1. Prompt identification of persons with SARS, their movements and contacts;
2. Effective isolation of SARS patients in hospitals;
3. Appropriate protection of medical staff treating these patients;
4. Comprehensive identification and isolation of suspected SARS cases;
5. Simple hygienic measures such as hand-washing after touching patients, use of appropriate and well-fitted masks, and introduction of infection control measures;
6. Exit screening of international travellers;
7. Timely and accurate reporting and sharing of information with other authorities and/or governments.

References

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TUBERCULOSIS

Tuberculosis is a specific infectious disease caused by *M. tuberculosis*. The disease primarily affects lungs and causes pulmonary tuberculosis. It can also affect intestine, meninges, bones and joints, lymph glands, skin and other tissues of the body. The disease is usually chronic with varying clinical manifestations. The disease also affects animals like cattle; this is known as "bovine tuberculosis", which may sometimes be communicated to man. Pulmonary tuberculosis, the most important form of tuberculosis which affects man, will be considered here.

Problem statement

WORLD

Tuberculosis remains a worldwide public health problem despite the fact that the causative organism was discovered more than 100 years ago and highly effective drugs and vaccine are available making tuberculosis a preventable and curable disease. Technologically advanced countries have achieved spectacular results in the control of tuberculosis. This decline started long before the advent of BCG or chemotherapy and has been attributed to changes in the "non-specific" determinants of the disease such as improvements in the standard of living and the quality of life of the people coupled with the application of available technical knowledge and health resources.

It is estimated that about one-third of the current global population is infected asymptomatically with tuberculosis, of whom 5–10 per cent will develop clinical disease during their lifetime. Most new cases and deaths occur in developing countries where infection is often acquired in childhood. The annual risk of tuberculosis infection in high burden countries is estimated to be 0.5–2 per cent *(1)*. Patients with infectious pulmonary tuberculosis disease can infect 10–15 persons in a year.

Tuberculosis remains a major global health problem. The current global picture of TB shows continued progress but not fast enough. During the year 2013, an estimated 9 million people developed TB, which is equivalent to 126 cases per 100,000 population. Most of the cases occurred in Asia (56 per cent) and the African regions (29 per cent). Of these incident cases 1.1 million (13 per cent) were HIV positives, and 3.5 per cent of the new and 20.5 per cent of previously treated cases were of MDR-TB. It is estimated that about 1.5 million people died of TB, of these 360,000 were HIV positive and 210,000 MDR-TB cases.

About 60 per cent of TB cases and deaths occur among men, but burden of disease (3.3 million) among women is high. In 2013, an estimated 510,000 women died as a result of TB, more than one-third of whom were HIV positive. An estimated 550,000 (6 per cent of total cases) children under 15 years of age had TB of whom 80,000 died.

TB detection and treatment outcome : During 2013, of the estimated 9 million cases, only 6.1 million cases were reported to WHO. Of these 5.7 million were people newly diagnosed and 0.4 million were already on treatment. The notification rate was about 64 per cent. About 3 million missed cases were either not diagnosed or diagnosed but not reported.

In 2013, the treatment success rate continued to be high at 86 per cent among all new TB cases.

The South East Asia Region accounts for 39 per cent of the global burden of TB in terms of incidence and India alone accounts for 24 per cent of the world's TB cases. It is estimated that about 3.4 million new cases of TB continue to occur each year in this Region, most of them in India, Bangladesh, Indonesia, Myanmar and Thailand. 6.2 per cent of the cases with HIV known status (39 per cent of total SEAR cases) were HIV-positive. 89 per cent of HIV-positive TB cases were on co-trimoxazole preventive therapy and 61 per cent of these cases were put on antiretroviral therapy. Level of MDR-TB is still low in the Region (less than 2.2 per cent), however, this translates into nearly 90,000 estimated MDR-TB cases among all the notified TB cases in 2012 *(3)*. Each year, more than 2 million TB cases are registered for treatment with more than 85 per cent success rate of new sputum smear positive cases. TB mortality rate has decreased more than 40 per cent since 1990 *(3)*.

The actual burden of paediatric TB is not known due to diagnostic difficulties. It is assumed that about 10 per cent of total TB load is found in children. Globally, about 1 million cases of paediatric TB are estimated to occur every year, with more than 100,000 deaths *(4)*. Childhood deaths from TB are usually caused by meningitis or disseminated disease *(1)*. Though MDR-TB and XDR-TB is documented among paediatric age groups, there are no estimates of overall burden because of diagnostic difficulties and exclusion of children in most of the drug resistant surveys *(4)*.

In many developing countries, acquired drug resistance remains high, because national tuberculosis control programmes in these countries have not been able to achieve a high cure rate over a very long period of time, even after the introduction of short-course chemotherapy. Poverty, economic recession, malnutrition, overcrowding, indoor air pollution, tobacco, alcohol abuse and diabetes make populations more vulnerable to tuberculosis. Increase in human migration has rapidly mixed infected with uninfected communities. To make global situation worse, tuberculosis has formed a lethal combination with HIV.

DOTS remains central to the public health approach to tuberculosis control, which is now presented as *Stop TB Strategy*. To be classified as DOTS, a country must have officially accepted and adopted the strategy by 2004, and must have implemented the four technical components of DOTS in at least part of the country. DOTS coverage is defined as the percentage of the national population living

in areas where health services have adopted DOTS. "Areas" are the lowest administrative or management units in the country (township, district, counties, etc.). The target of DOTS programme is successful treatment or cure rate of 85 per cent of new smear positive cases, and detection of 70 per cent of such cases.

The advantages of DOTS are : (a) Accuracy of TB diagnosis is more than doubled; (b) Treatment success rate is upto 95 per cent; (c) Prevents the spread of the tuberculosis infection, thus reducing the incidence and prevalence of tuberculosis; (d) Improves quality of health care and removes stigma associated with TB; (e) Prevents failure of treatment and the emergence of MDR-TB by ensuring patient adherence and uninterrupted drug supply; (f) Helps alleviate poverty by saving lives, reducing duration of illness and preventing spread of infection; (g) Lends credibility to TB control efforts.

The WHO has set *International Standards for Tuberculosis Care*. These standards are intended to facilitate the effective engagement of all care-providers in delivering high-quality care for patients of all ages, including those with smear-positive, smear-negative, extrapulmonary tuberculosis, drug-resistant tuberculosis, and tuberculosis combined with HIV infection. The basic principles of care for people with, or suspected of having tuberculosis are the same worldwide. The standards are intended to be complementary to local and national tuberculosis control policies that are consistent with WHO recommendations. They are not intended to replace local guidelines. There are 6 standards for diagnosis, 9 standards for treatment and 2 standards for public health responsibilities. Please refer to WHO publication : Weekly Epidemiological Record, No. 5, dated 3rd Feb. 2006 for further details.

The WHO has launched global plan for *Stop TB Strategy* (2006-2015), with the objective of reducing incidence of tuberculosis. Please refer to page 200 for further details.

INDIA

India is the highest TB burden country in the world in terms of absolute number of incident cases that occur each year. It accounts for one-fourth of the estimated global incident TB cases in 2013.

As per WHO estimations, tuberculosis prevalence per lac population has reduced from 465 in year 1990 to 211 in 2013. In absolute numbers, prevalence has reduced from 40 lacs to 26 lacs annually. Incidence per lac population has reduced from 216 in year 1990 to 171 in 2013. Tuberculosis mortality has reduced from 38 per lac population in 1990 to 19 in 2013. In absolute numbers, mortality due to TB has reduced from 3.3 lacs to 2.4 lacs annually. Among the new TB cases, 5 per cent of patients were in paediatric age-group (0-14 years). HIV among estimated incident cases of TB was about 5 per cent. MDR-TB among notified new pulmonary TB patients was about 2.2 per cent, and among retreatment cases was about 15 per cent *(4)*.

The first nation-wide standardized tuberculin survey was carried out during the period 2000-2003. For the purpose of survey, country was stratified into 4 zones (north, west, south and east). An identical methodology of sampling was used across all zones to estimate ARTI (annual risk of TB infection), allowing for stratified analysis for children with and without BCG scar. The survey showed the national ARTI was about 1.5 per cent. The second survey (2009-2010) shows that the national ARTI is 1.1 per cent, but the sample size of survey 2 was substantially smaller *(5)*. The first survey showed that BCG scar did not influence ARTI interpretation *(5)*.

Table 1 shows the burden of tuberculosis in India (the estimated and reported rates etc.). The Indian scenario about DOTS programme has been discussed in detail in chapter 7.

TABLE 1

Burden of tuberculosis in India (2013)
(Population 1,252 million)

	Number (thousands)	Rate (per 100,000 population)
Estimates of TB burden 2013		
Mortality (excludes HIV + TB)	240 (150–350)	19 (12–28)
Mortality (HIV + TB only)	38 (31–44)	3 (2.5–3.5)
Prevalence (includes HIV + TB)	2,600 (1,800–3,700)	211 (143–294)
Incidence (includes HIV + TB)	2,100 (2,000–2,300)	171 (162–184)
Incidence (HIV + TB only)	120 (100–140)	9.7 (8.3–11)
Case detection, all forms (%)	58 (54–61)	
Estimates of MDR-TB burden 2013		
	New	Retreatment
% of TB cases with MDR-TB	2.2 (1.9–2.6)	15 (11–19)
MDR-TB cases among notified pulmonary TB cases	20,000 (17,000–24,000)	41,000 (30,000–52,000)
TB case notifications 2013		
	New	Relapse
Pulmonary, bacteriologically confirmed	621,762	102,660
Pulmonary, clinically diagnosed	292,926	
Extrapulmonary	226,557	
Total new and relapse	1,243,905	
Previously treated, excluding relapses	171,712	
Total cases notified	1,415,617	
Among 1,243,905 new and relapse cases: 64,726 (5%) cases aged under 15 years		
Reported cases of RR-/MDR-TB 2013		
		Total
Cases tested for RR-/MDR-TB		248,341
Laboratory-confirmed RR-/MDR-TB cases		35,385
Patients started on MDR-TB treatment		20,763
TB/HIV 2013		
	Number	(%)
TB patients with known HIV status	887,903	(63)
HIV-positive TB patients	44,027	(5)
HIV-positive TB patients on co-trimoxazole preventive therapy (CPT)	41,827	(95)
HIV-positive TB patients on antiretroviral therapy (ART)	38,754	(88)
HIV-positive people screened for TB	1,063,644	
Treatment success rate (%)		
New and relapse cases registered in 2012		88
Previously treated cases, excluding relapse, registered in 2012		74
HIV-positive TB cases, all types, registered in 2012		77
RR-/MDR-TB cases started on second-line treatment in 2011		50

Source : *(1)*

AGE DISTRIBUTION : In India tuberculosis is more prevalent in adults than in children. It affects adults in the most productive age group (15–54 years). More than 80 per cent of TB cases are in this age group, as shown in Table 2.

TABLE 2
Percentage of new smear positive cases in different age groups (2006)

Age group (Years)	No. of cases	Percentage
0–14	11,872	2.0
15–24	1,24,206	20.9
25–34	1,33,389	22.50
35–44	1,20,481	20.32
45–54	96,727	16.32
55–64	66,617	11.24
65 +	39,341	6.63

Source : *(6)*

THE ECONOMIC AND SOCIAL BURDEN OF DISEASE : Besides the disease burden, TB also causes an enormous socio-economic burden to India. TB primarily affects people in their most productive years of life. While two-thirds of the cases are male, TB takes disproportionately larger toll among young females, with more than 50 per cent of female cases occurring before the age of 34 years *(7)*.

Tuberculosis kills more women in reproductive age group than all causes of maternal mortality combined, and it may create more orphans than any other infectious disease. Nearly one-third of female infertility in India, is caused by tuberculosis. The indirect impact of tuberculosis on children is considerable, as nearly 3 lacs children of tuberculosis patients, either leave the school or take up employment to help support their families *(6)*. A patient of tuberculosis takes an average of three to four months to recuperate, losing that much income. The loss is disastrous for those struggling against poverty. They are most likely to be defaulters of treatment. The vast majority (more than 90 per cent) of the economic burden of TB in India is caused by the loss of life rather than morbidity.

In India, tuberculosis is mainly a disease of the poor. The majority of its victims are migrant labourers, slum dwellers, residents of backward areas and tribal pockets. Poor living conditions, malnutrition, shanty housing and overcrowding are the main reasons for the spread of the disease *(6)*.

HIV increases a person's susceptibility to tuberculosis infection, and tuberculosis is one of the earliest opportunistic disease to develop amongst persons infected with HIV. It increases morbidity and mortality in HIV infected persons. HIV is the most potent risk factor for progression of TB infection to disease.

Since death rate is declining and the disease is showing a decline in younger age groups, epidemiologists are beginning to think that perhaps we may have crossed the peak of the secular epidemic curve and are somewhere at the beginning of the declining limb.

Epidemiological indices *(2)*

Indices or parameters are needed to measure the tuberculosis problem in a community as well as for planning and evaluation of control measures. Indices are also required for international comparison. The following epidemiological indices are generally used in tuberculosis problem measurement and programme strategy :

1. **Incidence** is defined as the number of new and recurrent (relapse) episodes of TB (all forms) occurring in a given year. Recurrent episodes are defined as a new episode of TB in people who have had TB in the past and for whom there was bacteriological confirmation of cure and/or documentation that treatment was completed. Relapse cases are referred to as recurrent cases because the term is more useful when explaining the estimation of TB incidence. Recurrent cases may be true relapses or a new episode of TB caused by reinfection. In current case definitions, both relapse cases and patients who require a change in treatment are called 'retreatment cases'. However, people with a continuing episode of TB that requires a treatment change are prevalent cases, not incident cases.

2. **Prevalence** is defined as the number of TB cases (all forms) at a given point in time. It is the best available practical index to estimate the case load in a community. The age-specific prevalence of patients is considered the most relevant index.

3. **Mortality** from TB is defined as the number of deaths caused by TB in HIV-negative people, according to the latest revision of the International Classification of Diseases (ICD-10). TB deaths among HIV-positive people are classified as HIV deaths in ICD-10. For this reason, estimates of deaths from TB in HIV-positive people are presented separately from those in HIV-negative people.

4. The **case fatality rate** is the risk of death from TB among people with active TB disease.

5. The **case notification rate** refers to new and recurrent episodes of TB notified to WHO for a given year, expressed per 100,000 population. The case notification rate for new and recurrent TB is important in the estimation of TB incidence. In some countries, however, information on treatment history may be missing for some cases. When data on treatment history are not available, recurrent cases cannot be distinguished from cases whose treatment was changed, since both are registered and reported in the category "retreatment". Patients reported in the "unknown history" category are considered incident TB episodes (new or relapse). This is a change from previous years in view of past difficulties to estimate with NTPs the proportion of true new, or relapse TB episodes in this category of patients.

6. **Case detection rate** : The case detection rate is calculated as the number of notification of new and relapse cases in a year divided by the estimated incidence of such cases in the same year.

7. **Prevalence of drug-resistant cases** : It is the prevalence of patient excreting tubercle bacilli resistant to anti-tuberculosis drugs. This index is directly related to chemotherapy.

(a) *Prevalence of infection* : It is the percentage of individuals who show a positive reaction to the standard tuberculin test. When the test is done in defined age-groups, it yields age-specific prevalence which is a far superior indicator than the mere percentage of positive reactors in the total population *(8)*. Prevalence represents a cumulative experience of a population to recent and remote infection with Myco. tuberculosis. It may be mentioned that the interpretation of tuberculin test has become complicated in countries with a high coverage of BCG vaccination at birth, since most of the vaccinees become positive reactors to tuberculin test. This presents a problem in identifying true prevalence of infection. Further, cross-sensitivity to atypical mycobacteriae, where it occurred, has also caused the

prevalence to be over-estimated. Despite these limitations, tuberculin-testing is widely used for estimating the prevalence of tuberculous infection in a population.

(b) *Incidence of infection* : (Annual Infection Rate) : It is the percentage of population under study who will be newly infected by Mycobacterium tuberculosis among the non-infected of the preceding survey during the course of one year. It reflects the annual risk of being infected (or reinfected) in a given community. In other words, it expresses the attacking force of tuberculosis in a community *(9)*. In developing countries, every 1% of annual risk of infection is said to correspond to 50 new cases of smear-positive pulmonary tuberculosis, per year for 100,000 general population *(10)*. Also known as "tuberculin conversion" index, this parameter is considered one of the best indicators for evaluating the tuberculosis problem and its trend. The higher the rate, the greater the problem *(9, 11)*. It may be mentioned that a good treatment programme, lowers the risk of tuberculosis infection in the community.

Revised (2013) definitions of tuberculosis cases and treatment *(12)*

WHO has issued updated guidance on definitions of cases and treatment outcomes and associated reporting framework in March 2013. These updates were necessary to accomodate diagnosis using Xpert MTB/RIF and other WHO-endorsed molecular tests, as well as offering an opportunity to improve aspects of the existing (2006) framework, such as inclusion of more comprehensive reporting of TB cases among children. The updated definitions will be used from 2014 in global data collection *(2)*.

