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ERS TASK FORCE

Tuberculosis management in Europe

Recommendations of a Task Force of the European Respiratory Society (ERS), the World Health Organisation (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) Europe Region.

Task Force of ERS, WHO and the Europe Region of IUATLD

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The objective of tuberculosis (TB) control is the elimination of TB by stopping the transmission of the disease [1–3]. This is achieved through the rapid identification and effective treatment of infectious cases [1–3]. Modern anti-TB chemotherapy is based on the principle of administering properly selected standardized therapeutic schemes at proper dosage for a sufficient duration [4]. Although, in several European countries, national guidelines, have been produced to standardize diagnostic and treatment procedures, as suggested by the World Health Organization (WHO) and the International Union against Tuberculosis and Lung Disease (IUATLD) [1–3], a comprehensive document focused on TB management in Europe is not available. [1, 5–7].

As TB still remains a relevant public health problem in Europe [8–11], a European Task Force was established within the European Respiratory Society (ERS), involving ERS, WHO and IUATLD experts, to produce guidelines on TB management in Europe specifically designed for specialists treating TB patients. The guidelines, which are consistent with WHO/IUATLD documents previously published in Europe, are particularly focused on standardized anti-TB treatment, treatment result monitoring and treatment in special situations.

Treatment and treatment result monitoring in Europe

Information on treatment and treatment result monitoring in Europe is available from published surveys [8, 9, 12] and WHO sources [11, 13].

Treatment

In Central/Eastern Europe, in the early 1990s, only the Czech Republic, Slovakia and Poland were using the

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WHO-recommended initial phase of treatment, consisting of 2 months of isoniazid (H), rifampicin (R), pyrazinamide (Z) and ethambutol (E) or streptomycin (S) (2 HRZE or HRZS). All the other countries reported using a variety of approaches in the intensive phase, such as longer durations (3 months. Albania and Romania), intermittency, twice a week (Romania), three drugs only (Bosnia, Bulgaria, Croatia, Hungary and Slovenia) or without Z (Estonia). Similarly, the WHO-recommended continuation phase of treatment, consisting of H and R for 4 months (4 HR), was used in only a few countries. Most used much longer durations (Albania, Bulgaria, Hungary and Croatia), or additional drugs such as E (Estonia and Poland) [9, 12, 13]. With regard to retreatment, no country was using the regimens recommended by the WHO [9, 12, 13].

The situation has recently improved in many countries. Standardized WHO-recommended regimens are now applied in Armenia, Azerbaijan (pilot project), Croatia, the Czech Republic, Georgia (pilot project), Kazakhstan (pilot project), Kyrgyzstan (pilot project), Latvia, Poland, the Russian Federation (three oblasts), Slovakia and Slovenia, and most of the remaining countries are probably on their way to adopting modem regimens [11].

In Western Europe, adequate short-course chemotherapy regimens, in some cases standardized, are presently used in Andorra, Denmark, Finland, Ireland, Israel, Italy, Germany, Malta, Norway, Portugal, Sweden, Switzerland, the Netherlands and the UK for both new and retreatment cases.

The available data are summarized in table 1.

Treatment result monitoring

The countries adopting the WHO-recommended strategy of TB control (directly observed treatment (DOT), short course (DOTS) countries) are those in which treatment, result monitoring, based on cohort analysis, is performed [11]. In 1995, standardized treatment result data were available from the following countries: 1) Central/Eastern Europe: Armenia, Azerbaijan, the Czech Republic, Georgia, Kyrgyzstan, Latvia, the Russian Federation, Slovakia and Slovenia; and 2) Western Europe: Italy, Malta, the Netherlands, Norway and Portugal. In addition, nonstandardized treatment results (to be interpreted with caution as definitions vary and quality of information systems may not be high) are also available from several non-DOTS countries (Bosnia and Herzegovina, Yugoslavia, Iceland, Luxembourg, Romania, Tajikistan, FYROM, Turkmenistan, Ukraine and Uzbekistan).

Reference documents and definitions

The core group of documents published by WHO/IUATLD task forces [1, 5–7] and two pivotal WHO documents [3, 14], all of them using consistent definitions, were used as reference documents.

The following definitions were adopted. 1. "Infection with *Mycobacterium tuberculosis*" is defined as infection with *M. tuberculosis*, manifested by a significant tuberculin skin test reaction without any sign of clinically and/or radiologically active disease [1, 5]. 2. "Tuberculosis" refers to clinically, bacteriologically, histologically and/or radiologically active disease [1, 5]. 3. A "definite case" of TB is a case with culture-confirmed disease caused by *M. tuberculosis* complex (in countries in which level II laboratories are not routinely available or in which routine culture of specimens from all cases cannot be afforded or expected, a patient with two consecutive sputum smear

Table 1. – Tuberculosis control policies in Europe

Country	DOTS strategy	SCC	DOT
Albania	-	0	**
Andorra	-	**	0
Armenia	++	**	*
Austria	-	0	0
Azerbaijan	++	*	*
Belarus	-	*	**
Belgium	-	0	0
Bosnia and Herzegovina	-	**	**
Bulgaria	-	0	0
Croatia	-	**	**
The Czech Republic	+++	**	**
Denmark	-	**	**
Estonia	-	0	**
Finland	-	**	**
France	-	0	0
Georgia	++	**	**
Germany	-	**	0
Greece	-	0	0
Hungary	-	*	**
Iceland	-	**	0
Ireland	-	**	*
Israel	-	**	0
Italy	++	*	*
Kazakhstan	-	*	**
Kyrgyzstan	+	*	*
Latvia	+++	**	**
Lichtenstein	-	0	0
Lithuania	-	**	**
Luxembourg	-	**	**
Malta	+++	**	**
Monaco	-	0	0
The Netherlands	+++	**	*
Norway	+++	**	*
Poland	-	**	**
Portugal	+++	**	**
Moldavia	-	*	**
Romania	-	**	0
The Russian Federation	+	*	*
San Marino	+++	**	**
Slovakia	+++	**	**
Slovenia	+++	**	**
Spain	-	**	0
Sweden	-	**	*
Switzerland	-	**	**
Taijikistan	-	0	0
FYROM	-	0	**
Turkey	-	**	*
Turkmenistan	-	0	**
Ukraine	-	0	**
UK	-	**	0
Uzbekistan	-	0	0
Yugoslavia	-	**	**

DOTS: directly observed treatment (DOT), short course; SCC: short course chemotherapy. -: not known/not implemented; +: implemented in <10% of the total population; ++: implemented in 10–90% of the total population; +++: implemented in >90% of the total population; 0: absent; *: present in part of the country; **: fully implemented.

examinations positive for acid-fast bacilli or one positive sputum examination, radiological signs and a clinician′s decision to treat is also considered a "definite case"). "Other than definite cases" are those meeting both of the following conditions. 1) a clinician′s judgement that the patient′s clinical, and/or radiological signs and/or symptoms are compatible with TB, and 2) a clinician′s decision to treat the patient with a full courses of chemotherapy [6]. 4. A "new case" is a patient who has never had drug treatment for TB or who has taken anti-TB drugs for <4 weeks [14]. 5. A "relapse" is a patient who has been declared cured of any form of TB in the past by a physician, after one or more full courses of chemotherapy, and has developed sputum smear-positive or culture-positive disease [14]. 6. A "treatment failure" is a patient who, while on treatment, remains or reverts to being smear-positive and/or culture-positive ≥5 months after commencing treatment, or a patient who was initially smear-negative before starting treatment and becomes smear- and/or culture-positive after the second month of treatment [14]. 7. A "treatment after interruption" is a patient who interrupted treatment for 2 months, and returned to the health service with smear-positive and/or culture-positive sputum (also a smear-negative patient, but still with active TB as judged by clinical and radiological assessment) [14]. 8. A "chronic case" is a patient who remains or again becomes smear- and/or culture-positive after completing a fully supervised standard retreatment regimen [14]. The definitions of treatment outcome categories (cure, treatment completed, failure, death, treatment interrupted/default and transfer out) are summarized in table 2 [7]. In particular, patients are declared "cured" if they have completed a full course of treatment and diagnosis was: 1) confirmed by culture and there is a documented conversion (culture-negative) on at least one occasion during, the continuation phase, or 2) based on microscopy and there is documented evidence of two negative sputum smears during the continuation phase. When the bacteriological evidence is not available, the result of treatment is defined as "treatment completed". The sum of cases cured and completing treatment represents cases "treated successfully". "Treatment failure" is a patient who failed to achieve bacteriological conversion within 5 months from the start of treatment, or who, after previous conversion, becomes sputum smear- or culture-positive again, and in whom the first-line treatment is replaced by second-line treatment [7]. 9. "High-risk groups" are population sections with an incidence clearly in excess of that in the general population [1, 5], defined as having an incidence of >100 cases per 100,000 population [1, 7]. 10. "Preventive chemotherapy" is defined as the treatment of infection with *M. tuberculosis* in order to prevent progression to active TB [5]. 11. "Chemoprophylaxis" is defined as the treatment of individuals at risk of acquiring TB who are not infected [15]. 12. "Recent infection" is defined as a positive tuberculin skin test reaction after documentation of a negative tuberculin skin test within the preceding 2 yrs [5]. 13. "Fibrotic lesions" are defined as well-delineated radiographic lesions compatible with healed TB [5]. 14. "Low incidence countries" are those countries in which the incidence of all forms of notified TB is <20 cases per 100,000 population [1, 7]. 15. "DOT" (direct observation of the patient swallowing the pills) is a technical element, as part of the DOTS strategy [3]. 16. "DOTS" is the WHO-recommended strategy of TB control. It implies political commitment and includes several technical elements: 1) case detection among symptomatic patients who self-report to health services and are diagnosed by sputum smear microscopy; 2) standardized short-course chemotherapy to, at least, all confirmed sputum smear-positive cases under proper case management conditions and using DOT during, at least, the intensive phase of treatment; 3) regular drug supply and 4) the establishment and maintenance of a standardized recording and reporting system, which enables assessment of treatment results [3, 11].

