin surveys, and the first is to select an appropriate sample. For example, if we wished to investigate the tuberculin sensitivity of 10-year-old children, it may not be sufficient only to test children at a school, since those from poorer families may not attend the school and thus the sample would not be representative of the population of 10-year-olds.

The technique should be as follows:

a. **Equipment required:**

- Heaf multiple puncture apparatus
- tuberculin PPD 100,000 units/ml
- spirit for cleaning skin
- spirit lamp for flaming apparatus

b. **Method:**

- clean a portion of the front of the forearm in an area not crossed by veins;
- place a drop of tuberculin on the skin covering about 1cm;
- hold the skin taut and place the end plate of the Heaf gun firmly onto the skin;
- press the handle to release the needles;
- dip the needles of the gun in methylated spirit and flame before repeating the procedure in the next child.

The test is read after three days:

Negative: no reaction

Grade I: discrete palpable induration at three or more puncture sites

Grade II: indurated points join together to form a ring

Grade III: induration fills the central area

Grade IV: more extensive induration with blister formation

In simple terms Grades III and IV may be taken as positive, i.e. indicating TB infection. However, in many areas *false positives* may be given due to other non-specific infections. Because of this, tuberculin surveys should be fully discussed with the Ministry of Health to determine whether useful results can be obtained.

Appendix 2

Methods of sputum microscopy

This method is based on that recommended by the IUAT. This is only an outline, and workers using laboratories are recommended to obtain the IUAT 'Technical Guide for Sputum Examination for Tuberculosis by Direct Microscopy', or refer to the laboratory manuals listed in Appendix 7.

Equipment required (assuming no electricity or running water):

- standard light microscope with X100 oil immersion lens
- cartons for sputum collection
- microscope slides
- slide marker
- wire loops (for spreading sputum on slide)
- methylated spirit burner
- buckets
- racks to hold slides over buckets while staining
- forceps
- carbol fuchsin stain (Solution 1)
- Acid-Alcohol (methylated spirit 970ml: Hydrochloric acid 30ml per litre) litre) for decolourising (Solution 2)
- Methylene blue for counterstaining (Solution 3)

Method:

Handling of sputums is potentially very dangerous. Ideally an extractor fume cupboard should be available; as this is often not possible, each laboratory must ensure it has a system of safe handling to minimise the risk of infection to laboratory staff.

1. The sample is received from the patient, given a number, and the number and patient's name entered in the register.
2. A slide is given the appropriate number.
3. Flame the wire loop in the spirit burner, allow to cool, take a small portion of sputum from the container and spread as thinly as possible on the slide.
4. Re-flame the loop. Discard sputum container and lid into a rubbish bin containing strong disinfectant solution (e.g. 5% phenol). The containers must then be burnt.
5. Allow the slide to air-dry for 30 minutes.

6. Fix the slide by holding with forceps, smear uppermost, and passing three times through the spirit lamp flame. Allow the slide to cool.
7. Place the slide on the slide rack over the bucket or a special tray, with the smear uppermost.
8. Cover the slide surface with carbol fuschin stain.
9. Warm the slide by moving the spirit burner beneath it until vapour rises, but do not let the carbol fuschin boil. Leave the warm stain for five minutes.
10. Rinse the slide in a gentle stream of water.
11. Cover slide with Acid-Alcohol. Leave for three minutes. Rinse with water.
12. Cover slide with methylene blue. Leave for one minute. Rinse with water.
13. Allow the slide to air-dry.
14. When dry, examine the slide under the X100 oil immersion objective, for the presence of acid-fast bacilli.

It is useful to indicate the number of bacteria present using the following method:

No AFB	per 100 immersion fields	0
1-9 AFB	per 100 immersion fields	record actual figure
10-99 AFB	per 100 immersion fields	+
1-10 AFB	per field	++
More than 10 AFB	per field	+++

Further details of stain preparation, laboratory equipment, etc. are given in the reference in Appendix 7.

Appendix 3

Drug dosages

Although dosages of individual drugs are given, they must only be used in the appropriate combined regimens as described in Chapter 10.

Drug	Adult daily dose	Child 6–15 yrs. daily dose	Child under 6 years
Streptomycin	0.75g	0.5g	0.25g
Isoniazid	300mg	150mg	100mg
Thiacetazone	150mg	100mg	50mg
Rifampicin	450mg	300mg	15mg/kg
Pyrazinamide	1.5g	1g	*
Ethambutol	800mg	400mg	*
Capreomycin	1g	*	*
Cycloserine	250mg b.d.	*	*

* Best avoided — seek paediatric advice.