Presumptive case: Presumptive TB refers to a patient who presents with symptoms or signs suggestive of TB (previously known as a TB suspect).

A. CASE DEFINITIONS

a. *A bacteriologically confirmed TB case* is one from whom a biological specimen is positive by smear microscopy, culture or WRD (such as Xpert MTB/RIF). All such cases should be notified, regardless of whether TB treatment has started.

b. *A clinically diagnosed TB case* is one who does not fulfil the criteria for bacteriological confirmation but has been diagnosed with active TB by a clinician or other medical practitioner who has decided to give the patient a full course of TB treatment. This definition includes cases diagnosed on the basis of X-ray abnormalities or suggestive histology and extrapulmonary cases without laboratory confirmation. Clinically diagnosed cases subsequently found to be bacteriologically positive (before or after starting treatment) should be reclassified as bacteriologically confirmed.

Bacteriologically confirmed or clinically diagnosed cases of TB are also classified according to:

1. anatomical site of disease;
2. history of previous treatment;
3. drug resistance;
4. HIV status.

1. Classification based on anatomical site of disease

a. *Pulmonary tuberculosis (PTB)* refers to any bacteriologically confirmed or clinically diagnosed case of TB involving the lung parenchyma or the tracheobronchial tree. Miliary TB is classified as PTB because there are lesions in the lungs. Tuberculous intra-thoracic lymphadenopathy (mediastinal and/or hilar) or tuberculous pleural effusion, without radiographic abnormalities in the lungs, constitutes a case of extrapulmonary TB. A patient with both pulmonary and extrapulmonary TB should be classified as a case of PTB.

b. *Extrapulmonary tuberculosis (EPTB)* refers to any bacteriologically confirmed or clinically diagnosed case of TB involving organs other than the lungs, e.g. pleura, lymph nodes, abdomen, genitourinary tract, skin, joints and bones, meninges.

2. Classification based on history of previous TB treatment (patient registration group)

Classifications based on history of previous TB treatment are slightly different from those previously defined. They focus only on history of previous treatment and are independent of bacteriological confirmation or site of disease.

New patients: Patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month.

Previously treated patients: Patients who received 1 month or more of anti-TB drugs in the past. They are further classified by the outcome of their most recent course of treatment as follows:

a. *Relapse patients* have previously been treated for TB, were declared cured or treatment completed at the end of their most recent course of treatment, and are now diagnosed with a recurrent episode of TB (either a true relapse or a new episode of TB caused by reinfection).

b. *Treatment after failure patients* are those who have previously been treated for TB and whose treatment failed at the end of their most recent course of treatment.

c. *Treatment after loss to follow-up patients* have previously been treated for TB and were declared lost to follow-up at the end of their most recent course of treatment. (These were previously known as treatment after default patients.)

d. *Other previously treated patients* are those who have previously been treated for TB but whose outcome after their most recent course of treatment is unknown or undocumented.

e. *Patients with unknown previous TB treatment history* do not fit into any of the categories listed above. New and relapse cases of TB are incident TB cases.

3. Classification based on drug resistance

Cases are classified in categories based on drug susceptibility testing (DST) of clinical isolates confirmed to be M. tuberculosis:

a. *Monoresistance*: resistance to one first-line anti-TB drug only.

b. *Polydrug resistance*: resistance to more than one first-line anti-TB drug (other than both isoniazid and rifampicin).

c. *Multidrug resistance*: resistance to at least both isoniazid and rifampicin.

d. *Extensive drug resistance*: resistance to any fluoroquinolone and at least one of three second-line injectable drugs (capreomycin, kanamycin and amikacin), in addition to multidrug resistance.

e. *Rifampicin resistance:* resistance to rifampicin detected using phenotypic or genotypic methods, with or without resistance to other anti-TB drugs. It includes any resistance to rifampicin, whether monoresistance, multidrug resistance, polydrug resistance or extensive drug resistance.

These categories are not all mutually exclusive. When enumerating rifampicin-resistant TB (RR-TB), for instance, multidrug-resistant TB (MDR-TB) and extensively drug-resistant TB (XDR-TB) are also included. While it has been the practice until now to limit the definitions of monoresistance and polydrug resistance to first-line drugs only, future drug regimens may make it important to classify patients by their strain resistance patterns to fluoroquinolones, second-line injectable agents and any other anti-TB drug for which reliable DST becomes available.

4. Classification based on HIV status

a. *HIV-positive TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a positive result from HIV testing conducted at the time of TB diagnosis or other documented evidence of enrolment in HIV care, such as enrolment in the pre-ART register or in the ART register once ART has been started.

b. *HIV-negative TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has a negative result from HIV testing conducted at the time of TB diagnosis. Any HIV-negative TB patient subsequently found to be HIV-positive should be reclassified accordingly.

c. *HIV status unknown TB patient* refers to any bacteriologically confirmed or clinically diagnosed case of TB who has no result of HIV testing and no other documented evidence of enrolment in HIV care. If the patient's HIV status is subsequently determined, he or she should be reclassified accordingly.

B. TREATMENT OUTCOME DEFINITIONS

The new treatment outcome definitions make a clear distinction between two types of patients:

- patients treated for drug-susceptible TB;
- patients treated for drug-resistant TB using second-line treatment (defined as combination chemotherapy for drug-resistant tuberculosis which includes drugs other than those in Group 1 (see page 187).

The two groups are mutually exclusive. Any patient found to have drug-resistant TB and placed on second-line treatment is removed from the drug-suscepitble TB outcome cohort. This means that management of the standard TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment.

1. Treatment outcomes for TB patients (excluding patients treated for RR-TB or MDR-TB)

All bacteriologically confirmed and clinically diagnosed TB cases should be assigned an outcome from this list except those with RR-TB or MDR-TB, who are placed on a second-line drug regimen.

Outcome	Definition
Cured	A pulmonary TB patient with bacteriologically confirmed TB at the beginning of treatment who was smear or culture-negative in the last month of treatment and on at least one previous occasion.
Treatment completed	A TB patient who completed treatment without evidence of failure BUT with no record to show that sputum smear or culture results in the last month of treatment and on at least one previous occasion were negative, either because tests were not done or because results are unavailable.
Treatment failed	A TB patient whose sputum smear or culture is positive at month 5 or later during treatment.
Died	A TB patient who dies for any reason before starting or during the course of treatment.
Lost to follow-up	A TB patient who did not start treatment or whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A TB patient for whom no treatment outcome is assigned. This includes cases "transferred out" to another treatment unit as well as cases for whom the treatment outcome is unknown to the reporting unit.
Treatment success	The sum of cured and treatment completed.
Cohort	A group of patients in whom TB has been diagnosed, and who were registered for treatment during a specified time period (e.g. the cohort of new smear-positive cases registered in the calendar year 2011). This group forms the denominator for calculating treatment outcomes. The sum of the treatment outcomes, plus any case for which no outcome is recorded (eg still on treatment) should equal the number of cases registered *(2)*.

Patients found to have an RR-TB or MDR-TB strain at any point in time should be started on an adequate second-line drug regimen. These cases are excluded from the main TB cohort when calculating treatment outcomes and included only in the second-line TB treatment cohort analysis. If treatment with a second-line drug regimen is not possible, the patient is kept in the main TB cohort and assigned an outcome from above table.

2. Outcomes for RR-TB/MDR-TB/XDR-TB patients treated using second-line treatment

Outcome	Definition
Cured	Treatment completed as recommended by the national policy without evidence of failure AND three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment completed	Treatment completed as recommended by the national policy without evidence of failure BUT no record that three or more consecutive cultures taken at least 30 days apart are negative after the intensive phase.[a]
Treatment failed	Treatment terminated or need for permanent regimen change of at least two anti-TB drugs because of: - lack of conversion[b] by the end of the intensive phase,[a] or - bacteriological reversion[b] in the continuation phase after conversion[b] to negative, or - evidence of additional acquired resistance to fluoroquinolones or second-line injectable drugs, or - adverse drug reactions (ADRs).
Died	A patient who dies for any reason during the course of treatment.
Lost to follow-up	A patient whose treatment was interrupted for 2 consecutive months or more.
Not evaluated	A patient for whom no treatment outcome is assigned. (This includes cases "transferred out" to another treatment unit and whose treatment outcome is unknown)
Treatment success	The sum of cured and treatment completed

Cohort	A group of patients where RR-TB has been diagnosed (including MDR-TB and XDR-TB), and who were started on a full course of a second-line MDR-TB drug regimen during a specified time period (e.g. the cohort of MDR-TB cases registered in the calendar year 2010). This group forms the denominator for calculating treatment outcomes. With the revised definitions, any patient found to have drug-resistant TB and placed on second line treatment is removed from the drug-susceptible TB outcome cohort. This means that management of the basic management unit TB register and of the second-line TB treatment register needs to be coordinated to ensure proper accounting of the outcomes of treatment *(2)*

* For *Treatment failed*, lack of conversion by the end of the intensive phase implies that the patient does not convert within the maximum duration of intensive phase applied by the programme. If no maximum duration is defined, an 8-month cut-off is proposed. For regimens without a clear distinction between intensive and continuation phases, a cut-off 8 months after the start of treatment is suggested to determine when the criteria for Cured, Treatment completed and Treatment failed start to apply.

* The terms "conversion" and "reversion" of culture as used here are defined as follows:

Conversion (to negative) : culture is considered to have converted to negative when two consecutive cultures, taken at least 30 days apart, are found to be negative. In such a case, the specimen collection date of the first negative culture is used as the date of conversion.

Reversion (to positive) : culture is considered to have reverted to positive when, after an initial conversion, two consecutive cultures, taken at least 30 days apart, are found to be positive. For the purpose of defining treatment failed, reversion is considered only when it occurs in the continuation phase.

The revised definitions should be applied by the NTP at a set changeover date (e.g. 1 January): all cases on treatment on that date should be assigned outcomes according to the revised definitions. This means that patients started on treatment in the previous year may be assigned outcomes according to two different definitions of cured or treatment failed, depending on whether they completed treatment before or after the changeover date. This may be the most practical option for the transition period, given that retrospective reassignment of outcomes is not always feasible.

NATURAL HISTORY OF TUBERCULOSIS

Agent factors

(a) AGENT : *M. tuberculosis* is a facultative intracellular parasite, i.e., it is readily ingested by phagocytes and is resistant to intracellular killing *(13)*. Of importance to man are the human and bovine strains. The human strain is responsible for the vast majority of cases. The bovine strain affects mainly cattle and other animals. Regarding virulence, the Indian tubercle bacillus is said to be less virulent than the European bacillus. In recent years, a number of "atypical" mycobacteria have been isolated from man *(14)*. These have been classified into four groups – (i) photochromogens (e.g., *M. Kansasii*); (ii) scotochromogens (e.g., *M. scrofulaceum*); (iii) non-photochromogens (e.g., *M. intercellulare*)) and, (iv) rapid growers (e.g., *M. fortuitum*). All these are mainly saprophytic. Diseases attributed to them have resembled pulmonary tuberculosis and chronic cervical lymphadenitis.

(b) SOURCE OF INFECTION : There are two sources of infection – human and bovine. (i) *Human source* : The most common source of infection is the human case whose sputum is positive for tubercle bacilli and who has either received no treatment or has not been treated fully. An estimated annual average of 10–15 persons contract the infection from one case of infectious pulmonary TB. Such sources can discharge the bacilli in their sputum for years. The tubercle bacilli in a human case are usually a mixed group – some multiply very rapidly and some slowly. The more rapidly a bacillary strain multiplies the more susceptible it is to the bactericidal action of chemotherapeutic drugs. The slow multipliers are the source of persister or dormant bacilli; they can remain alive for years without causing harm to the host, but when conditions are favourable they may start multiplying again and cause active disease. That is, they are the seeds of a future relapse *(15)*. (ii) *Bovine source* : The bovine source of infection is usually infected milk. There is no definite evidence that bovine tuberculosis is a problem in this country because of the practice of boiling milk before consumption.

(c) COMMUNICABILITY : Patients are infective as long as they remain untreated. Effective anti-microbial treatment reduces infectivity by 90 per cent within 48 hours *(16)*.

Host factors

(a) AGE : Tuberculosis affects all ages. Developing countries show a sharp rise in infection rates from childhood to adolescence. In India, from an average of 2 per cent in the "0–14 years age group", the infection rate climbs to about 20 per cent at age 15–24 years age group (Table 2). In the developed countries, the disease is now more common in the elderly. (b) SEX : More prevalent in males than in females. (c) HEREDITY : Tuberculosis is not a hereditary disease. However, twin studies *(17)* indicate that inherited susceptibility is an important risk factor. (d) NUTRITION : Malnutrition is widely believed to predispose to tuberculosis. As malnutrition is widely prevalent in developing world, it will continue to affect the development of active disease, out- come of treatment and spread of the disease. (e) IMMUNITY : Man has no inherited immunity against tuberculosis. It is acquired as a result of natural infection or BCG vaccination. Past infection with atypical mycobacteria is also credited with certain amount of naturally acquired immunity. It is now known that both delayed hypersensitivity and acquired resistance to tuberculosis are cell-mediated responses. In most cases, the cellular immunity proves adequate to limit further multiplication and spread of bacilli.

Social factors

Tuberculosis is a social disease with medical aspects. It has also been described as a barometer of social welfare. The social factors include many non-medical factors such as poor quality of life, poor housing, and overcrowding, population explosion, undernutrition, smoking, alcohol abuse, lack of education, large families, early marriages, lack of awareness of causes of illness, etc. All these factors are interrelated and contribute to the occurrence and spread of tuberculosis. In fact, tuberculosis began to decline in the western world long before the advent of chemotherapeutic drugs. This has been attributed to improvements in the quality of life.

Mode of transmission

Tuberculosis is transmitted mainly by droplet infection and droplet nuclei generated by sputum-positive patients with pulmonary tuberculosis. To transmit infection, the particles must be fresh enough to carry a viable organism. Coughing generates the largest number of droplets of all sizes. The frequency and vigour of cough and the ventilation of the environment influence transmission of infection.

Tuberculosis is not transmitted by fomites, such as dishes and other articles used by the patients. Sterilization of these articles is therefore of little or no value. Patients with extrapulmonary tuberculosis or smear-negative tuberculosis constitute a minimal hazard for transmission of infection

Incubation period

The time from receipt of infection to the development of a positive tuberculin test ranges from 3 to 6 weeks, and thereafter, the development of disease depends upon the closeness of contact, extent of the disease and sputum positivity of the source case (dose of infection) and host-parasite relationship. Thus the incubation period may be weeks, months or years.

THE CONTROL OF TUBERCULOSIS

Tuberculosis control means reduction in the prevalence and incidence of disease in the community.

Since tuberculosis is an infectious disease, the basic principles of prevention and control are the same as for any other infectious disease. The control measures consist of a **curative** component – namely case finding and treatment; and a **preventive** component – namely BCG vaccination. These are the two fundamental components of a national tuberculosis programme. The most powerful weapon, however, is the combination of case-finding and treatment.

Case-finding

a. THE CASE

The first step in a tuberculosis control programme is early detection of sputum-positive cases. This should be an intensive, on-going programme.

b. TARGET GROUP

An overwhelming majority of patients of pulmonary tuberculosis have one or more of the symptoms referable to chest, such as persistent cough and fever, and many of them (over 60 per cent) seek medical advice on their own initiative. The chest symptoms often develop early, that is before the disease has gone on to an advanced stage. This is the most fertile group for case-finding.

c. CASE-FINDING TOOLS

(i) **Sputum examination :** Sputum smear examination by direct microscopy is now considered the method of choice. The reliability, cheapness and ease of direct microscopic examination has made it number one case-finding method all over the world. It enables us to discover the epidemiologically most important cases of pulmonary tuberculosis, i.e., those excreting tubercle bacilli in their sputum. This is the group which contributes most of the new cases to the "pool of infection" every year.

Collection of sputum samples

A pulmonary tuberculosis suspect should submit two sputum samples for microscopy. The chances of finding TB bacilli are greater with two samples than with one sample. Secretions build up in the airways overnight. So an early morning sputum sample is more likely to contain TB bacilli than one taken later in the day. It may be difficult for an out-patient to provide two early morning sputum samples. Therefore in practice an out-patient usually provides sputum samples as follows:

day 1	sample 1	Patient provides an "on-the-spot" sample under supervision when presenting to the health facility. Give the patient a sputum container to take home for an early morning sample the following morning.
day 2	sample 2	Patient brings an early morning sample.

If the patient is coming from a long distance or there is likelihood that the patient may default to give a second sample, 2 spot specimens are collected with a gap of one hour *(18)*.