Rationale for standardized treatment

New cases

Treatment regimens comprise an initial (intensive) phase of 2 months and a co continuation phase usually lasting 4–6 months [14–20]. During the intensive phase, during which four drugs are given, there is a rapid killing of tubercle bacilli. During this phase, adequately treated patients become rapidly noninfectious (in the presence of

Table 2. – Definitions of treatment outcome categories of definite cases of pulmonary tuberculosis

	Culture-confirmed	Sputum smear microscopy-confirmed
Cured	Documented conversion of culture during the continuation phase	Sputum smears negative on two occasions during the continuation phase of treatment
Treatment completed	Documented treatment completion, but no documented culture conversion	Documented treatment completion, but no sputum smear microscopy available at the end of treatment
Treatment failure	Culture remaining or becoming positive again after ≥5 months of treatment	Sputum smears remaining or becoming positive again after ≥5 months of treatment
Death	Death of the patient irrespective of cause at any time before the envisaged end of treatment	Death of the patient irrespective of cause at any time before the envisaged end of treatment
Treatment interrupted	Patient off treatment for ≥2 consecutive months, failure to complete treatment within 9 months for a 6-month or within 12 months for a 9-month regimen, or drug intake <80%	Patient off treatment for ≥2 consecutive months, failure to complete treatment within 9 months for a 6-month or within 12 months for a 9-month regimen, or drug intake <80%
Transfer out	Patient referred to another clinician/unit for treatment for whom information on treatment outcome cannot be obtained	Patient referred to another clinician unit for treatment for whom information on treatment outcome cannot be obtained

(modified from [7].)

Table 3. – Essential antituberculosis drugs

Drug	Recommended dose mg·kg body weight^{-1}·day^{-1}		
	Daily	Intermittent, three times weekly	Intermittent, twice weekly
Isoniazid	5 (4–6)	10 (8–12)	15 (13–17)
Rifampicin	10 (8–12)	10 (8–12)	10 (8–12)
Pyrazinamide^{+}	25 (20–30)	35 (30–40)	50 (40–60)
Streptomycin	15 (12–18)	15 (12–18)	15 (12–18)
Ethambutol	15* (15–25)	30 (25–35)	45 (40–50)

Data are presented as mean (range). *: as a dose of 15 mg·kg body weight^{-1} day^{-1} is considered safer and a dose of 25 more effective [22], the American Thoracic Society recommends 25 mg·kg body weight^{-1}·day^{-1} during the intensive phase (8 weeks) followed by 15 during the continuation phase of treatment [23]; $^{+}$: The British Thoracic Society [22] recommends a daily dose of 35 mg·kg body weight^{-1}·day^{-1}. When the administration is intermittent, the recommended dose is 50 mg·kg body weight^{-1}·day^{-1} (three times weekly) or 75 mg·kg body weight^{-1}·day^{-1} (twice weekly). (Modified from [14].)

susceptible strains) and symptoms improve. The vast majority of sputum smear-positive patients, when correctly treated, achieve sputum conversion (*i.e.*, a negative sputum smear examination) within 2 months. In the continuation phase, fewer drugs are necessary, but for a longer duration. The sterilizing effect of the drugs eliminates the remaining bacilli and prevents subsequent relapse [16, 17].

In sputum smear-positive patients, there is a risk of selecting resistant strains, as these patients harbour and excrete a large number of metabolically active bacilli, Short-course regimens consisting of four drugs during the intensive phase (*e.g.* HRZE or HRZS) and two drugs during the continuation phase (*i.e.* HR) significantly reduce this risk. These regimens are as effective in patients with organisms initially resistant to one of the drugs (excluding R) as in those with sensitive organisms [16–21].

In pulmonary sputum smear-negative and extrapulmonary patients, the risk of selecting resistant mutants is significantly lower, as these patients harbour fewer bacilli. Properly designed controlled clinical trials have proved the efficacy of chemotherapy regimens consisting of three drugs during the intensive phase (*e.g.* HRZ) and two drugs during the continuation phase (*i.e.* HR) [14–21].

Retreatment cases

As previously treated patients are more likely to have acquired drug resistance to at least H, the standard WHO-recommended retreatment regimen includes: 1) five drugs for 2 months followed by four drugs for 1 month during the intensive phase (which is administered for 3 months), and 2) three drugs during the continuation phase (which is administered for 5 months, *e.g.* 2 SHRZE/1 HRZE/5 HRE). This approach allows the patient to receive at least three active drugs during the initial phase, reducing, the risk of selecting further resistant bacilli [14, 21].

The treatment regimens and dosages recommended by the WHO are summarized in tables 3 and 4 [14, 21]. Patients are classified into four treatment categories (I: new sputum smear-positive and other severe cases; II: retreatment cases; III: new sputum smear-negative and nonsevere extrapulmonary cases; and IV: chronic cases).

The use of four drugs in the intensive phase in communities in which there is even a small risk (>2%) of single drug resistance has been recommended [15]. In specific areas at higher risk of multidrug resistance (*e.g.*, New York), at least five drugs may be needed during the intensive phase in new cases and at least flour (but possibly as many as six or seven) in retreatment cases [15].

Regimens comprising three drugs in new cases or four in retreatment cases can be applied only in populations in which the prevalence of drug resistance is known to be very low. Simultaneous use of DOT and/or fixed-dose combination (FDC) tablets may prevent the spread of drug resistance [14].

Use of fixed-dose combination tablets

The WHO and the IUATLD strongly recommend the use of FDC tablets (incorporating two or three drugs within the same tablet) of proven bioavailability [24, 25]. Pharmacokinete studies in humans have demonstrated that the plasma concentrations of H, R and Z administered in free combination or FDC are similar [26, 27]. The majority of studies confirm that no significant differences exist between FDC tablets and single drugs as far as sputum smear conversion rate and frequency of side-effects and relapses are concerned [28–33]. The differences found in some studies comparing FDC *versus* separate formulations are

Table 4. – Recommended tuberculosis (TB) treatment regimens for each treatment category according to the World Health Organization

Treatment category	TB patients	Recommended regimens	
		Initial phase (daily or three times weekly)	Continuation phase
I	New smear-positive pulmonary TB; New smear-negative pulmonary TB with extensive parenchymal involvement; New cases of severe forms of extrapulmonary TB	2 HRZE (HRZS) 2 HRZE (HRZS) 2 HRZE (HRZS)	4 HR 4 H_3R_3 6HE*
II	Sputum smear-positive: relapse; treatment failure; treatment after interruption	2 HRZES/1 HRZE2 HRZES/1 HRZE	5 $H_3R_3E_3$ 5 HRE
III	New smear-negative pulmonary TB (other than in category 1); new less severe forms of extrapulmonary TB	2 HRZ 2 HRZ 2 HRZ	4 HR 4H_3R_3 6 HE*
IV	Chronic case (still sputum-positive after supervised retreatment	Not applicable (use of second-line drugs in specialized centres)	

*: only when R is not tolerated. H_3/R_3/E_3: drug-administered three times weekly. (Modified from [14].)

controversial. The US Trial 21 found quicker sputum conversion and a higher incidence of side-effects using the FDC regimen [33]. The Singaporean study found a slight higher relapse rate after 24 months, confirmed (and achieving statistical significance) after 5 yrs of follow-up [34]. The Hong Kong study found a better acceptability to patients in comparison with separate formulations [35] and the Algerian study a lower incidence of side-effects with FDC tablets [36]. Advantages offered by FDC tablets include a reduced risk of selecting resistant mutants in the event of treatment interruption or relapse [24, 25, 31, 36, 37], concrete help for physicians in prescribing effective regimens and reducing inadvertent medication errors [24, 25, 28–35]; simplification of drug procurement, management and handling; a simplified regimen for the patient leading to improved compliance [34–37]; and a reduction in inappropriate use of R [14, 24, 25, 31, 36, 37]. At present, FDC tablets consist of combinations of HR, HRZ and HRE. A four-drug combination tablet is expected to be available in the future.