'Shelf-life' of anti-tuberculosis drugs

Using the term 'shelf-life' to mean the period between the day of manufacture and the date of expiry (which should be marked on all drugs by any reliable manufacturer), anti-tuberculosis drugs, if stored properly and protected from extremes of temperature and humidity, will last as follows — isoniazid, ethambutol and thiacetazone last for 5 years; streptomycin, rifampicin and pyrazinamide last for 3 years. If the above dates are known it is utterly pointless and hazardous to use drugs which are out of date. In fact the 'shelf-life' for all the main drugs is clearly quite long and should fall well within the period during which they are ordered and used in most programmes.

Appendix 4

Drug adverse effects

All anti-tuberculous drugs may give adverse side effects, some potentially serious. This is why anti-tuberculous drugs should *only* be available through TB programmes which are part of the health services, and only given to patients registered in the programme.

Some drugs have *absolute* contra-indications where they must not be used. These are:

Drug	Absolute contra-indication
Streptomycin	Pregnancy *
Isoniazid	Liver disease caused by other drugs
Thiacetazone	Jaundice
Rifampicin	Jaundice
Pyrazinamide	Jaundice
Ethambutol	Very young/very old patients
Capreomycin	Pregnancy
Cycloserine	Epilepsy, alcoholism

* Although only two drugs are absolutely contra-indicated in pregnancy, all drugs should be used with caution. However, it must be remembered that pregnancy may not be diagnosed until the second or third month, and little can be done to prevent drugs being used in this period.

Side effects of individual drugs. (NB The drugs should be stopped and medical advice sought if these effects occur)

Streptomycin

- Problems with hearing and balance
- Hypersensitivity reactions
- Renal impairment

Isoniazid

- Hypersensitivity
- Peripheral neuritis (treat with pyridoxine)

Thiacetazone

- Hypersensitivity
- Gastro-intestinal symptoms
- Jaundice

Rifampicin (NB In *normal* doses the urine will be red)

Gastro-intestinal symptoms

Influenza-like symptoms

Liver impairment and jaundice

Pyrazinamide

Nausea and vomiting

Liver impairment and jaundice

Ethambutol

Peripheral neuritis

Visual defects

Capreomycin

Hypersensitivity reactions

Liver and renal damage

Hearing loss

Cycloserine

Headaches

Dizziness

Drowsiness

Appendix 5

Drugs for resistant cases

Chapter 11 has emphasised that the principal reason for treatment failure is poor drug compliance and not drug resistance.

Many programmes put patients who are not responding to treatment onto 'second-line drugs' rather than attempting to improve compliance with the standard regimen. This is very bad practice, and leads to the indiscriminate use of drugs with severe side effects and may lead to real drug resistance.

The decision to start a patient on second line drugs must be taken by a doctor, and should be based on resistance proven by the government central laboratory. If more than 5% of patients require second line drugs, a thorough review of the programme is required.

One possible alternative regimen is the following;

Previous regimen: streptomycin, isoniazid, thiacetazone.

Second line: Rifampicin plus ethambutol.

Because of the potential serious side effects of further second line drugs their use beyond hospital inpatients can rarely be justified.

Appendix 6

Measuring drug compliance

Tablet-counting method

Some idea of compliance can be determined by health workers checking how many tablets patients have remaining a certain number of days after they have collected a weekly or monthly supply. While there are many sources of error, it is a valuable indicator.

Urine-testing method

A method is available for detecting the presence of isoniazid products in urine. Special chemicals are required but the method could be used by a survey team rather than as a routine process. Details of the method are available in the 'Journal of Clinical Pathology', Vol. 30, pp. 84–87.

For rifampicin, a simple method of checking ingestion is to collect a urine sample between 2 and 10 hours after a dose should have been taken to see if the drug has produced its characteristic orange/red colouration.

Appendix 7

Useful addresses and literature

a. Organisations

International Union Against Tuberculosis and Lung Disease (IUATLD).
3, Rue Georges Ville,
75116 Paris, France.

WHO Tuberculosis Unit,
World Health Organisation,
Geneva, Switzerland.

Medical Research Council (UK),
Tuberculosis Unit,
Brompton Hospital,
Fulham Road,
London SW3, UK.

Oxfam Health Unit,
274 Banbury Road,
Oxford OX2 7DZ, UK.

ECHO (Supplies drugs and equipment to charitable hospitals),
Ullswater Crescent,
Coulston,
Surrey CR3 2HR, UK.

UNICEF (Supplies BCG immunisation kit),
United Nations,
New York,
NY 10017, USA.

Also — contact National Tuberculosis Programme in your country.

b. Books

J. Crofton and A. Douglas, *Respiratory Diseases*, Blackwells, Oxford, 1981.

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