Ziehl-Neelsen acid-fast stain

This simple stain detects acid fast bacilli. The procedure is as follows:

1. Fix the smear on the slide by passing the slide with the smear up about three times slowly through a flame. It can also be done by covering the smear with alcohol and letting this evaporate.
2. Cover with carbol fuchsin, steam gently for 5 minutes over direct flame (or for 20 minutes over a water bath). Do not permit slide to boil or dry out.
3. Wash with deionized water.
4. Decolourize in 3.0 per cent acid-alcohol (95 per cent ethanol and 3.0 per cent hydrochloric acid) until only a faint pink colour remains.
5. Wash with water.
6. Counter stain for 1 minute with Loeffler's methylene blue.
7. Wash with deionized water and let it dry.

Slide reporting *(19)*

The number of bacilli seen in a smear reflects disease severity and patient infectivity. Therefore, it is important to record the number of bacilli seen on each smear. The table below shows the standard method of reporting using 1000 X magnification.

Number of bacilli			Result reported
No	AFB	per 100 oil immersion fields	0
1-9	AFB	per 100 oil immersion fields	scanty (or number AFB seen)
10-99	AFB	per 100 oil immersion fields	+ (1+)
1-10	AFB	per oil immersion field	++ (2+)
> 10	AFB	per oil immersion field	+++ (3+)

Laboratory technicians should examine both the sputum samples from each TB suspect. They must record the result of each sputum sample with the laboratory reference number in the laboratory register and on the sputum request form. Results as indicated above are made available to the clinician who can then categorize the patient. It is advised that the smear examined by one microscopist should not exceed 20 per day as visual fatigue leads to a deterioration of reading quality *(20)*.

One positive specimen out of the two is enough to declare a patient as smear positive TB. Smear positive TB is further classified as new or retreatment cases, based on their previous treatment history, and appropriate therapy is prescribed. Patients in whom both specimens are smear negative should be prescribed symptomatic treatment and broad-spectrum antibiotic for 10–14 days. In such cases

antibiotics such as fluoroquinolones (ciprofloxacin, ofloxacin, etc.), rifampicin or streptomycin, which are active against TB, should not be used. Most patients are likely to improve with antibiotics if they are not suffering from TB. If the symptoms persist after a course of broad-spectrum antibiotic, repeat sputum smear examination (2 samples) must be done for such patients. If one or more smears are positive, the patient is diagnosed as having smear-positive pulmonary TB. If none of the repeat sputum specimen is positive, a chest X-ray is taken, and if findings of the X-ray are consistent with pulmonary TB, the patient is diagnosed as a case of sputum-negative pulmonary TB *(7)*.

Sputum smear microscopy for tubercle bacilli is positive when there are at least 10,000 organisms present per ml of sputum. The sputum smear positivity rate in TB/HIV patient depends on the degree of immunocompromise. If the degree of immunocompromise is mild, the likelihood of positive sputum smear is similar to HIV negative patient. If immunocompromise is severe, the likelihood of positive sputum smear is decreased because of decreased inflammation in lungs *(19)*.

False-positive results of sputum smear microscopy

A false-positive result means that the sputum smear result is positive even though the patient does not really have sputum smear-positive PTB. This may arise because of the following: red stain retained by scratches on the slide, accidental transfer of AFBs from a positive slide to a negative one; contamination of the slide or smear by environmental mycobacteria; presence of various particles that are acid-fast (e.g. food particles, precipitates, other microorganisms).

False-negative results of sputum smear microscopy

A false-negative result means that the sputum smear result is negative even though the patient really does have sputum smear-positive PTB. This may arise because of problems in collecting (patient provides inadequate sample, inappropriate sputum container used or sputum stored too long before smear microscopy), processing (faulty sampling of sputum for smear or faulty smear preparation and staining), or interpreting sputum smears (inadequate time spent examining smear or inadequate attention to smear examination), or because of administrative errors (misidentification of patient, incorrect labelling of sample or mistakes in documentation).

Fluorescence microscopy

Fluorescence microscopy is mainly used in industralized countries. It is performed with auramine stain. The advantage of FA microscopy is from the speed of examination. The field of view is 5–10 times bigger. Scanning of one length of smear will require only 1–2 minutes.

Light-emitting diode fluorescence microscopy (LEDs)

LEDs provide a much less expensive light source for fluorescence microscopy. In a recent WHO evaluation, the diagnostic accuracy of LED microscopy was found to be comparable to that of conventional fluorescence microscopy and superior to that of conventional Ziehl-Neelsen microscopy. It is therefore recommended that LED microscopy be phased in as an alternative to conventional Z-N light microscopy in both high and low-volume laboratories *(20)*.

Radiography

Chest X-rays are useful for the diagnosis of smear negative pulmonary TB and TB in children. It is not routinely indicated in smear-postive cases. X-rays are valuable tools for the diagnosis of pleural and pericardial effusion, especially in early stages of the disease when clinical signs are minimal. It is essential in the diagnosis of miliary TB. The other indications are frequent or severe haemoptysis to exclude bronchiectasis or aspergilloma and in patients needing specific treatment for pneumothorax.

Sputum culture *(21)*

Isolation of mycobacteria from clinical samples by culture still represents the corner-stone on which definitive diagnosis of tuberculosis and other mycobacterioses relies. At present, mycobacterial culture can be performed on conventional egg based solid medium such as Lowenstein-Jensen medium and agar based ones, such as Middle brook 7H10 or 7H11 and liquid media such as Kirchner's or Middle brook 7H9 broth. The major constraint of culturing mycobacteria in conventional media is its slow growth which necessitates a mean incubation period of at least 4 weeks. The drug susceptibility tests to anti-tuberculosis drugs require additional 4 weeks. Most of the laboratories in the developing world rely on solid media for culture of mycobacteria. The choice and preparation of specimens by various pretreatment procedures has tremendous influence on the sensitivity of results. The positively of culture largely dependens on the technique of decontamination used by various laboratories, viz the chemicals used for decontamination and the centrifugation method adopted for processing specimens for culturing mycobacteria by inoculating into solid or liquid media.

Although a combination of solid and liquid media is currently the gold standard for the primary isolation of mycobacteria, a few modern, rapid methods are also available. These include micro colony detection on solid media (including the rapid slide culture technique), septi-check AFB method, microscopic observation of in-broth culture (MODS), the BACTEC 460 radiometric system, BACTEC MGIT 960 system (Becton Dickinson), MB/BaCT system (Organon Teknika), and the ESP II culture system.

Micro colony detection on solid media *(21)*

In this method, plates poured with thin layer of middle brook 7H11 agar medium are incubated and examined microscopically on alternate days for the first 2 days and less frequently thereafter. In less than 7 days, micro colonies of *M. tuberculosis* can be detected. Though this method is less expensive and requires about half the time needed for conventional culture, the recovery of mycobacteria is less efficient and it is labour intensive. Since *M. tuberculosis* grows more rapidly in liquid medium forming strings and tangles, which can be observed under the inverted light microscope with 40x magnification, this method is a better alternative for culturing tubercle bacilli.

Radiometric BACTEC 460 TB method *(21)*

This technique is specific for mycobacterial growth, wherein C labeled palmitic acid in 7H12 medium is used. This system detects the presence of mycobacteria based on

their metabolism rather than visible growth. When the C labeled substrate present in the medium is metabolized, CO_2 is produced and measured by the BACTEC system instrument and reported in terms of growth index (GI) value. The BACTEC system is also useful in the identification of *M. tuberculosis* using specific inhibitor, para-nitro-a-acetylamino-b-hydroxypro-piophenone. Using the same system, drug susceptibility tests can also be performed for all the anti-tuberculosis drugs when sufficient GI is observed. Mycobacteria in clinical samples can be detected in half the time compared to conventional culture methods.

MGIT 960 mycobacteria detection system *(21)*

It is an automated system for the growth and detection of mycobacteria with a capacity to incubate and continuously monitor 960 mycobacteria growth indicator tube (MGIT) every 60 minutes for increase in fluorescence. Growth detection is based on the AFB metabolic O_2 utilization and subsequent intensification of an O_2 quenched fluorescent dye contained in a tube of modified MGIT. A series of algorithms are used to determine presumptive positivity and alert the operator to the presence and location of positive tubes.

MB/BaCT system

This is a non-radiometric continuous monitoring system with a computerized database management. The system is based on colorimetric detection of CO_2.

Detection and identification of mycobacteria directly from clinical samples

Both genotypic (molecular) and phenotypic methods are available with newer modifications for the diagnosis of tuberculosis as an alternative for smear microscopy.

Genotypic methods *(21)*

Polymerase chain reaction

The PCR allows sequences of DNA present in only a few copies of mycobacteria to be amplified *in vitro* such that the amount of amplified DNA can be visualized and identified. If appropriate sequences specific for *M. tuberculosis* are selected, 10–1000 organisms can be readily identified. The PCR methodology is rapid; results are available within a day of DNA extraction from the sample. A number of target genes of mycobacterial DNA have been evaluated for diagnosis by PCR and various other genotypic methods. The most common target used in the PCR is IS6110.

A variety of PCR methods have been described in the search for a sensitive and reliable screening test for tuberculosis in clinical specimens. Species-specific and genus-specific PCR methods are being used with various targets and modifications of PCR. The following are some of the methods used for identification of *M. tuberculosis* and non-tuberculous mycobacteria (NTM).

Transcription mediated amplification (TMA) and nucleic acid amplification (NAA)

This approach identifies the presence of genetic information unique to *M. tuberculosis* complex directly from pre-processed clinical specimens. The NAA technique uses chemical, rather than biological amplification to produce nucleic acid, so that within a few hours these tests distinguish between *M. tuberculosis* complex and NTM in an AFB-positive specimen.

Cartridge based nucleic acid amplification test

The second generation NAAT-based TB diagnostics offer the prospect of very high sensitivity, approaching that of liquid culture – the current gold standard for TB diagnosis. In addition, some versions of NAAT also provide information on drug susceptibility to rifampicin, which is a surrogate marker in most countries for identification of patients who are most likely to have MDR-TB, thus allowing the early initiation of standardized 2nd line TB treatment *(4)*.

GeneXpert MTB/RIF

The Xpert MTB/RIF detects DNA sequences specific for Mycobacterium tuberculosis and rifampicin resistance by polymerase chain reaction. It is based on the Cepheid GeneXpert system, a platform for rapid and simple-to-use nucleic acid amplification tests (NAAT). The Xpert MTB/RIF purifies and concentrates *Mycobacterium tuberculosis bacilli* from sputum samples, isolates genomic material from the captured bacteria by sonication and subsequently amplifies the genomic DNA by PCR. The process identifies all the clinically relevant rifampicin resistance inducing mutations in the RNA polymerase beta (rpoB) gene in the *mycobacterium tuberculosis* genome in a real time format using fluorescent probes called molecular beacons. Results are obtained from unprocessed sputum samples in 90 minutes, with minimal biohazard and very little technical training required to operate.

Phenotypic method *(21)*

FAST Plaque TB

This is an original phage based test, which uses the mycobacteriophage to detect the presence of *M. tuberculosis* directly from sputum specimens. It is a rapid, manual test, easy to perform and has an overall higher sensitivity when compared with sputum smear microscopy, in newly diagnosed smear positive TB.

Serological diagnosis of tuberculosis

Most of the serological tests have low turn around time, high negative predictive value and are useful as screening tests. The limitation of these tests is low sensitivity in smear negative patients, HIV positive cases, and in disease endemic countries with a high infection rate. The tests are also expensive, require trained personnel and often have difficulty in distinguishing between *M. tuberculosis* and NTM *(21)*.

TB STAT-PAK

Immunochromatographic test based on the detection of antibodies has been evolved with a capability to differentiate between active or dormant TB infection in whole blood, plasma or serum. Its value in disease endemic countries such as India is yet to be ascertained *(21)*.

Insta test TB *(21)*

It is a rapid *in vitro* assay for the detection of antibody in active TB disease using whole blood or serum. The test employs an antibody binding protein conjugated to a colloidal gold particle and a unique combination of TB antigens immobilized on the membrane.

Some of the other commercially available antibody tests for pulmonary TB are listed below.

Name of the assays	Antigen used
MycoDot (Dot-blot)	Lipo arabino mannan (LAM)
Detect- TB (ELISA)	Recombinant protein peptide
Pathozyme Myco (ELISA)	38 kDa (recombinant Ag) and LAM
Pathozyme TB (ELISA)	38 kDA (recombinant)
Antigen A60 (ELISA)	Antigen-60
ICT diagnostics (membrane based)	38 kDa (recombinant)

Sourcde : *(21)*

TUBERCULIN TEST

The tuberculin test was discovered by Von Pirquet in 1907. A positive reaction to the test is generally accepted as evidence of past or present infection by *M. tuberculosis*. The tuberculin test is the only means of estimating the prevalence of infection in a population.

Tuberculin : Only two tuberculins have been accepted as standard tuberculin by WHO, i.e., purified protein derivative-S (PPD-S) and PPD-RT 23. PPD is standardized in terms of its biological reactivity as tuberculin units (UT). A standard 5 tuberculin unit (5 TU) dose of PPD-S is defined as delayed skin activity contained in a 0.1 µg/0.1 ml dose of PPD-S. 1 TU of PPD-RT 23 is equivalent to 5 TU of PPD-S. In India PPD-RT 23 with Tween 80 is used. Tween 80 is a detergent added to tuberculin to prevent their adsorption on glass or plastic surface. Use of tuberculin strength of 1 TU is recommended for standard Mantoux test in India.

MANTOUX TEST : The Mantoux test is carried out by injecting 1 TU of PPD in 0.1 ml intradermally on the flexor surface of the left forearm, mid-way between elbow and wrist. The injection should be made with a tuberculin syringe, with the needle bevel facing upward. When placed correctly, injection should produce a pale wheal of the skin, 6 to 10 mm in diameter. The result of the test is read after 48–96 hours but 72 hours (3rd day) is the ideal.

Tuberculin reaction consists of erythema and induration. Since erythema is sometimes difficult to measure, induration alone is measured (horizontal transverse diameter of induration in millimetres, using a transparent plastic ruler or callipers). Reactions exceeding 10 mm are considered "positive". Those less than 6 mm are considered "negative". Those between 6 and 9 mm are considered "doubtful", i.e., the reaction may be due to *M. tuberculosis* or atypical mycobacteria. If there is no induration, the result should be recorded as '0'.

It has been further observed that strong reactors (i.e., those showing 20 mm or more induration) have greater chances of developing tuberculosis than those showing 10 mm induration. Those with less than 5 mm induration have more risk of developing tuberculosis than those with 6–9 mm induration. Studies indicate that 92 per cent of new cases occur in persons who are already tuberculin reactors *(22)*. These findings illustrate the prognostic significance of the test.

Classification of positive tuberculin skin test reaction *(23)*

A tuberculin skin test reaction is considered positive if the transverse diameter of the indurated area reaches the size required for the specific group. All other reactions are considered negative. The classificaiton is as follows:

Induration size	Group
≥ 5 mm	1. HIV-positive persons. 2. Recent contacts of individuals with active tuberculosis. 3. Persons with fibrotic changes on chest films suggestive of prior tuberculosis. 4. Patients with organ transplants and other immunosuppressed patients (receiving the equivalent of > 15 mg/d of prednisone for 1 month or more).
≥ 10 mm	1. Recent immigrants (< 5 years) from countries with a high prevalence of tuberculosis (eg. Asia, Africa, Latin America). 2. HIV-negative injection drug users. 3. Mycobacteriology laboratory personnel. 4. Residents of and employees in the following high-risk congregate settings: correctional institutions; nursing homes and other long-term facilities for the elderly; hospitals and other health care facilities; residential facilities for AIDS patients; and homeless shelters. 5. Persons with the following medical conditions that increase the risk of tuberculosis: gastrectomy, ≥ 10% below ideal body weight, jejunoileal bypass, diabetes mellitus, silicosis, advanced chronic kidney disease, some hematologic disorders, (eg. leukemias, lymphomas) and other specific malignancies (eg. carcinoma of the head or neck and lung). 6. Children < 4 years of age or infants, children and adolescents exposed to adults at high risk.
≥ 15 mm	1. Persons with no risk factors for tuberculosis.

A negative tuberculin test must also be interpreted with caution. For many years, it has been assumed that a negative test constituted strong evidence against the presence of active tuberculous disease in the majority of cases. It has been shown that in the majority of patients with tuberculosis, the cellular immune response may be depressed. It means a negative tuberculin test cannot be relied upon to exclude tuberculosis. The dermal hypersensitivity to tuberculin can also be lost in various states of immune suppression, e.g., malignancy, Hodgkin's disease, HIV infection, malnutrition, severe bacterial infection (including TB itself), viral infections (e.g. measles, chickenpox, glandular fever), recent live-virus vaccination (e.g. measles), immunosuppresive drugs (e.g. steroids) and incorrect injection of PPD. Therefore, too great a diagnostic significance should not be placed on a negative tuberculin test *(13)*.