Patient monitoring

The patient undergoing anti-TB chemotherapy should be monitored to evaluate response to treatment and to promptly identify and manage drug-induced toxicity and evaluate the performance of the programme [7, 14].

Bacteriological monitoring is possible only among "definite cases" (table 5). If a patient is smear- and culture-positive, the minimum requirement is to carry out a smear examination after the initial phase of treatment. If sputum smear conversion is achieved, a negative culture result during the continuation phase is sufficient to declare the patient cured if the full course of treatment has been completed. If the patient is culture-positive and smear-negative, both culture and sputum smear should be monitored at the end of the intensive phase. If the smear remains negative, cure is defined by culture result.

If the patient is smear-positive and culture-negative or culture is not performed, the smear examination should be performed at the end of the initial phase (end of second month), during the continuation phase (end of fourth month) and at end of treatment. Bacteriological monitoring at the end of treatment is strictly recommended in definite cases in order to assess precisely that the patient has been cured. In patients unable to produce sputum (*e.g.* because they do not cough), induction of sputum with hypertonic saline may be a noninvasive way of obtaining an adequate sample.

Radiological and clinical monitoring represent the only possible means of monitoring pulmonary smear/culture negative and extrapulmonary cases. While also used in definite cases, radiological and clinical monitoring of treatment is not fully reliable due to the limitations of chest radiography (observer error, over- and under-reading, influence of experience on radiograph reading results, and disagreement between readings of chest radiographs for follow-up) and clinical signs and symptoms [7, 38].

Directly observed therapy

Recommended by the WHO as part of the DOTS strategy [3], DOT is mandatory in countries in which treatment results are poor or likely to be poor. Whenever the treatment success rate (cure and completion) is unequivocally shown to be satisfactory (>85%), the national health authorities (National Programme, Ministry of Health) should decide under what circumstances DOT is necessary (during hospitalization, in specific groups at risk of lower success rates, in relapses, etc.).

Table 5. – Treatment monitoring of new "definite" cases using either the culture-based method or the smear-based method depending on the initial bacteriological diagnosis*

Bacteriology at diagnosis	Initial phase	Action to be taken	Continuation phase	Final outcome
Culture-positive (regardless of smear result) (DST performed)	End month 2 Smear Culture (DST result known)	Clinical improvement, smear negative: start continuation regardless of DST result[+]	Culture (during continuation)	
		No clinical improvement, smear positive: look at DST: 1) if resistant strain: consider regimen modification[+]; and 2) if susceptible strain: One additional month initial phase, same regimen, ensure DOT Repeat smear/culture (end month 3) Start continuation	End month 5 Smear Culture	If negative: cured If positive: failure* (individualized regimen based on DST result)
Smear-positive	Smear (end month 2)			
	Negative Positive	Start continuation One additional month initial phase, same regimen Repeat smear/culture (end month 3) Start continuation	Smear end month 4 followed by final smear (end month 6)	If negative: cured If positive: failure

*: in treatment cases, the monitoring is similar, taking into account the different duration of the intensive phase (3 months); [+]: multidrug-resistant tuberculosis requires modification of regimen; [#]: re-evaluate causes of failure. DST: drug sensitivity test; DOT: directly observed therapy.

Preventive chemotherapy and chemoprophylaxis

Preventive chemotherapy (*i.e.*, the treatment of persons infected with *M. tuberculosis*) has proved very effective in preventing progression to TB or reactivation of disease [23, 39–41]. Placebo-controlled randomized clinical trials have demonstrated that a 6–12-month course of H reduced the risk of developing active TB in infected persons by ≥80% [41]. If no reinfection occurs, the protective effect is presumed to be lifelong. More recently, clinical trials have also shown that H chemotherapy may reduce the occurrence of TB among human immunodeficiency virus (HIV)-infected individuals [39, 42, 43]. Individual candidates for preventive chemotherapy should be identified by purified protein derivate of tuberculin (PPD) skin testing using the Mantoux technique. As reliable data for developing new recommendations are not yet available in Europe, other pre-existing recommendations are discussed.

Individuals recommended for receipt of preventive chemotherapy, according to the American Thoracic Society (ATS), are listed in table 6 [23]. The cut-off for defining a "positive" skin test, and thus whether an individual should be given preventive chemotherapy, is related to the probability that the reaction represents true infection and to the likelihood that the individual, if truly infected, will develop TB, Thus, different cut-offs were suggested by the ATS (5-mm induration: close contacts, HIV-infected, fibrotic lesions; 10-mm: most at risk persons; 15-mm: low-risk persons) [23].

PPD-negative infants and children who are contacts of infectious cases should be given chemoprophylaxis and undergo a repeat PPD test 2–3 months after the contact is broken. Those who remain PPD-negative should stop chemoprophylaxis [23]. While, HIV-infected anergic individuals may be considered for chemoprophylaxis, due to their increased risk of TB, a recent study in the USA did not show a benefit from this practice [39] (table 3). For preventive chemotherapy and chemoprophylaxis, H is recommended at a dose of 5 $mg \cdot kg^{-1} \cdot day^{-1}$ up to 300 $mg \cdot m^2$ body $surface^{-1}$ (200 mg in children) for ≥6 months. If supervised administration is feasible, intermittent doses (15 $mg \cdot kg^{-1} \cdot day^{-1}$, up to 900 $mg \cdot day^{-1}$) may be given two or three times a week [21]. Contraindications to H preventive chemotherapy and chemoprophylaxis include the presence of liver disease. The major adverse reaction is drug-induced hepatitis, which may be fatal [44]. Close monitoring of clinical tolerance is therefore mandatory [44].

Table 6. – Recommendations of the American Thoracic Society (1994) for preventive chemotherapy

Risk group	Tuberculin reaction size	Treatment of duration
HIV-infected persons	≥5 mm*	12 months 6 months
Close contacts of TB patients	≥5 mm+	(9 for children)
Fibrotic lesions on chest radiography	≥5 mm	12 month
Recently infected persons	≥10 mm	6 months
High-risk medical conditions[#]	≥10 mm	6–12 months
High-risk group, <35 yrs[§]	≥10 mm	6 months
No high risk, <35 yrs	≥15 mm	6 months

*: anergic human immunodeficiency virus (HIV)-infected persons with an estimated risk of *Mycobacterium tuberculosis* infection of 10% may also be considered for isoniazid preventive chemotherapy; [+]: tuberculin-negative contacts, especially children, should be given chemoprophylaxis for 2–3 months after contact is ended and then retested with Siebert purified protein derivate of tuberculin. (Modified from [23].). Those remaining negative should stop receiving preventive therapy; [#]: includes diabetes mellitus, prolonged therapy with systemic corticosteroids, other immunosupressive therapy, some haematological and reticuloendothelial diseases, HIV-seronegative injecting drug users, end-stage renal disease and clinical situations associated with rapid weight loss; [§]: includes persons born in high-prevalence countries, medically underserved low-income populations and residents of long-term care facilities. TB: tuberculosis.

Economic considerations

The competition of health programmes for limited economic resources within national health systems has spawned an abundance of studies on economic evaluation of healthcare. Economic evaluation is the comparative analysis of alternative courses of action in terms of costs and consequences, and is most useful when preceded by an evaluation of efficacy (capability of the programme to meet the planned objectives) and effectiveness (capability of the programme to meet the planned objectives at lower costs). Although, in developing countries, the treatment of TB cases proved to be among the most cost-effective health interventions [45, 46], few studies had evaluated the economic impact of TB control in low-prevalence countries [47]. Economic evaluation should become a guide for the physician in selecting the most cost-effective option during clinical activity.

Hospital admission and treatment

A cost-effectiveness study was recently performed in the Russian Federation aimed at comparing the WHO strategy, based on case findings among symptomatic patients using shorter standardized regimens, with the old strategy, based on active screening of the asymptomatic population and longer regimens. The cost per case cured, at a cure rate of 85%, ranged from US$1,197 (new strategy) to US$6,293 (old strategy), with potentially relevant monetary savings. Hospital admission costs were the main determinants of the difference between the cost of the new and the old strategy [48], In Armenia, the adoption of the WHO strategy decreased the cost per case cured by 38% (W.J. Meerding, personal communication). Although no universally accepted indications for hospital admission are available, there is agreement in considering admission appropriate for severe smear-positive and extrapulmonary cases, multidrug-resistant cases, poorly compliant patients and patients with other severe medical problems [23, 48]. If patients are admitted, they should be isolated from non-TB patients until they are noninfectious [49].

Directly observed therapy

Among nine cost-effectiveness studies analysed in a recent review article [47], only one was performed in a

low-prevalence country. This study aimed at comparing self-administered treatment *versus* DOT. The study showed that directly observed intermittent therapy by health workers was slightly more costly than self-administered regimens, but this difference was reversed when the reduced need for monitoring was taken into account. In addition, further savings may be expected in the future due to the lower number of relapses and resistant cases [47].