Two-step testing

Some people who were previously infected with TB may have a negative reaction when tested years after infection, as the immune system response may gradually wane. This initial skin test, though negative, may stimulate (boost) the body's ability to react to tuberculin in future tests. Thus, a positive reaction to a subsequent test may be misinterpreted as a new infection, when in fact it is the result of the boosted reaction to an old infection. Giving a second TST after an initial negative TST reaction is called a two-step testing. Use of two-step testing is recommended for initial skin testing of adults who will be retested periodically (e.g. health care workers).

- The first test is read 48–72 hours after injection.
  - If the first test is positive, consider the person infected.
  - If the first test is negative, give a second test one to three weeks after the first injection.
- The second test is read 48–72 hours after injection.
  - If the second test is positive, consider the person previously infected.

- If the second test is negative, consider the person uninfected.

The validity of tuberculin test, like all medical tests, is subject to variability. It is limited by lack of specificity. Apart from errors associated with the mode of administration, reading of results and the test material used, there are other factors such as cross-reactions due to sensitization by other mycobacteria, which should be taken into account. In countries with a high coverage of BCG, which also produces tuberculin hypersensitivity, tuberculin test has lost its sensitivity as an indicator of the "true" prevalence of infection. The true prevalence rates of infection may be exaggerated by infection with atypical mycobacteria as well as the "boosting effect" of a second dose of tuberculin producing a larger reaction than the first *(24)*.

It is often assumed that delayed hypersensitivity as measured by tuberculin testing is a correlate of the protective immune response. But evidence indicates that this hypersensitivity is irrelevant to the ability of the host to combat the disease. Despite these limitations, the tuberculin test continues to be the only tool for measuring the prevalence of tuberculous infection in a community. It has been aptly said that tuberculin test "must be approached with respect, administered with care, read with deliberation and interpreted with sentient discrimination".

Case-finding should not be an end in itself. It is of little value as a control measure unless followed by chemotherapy. Resources and efforts should be directed towards primary health care, rather than irrational case finding.

Please refer to chapter 7 for the flow chart for diagnosis of tuberculosis in adults, as followed by RNTCP.

Chemotherapy

The development of effective treatment for tuberculosis has been one of the most significant advances during this century. With the evolution of controlled trials (see page 81), the chemotherapy of tuberculosis is now more rationally based, than in the treatment of other infectious diseases.

Chemotherapy is indicated in every case of active tuberculosis. The objective of treatment is cure – that is, the elimination of both the fast and slowly multiplying bacilli (including the persisters) from the patient's body. The effects of chemotherapy are judged not by the anatomic healing of lesions, but mainly by the elimination of bacilli from the patient's sputum. Chemotherapy should be easily available, free of charge to every patient detected. It should be adequate, appropriate and applied to the entire pool of infectors in the community. Patient compliance is critically important, the patient must take the correct drugs at the correct dosage for the correct length of time. Incomplete treatment puts the patient at risk of relapse and the development of bacterial resistance and, importantly, the community at risk of infection with resistant organisms.

Anti-tuberculosis drugs

There are now twelve or thirteen drugs active against ***M. tuberculosis***, of which, six are considered to be essential. An antitubercular drug should satisfy the following criteria : (a) highly effective (b) free from side-effects (c) easy to administer, and (d) reasonably cheap. The currently used drugs may be classified into two groups : bactericidal and bacteriostatic. The bactericidal drugs kill the bacilli *in vivo*. The bacteriostatic drugs inhibit the multiplication of the bacilli and lead to their destruction by the immune mechanism of the host. A brief review of these drugs is given below.

THE FIRST-LINE DRUGS

BACTERICIDAL DRUGS

Rifampicin (RMP)

RMP is a powerful bactericidal drug. It is a better sterilizing agent than INH. It permeates all tissue membranes including the blood-brain and placental barriers. It is equally effective against intracellular as well as extracellular bacilli. It is the only bactericidal drug active against the "persisters" or dormant bacilli which are found in the solid caseous lesions, all other drugs being inactive *(25)*. In this regard, it has a distinct advantage over INH. Rifampicin is of special value when the bacilli resists other drugs. In combination with INH, it can cure even extensive tuberculosis, in about 9 months.

RMP is used only as oral drug. It is so well absorbed that there is little need for parenteral administration. The dose should be taken at least one hour before or 2 hours after food because absorption is reduced by food. It is never used alone for the treatment of tuberculosis, but always used in combination with INH or another drug.

Many patients develop nausea at the start of treatment, but this passes off. The toxic effects include hepatotoxicity, gastritis, influenza-like illness, purpura, thrombocytopenia and nephrotoxicity. The patient should be told that the drug will turn the urine red; this can be used as test of compliance.

PAS delays its absorption; hence concurrent administration with PAS should be avoided. If RMP is stopped for some reason, it should not be restarted within 3 weeks to avoid hypersensitivity.

INH

INH ranks among the most powerful drugs in the treatment of tuberculosis. It can easily penetrate the cell membrane, and is thus active against intracellular and extracellular bacilli. Its action is most marked on rapidly multiplying bacilli. It is less active against slow multipliers. INH gets widely distributed in the body including CSF. Its ease of administration, freedom from toxicity and low cost makes it an ideal component for any drug regimen.

INH should be given as a single dose. INH reaches its peak level in blood 1 to 2 hours after the dose. It has been found that its peak level in serum is more important than sustained inhibitory level. It is for this reason, INH should not be given in divided doses *(26)*.

Patient may experience gastrointestinal irritation, peripheral neuropathy, blood dyscrasias, hyperglycaemia and liver damage. Those patients who are slow inactivators experience a higher incidence of toxicity. The addition of pyridoxine (10-20 mg daily) helps prevent the occurrence of peripheral neuropathy.

Streptomycin

Streptomycin is bactericidal. It acts entirely on rapidly multiplying bacilli. It has been shown that when bacilli are multiplying rapidly, they come out of the phagocytes and are mostly extracellular apd are, therefore, susceptible to streptomycin. Streptomycin is less active against slow multipliers. It has no action on persisters. It does not permeate cell walls or normal biological membranes such as meninges or pleura.

The daily dose of streptomycin is 0.75 g in a single injection. This is a disadvantage because of the organizational problem involved in the long term treatment. It can cause side-

effects which include vestibular damage and nystagmus rather than deafness. Renal damage may also occur.

Pyrazinamide

This drug is bactericidal and is particularly active against the slow-multiplying intracellular bacilli which are unaffected by other drugs. It has been found to increase the sterilizing ability of rifampicin. Therefore, pyrazinamide has been incorporated in short-course chemotherapy regimens.

Complications include hepatotoxicity and hyperuricaemia. Pyrazinamide achieves high levels in CSF and is, therefore, recommended in tuberculous meningitis.

BACTERIOSTATIC DRUGS

Ethambutol

Ethambutol is bacteriostatic and is used in combination to prevent the emergence of resistance to other drugs. It is given orally. Its major side-effect is retrobulbar neuritis; this however does not occur at the usual dosage. Ethambutol has replaced para-aminosalicylic acid (PAS) almost entirely among adults.

THE SECOND-LINE DRUGS

Fluoroquinolones

Ciprofloxacin, ofloxacin, levofloxacin, moxifloxacin and gatifloxacin are active against *M. tuberculosis*, even those resistant to other drugs. They are given orally or IV. They are useful in treating infections resistant to standard drugs and in cases with relapse.

Ethionamide

Ethionamide is structurally related to INH and acts by inhibiting the mycolic acid synthesis. It is effective against bacilli resistant to other drugs and has proved effective in infections due to atypical mycobacteria. It is effective against intracellular as well as extracellular organisms.

Capreomycin

It is bactericidal. Its mechanism of action, pharmacokinetics and adverse reactions are similar to those of streptomycin. It should be administered with caution in presence of renal impairment.

Kanamycin and Amikacin

They are bactericidal and are active against bacilli resistant to streptomycin, INH and cycloserine.

Cycloserine

The drug is mainly bacteriostatic. It is effective against bacilli resistant to INH or streptomycin and against atypical mycobacteria, although antitubercular activity is less than that of these two drugs. It acts by inhibiting the synthesis of the bacterial cell wall.

Thioacetazone

It is a bacteriostatic drug. It rapidly diffuses into various body tissues and also crosses the placenta barrier. It is also secreted in milk. It should never be used in HIV patients as it can cause severe and fatal skin reactions. Side-effects include gastrointestinal disturbances, blurring of vision, haemolytic anaemia and urticaria. The incidence of these side-effects seem to differ in different ethnic groups.

Macrolides

Newer macrolides azithromycin and clarithromycin also have action against tubercular bacilli. They are used to treat atypical mycobacterial infection and cases with relapse.

Antituberculosis drugs can also be grouped according to their efficacy, experience in use and drug class. The different groups are as follows *(27)* :

Alternative method of grouping anti-TB agents

Grouping	Drugs
Group 1 : First-line oral anti-TB agents	Isoniazid (H); Rifampicin (R); Ethambutol (E); Pyrazinamide (Z)
Group 2 : Injectable anti-TB agents	Streptomycin (S); Kanamycin (Km); Amikacin (Am); Capreomycin (Cm); Viomycin (Vm).
Group 3 : Fluoroquinolones	Ciprofloxacin (Cfx); Ofloxacin (Ofx); Levofloxacin (Lvx); Moxifloxacin (Mfx); Gatifloxacin (Gfx)
Group 4 : Oral second-line anti-TB agents	Ethionamide (Eto); Prothionamide (Pto); Cycloserine (Cs); Tertzadone (Trd); para-aminosalicylic acid (PAS)
Group 5 : Agents with unclear efficacy (not recommended by WHO for routine use in MDR-TB patients)	Clofazimine (Cfz); Linezolid (Lzd); Amoxicillin/Clavulanate (Amx/Clv); thioacetazone (Thz); imipenem/cilastatin (Ipm/Cln); high-dose isoniazid (high-dose H); Clarithromycin (Clr)

For dosage of different second-line drugs, kindly refer to page 191.

Most TB patients complete their treatment without any significant drug side-effects. However, a few patients do develop major reactions and it is important to monitor clinically all the patients. A patient who develops one of the following reactions must never receive that drug again *(19)* :

Reaction	Drug responsible
a. Severe rash, agranulocytosis	Thioacetazone
b. Hearing loss or disturbed balance	Streptomycin
c. Visual disturbance (poor vision and colour perception)	Ethambutol
d. Renal failure, shock or thrombocytopenia	Rifampicin
e. Hepatitis	Pyrazinamide

Two-phase chemotherapy

It is well recognized that there are two phases in the effective treatment of tuberculosis : (i) the first is a short, aggressive or intense phase, early in the course of treatment, lasting 1-3 months. During this intensive phase, three or more drugs are combined to kill off as many bacilli as possible. The more rapidly the bacilli are killed initially, the less likely are "persisters" to emerge. The risk of relapse is also lessened. (ii) the second or "continuation" phase is aimed at sterilizing the smaller number of dormant or persisting bacilli. In the standard anti-tuberculous therapy, the duration of treatment was not less than 18 months to achieve complete sterilization of the bacilli. With the introduction of rifampicin and pyrazinamide, this period is now successfully reduced to 6–9 months.

DOMICILIARY TREATMENT

The self-administration of drugs (generally oral drugs) by the patients themselves without recourse to hospitalization is called domiciliary or ambulatory treatment. The classical controlled clinical trials *(28)* carried out at the Tuberculosis Chemotherapy Centre, Chennai showed that the incidence of tuberculosis was no greater in the contacts of patients treated at home than in the contacts of patients treated in sanatoria. It is now universally accepted that with good chemotherapy, hospital treatment has no advantage over domiciliary

treatment, and domiciliary treatment is to be preferred because in the long run, it is so much cheaper than hospital treatment, and that it can be managed by the primary health care system and the general health services of the country. It may be mentioned that it was this study, the classical Chennai Study, that prompted a radical departure from the traditional sanatorium to ambulatory or domiciliary treatment.

LONG-COURSE REGIMENS

The classical (long-course) conventional chemotherapeutic regimens depended upon the use of INH along with one or two bacteriostatic or "companion" drugs. The main role of the bacteriostatic drugs was to prevent the emergence of INH-resistant strains. Sterilization of the lesions thus depended entirely on INH, and 18 months of treatment was required to avoid relapses. Two main types of drug regimens were formulated for application in India. These are :

a. daily regimens
b. bi-weekly or intermittent regimens

SHORT-COURSE CHEMOTHERAPY

For a long time, the standard duration of tuberculosis chemotherapy was 18 months. In 1972, Wallace Fox and his colleagues from the British Medical Research Council showed that the addition of rifampicin or of pyrazinamide to regimens containing INH made it possible to reduce the duration of treatment.

There are a number of advantages of short-course chemotherapy, viz. rapid bacteriological conversion, lower failure rates and a reduction in the frequency of emergence of drug-resistant bacilli. Patient compliance is improved, they become non-infectious earlier. The disadvantage is that the high cost of short-term chemotherapy militates against its wider use in developing countries.

There are now a number of short-course regimens of 6 months duration that are highly effective, of low toxicity, and well-tolerated. These potent regimens are based on an initial intensive phase with 4 drugs (INH, rifampicin and pyrazinamide, supplemented by either streptomycin or ethambutol) for a period of 2 months, followed by 2 drugs in the continuation phase. (INH plus rifampicin or thioacetazone) given daily or intermittently. The treatment must be fully supervised and monitored mainly by bacteriological examination.

DIRECTLY OBSERVED TREATMENT, SHORT COURSE (DOTS) CHEMOTHERAPY

DOTS is a strategy to ensure cure by providing the most effective medicine and confirming that it is taken. It is the only strategy which has been documented to be effective world-wide on a programme basis. In DOTS, during the intensive phase of treatment a health worker or other trained person watches as the patient swallows the drug in his presence. During continuation phase, the patient is issued medicine for one week in a multiblister combipack, of which the first dose is swallowed by the patient in the presence of health worker or trained person. The consumption of medicine in the continuation phase is also checked by return of empty multiblister combipack, when the patient comes to collect medicine for the next week. The drugs are provided in patient-wise boxes with sufficient shelf-life. In the programme alternate-day treatment is used.

The cases are divided into two types of categories – category I and category II. Table 3 shows the type of cases included in each kind of category, the treatment regimen and the duration of treatment *(29)*.

TABLE 3

Treatment categories and sputum examination schedule in DOTS chemotherapy in India

TREATMENT REGIMEN			SPUTUM EXAMINATIONS FOR PULMONARY TB			
Category of treatment	Type of patient	Regimen*	Pre-treatment sputum	Test at month	IF : result is	⟶ THEN :
New cases Category I Red Box	New sputum smear-positive New sputum smear-negative New extra-pulmonary** New others	$2(HRZE)_3$ + $4(HR)_3$	+	2	–	Start continuation phase, test sputum again at 4 and 6 months#
					+	Continue intensive phase for one more month# Complete the treatment in 7 months
Previously Treated Category II Blue Box	Sputum smear-positive Relapse*** Sputum smear-positive Failure*** Sputum smear-positive treatment after default others	$2(HRZES)_3$ + $1(HRZE)_3$ + $5(HRE)_3$	+	3	–	Start continuation phase, test sputum again at 5 months 6 months, completion of treatment#
					+	Continue intensive phase for one more month, test sputum again at 4 months if sputum is positive send sputum for culture and drug sensitivity as it might be a case of MDR-TB#

* The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week. H: Isoniazid (600 mg), R: Rifampicin (450 mg), Z: Pyrazinamide (1500 mg), E: Ethambutol (1200 mg), S: Streptomycin (750 mg). Patients who weigh more than 60 kg receive additional Rifampicin 150 mg. Patients more than 50 years old receive streptomycin 500 mg. Patients in categories I and II, who have a positive sputum smear at the end of the initial intensive phase, receive an additional month of intensive phase treatment.

** Examples of seriously ill extra-pulmonary TB cases are meningitis, disseminated TB, tuberculous pericarditis, peritonitis, bilateral or extensive pleurisy, spinal TB with neurological complications and intestinal and genito-urinary TB.

*** In rare and exceptional cases, patients who are sputum smear-negative or who have extra-pulmonary disease can have Relapse or Failure. This diagnosis in all such cases should always be made by an MO and should be supported by culture or histological evidence of current, active tuberculosis. In these cases, the patient should be categorized as 'Other' and given Category II treatment.

Any patient treated with Category I who has a positive smear at 5 months of treatment should be considered a Failure and started on Category II treatment, afresh. If category I sputum smear –ve case fails to improve or if patient develops pulmonary signs and positive smear at the end of intensive phase, it is considered treatment failure. Start category II treatment and confirm failure by culture and perform DST.

Source : *(30, 31)*

MANAGEMENT OF PATIENTS WHO INTERRUPT TREATMENT

Table 4, 5 and 6 show the management of patients who interrupt the treatment under revised national tuberculosis control programme.