Preventive chemotherapy and chemoprophylaxis

Compliance is crucial to obtaining satisfactory results, because it is more difficult to ensure, adherence among asymptomatic persons than among patients treated for TB. In a meta-analysis of available studies, only 60.5% of 1,084,760 patients completed preventive therapy [44]. Priorities for preventive chemotherapy and chemoprophylaxis take into consideration the risk of developing TB compared with the risk of H toxicity. Recommendations for the use of H are based on a comparison of the risk of hepatic injury during the period of treatment with the potential lifelong benefit of preventing TB. Also of importance in developed countries is the benefit to the community, because prevention of TB cases precludes the spread of new infection, This strategy can be considered a component of TB control in high-income countries only. Each national TB program should define which are the groups at particularly high risk and the appropriate cut-off values in order to apply this strategy, taking into account the likely compliance to preventive chemotherapy. If used indiscriminately, a large number of infected individuals would have to be treated to prevent the occurrence of a single case [23].

Bacille Calmette-Guérin

Based on scientific evidence and economic considerations, the WHO recommends bacille Calmette-Guérin vaccination in infants at birth in countries in which the incidence of TB is high. Repeated vaccination or multiple revaccinations are strongly discouraged [50, 51].

Free cost access of tuberculosis patients to healthcare

The Task Force strongly recommends free access of all TB patients to health services (diagnostic procedures, treatment and follow-up) [5].

Treatment in special situations

Those health conditions affecting TB treatment (chronic renal failure, liver disease, silicosis, *etc.*) and special situations requiring modifications of the standard regimens (pregnancy, lactation, paediatric age, *etc.*) are considered in this section [52].

Chronic renal failure

H, R and Z are predominantly metabolized by the liver and may be given in renal failure [52]. S and other aminoglycosides are excreted exclusively by the kidneys and should be used with caution in renal failure. Renal function should be measured before treatment is started. S levels should be measured in renal failure and not exceed 4 $mg \cdot L^{-1}$ in order to avoid toxicity. If the patient is receiving dialysis, S should be given 4–6 h before dialysis.

E dosage should be reduced in renal impairment. In patients with a creatinine clearance of 50–100 $mL \cdot min^{-1}$, 25 $mg \cdot kg$ body $weight^{-1}$ three times weekly should be used. If the clearance is 30–50 $mL \cdot min^{-1}$, the dose should be given twice weekly. If clearance is 10–30 $mL \cdot min^{-1}$, a dose of 15 $mg \cdot kg^{-1}$ 36–48 hourly has been suggested. Patients on dialysis should be given 25 $mg \cdot kg^{-1}$ 4–6 h before dialysis. Serum levels may be monitored [52–56].

Management of tuberculosis treatment in the presence of liver function abnormality

Liver function tests (LFTs) should be carried out before treatment is started [52–56]. If these are normal, the patient should be advised about possible symptoms arising from liver function disturbance such as malaise, nausea or jaundice. The patient should be advised not to drink alcohol during treatment.

Some authors do not consider routine LFTs necessary while on treatment. Should the patient complain of symptoms attributable to liver function abnormality while on treatment, liver function should be measured. If the results are abnormal (LFT results more than five times the upper limit of normal, see below), treatment with possible hepatitic drugs (H, R and Z) should be stopped until liver function returns to normal. The same procedure should be carried out if the patient becomes icteric on treatment. Once liver function returns to normal, drugs may be restarted in full dosage [57–59]. If liver disturbance occurs for a second time, hepatitic drugs should again be stopped and added one at a time in the presence of two non-hepatitic drugs (S and E) [57–59].

The presence of abnormal liver function test results before treatment is not necessarily a contraindication to treatment with hepatitic drugs. In this situation, a rise in bilirubin should lead to a discontinuation of these drugs. They may be retried, provided liver function returns to its pretreatment levels.

Some authorities advocate routine liver function testing during treatment and discontinuing hepatitic drugs if enzyme levels exceed five times the upper limit of normal [60–62]. There are no general data to support this practice. It should be borne in mind that serious untreated TB at most sites may be fatal [58, 59].

Silicosis

There is evidence that standard 6-month short-course chemotherapy may be inadequate in silico-TB [54, 63]. A treatment longer than the standardized one is recommended (up to 8 months) because of the difficulties in penetration of the drugs into fibrotic lung and impairment of macrophage function [53, 63]. If Z is not included during the initial intensive phase, it is recommended that the treatment be continued for up to 12 months [53]. TB in other pneumoconioses (*e.g.* coal workers′ pneumoconiosis) can be treated with standard regimens [64].

Diabetes mellitus

Diabetic patients are at major risk of TB [52, 61]. Standard regimens are adequate. It should be remembered that R reduces the serum levels of some oral hypoglycaemic drugs such as the sulphonylureas [52, 54, 60].

Human immunodeficiency virus

Patients with HIV-associated TB also present with extrapulmonary disease. When the disease is pulmonary, the classical upper zone infiltration with cavitation may be absent on chest radiography, and uncharacteristic patterns may be detected (hilar adenopathy, middle- and lower-zone noncavitating infiltrates) [65–68]. Those with very low CD4+ cell counts may present with disseminated disease. Mortality is higher than in HIV-negative disease [65–69].

As adherence to the prescribed regimen is the most important determinant of success, the same regimens recommended for HIV-negative individuals are effective for HIV-positive patients [14, 23, 66–70]. Though continuation of treatment beyond the standard length has been recommended [69], there is little scientific data to support this.

Adverse effects of medication are more frequent in HIV-positive patients. Thiacetazone, a drug not usually used in Europe, should be avoided [71]. In cases in which sterility of needles cannot be guaranteed, S should not be used in order to avoid potential HIV transmission.

Several nosocomial outbreaks of drug-resistant TB in HIV-positive patients have been recently described in Europe [72]. In cases in which drug resistance is suspected, regimens for drug-resistant TB should he used [73].

Many HIV positive patients are now started on combination anti-HIV drugs including protease inhibitors. These are metabolized by the P450 enzyme, which is induced by R. Protease inhibitors may therefore be reduced to negligible serum concentrations with concomitant use of R. There are four possible options for overcoming this problem [22]: 1) discontinue use of the protease inhibitor and use alternative antiviral agents until the end of anti-TB chemotherapy; 2) discontinue use of the protease inhibitor for the intensive phase of treatment and recommence its use during the continuation phase using a non-R-containing regimen such as H and E for 6 months; 3) omit R completely from the anti-TB drug regimen and continue for 18 months; and 4) use indinavir as the protease inhibitor and substitute rifabutin (in reduced dose) for R. It is recommended that the first option be selected whenever possible.

Immunosuppresion other than human immunodeficiency virus

Immunosuppression, induced iatrogenically through immunosuppressive drugs, or related reticuloendothelial neoplasms can act as risk factors for TB. There is evidence that standard regimens are adequate for these patients, although the underlying disease is responsible for excessive mortality [70].

Comatose patient

Standard treatment should be prescribed, avoiding the administration of E as visual acuity cannot be monitored. Different routes of administration need to be used. H and R can both be given by means of syrup, H, R and S by intravenous infusion, H and S by intramuscular injection, and Z, crushed, through a nasogastric tube [52]. Intravenous drugs should be available in units admitting comatose patients.

Pregnancy/lactation

In pregnancy, standard short-course chemotherapy can be given. According to WHO and IUATLD recommendations, all first-line drugs can be safely administered except S, because it may cause (as other aminoglycosides) foetal ototoxicity [14, 74, 75]. The effect of both combined oral contraceptives, and the progesterone-only pill is reduced by regimens containing R. The occurrence of pregnancy in women with TB taking R is not an indication for termination of pregnancy [52, 76]. Most anti-TB drugs are present in small concentrations in breast milk. However, these levels are well tolerated by infants, although they do not provide adequate therapy or preventive therapy. Breast feeding is not contraindicated, except in cases where the mother is highly infectious, *i.e.* sputum smear-positive [23, 53, 76]. Although isolation until sputum smear conversion has been suggested, evidence exists that H can protect the newborn from postnatal infection even when infants are not isolated from their mother [77–80].

Paediatric age

The basic principles of treatment of TB in children are essentially the same as in adults [14, 75, 77, 78]. 1) As TB in children is usually an immediate complication of primary infection, they typically demonstrate closed caseous lesions with relatively few mycobacteria. As the probability of acquiring drug resistance is proportional to the size of the bacillary population, children are considered to be at lower risk of developing acquired drug resistance during treatment. 2) The risk of developing extrapulmonary TB, especially disseminated disease and meningitis (requiring prompt and effective treatment), is greater than in adults. 3) Normally, due to pharmacokinetics, children tolerate larger doses of drugs per kg body weight and are less likely to develop side-effects than adults. However, children with disseminated TB or meningitis or who are malnourished may develop hepatotoxicity, especially when the daily dosage of H exceeds 10 mg·kg body weight^{-1}. 4) Owing to the lack of specific drug formulations, the administration of drugs in paediatric subjects may sometimes necessitate the crushing of pills or making up of unstandardized suspensions. If these problems are not considered in advance, they may cause delays and interruptions of treatment and/or administration of inappropiate doses.

The regimen for pulmonary TB is a 6-month regimen including H, R and Z during the intensive phase (first 2 months) and HR during the continuation phase (4 months). The same regimen is recommended for both disseminated

disease and lymp node TB. Some authors recommend a longer duration for meningitis and TB of the bones (9–12 months) and the use of a fourth drug when drug resistance is likely or suspected [79–81].

This standard regimen is generally well tolerated. Supplementation with pyridoxine is recommended in malnourished children [79]. Although transiently elevated liver transaminase levels are described in 3–10% of children taking H, the risk of developing hepatotoxicity is very low [79]. R is well tolerated and adverse reactions such as leukopenia, thrombocylopenia and flu-like syndrome are rare. Z, extensively used in children over the past 10 yrs, has proved to be well tolerated at a daily dose of 30–40 mg·kg body weight^{-1}. S, less frequently prescribed than in the past, is also well tolerated. The general use of E in children is not recommended in existing guidelines [79] because of the difficulties in monitoring optic toxicity, being limited to schoolchildren and adolescents and when drug-resistant TB is suspected [79]. In a recent review of the literature, no definite arguments against the use of E in children were found [82]. The author concluded that E can be recommended for children aged ≥5 yrs, at a dosage of 15 mg·kg body weight^{-1}·day^{-1}, for routine treatment, without taking more precautions than for adults.

Several second-line drugs, including ethionamide, polypeptides (capreomycin) and aminoglycosides (kanamycin, amikacin), are well tolerated. It is recommended that liver function is tested before the commencement of therapy and, in cases in which the patient is unconscious or uncooperative, every 2 weeks for the first 2 months. Liver function monitoring is mandatory when clinical signs and symptoms (fever, malaise, vomiting, jaundice, and weight loss) appear [79].

The list of drugs recommended and their daily doses are summarized in table 7.

Treatment of newborn

Prevention of infection and disease in the newborn is strictly related to the control of TB in the mother. When TB is suspected or diagnosed in the newborn, a standard short-course chemotherapy has to be given.

Treatment and drug interactions in geriatric subjects

The elderly with TB should receive standard short-course chemotherapy. However, as decreased renal and hepatic clearance have been described in elderly patients, they are more susceptible to adverse effects from drug treatment [54, 61, 87]. Furthermore, the drug half-life and organ response to a given anti-TB drug may be altered, and the elderly patient may have multiple illnesses requiring different drugs [54]. A few issues deserve special attention [87]. 1) As R induces liver enzymes, the clearance of several drugs often used in the elderly may be accelerated (warfarin and its analogues, steroids, hypoglycaemic agents, digoxin, theophylline, and β-blockers). Proper monitoring and adjustment of the dosages may, therefore, be needed. 2) Z can cause hyperuricaemia, although gout attacks are very rare. Uric acid measurement is not generally recommended, except in the case of previously documented hyperuricaemia. In the case of symptoms, appropriate treatment (allopurinol) should be prescribed. 3) As the risks of acquiring S-induced nephrotoxicity and ototoxicity are increased in the elderly, the recommended daily dose of S (10 mg·kg^{-1}·day^{-1}) should not exceed 750 mg.

Multidrug-resistant tuberculosis

The management of multidrug-resistant tuberculosis (resistance to at least isoniazid plus rifampicin) is particularly difficult. The World Health Organization recommendations [14] to refer these patients to highly specialized centres with the necessary appropriate experience is strongly endorsed. Those centres should have: 1) expertise in the clinical and laboratory aspects, which are based on relevant experience and validated quality, respectively; 2) high-level laboratory services, preferably

Table 7. – Essential antituberculosis drugs in children

Drug	Dosage forms	Recommended dose mg·kg body weight^{-1}·day^{-1} (maximum dose mg)					
		Daily		Intermittent three times weekly		Intermitent twice weekly	
		≤12 yrs	12–16 yrs	≤12 yrs	12–16 yrs	≤12 yrs	12–16 yrs
Isoniazid	Scored tablets, 50 and 150 mg	5* (300)	5 (300)	20–40 (900)	15 (900)	20–40 (900)	15 (900)
Rifampicin	Capsules, 300 mg; Syrup, 20 mg·mL^{-1}	10–20 (600)	10 (600)	10–20 (600)	10 (600)	10–20 (600)	10 (600)
Pyrazinamide	Scored tables, 500 mg	15–30 (2000)	15–30 (2000)	50–70 (3000)	50–70 (3000)	50–70 (4000)	50–70 (4000)
Streptomycin	Vials, 1 g	20–40 (1000)	15 (1000)	25–40 (1500)	25–40 (1500)	25–40 (1500)	25–40 (1500)
Ethambutol	Tablets, 250 and 500 mg; scored tablets, 400 mg	15–25 (2500)	15–25[§] (2500)	50 (2500)	50 (2500)	50 (2500)	50 (2500)

*: As the risk of isoniazid-induced hepatitis increases with dose when isoniazid is used in combination with rifampicin, some authors suggest not exceeding 10 mg·kg body weight^{-1}·day^{-1} [83, 84]. Evidence exists that a dose of 5 mg·kg body weight^{-1}·day^{-1} [85] is appropriate and safe; [+]: a dose of 50 mg·kg body weight^{-1}·day^{-1} is considered sufficient by other authors [86]; [§]: as a dose of 15 mg·kg body weight^{-1}·day^{-1} is considered safer and a dose of 25 more effective [22], the American Thoracic Society recommends 25 mg·kg body weight^{-1}·day^{-1} during the intensive phase of treatment (8 weeks) followed by 15 mg·kg body weight^{-1}·day^{-1} during the continuation phase [23].

Table 8. – Side-effects of antituberculosis drugs

Drug	Side-effects
Isoniazid	Hepatitis, neuritis, lupus erythematous syndrome, drowsiness, mood changes
Rifampicin	Drug interactions, hepatitis, thrombopenia, abdominal distress, diarrhoea
Pyrazinamide	Hepatitis, rash, arthralgia or arthritis, hyperuricaemia, abdominal distress
Ethambutol	Optic neuritis, abdominal distress
Streptomycin	Hearing loss, ataxia, nystagmus, azotaemia, proteinuria, eosinophilia, serum electrolyte abnormalites
Amikacin	
Kanamycin	
Capreomycin	
Ofloxacin	Abdominal distress, headache, anxiety, tremulousness, thrush
Ciprofloxacin	Abdominal distress, headache, anxiety, tremulousness, thrush, drug interactions
EthionamidePhothionamide	Abdominal distress, dysgeusia, diarrhoea, hepatitis, arthralgia
Aminosalicylic acid	Abdominal distress, nausea, bloating, diarrhoea, rash, oedema
Cycloserine	Mood and cognitive deterioration, psychosis, scizures

equipped with rapid diagnostic methods, with mandatory external quality assessment procedures; 3) available appropriate methods to prevent transmission of resistant strains in the laboratory and clinical setting (*e.g.* negative pressure rooms for inpatient care); and 4) intensive monitoring during the whole treatment regimen by means of clinical and laboratory methods, ensuring directly observed therapy for each dose administered, and early detection of side-effects of treatment.

Appendix: Side-effects and side-effects management

Table 8 summarizes the most frequent side-effects related to the use of antimycobacterial drugs.

Isoniazid. Hepatitis is the main toxic effect of H, and is directly correlated with age (incidence rate 0.5–1%, higher in females) [52, 56, 60, 88]. Alcohol consumption and the coexistence of acute or chronic hepatitis [16, 56, 61] are other important risk factors, Transient elevations of hepatic enzyme concentrations may be observed during the first period of therapy, but do not usually give rise to hepatitis.

H-induced neuropathy can be prevented by supplementation with pyridoxine (10 mg·day^{-1}) [89]. In the case of appearance of neuropathy, the drug should be stopped promptly.

Attention must be paid when H and phenytoin or carbamazepine are simultaneously given because their serum levels can increase: dose adjustment may be needed [90]. The commonest interactions of anti-TB drugs are summarized in table 9 [92].

The main contraindications to H use are known hypersensitivity [56, 60, 92]. Desesitization procedures should be managed in specialized TB units [58].

Rifampicin. Side-effects are more common with intermittent than with daily R-containing regimens [91]. Although liver transaminases can rise transiently at the beginning of treatment, accompanied by jaundice [34, 38], true hepatitis is a rare event. Gastrointestinal upset, pruritus and skin eruptions are known R-induced side-effects. A "flu-like" syndrome (fever, chills and headache) can occur. Thrombocytopenic purpura, haemolysis, severe renal failure and shock, more frequently with intermittent administration of the drug (particularly if the daily dosage of R is >600 mg or >10 mg·kg body weight^{-1} day can also occur. If these reactions occur, R should be stopped, replaced by another first-line drug [4, 44] and not used again in that patient.

As R is an important inducer of hepatic enzymes, the activity of other drugs metabolized in the liver may be reduced (table 9). In particular, females using the contraceptive pill should be advised of the potential risk related to the reduced effectiveness of the method [93]. The interaction with methadone may be important in drug addicts under treatment.