Daily self administered non-DOTS regime is followed in exceptional cases when there is adverse reaction to drugs used in short-course chemotherapy or when the patient cannot comply with this regime. The treatment is given as follows :

(1) Non-DOTS regime 1 (ND1) : For new smear positive pulmonary seriously ill patients and extrapulmonary seriously ill patients – 2 (SHE) + 10 (HE)

(2) Non-DOTS regime 2 (ND2) : For smear negative pulmonary not seriously ill patients and extra pulmonary not seriously ill patients – 12 (HE).

Please refer to page 180 for the treatment outcome definitions.

TABLE 4

Management of patients who were smear-negative at diagnosis and who interrupt treatment

Treatment received before interruption	Length of interruption	Do a sputum smear examination	Result of sputum smear examination	Outcome	Re-registration	Treatment
Less than 1 month	Less than 2 months	No	-	-	-	Resume treatment and complete all doses
	2 months or more	Yes	Negative	-	-	Resume treatment
			Positive	Default	New	Begin CAT I afresh
More than 1 month	Less than 2 months	No	-	-	-	Resume treatment and complete all doses
	More than 2 months	Yes	Negative	-	-	Resume treatment and complete all doses
			Positive	Default	Treatment after default	Begin CAT II treatment afresh

Source : *(29)*

TABLE 5

Management of new smear-positive cases who interrupt treatment (Category I)

Treatment received before interruption	Length of interruption	Do a sputum smear examination	Result of sputum smear examination	Outcome	Re-registration	Treatment
Less than 1 month	Less than 2 weeks	No	-	-	-	Continue CAT I*
	2-7 weeks	No	-	-	-	Start again on CAT I**
	8 weeks or more	Yes	Positive	Default	New	Start again on CAT I**
			Negative	-	-	Continue CAT I*
1-2 months	Less than 2 weeks	No	-	-	-	Continue CAT I*
	2-7 weeks	Yes	Positive	-	-	1 extra month of intensive phase of CAT I
			Negative	-	-	Continue CAT I*
	8 weeks or more	Yes	Positive	Default	Treatment After Default	Start on CAT II**
			Negative	-	-	Continue CAT I*
More than 2 months	Less than 2 weeks	No	-	-	-	Continue CAT I*
	2-7 weeks	Yes	Positive	Default***	Other	Start on CAT II**
			Negative	-	-	Continue CAT I*
	8 weeks or more	Yes	Positive	Default	Treatment After Default	Start on CAT II **
			Negative	-	-	Continue CAT I*

* A patient must complete all **24 doses** of the initial intensive phase. For example, if a patient has to continue his previous treatment and he took 1 month of treatment (12 doses) before interrupting, he will have to take 1 more month (12 doses) of the intensive phase treatment. He will then start the continuation phase of treatment.

** A patient who must 'start again' will *restart treatment from the beginning*

*** Although this patient does not strictly fit the definition of default, default most closely describes the outcome of this patient, although at re-registration they should be categorized as 'Other'.

Source : *(29)*

TABLE 6

Management or retreatment of smear-positive cases who interrupt treatment (Category II)

Treatment received before interruption	Length of interruption	Do a sputum smear examination	Result of sputum smear examination	Outcome	Re-registration	Treatment
Less than 1 month	Less than 2 weeks	No	–	–	–	Continue CAT II*
	2-7 weeks	No	–	–	–	Start again on CAT II**
	8 weeks or more	Yes	Positive	Default	Treatment After Default	Start again on CAT II**
			Negative	–	–	Continue CAT II*
1-2 months	Less than 2 weeks	No	–	–	–	Continue CAT II*
	2-7 weeks	Yes	Positive	–	–	1 extra month of intensive phase of CAT II
			Negative	–	–	Continue CAT II*
	8 weeks or more	Yes	Positive	Default	Treatment After Default	Start again on CAT II**
			Negative	–	–	Continue CAT II*
More than 2 months	Less than 2 weeks	No	–	–	–	Continue CAT II*
	2-7 weeks	Yes	Positive	Default**	Other	Start again on CAT II
			Negative	–	–	Continue CAT II*
	8 weeks or more	Yes	Positive	Default	Treatment After Default	Start again on CAT II
			Negative	–	–	Continue CAT II*

* A patient must complete all **36 doses** of the initial intensive phase.

** Although this patient does not strictly fit the definition of default, default most closely describes the outcome of this patient, although at re-registration they should be categorized as 'Other'.

Source : *(29)*

DOTS-PLUS TREATMENT FOR MDR-TB *(7)*

Recognizing that the diagnosis and treatment of MDR-TB is complex, RNTCP has developed national guidelines based on the WHO recommended international DOTS-Plus guidelines. Drug resistance may be suspected based on history of prior treatment (e g smear positive case after repeated treatment courses, category II failure etc.) and/or close exposure to a possible source case confirmed to have drug-resistant TB. Please refer to chapter 7 for diagnostic criteria followed by RNTCP. As per guidelines, the diagnosis of MDR-TB is at the Intermediate Reference laboratories accredited to perform culture and drug sensitivity testing (DST). After diagnosis, the treatment of MDR-TB is initiated at designated DOTS-Plus sites, which are established in tertiary care centres (like medical colleges, large speciality hospitals) at least one in each state. The DOTS-Plus sites have qualified staff available to manage patient; using DOTS-Plus regimen; using the second-line drugs, given under DOT and standardized follow-up protocol; and have system in place to deliver ambulatory DOT after an initial short period of in-patient care to stabilize the patient.

Pre-treatment evaluation *(18)*

Since the drugs used for the treatment of MDR-TB are known to produce adverse effects, a proper pre-treatment evaluation is essential to identify patients who are at increased risk of developing such adverse effects. The pre-treatment evaluation includes the following:

1. Detailed history (including screening for mental illness, drug/alcohol abuse etc.)
2. Weight
3. Height
4. Complete blood count
5. Blood sugar to screen for diabetes mellitus
6. Liver function tests
7. Blood urea and S. creatinine to assess the kidney function
8. TSH levels to assess the thyroid function
9. Urine examination – routine and miscroscopic
10. Pregnancy test (for all women in the child-bearing age group)
11. Chest X-ray

All MDR-TB cases are offered referral for counselling and HIV testing at the nearest centre. Patients should receive counselling on the nature and duration of treatment, need for regular treatment and possible side effects of these drugs and the consequences of irregular treatment or pre-mature cessation of treatment. It is advisable to involve close family members during the counselling, since family support is an essential component in the management. Patients should be advised to report any side-effects experienced by them. Female patients should receive special counselling on family planning.

While the MDR-TB case is undergoing pre-treatment evaluation, the DTO should ensure an initial home visit to verify the address and meet the family members. A DOT provider (who can either be a health care worker, a community worker or a community volunteer), should be identified in consultation with the patient. The DOT centre can be either at the sub-centre of the health system or in the community. The DOT provider should be given training for drug administration, identification of adverse effects during treatment and the frequency of follow up.

Regimen for MDR-TB *(18)*

This regimen comprises of 6 drugs - Kanamycin, Levofloxacin, Ethionamide, Pyrazinamide, Ethambutol and Cycloserine during 6–9 months of the intensive phase and 4 drugs-Levovfloxacin, Ethionamide, Ethambutol and Cycloserine during the 18 months of the continuation phase.

RNTCP regimen for MDR-TB :
6 (9) Km Lvx Eto Cs Z E / 18 Lvx Eto Cs E
(Reserve/substitute drugs : PAS, Mfx, Cm)

Special adjustments to the standard regimen for MDR-TB are as follows:

- In case of intolerance to Kanamycin, then Capreomycin (or PAS if injectable agent not feasible) is the available substitute drug.
- In case of intolerance leading to discontinuation of other oral second-line drug, p-aminosalicylic acid (PAS) is the available substitute drug.
- Baseline Kanamycin mono-resistance should lead to substitution of Kanamycin with Capreomycin.
- Baseline Ofloxacin mono-resistance should lead to substitution of Levofloxacin with the combination of Moxifloxacin and PAS.
- Baseline Ofloxacin and Kanamycin resistance (i.e. XDR-TB) should lead to declaration of outcome, referral to DR-TB Centre for pre-treatment evaluation for regimen for XDR-TB.

Drug dosage and administration

All drugs should be given in a single daily dosage under directly observed treatment (DOT) by a DOT provider. All patients will receive drugs under direct observation on 6 days of the week. On Sunday, the oral drugs will be administered unsupervised whereas injection Kanamycin will be omitted. If intolerance occurs to the drugs, Ethionamide, Cycloserine and PAS may be split into two dosages and the morning dose administered under DOT. The evening dose will be self-administered. The empty blister packs of the self-administered doses will be checked the next morning during DOT. Pyridoxine should be administered to all patients on regimen for MDR-TB.

The drug dosage for MDR-TB cases are decided according to the weight bands as shown in Table 7.

TABLE 7
Regimen for MDR-TB dosage and weight-band recommendations

Drug	16–25 kgs	26–45 kgs	46–70 kgs
Kanamycin	500 mg	500 mg	750 mg
Levofloxacin	250 mg	750 mg	1000 mg
Ethionamide	375 mg	500 mg	750 mg
Ethambutol	400 mg	800 mg	1200 mg
Pyrazinamide	500 mg	1250 mg	1500 mg
Cycloserine	250 mg	500 mg	750 mg
Pyridoxine	50 mg	100 mg	100 mg
Na-PAS (80% weight/vol)	5 gm	10 gm	12 gm
Moxifloxacin (Mfx)	200 mg	400 mg	400 mg
Capreomycin (Cm)	500 mg	750 mg	1000 mg

Source : *(18)*

If a patient gains 5 kgs or more in weight during treatment and crosses the weight-band range, the DR-TB centre committee may consider moving the patient to the higher weight-band drug dosages. Similarly if a patient loses 5 kgs or more in weight during treatment and crosses the weight band the DR-TB centre committee may consider moving the patient to the lower weight band. The new higher/lower dosages are provided whenever the patient is due for the next supply of drugs in the normal course of treatment and not as soon as change of weight is noted.

Large majority of the patients fall into one of the above weight bands. However, there are some cases weighing less than 16 kg and more than 70 kg who may require some alteration in the dosage of the drugs in the MDR-TB regimen.

1. The dosages of 2nd the line drugs for MDR-TB cases in paediatric age group weighing < 16 kg are as shown in Table 8.

TABLE 8
Dosage of regimen for MDR-TB for paediatric age group < 16 kg

Drug	Daily dose - mg/kg body weight
Kanamycin / Capreomycin	15–20 mg/kg
Levofloxacin / Moxifloxacin	7.5–10 mg/kg
Ethionamide	15–20 mg/kg
Cycloserine	15–20 mg/kg
Ethambutol	25 mg/kg
Pyrazinamide	30–40 mg/kg
(Na-PAS)	150 mg/kg

2. The dosages for > 70 kg higher weight patients include use of additional dosages of some 2nd line drugs, taking the dosage to Kanamycin/Capreomycin (1 gm), Ethionamide (1 gm), Cycloserine (1 gm), Ethambutol (1.6 gm) and Pyrazinamide (2 gm). Other drugs dosages would remain the same. All these are well within the maximum permissible dosage for each drug as per the WHO guidelines.

Treatment duration for regimen for MDR-TB (18)

The treatment is given in two phases, the intensive phase (IP) and the continuation phase (CP). The total duration of treatment for regimen for MDR-TB is 24–27 months, depending on the IP duration. IP should be given for at least six months. After 6 months of treatment, the patient will be reviewed and the treatment changed to CP if the 4th or 5th month culture result in solid or liquid culture is negative respectively. If the 4th or 5th month culture result remains positive, the treatment is extended by 1 month. Extension of IP beyond 1 month will be decided on the results of sputum culture of 5th or 6th and 6th or 7th months. If the result of the 4th month culture is still awaited after 6 months of treatment, the IP is extended until the result is available, with further treatment being decided according to the culture result. The IP can be extended upto a maximum of 3 months after which the patient will be initiated on the CP irrespective of the culture result. The recommended duration for CP is 18 months.

Discharge from DR-TB Centres and transition to decentralized supervised treatment

Patients admitted at the DR-TB centre, if clinically appropriate, may be discharged 7 days after treatment

initiation to their district of residence with a maximum of 7 day supply of drugs and arrangement for injections in transit. The respective DTO should be informed of the patients discharge three days prior to the actual time of discharge. The DTO will inform the respective MO-PHI and the identified DOT provider about the expected discharged of the patient. The monthly drug box and the patient records will be passed on to the identified DOT provider from the respective TU. Local arrangements will need to be made for daily injections during the intensive phase.

Regimen for XDR-TB *(18)*

All XDR-TB patients should also be subject to a repeat full pre-treatment evaluation, but also including consultation by a thoracic surgeon for consideration of surgery. MDR-TB patients diagnosed as XDR-TB would be given an outcome of "Switched to regimen for XDR-TB". The decision and initiation of regimen for XDR-TB is to be taken by the concerned DR-TB centre committee.

The *Intensive Phase* (6–12 months) consists of 7 drugs – Capreomycin (Cm), PAS, Moxifloxacin (Mfx), High dose INH, Clofazimine, Linezolid, and Amoxyclav

The *Continuation Phase* (18 months) consists of 6 drugs - PAS, Moxifloxacin (Mfx), High dose INH, Clofazimine, Linezolid, and Amoxyclav.

RNTCP regimen for XDR-TB :

6–12 Cm, PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv/
18 PAS, Mfx, High dose-H, Cfz, Lzd, Amx/Clv
(Reserve/Substitute drugs : Clarithromycin, Thiacetazone)

The dosage of the drugs would vary as per the weight of the patient (<45 Kg or >45 Kg). All drugs are to be given on a daily basis. Injections of Capreomycin will be given for 6 days/week (not on sundays). All morning doses are to be supervised by the DOT provider except on sundays. After taking DOT for morning doses on saturday, next day medicines would be given to the patient to be taken at home on sunday. Empty blisters of medicines taken unsupervised in the evening, and on sundays are to be collected by DOT provider.

Regimen for XDR-TB dosage and weight band recommendations are as follows

Drugs	Dosage/day	
	≤ 45 Kgs	> 45 Kgs
Inj. Capreomycin (Cm)	750 mg	1000 mg
PAS	10 gm	12 gm
Moxifloxacin (Mfx)	400 mg	400 mg
High dose INH (High dose-H)	600 mg	900 mg
Clofazimine (Cfz)	200 mg	200 mg
Linezolid (Lzd)	600 mg	600 mg
Amoxyclav (Amx/Clv)	875/125 mg BD	875/125 mg BD
Pyridoxine	100 mg	100 mg
Reserve/Substitute drugs		
Clarithromycin (Clr)	500 mg BD	500 mg BD
Thiacetazone (Thz)#	150 mg	150 mg

Depending on availability, not to be given to HIV positive cases.

Source : *(18)*

The reserve/substitute drugs would be used in the following conditions:

- In case the patient was on PAS, PAS will be replaced with one of the reserve drugs in the regimen for XDR-TB
- If the patient is unable to tolerate one or more of the drugs
- If the patient is found to be resistant to Capreomycin.

Duration of regimen for XDR-TB (18)

The Regimen for XDR-TB would be of 24–30 months duration, with 6–12 months Intensive Phase (IP) and 18 months Continuation Phase (CP). The change from IP to CP will be done only after achievement of culture conversion i.e. 2 consecutive negative cultures taken at least one month apart. In case of delay in culture conversion, the IP can be extended from 6 months upto a maximum of 12 months. In case of extension, the DR-TR centre committee, which will be responsible for initiating and monitoring the regimen for XDR-TB, can decide on administering Capreomycin injection intermittenly (3 times/week) for the months 7 to 12.

Direct observation of treatment remains even more crucial in XDR-TB as this is the last chance at successful treatment that these patients will have. Because of the use of drugs with different toxicity profiles, XDR-TB requires more intensive monitoring during follow-up.

- Complete blood count with platelets count : weekly in first month, then monthly to rule out bone marrow suppression and anaemia as a side-effect of Linezolid.
- Kidney function test: monthly creatinine and addition of monthly serum electrolytes to the monthly creatinine during the period that Inj. Capreomycin is being administered.
- Lever function tests : monthly in IP and 3 monthly during CP.
- CXR every 6 months.

Management of treatment interruptions and default for M/XDR-TB patients

All efforts should be made to ensure that M/XDR-TB patients do not interrupt treatment or default. Action should be taken to promptly retrieve patients who fail to come for DOT. The following situations may be seen in case of treatment interruption.

1. *Patients in IP/CP who miss doses*: All the missed doses during IP must be completed prior to switching the patient to CP. Similarly all missed doses during CP must be administered prior to ending treatment.

2. *Patients who interrupt treatment for less than 2 months during IP*: When the patient returns to resume treatment the IP should be continued, however the duration of treatment will be extended to complete IP. The follow up cultures should be done as per the revised schedule.