When used simultaneously, H and R can produce hepatitis (hepatocellular damage seldom associated with cholestasis) in 3–4% of patients [62]. These abnormalities usually appear during the first 2 weeks of treatment [39, 62].

A very low risk of hepatitis is described among children treated with H alone [78]. whereas its combination with R increases the risk significantly (up to 6.9%) [62]. In the recent study of Ormerod [94], no hepatitis occurred in 266 children treated for 3 or 4 months with H and R.

The main contraindication to R use is known hypersensitivity to rifamycins [14, 56, 60].

Pyrazinamide. Hepatitis, rash, abdominal distress and hyperuricaemia (with or without arthralgia) are the commonest side-effects of Z. The frequency of drug-induced hepatitis is not increased when Z is added to H and R, although Z-induced hepatitis has been described [92]. Liver injury, as well as tubulointerstitial nephritis and myoglobinuric renal failure, have been described and were often due to the doses >15–30 mg·kg body weight^{-1}·day^{-1} used in the 1950s [92. 95].

The facial flushing or erythematous rash with pruritus appearing in the first days of treatment are usually self-limiting. Hyperuricaemia, caused by the inhibition of renal tubular secretion is rarely symptomatic [54]. Patients with diabetes should be carefully monitored since blood glucose concentrations may become labile. Arthralgia, particularly of the shoulders, commonly occurs and is responsive to simple analgesics. It seems neither to correlate with the level of uric acid nor to respond to allopurinol [96]. Both hyperuricaemia and arthralgia may be reduced by intermittent administration of Z [54].

The main contraindications to Z use are known hypersensitivity and severe hepatic impairment [56, 60, 95].

Table 9. – Interactions with antituberculosis drugs

Drug	Interaction	Effect
Isoniazid	Phenytoin	↑ serum level of phenytoin
	Carbamazepine	↑ serum level of carbamazepi
	Warfarin	↑ serum level of warfarin
	Diazepan	↑ serum level of diazepan
	Prednisolone	↑ serum level of isoniazid
Rifampicin	Warfarin	↓ serum level of warfarin
	Sulphonylureas	↓ serum level of sulphonylureas
	Corticosteroids	↓ serum level of corticosteroids
	Oral contraceptives	↓ serum level of oral contraceptives
	Phenytoin	↓ serum level of phenytoin
	Digital glycosides	↓ serum level of digitalis glycosides
	Cyclosporin	↓ serum level of cyclosporin
	Cimetidine	↓ serum level of cimetidine
	Methadone	↓ serum level of methadone
	Theophylline	↓ serum level of theophylline
	Protease inhibitors	↓ serum level of protease inhibitors
Ethambutol	Aluminium hydroxide	↓ serum level of ethambutol
Pyrazinamide	Probenecid	↑ serum level of pyrazinamide
Streptomycin	Neuromuscular blocking agents	↑ serum level/effect of neuromuscular blocking agents

↑: increased; ↓: decreased.

Ethambutol. The main and most severe adverse effect of E is retrobulbar neuritis, which is usually dose-related. Although it is very rare at a dosage of 15 mg·kg body weight^{-1}·day^{-1} and with normal renal function, its frequency increases to almost 3% when doses of 25 mg·kg body weight^{-1}·day^{-1} are administered and/or in the presence of impaired renal function [14, 52, 97, 98]. Patients complain of blurred vision, red/green blindness (early symptoms) and, later, central scotomata. Visual acuity monitoring is strongly advised before administering E, and later if the patient reports visual symptoms. The drug should be stopped immediately if visual symptoms appear. As optic atrophy is usually reversible, proper clinical monitoring prevents irreparable ocular damage. Renal failure (determining higher blood levels of E) increases the probability that ocular side-effects might occur [53]. Owing to difficulties in monitoring visual acuity in children, the drug should be used with caution and only when really necessary [14, 52, 98, 99]. Signs of peripheral neuritis in the legs, rashes or abdominal distress may occasionally develop [14, 52, 98, 99].

Contraindications to E use include known hypersensitivity, pre-existing optic neuritis from any cause, inability to report symptomatic visual disturbances and creatinine clearance of <50 mL·min^{-1} [56, 60].

Streptomycin. Ototoxicity, due to the irreversible damage of the vestibular branch of the eighth cranial nerve, is the main side-effect of S. Vertigo, ataxia, nystagmus and somettimes hearing loss are the commonest symptoms. Nephrotoxicity, especially in those patients with pre-existing renal insufficiency, has been described [99]. The association of H and other ototoxic/nephrotoxic drugs (other aminoglycosid antibiotics, amphotericin B, cephalosponins, ethacrynic acid, cyclosporin, cisplatin, frusemide and vancomycin) might increase both the frequency and severity of symptoms [54].

The dosage should be reduced if headache, vomiting, vertigo and tinnitus occur [92, 54]. The minor side-effects are fever, skin rashes and eosinophilia [99]. The dosage should be reduced by 50% if urinary output falls, albuminuria occurs or tubular casts are detected in the urine [54].

S should be avoided, when possible, in children (the injections are painful and irreversible auditory nerve damage may occur), and the dosage reduced in the elderly and in the presence of renal impairment. In patients with renal impairment, renal function monitoring is mandatory and, where possible, serum levels of the drug should be monitored periodically to ensure plasma concentrations (measured when the next dose is due) do not exceed 4 mg·mL^{-1} [54, 56, 60]. S may potentiate the effect of neuromuscular blocking agents administered during anaesthesia [56, 60].

Contraindications to S use are represented by known hypersensitivity, auditory nerve impairment and myasthenia gravis [56, 60].

Second-line drugs

Cycloserine. The most serious adverse effects of cycloserine, which are dose-related, are those affecting the central nervous system: psychosis, depression, headache, seizures and vertigo. Alcoholics and those patients receiving dosages >500 mg·day^{-1} are at major risk of developing side-effects. Sedatives and anticonvulsant drugs are effective in controlling the symptoms. The monitoring of blood levels (to keep levels <30 g·mL^{-1}) has been suggested, especially in patients with impaired renal clearance [54, 56, 60].

Ethionamide/Prothionamide. Gastrointestinal intolerance (abdominal pain, nausea and vomiting) is the most frequent side-effect of ethionamide/prothionamide. The drugs are hepatotoxic and may cause hyperglycaemia in diabetics. They can increase cycloserine side-effects on the central nervous system.

Daily doses of 0, 5–1 g (given in two or three doses) usually limit the gastrointestinal upset [54, 56, 60].

Aminoglycosides (kanamycin and amikacin) and polypeptides (capreomycin). The major side-effects of aminoglycosides and polypeptides are nephrotoxicity, ototoxicity and neuromuscular blockade. Their dosages should be reduced in patients with renal impairment [54, 56, 60].

p-aminosalicylic acid. Gastrointestinal upset, rash, bloating, diarrhoea and nausea are the more frequently observed side-effects of *p*-aminosalicylic acid. Intravenous administration partially limits the gastrointestinal reactions [54].

Rifamycins. Rifabutin and rifapentine have similar adverse effects to R [54, 56].

The spectrum of rifabutin and rifapentine is similar to that of R, although rifabutin is also active against M. avium. Basically, the indication for both drugs in the treatment of TB is the same as R, and they should not be considered first-line drugs.

Rifabutin. Owing to partial cross-resistance, approximately one-third of R-resistant strains are susceptible to rifabutin [100]. The role of this drug is presently controversial, as, in a recent trial (rifabutin *versus* R), no difference in outcome was found [101].

Rifapentine. Rifapentine, having a rather long half-life (>14 h), might permit once-weekly administration [102]. Further evaluation is necessary.

Quinolones. Ofloxacin and ciprofloxacin have been demonstrated to be moderately effective against *M. tuberculosis* and *M. avium* complex and are used as second-line drugs in cases of resistance to or intolerance to first-line drugs. Side-effects are rare (3–7%) and usually mild and transient, including abdominal pain, nausea, vomiting, dizziness, headache and increased aspartate aminotransferase and alanine aminotransferase (ALT) [103]. As they may impair growth and produce injury to growing cartilage, permission for their use in growing children differs among European countries.

Corticosteroids. Corticosteroids are associated with anti-TB treatment in several conditions, although very few controlled clinical trials are available on this topic and the drugs, dosage and duration of treatment used in the different studies varied greatly [104–106]. Their use is justified by their potential anti-inflammatory activity in a disease in which the host response plays a major role. The long-term benefits are limited to the reduced mortality in pericarditis and decreased neurological sequelae of meningitis [104, 107, 108].

The short-term benefits include faster clinical improvement in tubercular meningitis, pericarditis and pleuritis. Their use in pulmonary TB should be limited to acute life-threatening conditions and to adrenal insufficiency [97].

Corticosteroids should be used with caution in HIV-infected patients. Their interactions with R should be taken into consideration [104].

In general, prednisone can be used at a dose of 20–60 $mg \cdot day^{-1}$ whereas in tubercular meningitis, dexamethasone is preferred (up to 12 $mg \cdot day^{-1}$) [104, 109].

Adherence to tuberculosis treatment.. As adherence to the prescribed treatment is crucial to achieving a cure, it should be promoted and evaluated taking into account the resources available. The strategies proposed [110–111] include: 1) accessible and appropriate healthcare; 2) training, motivation and supervision of health staff; 3) promotion of patient adherence by means of counselling/education; 4) reminder cards; 5) increasing motivation (persuation, incentives); 6) DOT; 7) monitoring of side-effects. 8) FDC tablets and blisters; and 9) collaboration with social services.

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References

1. Clancy L, Rieder HL, Enarson DA, Spinaci S. Tuberculosis elimination in the countries of Europe and other industrialized countries. *Eur Respir J* 1991; 4: 1283–1295.
2. Enarson DA. The International Union Against Tuberculosis and Lung Disease model National Tuberculosis Programmes. *Tuberc Lung Dis* 1995; 76: 95–99.
3. World Health Organization. WHO framework for effective tuberculosis control. Geneva, 1994. WHO/TB/94.179: 1–13.
4. Crofton J. The prevention and management of drug-resistant tuberculosis. *Bull Int Union Tuberc Lung Dis* 1987; 62: 6–11.
5. Rieder HL, Zellweger JP, Raviglione MC, Keizer ST, Migliori GB. Tuberculosis control in Europe and international migration. *Eur Respir J* 1994; 7: 1545–1553.
6. Rieder HL, Watson JM, Raviglione MC, *et al*. Surveillance of tuberculosis in Europe. *Eur Respir J* 1996; 9: 1097–1104.
7. Veen J, Raviglione MC, Rieder HL, Migliori GB, Graf P, Grzemska M, Zalesky R. Standardised outcome monitoring in Europe. Recommendations of a Working group of WHO and IUATLD (Europe Region). *Eur Respir J* 1998; 12: 505–510.
8. Raviglione MC, Sudre P, Rieder HL, Spinaci S, Kochi A. Secular trends of tuberculosis in Western Europe. *Bull World Health Organ* 1993; 71: 297–306.
9. Raviglione MC, Rieder HL, Styblo K, Khomenko AG, Esteves K, Kochi A. Tuberculosis trends in Eastern Europe and the former USSR. *Tuberc Lung Dis* 1994; 75: 400–416.

10. EuroTB (CESES/KNCV) and the national coordinators for tuberculosis surveillance in the WHO European region. Surveillance of tuberculosis in Europe. Report on the feasibility study (1996-1997). Tuberculosis cases notified in 1995. CESES/KNCV, Saint- Maurice (France), October 1997: pp 1–63.
11. Global Tuberculosis Programme World Health Organization. Global tuberculosis control. WHO Report 1998, WHO/TB/98.237: 101–116.
12. Migliori GB, Raviglione MC. Specific problems in developing areas of the world. Central and Eastern Europe *In*: Davies PDO"Clinical Tuberculosis" 2nd Edition. Chapman & Hall Medical, London, 1998: pp. 643–660.
13. National Tuberculosis and Lung Diseases Research Institute/World Health Organization Collaborating Centre for Tuberculosis. Report on the Second Meeting of National TB Programme managers from Central and Eastern Europe and the former USSR. Bulletin No. 3, WHO Collaborating Centre for Tuberculosis, Warsaw 1997: 1–30.
14. World Health Organization. Treatment of tuberculosis. Guidelines for national programmes. World Health Organization, Geneva, 1997; WHO/TB/97.220: 1–77.
15. Iseman MD. Treatment of multidrug-resistant tuberculosis. *N Engl J Med* 1993; 328: 784–791.
16. Mitchinson DA. The action of antituberculosis drugs in short-course chemotherapy. *Tubercle* 1985; 66: 219–225.
17. Mitchinson DA. Mechanisms of drug action in short-course chemotherapy. *Bull Intern Union Tuberc* 1985; 60: 34–37.
18. Fox W, Mitchinison DA. Short-course chemotherapy for pulmonary tuberculosis. *Am Rev Respir Dis* 1975; 111: 325–353.
19. Fox W. The chemotherapy of pulmonary tuberculosis: a review. *Chest* 1979 (suppl) 76: 785–796.
20. Grosset JH. Present status of chemotherapy of tuberculosis. *Rev Infect Dis* 1989; 11 (suppl 2): S347–S352.
21. Raviglione MC, O′Brien RJ. Tuberculosis. *In*: Fauci AS, Braunwald E, Isselbacher KJ, *et al*, eds. "Harrison′s Principles of Internal Medicine", 14th Edn. McGraw Hill, Inc., New York, USA, 1998, chapter 171: pp. 1004–1014.
22. Joint tuberculosis committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in United Kingdom: recommendations 1998. *Thorax* 1998; 53: 536–548.
23. American Thoracic Society. Treatment of tuberculosis and tuberculosis infection in adults and children. *Am J Respir Crit Care Med* 1994; 149: 1359–1374.
24. Acocella G, Angel JH. Short-course chemotherapy of pulmonary tuberculosis: a new approach to drug dosage during the initial intensive phase. *Am Rev Respir Dis* 1986; 134: 1283–1286.
25. IUATLD/WHO. The promise and reality of fixed-dose combination with rifampicin, A joint statement of the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the World Health Organization. *Tubercle Lung Dis* 1994; 75: 180–181.
26. Acocella G, Luisettil M, Gialdroni Grassi G, Peona V, Pozzi E, Grassi C. Bioavailability of isoniazid, rifampicin and pyrazinamide (in free combination or fixed- triple formulation) in intermittent antitubercolous chemotherapy. *Monaldi Arch Chest Dis* 1993; 48: 205–209.
27. Ellard GA, Ellard DR, Allen BW, *et al*. The bioavailability of isoniazid, rifampicin and pyrazinamide in two commercial available combined formulations designed for use in the short-course treatment of tuberculosis. *Am Rev Respir Dis* 1986; 133: 1076–1080.
28. Chrétien J, Pretet S, Rochemaure J, *et al*. Chimiothérapie de la courte duréé de la tuberculose pulmonaire utilisant une association triple fixe isoniazide, rifampicine et pyrazinamide, suivie d′une combinaison fixe isonoazide-rifampicine. Etude coopérative française. *Bull Un Int Tub* 1996; 61: 22.
29. Gunardi AS. Résultats d′une étude du rifater sur le terrain en Indonésie. *Bull Und Int Tub* 1986; 61: 23.
30. Embran P, Wibowo S, Handojo RA, *et al*. Essal thérapeutique controlé: traitement de la tuberculose pulmonaire par un régime comportant: rifampicine, isoniazide et pyrazinamide. *Bull Un Int Tub* 1986; 61: 24.
31. Leonin TA. Essai clinique controlé d′une chimiothèrapie de courte duréé effectué dans plusieurs centres des Philippines. *Bull Unt Int Tub* 1986; 61: 23.
32. Lopez JS. Essai sur le terrain d′une chimiotherapic de la tuberculose pulmonaire dans les conditions courantes d′ exécution du programme. *Bull Und Int Tub* 1986; 61: 24.
33. United States Public Health Service Tuberculosis Therapy Trial 21. Preliminary results of an evaluation of a combination tablet of isoniazid, rifampicin and pyrazinamide. *Tubercle* 1987; 68 (suppl): S41–S46.
34. Teo SK. Assessment of a combined preparation of isoniazid, rifampicin and pyrazinamide (Rifater®) in the initial phase of chemotherapy in three 6-month regimens for smear positive pulmonary tuberculosis. a five-year follow-up report. *Tuberc Lung Dis* 1999; 3: 120–132.
35. Hong Kong Chest Service/British Medical Research Council. Acceptability, compliance and adverse reactions when Isoniazid, Rifampin, and Pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. *Am Rev Respir Dis* 1989; 140: 1618–1622.
36. Chaulet P, Boulahbal F. Essai clinique d′une combinaison en proportions fixes de trois medicaments dans le traitement de la tuberculose. *Tuberc Lung Dis* 1995; 76: 407–412.
37. Acocella G. The use of fixed-dose combinations in antituberculous chemotherapy. Rationale for their application in daily, intermittent and pediatric regimens. *Bull Intern Union Tuberc Lung Dis* 1990; 65: 77–83.
38. Toman K. Tuberculosis case-finding and chemotherapy. Questions and answers. World Health Organization, Geneva (Switzerland), 1979: pp. 1–239.
39. Gordin FM, Matts JP, Miller C, *et al*. A controlled trial of isoniazid in persons with anergy and human immuno deficiency virus infection who are at high risk for tuberculosis. *N Engl J Med* 1997; 337: 315–320.
40. Ferebee SH. Controlled chemoprophilaxis trials in tuberculosis. *Adv Tuberc Res* 1970; 17: 28–106.
41. O′Brien RJ. Preventive therapy of tuberculosis. *In*: Porter JDH, McAdam KPWJ, eds. "Tuberculosis: back to the future". John Wiley & Sons Ltd., United Kingdom, 1994.
42. Pape JW, Jean SS, HO JL, Hafner A, Johnson WD Jr. Effect of isoniazid prophylaxis on incidence of active tuberculosis and progression of HIV inflection. *Lancet* 1993; 342: 268–272.
43. Whalen CC, Johnson JL, Okwera A, *et al*. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *N Engl J Med* 1997; 337: 801–808.
44. Snider DE Jr, Caras GJ. Isoniazid-associated hepatitis deaths: a review of available information. *Am Rev Respir Dis* 1992; 145: 494–497.
45. Murray CJL, DeJonghe E, Chum HJ, Nyangulu DS, Salomao A, Styblo K. Cost effectiveness of chemotherapy for