3. *Patients who interrupt treatment for less than 2 months during CP*: When the patient returns to resume treatment, the CP should be continued, however the duration of treatment will be extended to complete the CP. The follow up cultures should be done as per the revised schedule.

4. *Patients who default (interrupt treatment for 2 or more months) and return back for treatment*: Such patients should be given an outcome of "default" and then re-registered for further treatment which is based on the duration of default as shown in Fig. 1 and 2. Re-registration of patients will be done by the DR-TB Centre.

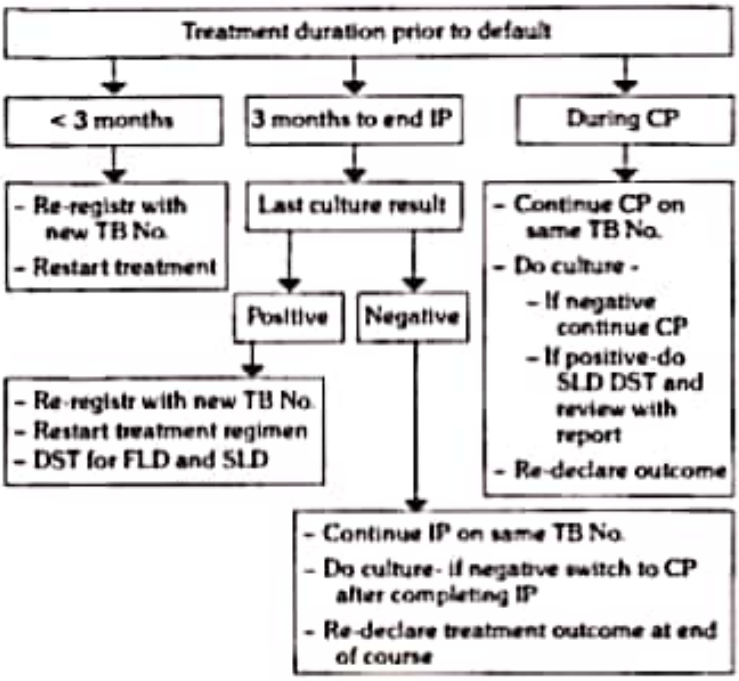

FIG. 1
Algorithm for management of M/XDR patients who default and return for treatment within 6 months of discontinuing regimen for M/XDR-TB

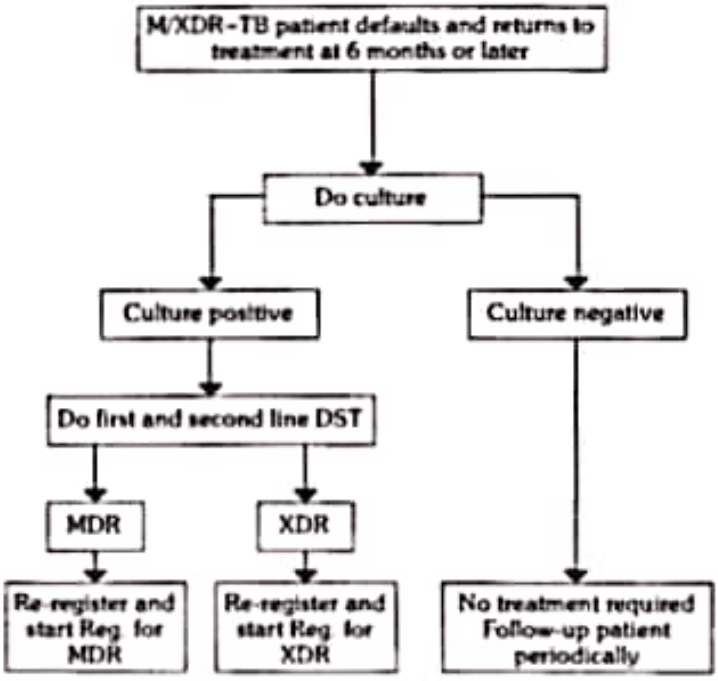

FIG. 2
Algorithm for management of M/XDR patients who default and return for treatment after 6 months.

Follow-up schedule during DR-TB treatment (18)

Schedule for sputum smear microscopy, culture and sensitivity follow up examinations

	IP monthly follow-up examinations				Extension of IP (1-3 months)			CP Quarterly follow-up examination in months						
	1st FU	2nd FU	3rd FU	4th FU				I qtr	II qtr	III qtr	IV qtr	V qtr	VI qtr
No IP extension	3	4	5	6	-	-	-	7	9	12	15	18	21	24
IP extension 1 month	3	4	5	6	7	-	-	8	10	13	16	19	22	25
IP extension 2 months	3	4	5	6	7	8	-	9	11	14	17	20	23	26
IP extension 3 months	3	4	5	6	7	8	9	10	12	15	18	21	24	27

* The number in each cell indicates the month of follow-up examination
** CP will have follow up sputum examination on 7 occasions irrespective of the duration of treatment

The first quarter in the CP will have two examinations and the rest 5 will be in the subsequent quarters till the end of treatment

- Two specimens for AFB at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Two specimens for culture at the end of 3, 4, 5, 6, 7, 9, 12, 15, 18, 21, 24 months
- Monthly weight
- Chest radiograph during pre-treatment evaluation, end of IP, end of treatment and whenever clinically indicated
- Physician evaluation including adverse drug reaction monitoring every month for six months, then every three months for two years
- S. Creatinine monthly for first 3 months, then every 3 months during the injectable phase
- Thyroid Function Test during pre-treatment evaluation and when indicated

Please refer to page 180 for the treatment outcome definitions of DOTS-Plus regimen.

CHILDHOOD TUBERCULOSIS

Cases of tuberculosis in children usually represent between 6–8 per cent of all tuberculosis in the age group of under 15 years *(4)*. The source of infection to a child is usually an adult, often a family member with sputum smear-positive tuberculosis. The frequency of childhood TB in a given population depends on : (a) the number of infectious cases; (b) closeness of contact with an infectious case; (c) the age of child when exposed to TB; and the age structure of the population.

Children rarely have sputum smear-positive TB and it is unlikely that they are a powerful source of transmission of TB. Tuberculosis in children is mainly due to failure of TB control in adults. The risk of infection to a child depends on extent of exposure to infectious droplet nuclei. An infant whose mother has sputum smear-positive PTB has a high chance of becoming infected. The chance of developing disease is greatest shortly after infection, and steadily decreases as the time goes by. Because of less-developed immune system, children under 5 years of age are more prone to develop (up

to 20 per cent) the disease mostly within 2 years following infection *(19)*. The commonest age of childhood TB disease is 1 to 4 years. Young age is a risk factor for spread of disease to other parts of the body, i.e. dissemination.

In order to simplify the management of paediatric TB, RNTCP in association with Indian Academy of Paediatrics (IAP) has described criteria for suspecting TB among children, has separate algorithms for diagnosing pulmonary TB and peripheral TB lymphadenitis and a strategy for treatment and monitoring patients who are on treatment. In brief, TB diagnosis is based on clinical features, smear examination of sputum where this is available, positive family history, tuberculin skin testing, chest radiography and histo-pathological examination as appropriate. The treatment strategy comprises of components. First, as in adults, children with TB are classified, categorized, registered and treated with intermittent short-course chemotherapy (thrice-weekly therapy from treatment initiation to completion), given under direct observation of a treatment provider (DOT provider) and the disease status is monitored during the course of treatment. Based on their pre-treatment weight, children are assigned to one of the pre-treatment weight bands and are treated with good quality anti-TB drugs through "ready-to-use" patient-wise boxes containing the patients' complete course of anti-TB drugs, made available to every registered TB patient according to programme guidelines. India is the first country to introduce paediatric patient wise boxes *(4)*.

Diagnosis of Paediatric TB (0–14 years)

A new diagnostic algorithm is developed for pulmonary TB, the commonest type of extra pulmonary TB (Lymph node TB) and for other types of extra-pulmonary TB (Fig. 3 a & b).

a. All efforts should be made to demonstrate bacteriological evidence in the diagnosis of paediatric TB. In cases where sputum is not available for examination or sputum microscopy fails to demonstrate AFB, alternative specimens (gastric lavage, induced sputum, bronco-alveolar lavage) should be collected, depending upon the feasibility, under the supervision of a paediatrician.

b. A positive tuberculin skin test / mantoux positive is defined as 10 mm or more induration. The optimal strength of tuberculin 2 TU (RT 23 or equivalent) is to be used for diagnosis in children.
   - There is no role for inaccurate and inconsistent diagnostics like serology (IgM, IgG, IgA antibodies against MTB antigens), various non-validated commercial PCR tests and BCG test.
   - There is no role of IGRAs in clinical practice for the diagnosis of TB.

c. Loss of weight was defined as a loss of more than 5% of the highest weight recorded in the past three months.

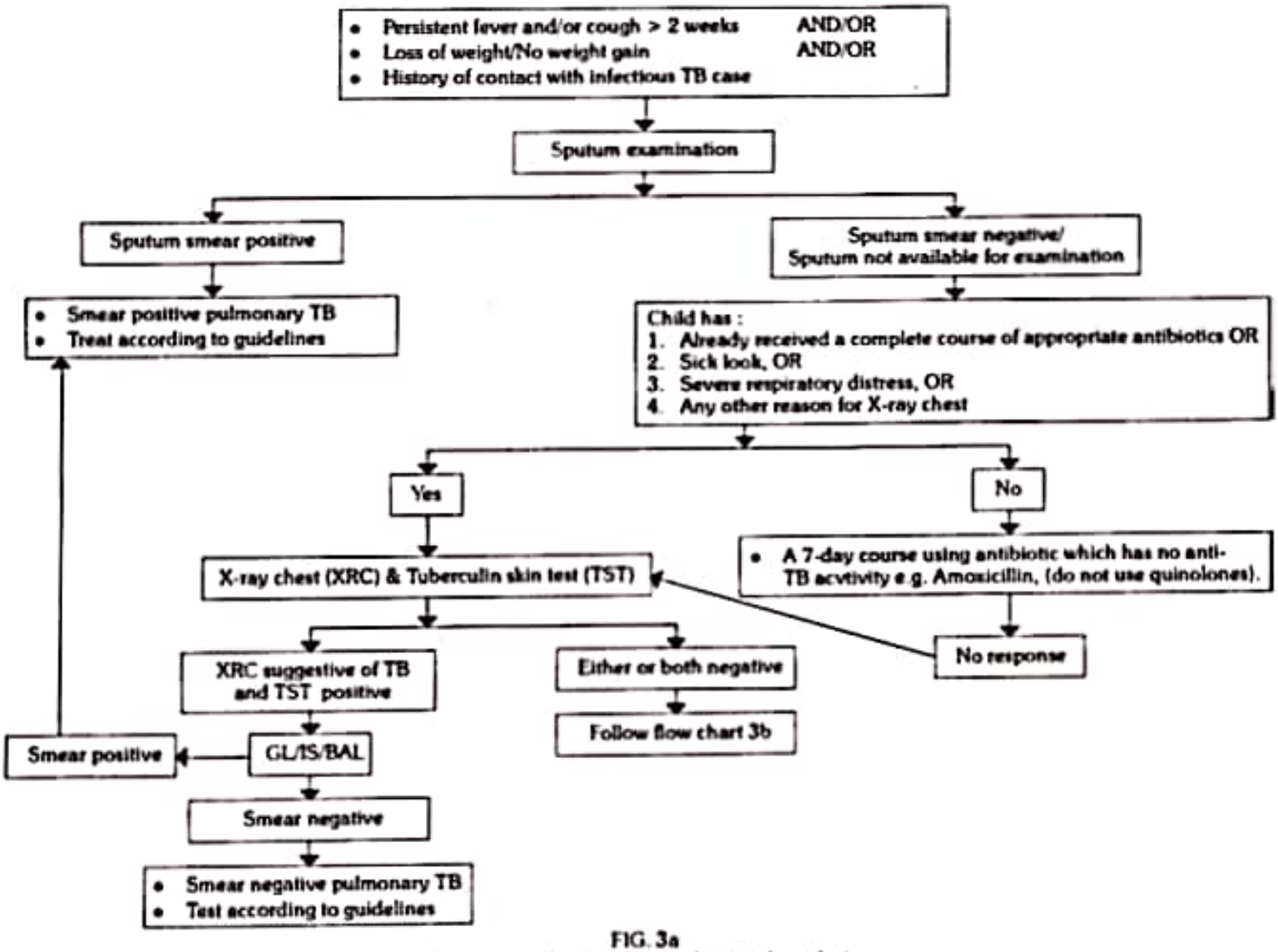

FIG. 3a
Diagnostic algorithm for paediatric tuberculosis

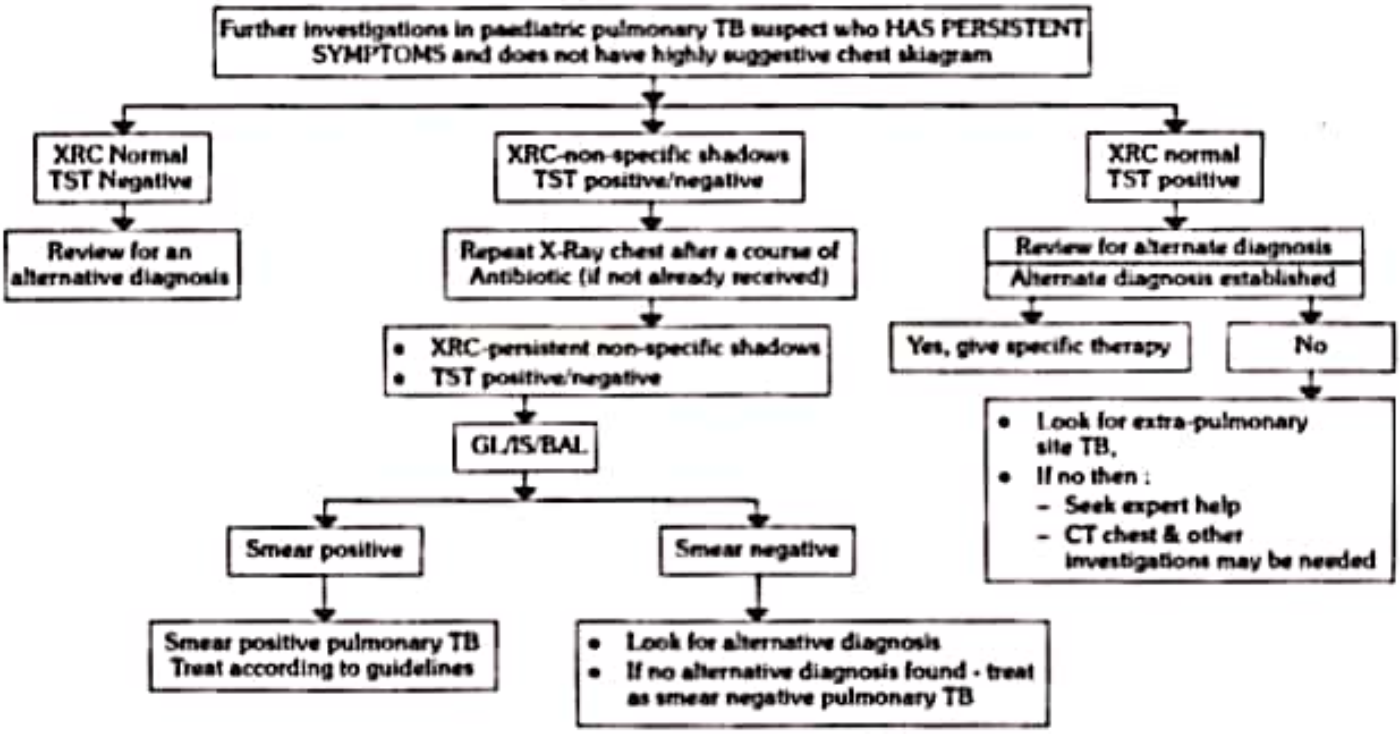

FIG. 3b
Diagnostic algorithm for paediatric tuberculosis

Source : *(5)*

Treatment

The intermittent therapy will remain the mainstay of treating paediatric patients. However, children with severe disseminated disease, neuro-tuberculosis and seriously ill hospitalized children having high likelihood of vomiting and intolerance to oral drugs, an initial daily supervised therapy during their stay in the hospital is needed. After discharge they will be given thrice weekly DOT regimen dosage.

The daily doses (mg per kg of body weight per day) are as follows : Rifampicin 10–12 mg/kg (max 600 mg/day), Isoniazid 10 mg/kg (max 300 mg/day), Ethambutol 20–25 mg/kg (max 1500 mg/day), PZA 30–35 mg/kg (max 2000 mg/day) and Streptomycin 15 mg/kg (max 1 gm/day). Table 9 shows the treatment categories and regimens for paediatric cases.

Drug dosages in children : There will be six weight bands and three generic patient-wise boxes to be used in combination to treat patients in these six weight bands. The newer weight bands are 6–8 kg., 9–12 kg., 13–16 kg., 17–20 kg., 21–24 kg. and 25–30 kg. However, a lead time of at least 2 years is required for the programme to procure and introduce the newer generic patient-wise boxes.

TB preventive therapy : The dose of INH for chemoprophylaxis is 10 mg/kg (instead of earlier recommended dosage of 5 mg/kg) administered daily for 6 months. TB preventive therapy should be provided to:

a. All asymptomatic contacts (under 6 years of age) of a smear positive case, after ruling out active disease and irrespective of their BCG or nutritional status.
b. Chemoprophylaxis is also recommended for all HIV infected children who either had a known exposure to an infectious TB case or are tuberculin skin test (TST) positive (≥5 mm induration) but have no active TB disease.
c. All TST positive children who are receiving immunosuppressive therapy (e.g. children with nephrotic syndrome, acute leukemia, etc).
d. A child born to mother, who was diagnosed to have TB in pregnancy, should receive prophylaxis for 6 months, provided congenital TB has been ruled out. BCG vaccination can be given at birth even if INH chemoprophylaxis is planned.

TABLE 9

Treatment categories and regimens for childhood tuberculosis

Category of treatment	Type of patients	TB treatment regimens	
		Intensive phase	Continuation phase
New cases	– New smear-positive pulmonary tuberculosis (PTB) – New smear-negative PTB – New extra-pulmonary TB.	$2H_3R_3Z_3E_3$*	$4H_3R_3$
Previously treated cases	– Relapse, failure to respond or treatment after default – Re-treatment others	$2S_3H_3R_3Z_3E_3$ + $1H_3R_3Z_3E_3$	$5H_3R_3E_3$

H = Isoniazid, R = Rifampicin, Z = Pyrazinamide, E = Ethambutol, S = Streptomycin

Source : *(4)*

Treatment during pregnancy *(18)*

Tuberculosis in pregnancy is usually treated with isoniazid, rifampicin and ethambutol for 2 months, followed by isoniazid and rifampicin for an additional 7 months. Ethambutol can be stopped after the first month if isoniazid and rifampicin susceptibility is confirmed. Since the risk of teratogenicity with pyrazinamide has not been clearly defined, pyrazinamide should be used only if resistance to other drugs is documented and susceptibility to pyrazinamide is likely. Streptomycin is contraindicated in pregnancy because it may cause congenital deafness. Pregnant women taking isoniazid should receive pyridoxin (Vitamin B_6), 10-25 mg orally once a day, to prevent peripheral neuropathy.

Pregnancy with MDR-TB

All MDR-TB suspects and patients of child-bearing age should be tested for pregnancy as part of pre-treatment evaluation and while on treatment, if there is a history of amenorrhoea of any duration. They should be advised to use birth control measures because of the potential risk to both mother and foetus. Oral contraceptives should be avoided. Use of barrier methods (condoms/diaphrams), IUDs are recommended, based on individual preference and eligibility. The management of MDR-TB patients with pregnancy is summarized in Fig. 4.

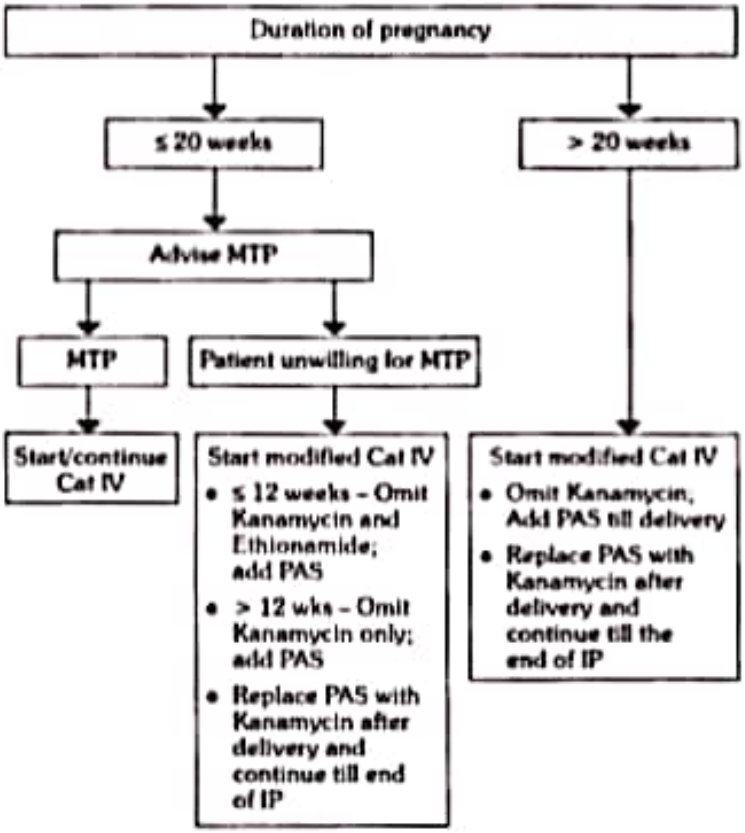

FIG. 4
Management of pregnancy with MDR-TB

In the end it may be stated that the main problem of chemotherapy today is not the need to introduce new regimens or more potent drugs, but to apply the existing ones successfully. The cornerstone of successful chemotherapy is adequate and regular drug intake. Patient compliance is critically important throughout the prescribed period of treatment. All other considerations are secondary.

BCG VACCINATION

Ever since Koch discovered *M. tuberculosis*, attempts have been made to prepare a prophylactic vaccine against tuberculosis using either attenuated or killed tubercle bacilli. Initially BCG was given orally during 1921 to 1925. The first human was vaccinated by the intradermal technique in 1927. Recognition of the value of BCG came in 1948 when it was accepted by tuberculosis workers from all over the world as a safe preventive measure.

(1) AIM : The aim of BCG vaccination is to induce a benign, artificial primary infection which will stimulate an acquired resistance to possible subsequent infection with virulent tubercle bacilli, and thus reduce the morbidity and mortality from primary tuberculosis among those most at risk.

(2) VACCINE : BCG is the only widely used live bacterial vaccine. It consists of living bacteria derived from an attenuated *bovine* strain of tubercle bacilli. The bacilli used for vaccine production are descendants of the original Calmette strain of BCG. Due to different methods of maintenance in various vaccine-production laboratories, many substrains have evolved during the past few decades. The WHO has recommended the "Danish 1331" strain for the production of BCG vaccine. Since January 1967, the BCG Laboratory at Guindy, Chennai, has been using the "Danish 1331" strain for the production of BCG vaccine *(32)*. Emphasis has been laid on regular checking of the quality of vaccines at the International Reference Centre for BCG quality control at Copenhagen.

(3) TYPES OF VACCINE : There are two types of BCG vaccine - the liquid (fresh) vaccine and the freeze-dried vaccine. Freeze-dried vaccine is a more stable preparation than liquid vaccine with vastly superior keeping qualities. Present-day vaccines are distributed in the freeze-dried form.

BCG vaccine is stable for several weeks at ambient temperature in a tropical climate, and for up to 1 year if kept away from direct light and stored in a cool environment preferably refrigerated at a temperature below 10 deg C *(33)*.

The vaccine must be protected from exposure to light during storage (wrapped up in a double layer of red or black cloth) and in the field. Normal saline is recommended as a diluent for reconstituting the vaccine, as distilled water may cause irritation. The reconstituted vaccine may be used up within 3 hours, and the left-over vaccine should be discarded.

(4) DOSAGE : For vaccination, the usual strength is 0.1 mg in 0.1 ml volume *(34)*. The dose to newborn aged below 4 weeks is 0.05 ml. This is because the skin of newborn is rather thin and an intradermal injection with full dose (0.1 ml) in some of them might penetrate into deeper tissue and give rise to local abscess formation and enlarged regional (axillary) lymph nodes.

(5) ADMINISTRATION : The standard procedure recommended by WHO is to inject the vaccine intradermally using a "Tuberculin" syringe (Omega microstat syringe fitted with a 1 cm steel 26 gauge intradermal needle). The syringe and needle technique remains the most precise way of administering the desired dose. All other techniques (e.g., bifurcated needle, dermo-jet) are reported to be less accurate, and do not permit the desired dose to be injected *(35)*. If the vaccine is injected subcutaneously an abscess is more likely to develop *(36)*. The site of injection should be just above the insertion of the left deltoid muscle. If it is injected too high, too forward or too backward, the adjacent lymph nodes may become involved and tender.

A satisfactory injection should produce a wheal of 5 mm in diameter.

The vaccine must not be contaminated with an antiseptic or detergent. If alcohol is used to swab the skin, it must be allowed to evaporate before the vaccine is given.

(6) AGE : The national vaccination policies differ from country to country *(34)*. In countries where tuberculosis is prevalent and the risk of childhood infection is high (as in India), the national policy is to administer BCG very early in infancy either at birth (for institutional deliveries) or at 6 weeks of age simultaneously with other immunizing agents such as DPT and polio. BCG administered early in life provides a high level of protection, particularly against the severe forms of childhood tuberculosis and tuberculous meningitis.

In countries with a low prevalence of tuberculosis, perhaps there is a diminishing need for widespread BCG vaccination. In this situation, it would seem reasonable to restrict BCG vaccination to high risk groups, for example, hospital personnel and tuberculin-negative contacts of known cases of tuberculosis particularly multi-drug resistant TB (MDR-TB) *(33, 37)*.

(7) PHENOMENA AFTER VACCINATION : Two to three weeks after a correct intradermal injection of a potent vaccine, a papule develops at the site of vaccination. It increases slowly in size and reaches a diameter of about 4 to 8 mm in about 5 weeks. It then subsides or breaks into a shallow ulcer, rarely open, but usually seen covered with a crust. Healing occurs spontaneously within 6 to 12 weeks leaving a permanent, tiny, round scar, typically 4–8 mm in diameter. This is a normal reaction *(38)*. However, with overdosage, the local lesion and the later scar may be considerably larger and of irregular size. Normally the individual becomes Mantoux-positive after a period of 8 weeks has elapsed, but sometimes about 14 weeks are needed.

(8) COMPLICATIONS : BCG has been associated with adverse reactions which include : prolonged severe ulceration at the site of vaccination, suppurative lymphadenitis, osteomyelitis, disseminated BCG infection and death. Ulceration and lymphadenitis occur in 1–10 per cent of vaccinations, and disseminated infection occurs in less than one per million vaccinations. The disseminated infection is usually associated with severe abnormalities of cellular immunity. The risk of adverse reactions is related to the BCG strain used by different manufacturers, the dose, the age of the child, the method of immunization and the skill of the vaccinator *(39)*.

If there is a local abscess formation, it should be treated by aspiration, in case it does not clear spontaneously. If this is not successful, it should be incised and treated with local applications daily with PAS or INH powder. There is no need for systemic treatment with INH. The patient should be assured of the harmless nature of the lesion *(40)*. In order to avoid these complications, the vaccination should be strictly intradermal and no other injection should be given for at least 6 months into the arm which received BCG vaccine *(41)*.

(9) PROTECTIVE VALUE : The duration of protection is from 15 to 20 years. The local BCG infection generates an immunity response, which is associated with the development of tuberculin hypersensitivity and with it, possibly, some immunity. The first prospective control trial of BCG showed it to be 80 per cent effective over an observation period of 20 years *(42)*. Since then several well-planned, controlled trials have been conducted in various parts of the world, including the "Tuberculosis Prevention Trial" in South India *(43, 44)*.

Studies have shown that the range of protection offered by BCG varied from 0 to 80 per cent in different parts of the world. The full explanation for the varying degrees of protection has yet to be found *(45, 46)*. One suggestion for which there is an increasing epidemiological support, is that prior exposure to some non-tuberculous environmental mycobacteria (e.g., *M. vaccae*, *M. non-chromogenicum*) may have conferred partial immunity on the population and thus masked the potential benefit of BCG vaccination *(47)*. There is also evidence that exposure to other species (e.g., *M. kansasii*, *M. scrofulaceus*) have an antagonistic action against BCG *(48)*. This may be one reason why BCG was not found to be protective in the South Indian trial *(38)*. However, infants and young children, BCG-vaccinated before they had contact with environmental mycobacteria, derived protection.

There is a large body of evidence which supports the conclusion that BCG gives an appreciable degree of protection against childhood tuberculosis *(48)*. The WHO, on the basis of an extended review of BCG including the South Indian trial *(50)* holds that it would seem unreasonable to stop current BCG vaccination programmes *(46)* and recommends that the use of BCG should be continued as an antituberculosis measure *(50)*.

(10) REVACCINATION : The duration of protection conferred by BCG is a matter of dispute. Even 90 years after the development of the vaccine, it is not known whether booster doses are indicated or advisable. In fact, BCG revaccination has not been included in the official immunization schedule in India under the expanded programme on immunization.

(11) CONTRAINDICATIONS : Unless specifically indicated, BCG should not be given to patients suffering from generalized eczema, infective dermatosis, hypogammaglobulinaemia, to those with a history of deficient immunity (symptomatic HIV infection, known or suspected congenital immunodeficiency, leukaemia, lymphoma or generalized malignant diseases), patients under immunosuppressive treatment (corticosteroids, alkylating agents, antimetabolites, radiation), and in pregnancy. The effect of BCG may be exaggerated in these patients.

(12) DIRECT BCG VACCINATION : Direct BCG vaccination, i.e., vaccination without a prior tuberculin test, has been adopted as a national policy in many developing countries, including India. It permits a more rapid and complete coverage of the eligible population, while reducing the cost. No adverse effects have been reported even if BCG is given to tuberculin-positive reactors *(38)*. However, it is sound practice to administer BCG during infancy before the child has had contact with environmental mycobacteria, than to resort to direct BCG at a later date, when the benefits of BCG are doubtful as shown by the South Indian trial *(49)*.

(13) IMPACT : BCG vaccination is less effective in controlling tuberculosis as compared to active case finding and chemotherapy, as BCG offers only partial protection. In 1982, a WHO Expert Committee *(51)* concluded that although BCG vaccination of uninfected individuals (usually children) can prevent tuberculosis in them, it can have only a relatively small epidemiological effect in that it will not contribute significantly to the reduction in the overall risk of infection in the community as a whole.

(14) BCG VACCINATION AND HIV INFECTION : Following a review of relevant data, the Global Advisory Committee on Vaccine Safety (GACVS) has revised its previous recommendations concerning BCG vaccination of children infected with HIV.

WHO had previously recommended that in countries with a high burden of TB, a single dose of BCG vaccine should be given to all healthy infants as soon as possible after birth unless the child presented with symptomatic HIV infection. However, evidence shows that children who were HIV-infected, when vaccinated with BCG at birth, and who later developed AIDS, were at an increased risk of developing disseminated BCG disease. Among these children, the benefits of potentially preventing severe TB are out weighted by the risks associated with the use of BCG vaccine. GACVS, therefore, advised WHO to change its recommendation such that *children who are known to be HIV-infected, even if asymptomatic, should no longer be immunized with BCG vaccine (52)*. However, population with high prevalence of HIV also have the greatest burden of TB, and in such populations, uninfected children will benefit from the use of BCG vaccine. Furthermore, with the increasing range and coverage of interventions to prevent vertical transmission from mother to child – including early diagonsis of maternal HIV infections, management of sexually transmitted infections; safe delivery practices; maternal and infant preventive antiretroviral medicines or maternal antiretroviral therapy; and safe infant feeding – the majority of infants born to HIV-infected mothers are not infected and would also be expected to benefit from BCG vaccination *(52)*.

Unfortunately, accurate diagnosis of HIV infection in the first year of life relies upon direct demonstration of the HIV virus, as maternal HIV antibody is passively transferred to the infant in utero. Currently available assays that can be used to diagnose HIV in the first year of life are expensive and technically demanding in many countries with generalized HIV epidemics. WHO recommends that these tests are first performed at or around 6 weeks age, yet this is often after BCG vaccination has already been given *(53)*.

(15) COMBINED VACCINATION : BCG may be given at the same time as oral polio vaccine. DPT vaccine may also be given at the same time as BCG, but in different arm without reducing the immune responses or increasing the rate of complications *(43)*. Mixed vaccines containing BCG have not yet been introduced.

An increasing number of industrialized countries are likely to reconsider their BCG vaccination policy during the coming years. To change from general to selective BCG vaccination, an efficient notification system must be in place in addition to the following "low endemicity" criteria : (a) an average annual notification rate of smear-positive pulmonary TB cases below 5 per 100,000; or (b) an average annual notification rate of tubercular meningitis in children aged under five years, below 1 per 10 million population during the previous five years; or (c) an average annual risk of tuberculosis infection below 0.1 per cent *(53)*

To sum up, BCG vaccination is a fundamental component of a national tuberculosis programme. Despite the contradictory evidence of controlled trials, there is evidence that BCG plays a valuable role in preventing severe forms of childhood tuberculosis, viz meningitis and miliary tuberculosis. Today, BCG vaccination is part of WHO Expanded Programme on Immunization. The greatest need for BCG vaccination today is undoubtedly in the developing countries of the world where tuberculosis is still a major health problem.

CHEMOPROPHYLAXIS

Chemoprophylaxis (now termed preventive treatment) with INH for one year or INH plus ethambutol for 9 months has been tried in contact reactors.

The case against INH chemoprophylaxis rests on three points : (a) First, it is a costly exercise *(54)*; (b) Secondly, it is not strikingly effective. For the majority of tuberculin-reactors, the risk of developing tuberculosis is small and the potential benefit offered by chemoprophylaxis is not great enough to justify its use *(55)*, and (c) INH prophylaxis carries a small risk of drug-induced hepatitis. Chemoprophylaxis is, therefore, not a worthwhile exercise of tuberculosis control, especially in developing countries such as India where resources are limited and a large segment of the population is infected. A WHO expert committee in 1982 *(51)* concluded that chemoprophylaxis with INH can prevent the development of tuberculosis in infected individuals, but its impact on the community will be minimal because it cannot be applied on a mass scale, even in technically advanced countries. An earlier WHO expert committee on tuberculosis *(8)* emphasized that preventive treatment is irrational even for special risk groups, unless case-finding and treatment programme for infectious tuberculosis is widespread and well-organized and achieves a high rate of cure. In this context, BCG gets priority over chemoprophylaxis.

Rehabilitation

In recent years, there has been a good deal of fresh thinking on the subject of rehabilitation, because of the success achieved in treating patients on domiciliary lines without interfering with their normal work and life. The proportion of patients who need rehabilitation and work under sheltered conditions is becoming less and less. The groups that need rehabilitation are those who are chronically ill and are still excreting tubercle bacilli. Some of those who had lung resection may require rehabilitation to suit their physical and mental abilities.

Surveillance

Surveillance is an integral part of any effective tuberculosis programme. It should be concerned with two distinct aspects : (a) surveillance of the tuberculosis situation, for example, by measuring the "annual infection rates" which will guide the epidemiologist and health administrator by indicating whether the TB problem is static, increasing or decreasing; (b) surveillance of control measures applied such as BCG vaccination and chemotherapy.

Role of hospitals

Inspite of effective domiciliary treatment services, there will always be some patients who will be needing hospitalization. The main indications for hospitalization are : (a) emergencies such as massive haemoptysis and spontaneous pneumothorax (b) surgical treatment (c) management of serious types of tuberculosis such as meningeal tuberculosis, and (d) certain social indications, such as when there is no one to look after the patient at home.

DRUG RESISTANCE

All drugs used in the treatment of tuberculosis tend to produce resistant strains. The resistance may be of two types : (a) *PRIMARY OR PRE-TREATMENT RESISTANCE* : It is the resistance shown by the bacteria in a patient, who has not received the drug in question before. That this is not

always due to infection of the individual with drug-resistant bacilli, is well known. It is an accepted fact that when the bacilli are rapidly multiplying, resistant mutants appear irrespective of the administration of any particular drug. According to one hypothesis, drug resistance is induced by transference through what are called "episomes". Episomes are non-chromosomal heritable genes which can pass from one bacterial cell to another. If there is a direct contact between the cell containing episomes, the episomes leave the resistant cell and invade susceptible cells *(56)*.
(b) *SECONDARY OR ACQUIRED RESISTANCE* : Here the bacteria were sensitive to the drug at the start of the treatment but became resistant to the particular drug during the course of treatment with it.

Drug resistance means that certain strains of tuberculosis bacilli are not killed by the anti-tuberculosis drugs given during the treatment. Some strains can be resistant to one or more drugs.

Definitions

Please refer to page 179 for classification of cases based on drug resistance.

Causes of drug-resistant tuberculosis *(18)*

Drug-resistant TB has microbial, clinical and programmatic causes. From a microbiological perspective, the resistance is caused by a genetic mutation that makes a drug ineffective against the mutant bacilli. An inadequate or poorly administered treatment regimen allows drug-resistant mutants to become the dominant strain in a patient infected with TB. Table 10 summarizes the common causes of inadequate treatment. However it should be stressed that MDR-TB is man-made phenomenon – poor treatment, poor drugs and poor adherence lead to the development of MDR-TB.

In all countries and especially those where the number of cases of tuberculosis is rising rapidly because of the association with HIV, the development of resistant strains of tuberculosis is a serious concern. In 2012, about 0.45 million people worldwide, are estimated to be infected with strains of drug resistant tuberculosis. An accurate picture of drug resistance is not available because few countries have a reliable drug resistance surveillance system *(2)*.

It is estimated that primary MDR-TB in India is around 2.2 per cent. The drug resistance in re-treatment cases is 15 (11-19) per cent. Although the level of MDR-TB in the country is low in relation to percentage and proportion, it translates into large absolute numbers *(2)*. For details please refer to page 430.

XDR-TB has been reported in India by isolated studies with non-representative and highly selected clinical samples. The magnitude of the problem remains to be determined due to the absence of laboratories capable of conducting quality assured second line drug susceptibility test *(6)*.

It has been observed that resistance to isoniazid alone does not affect the results of treatment so much, if proper regimens for treatment or retreatment are prescribed, but simultaneous resistance to isoniazid and rifampicin limits severely the results of the treatment.

The most serious danger of MDR Tuberculosis is that it is much more difficult to treat, even where second line drugs are available. Treatment of MDR tuberculosis can take at least two years and the results are poor. Second line drugs cost 30 times as much as drugs used in SCC treatment of non-resistant tuberculosis patients. Patients with MDR tuberculosis may need to be hospitalised and isolated which adds to the cost of treatment, to prevent transmission of primary resistant strains to others. Careful precautions are necessary to prevent transmission, especially to health workers caring for MDR tuberculosis patients *(57)*.

DOTS-Plus for MDR-TB is a comprehensive management initiative built upon 5 elements of DOTS strategy. However, DOTS-Plus also takes into account specific issues, such as use of second-line anti-TB drugs. The goal of DOTS-Plus is to prevent further development and spread of MDR-TB. DOTS-Plus is not intended for universal application and is not required in all settings. The aim of implementation of DOTS-Plus in selected areas with significant levels of MDR-TB is to combat an emerging epidemic. The underlying principle is that the first step in controlling MDR-TB is prevention by full implementation of DOTS. An effective DOTS-based TB control programme is a prerequisite for implementation of DOTS-Plus *(19)*.

The emergence of XDR-TB and high case fatality rate in patients with HIV infection was the subject of an emergency consultations held in Johannesburg on 7-8 September, 2006. The issues include strengthening treatment adherence to achieve high levels of completion (≥ 85 per cent) for all TB patients ensuring that second line drugs used to treat MDR-TB and XDR-TB are strictly controlled and properly used according to WHO guidelines. The steps required to limit the impact of MDR-TB and XDR-TB were identified and incorporated into a 7-point plan of action *(58)*.

In the short term, countries should:

1. develop national emergency response plans for MDR-TB and XDR-TB and ensure that basic TB control measures meet international standards for TB care and are fully implemented;
2. conduct rapid surveys of MDR-TB and XDR-TB using a standardized protocol to assess the geographical and

TABLE 10

Causes of inadequate treatment

Providers/programmes : Inadequate regimens	Drugs: Inadequate supply/quality	Patients: Inadequate drug intake
– Absence of guidelines or inappropriate guidelines	– Non-availability of certain drugs (stock-outs or delivery disruptions)	– Poor adherence (or poor DOT)
– Non-compliance with guidelines	– Poor quality	– Lack of information
– Inadequate training of health staff	– Poort storage conditions	– Non-availability of free drugs
– No monitoring of treatment	– Wrong dosages or combination	– Social and economic barriers
– Poorly organized or funded TB control programmes		– Malabsorption – Substance abuse disorders

temporal distribution of XDR-TB in vulnerable populations;

3. strengthen and expand national TB laboratory capacity by addressing all aspects of laboratory procedures and managment;
4. implement infection control precautions in health-care facilities according to WHO guidelines, with special emphasis on those facilities providing care for people living with HIV/AIDS.

In the long term, countries should:

5. establish capacity for clinical and public health managers to respond effectively to MDR-TB and XDR-TB;
6. promote universal access to antiretroviral therapy for all TB patients through close collaboration with treatment and care programmes for people living with HIV/AIDS;
7. support and increase funding for research into the development of new anti-tuberculosis drugs and rapid diagnostic tests for MDR-TB and XDR-TB.

Prevention of Drug Resistance : Since incomplete, inadequate and irregular treatment is the main cause of drug resistance, this can be prevented by (a) treatment with two or more drugs in combination (b) using drugs to which the bacteria are sensitive, and (c) ensuring that the treatment is complete, adequate and regular.

Revised National Tuberculosis Programme

For details of RNTCP activities, refer to chapter 7 page 427.

STOP TB Strategy

In 2006, WHO launched the new Stop TB Strategy. The core of this strategy is DOTS. The strategy is to be implemented over the next 10 years as described in the Global Plan to Stop TB 2006-2015. The targets and indicators for TB control are as defined within the framework of MDGs. These will be used to measure the progress made under the stop TB strategy. It focuses on the five principal indicators that are used to measure the implementation and impact of TB control. They are : case detection, treatment success, incidence, prevalence and deaths. The global targets for case detection and treatment success have been set by WHO's World Health Assembly *(59)*.

Stop TB Partnership targets

By 2015 : The global burden of TB (prevalence and death rates) will be reduced by 50% relative to 1990 levels. This means reducing prevalence to 150 per 100 000 or lower and deaths to 15 per 100 000 per year or lower by 2015 (including TB cases coinfected with HIV). The number of people dying from TB in 2015 should be less than approximately 1 million, including those coinfected with HIV.

By 2050 : The global incidence of TB disease will be less than or equal to 1 case per million population per year.

Components of the strategy and implementation approaches of stop TB strategy are as follows :

1. Pursuing high-quality DOTS expansion and enhancement
   a. Political commitment with increased and sustained financing
   b. Case detection through quality-assured bacteriology
   c. Standardized treatment with supervision and patient support
   d. An effective drug supply and managment system
   e. Monitoring and evaluation system, and impact measurement
2. Addressing TB/HIV, MDR-TB and other challenges
   - Implement collaborative TB/HIV activities
   - Prevent and control MDR-TB
   - Address prisoners, refugees, other high-risk groups and special situations
3. Contributing to health system strengthening
   - Actively participate in efforts to improve system-wide policy, human resources, financing, management, service delivery and information systems
   - Share innovations that strengthen health systems, including the Practical Approach to Lung Health (PAL)
   - Adapt innovations from other fields
4. Engaging all care providers
   - Public-Public and Public-Private Mix (PPM) approaches
   - Implement international standards for tuberculosis care
5. Empowering people with TB, and communities
   - Advocacy, communication and social mobilization
   - Community participation in TB care
   - Patients' charter for tuberculosis care
6. Enabling and promoting research
   - Programme based operational research
   - Research to develop new diagnostics, drugs and vaccines.

TUBERCULOSIS AND HIV

Worldwide the number of people infected with both HIV and tuberculosis is rising. The HIV virus damages the body's natural defences – the immune system – and accelerates the speed at which tuberculosis progresses from a harmless infection to life-threatening condition. The estimated 10 per cent activation of dormant tuberculosis infection over the life span of an infected person, is increased to 10 per cent activation in one year, if HIV infection is superimposed. Tuberculosis is already the opportunistic infection that most frequently kills HIV-positive people.

Even in HIV positive cases, tuberculosis can be cured if diagnosed in time and treated properly. Good TB control programme (DOTS) is the best thing that can be done to cure and extend the lives of HIV positive individuals. With correct TB treatment, the HIV positive person having tuberculosis can gain, on an average two additional years of life *(60)*.

Epidemiological Impact

HIV and tuberculosis interact in several ways *(57)* :

1. *Reactivation of latent infection* : People who are infected with both tuberculosis and HIV, are 25-30 times more likely to develop tuberculosis disease, than people infected only with tuberculosis. This is because HIV stops the

immune system working effectively and tuberculosis bacilli are able to multiply rapidly. In developing countries HIV associated tubercular disease is very common.

2. *Primary infection :* New tubercular infection in people with HIV can progress to active disease very quickly. In the USA active tubercular disease in two-thirds of people with both infections is due to recent infection, rather than reactivation of latent infection. People with HIV are at risk of being newly infected, if they are exposed to tuberculosis because their weakened immune system makes them more vulnerable.

3. *Recurring infection :* People with HIV who have been cured of tuberculosis infection may be more at risk of developing tuberculosis again. However, it is not clear whether this is because of reinfection or relapse.

4. *In the community :* There are more new cases of active tuberculosis because more people infected with tuberculosis develop active disease, and those newly infected become ill faster. This means that there are more people in the community who are infectious to others. Larger number of people with active disease mean more people will die from tuberculosis unless they are treated. The association of tuberculosis with HIV means that people suffer additional discrimination. Community education is needed to increase awareness that tuberculosis is curable and, most important, that people are no longer infectious after the first few weeks of treatment.

Diagnosis of tuberculosis in people with HIV

In most people in the early stages of HIV infection, symptoms of tuberculosis are similar as in people without HIV infection. In areas where many people have HIV infection, tuberculosis programmes should continue to focus on identifying infectious sputum-smear-positive cases through microscopy. However, diagnosis of tuberculosis in individual patients using the standard diagnostic tools can be more difficult if they have advanced HIV infection because :

(a) HIV positive people with pulmonary tuberculosis may have a higher frequency of negative sputum smears. Confirming the diagnosis may require sputum culture.

(b) The tuberculin skin test often fails to work in people who are HIV positive because it relies on measuring the response of a person's immune system. If the immune system has been damaged by HIV, it may not respond even though the person is infected with tuberculosis. HIV positive people with tuberculosis, therefore, have a higher frequency of false negative tuberculin skin test results.

(c) Chest radiography may be less useful in people with HIV because they have less cavitation. Cavities usually develop because the immune response to the tubercular bacilli leads to some destruction of lung tissue. In people with HIV, who do not have a fully functioning immune system, there is less tissue destruction and hence less lung cavitation.

(d) Cases of extra-pulmonary tuberculosis seem to be more common in people who are co-infected.

In short-screen for tuberculosis using sputum smear microscopy, if the result is positive, start treatment; if the result is negative, but it is suspected that the patient has tuberculosis, sputum culture should be carried out where feasible to confirm the diagnosis and give treatment to those with positive culture results. Alternatively, where culture cannot be done, treatment can be given to those judged by a doctor to have active tuberculosis on the basis of X-ray and clinical symptoms.

Initiating ART (Anti-Retroviral Therapy) in patients with MDR-TB *(18)*

The use of ART in HIV infected patients with TB improves survival for both drug resistant and susceptible disease cases. However HIV infected MDR patients without the benefit of ART may experience mortality rates exceeding 90%. The likelihood of adverse effects could compromise the treatment of HIV or MDR-TB if both treatments are started simultaneously. On the other hand undue delay in starting ART could result in significant risk of HIV related death amongst MDR patients. Table 11 is based on the WHO guidelines for initiating ART in relationship to treatment for MDR-TB.

TABLE 11

CD 4 cell count	ART recommendation	Timing of ART in relation to treatment for MDR-TB
≤ 350 cells/mm³	Recommend ART	After 2 weeks, as soon as the treatment for MDR TB is tolerated.
> 350 cells/mm³	Defer ART	Re-evaluate patient monthly for consideration of ART. CD4 testing is recommended every 3 months during treatment for MDR TB
Not available	Recommend ART	After 2 weeks, as soon as the treatment for MDR TB is tolerated

For patients who are already on ART at the time of MDR-TB diagnosis be continued on ART when TB therapy is initiated. Occasionally, patients with HIV-related TB may experience a temporary exacerbation of symptoms, signs of radiographic manifestations of TB after beginning TB treatment. This paradoxical reaction occurs in HIV-infected patients with active TB and is thought to be a result of immune restitution due to the simultaneous administration of antiretroviral and tuberculosis medication. Symptoms and signs may include high fever, lymphadenopathy, expanding intra-thoracic lesions and worsening of chest radiographic findings. The diagnosis of paradoxical reaction should be made only after a thorough evaluation has excluded other aetiologies, particularly TB treatment failure. For severe paradoxical reactions prednisone (1-2 mg/kg for 1-2 weeks, then gradually decreasing doses) may be used.

Diagnosis of HIV in TB patients

The diagnosis of HIV relies in serological testing. In areas where there is high prevalence of HIV (>1 per cent in pregnant women), HIV testing should be systemetically offered to all TB patients, including children. Pre-test counselling must be available to all patients so that they understand what the implications of the results might be and make a informed choice. Patients should be counselled on behaviour risk and methods to prevent transmitting or acquiring the infection.

TUBERCULOSIS AND DIABETES

Diabetes has been shown to be an independent risk factor for tuberculosis in community based study from south India and multiple studies globally. It is suggested that diabetes accounts for 14.8 per cent of all tuberculosis and