pulmonary tuberculosis in three sub-Saharan countries. *Lancet* 1991; 338: 1305–1308.
46. Sawert H, Kongsin S, Payanandana V, *et al*. Costs and benefits of improving tuberculosis control: the case of Thailand. *Soc Sci Med* 1997; 44: 1805–1816.
47. Fryatt RJ. Review of published cost-effectiveness studies on tuberculosis treatment programmes. *Tuberc Lung Dis* 1997; 2: 101–109.
48. Migliori GB, Khomenko AG, Punga VV, *et al*. Cost-effectiveness analysis of different policies of tuberculosis control in Ivanovo Oblast, Russian Federation. *Bull World Health Organ* 1998; 76: 475–483.
49. Clancy LJ, Kelly P, O′Reilly L, Byrne C, Costello E. The pathogenicity of *Mycobacterium tuberculosis* during chemotherapy. *Eur Respir J* 1990; 3: 399–402.
50. WHO Global Tuberculosi Programme and Global Programme on Vaccines. Statement on BCG revaccination for the prevention of tuberculosis. *Week Epidemiol Record* 1995; 70: 229–236.
51. Trnka L, Dankova D, Zitova J, *et al*. Survey of BCG vaccination policy in Europe: 1994–96. *Bull World Health Organ* 1998; 76: 85–91.
52. Ormerod LP. Chemotherapy of tuberculosis. *In:* Wilson R ed. "Tuberculosis" European Respiratory Monograph 1997; 4: 273–297.
53. O′Brien RJ. The treatment of tuberculosis. *In:* Reichman LB, Hershfield ES, eds. "Tuberculosis, a comprehensive international approach". M. Dekker Inc., New York, Basel, Hong Kong, 1993, pp. 207–240.
54. Patel AM, McKeon J. Avoidance and management of adverse reactions to antituberculosis drugs. *Drug Safety* 1995; 12: 1–25.
55. Varughese A, Brater DC, Benet LZ, Lee CC. Ethambutol kinetics in patients with impaired renal function. *Am Rev Respir Dis* 1986; 134: 34–38.
56. Winstanley PA. Clinical pharmacology of antituberculosis drugs. *In:* Davies PDO, eds. "Clinical Tuberculosis", 2nd Edition, Chapman & Hall Medical, London, 1998; pp. 225–242.
57. Dossing M, Wilke JTR, Askgaard DS, Nybo B. Liver injury during anti tuberculosis treatment: an 11-yr study. *Tuberc Lung Dis* 1996; 77: 335–340.
58. Davies PDO, Girling DJ, Grange JM. Tuberculosis. *In:* Weatherall DJ, Gledingham JG, Warrel DA, eds. "Oxford Texbook of Medicine", 3rd Edition Oxford, 1995; pp. 638–661.
59. Chan SL, Yew WW. Chemotherapy. *In:* Davies PDO, eds. "Clinical Tuberculosis", 2nd Edition, Chapman & Hall Medical, London, 1998; pp. 243–264.
60. Goodman & Gilman′s. "The pharmacological basis of therapeutics", 9th Edition edited by Hardman JG and Limbird LE, McGraw Hill Inc., New York, USA, 1996; pp. 1155–1174.
61. Schaberg T, Rebhan K, Lode H. Risk factors for side-effects of isoniazid, rifampin and pyrazinamide in patients hospitalized for pulmonary tuberculosis. *Eur Respir J* 1996; 9: 2026–2030.
62. Steel MA. Toxic hepatitis with isoniazid and rifampicin: a meta-analysis. *Chest* 1991; 99: 465–471.
63. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. A controlled clinical comparison of 6 and 8 months of antituberculosis chemotherapy in the treatment of patients with silicotuberculosis in Hong Kong. *Am Rev Respir Dis* 1991; 143: 262–267.
64. Jones FL. Rifampin- containing chemotherapy for pulmonary tuberculosis associated with coal workers′ pneumoconiosis. *Am Rev Respir Dis* 1982; 125: 681–683.
65. Sunderam G, McDonald R, Maniatis RJ, *et al*. Tuberculosis as a manifestation of the acquired immunodeficiency syndrome (AIDS). *JAMA* 1986; 256: 362–366.
66. Perriens JH, St Louis ME, Yiadul B, *et al*. Pulmonary tuberculosis in HIV infected patients in Zaire. *N Engl J Med* 1995; 332: 779–784.
67. Gnaore E, Sassa-Morokro M, Kassim S, *et al*. A comparison of the clinical features in tuberculosis associated with infection with human immunodeficiency viruses 1 and 2. *Trans R Soc Trop Med Hyg* 1993; 87: 57–59.
68. Harries AD. The association between HIV and tuberculosis in the developing world. *In*: Davies PDO, eds. "Clinical Tuberculosis", 2nd Edition, Chapman & Hall Medical, London, 1998; pp. 315–345.
69. Small PM, Schecter GF, Goodman PC, *et al*. Treatment of tuberculosis in patients with advanced human immunodeficiency virus infection. *N Engl J Med* 1991; 324: 289–294.
70. Dautzenberg B, Grosset J, Fechner J, *et al*. The management of thirty immunocompromised patients with tuberculosis. *Am Rev Respir Dis* 1984; 129: 494–496.
71. Nunn PM, Kibuga D, Gathua S, *et al*. Cutaneous hypersensitivity reactions to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet* 1991; 337: 627–63.
72. Di Perri G, Cruciani M, Danzi MC, *et al*. Nosocomial epidemic of active tuberculosis among HIV-infected patients. *Lancet* 1989; 2: 1502–1504.
73. Simone PM , Dooley SW. Drug resistant tuberculosis in USA. *In:* Davies PDO, eds. "Clinical Tuberculosis", 2nd Edition, Chapman & Hall Medical, London, 1998; pp. 265–287.
74. World Health Organization, WHO model prescribing information. Drugs used in Mycobacterial diseases. Geneva 1991. WHO/TB/91.191 14–22.
75. Antituberculosis regimens of chemotherapy. Recommendations from the Committee on Treatment of the IUATLD *Bull Intern Union Tuberc Lung Dis* 1988; 63: 63–68.
76. Fignon A, Descamps P, Body G. Maladies infectieuses au cours de la grossesse. *Rev Prat* 1991; 41: 1313–1323.
77. Starke J. Tuberculosis in children. *In*: Reichman LB, Hershfield ES, "Tuberculosis, a comprehensive international approach". M. Dekker Inc., New York, Basel, Hong Kong, 1993; pp. 329–367.
78. Scheinmann P, Refabert C, Delacourt C, Le Bourgeois M, Paupe J, de Blic J. Paediatric tuberculosis. *In*: Wilson R, eds. "Tuberculosis", European Respiratory Monograph, 1997; 4: 144–174.
79. American Academy of Paediatrics. Committee on infectious disease. Chemotherapy for tuberculosis in infants and children. *Paediatrics* 1992; 89: 161–165.
80. Light IJ, Saidelman M, Sutherland JM. Management of newborns after nursery exposure to tuberculosis. *Am Rev Respir Dis* 1974; 109: 415–418.
81. Dutt AK, Moers D, Stead WW. Short course chemotherapy for extrapulmonary tuberculosis. *Ann Intern Med* 1986; 107: 7–12.
82. Trébucq A. Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *Int J Tuberc Lung Dis* 1997; 1: 12–15.
83. Bartmann K, Massman W. Die Blutsplegel des INH bei Erwachsenen und Kindern. *Beitr Klin Tuberk* 1961; 124: 310–319.
84. Scholz H, Belohradsky BH, Kreth W, Roos R, Stehr K. Handbuch 1997. Infektionen bei Kindern und Jugendlichen. Futuranned Verlag, Munchen, 1977, pp. 577.

85. Roy V, Tekur U, Chopra K. Pharmacokinetics of isoniazid in pulrnonary tuberculosis: a comparative study of two dosage levels. *Indian Pediatr* 1996; 33: 287–291.
86. Starke JR, Correa AG. Management of mycobacterial infection and disease in children. *Paediatr Infect Dis* 1995; 14: 455–470.
87. MacDonald JR. Tuberculosis in the elderly. *In*: Reichman LB, Hershfield ES, "Tuberculosis, a comprehensive international approach", M. Dekker Inc., New York, Basel, Hong Kong, 1993, pp. 413–432.
88. Kopanoff DE, Snider DE, Cacas GJ. Isoniazid related hepatitis. *Am Rev Respir Dis* 1978; 117: 991–1001.
89. Snider DE. Pyridoxine supplementation during isoniazid therapy. *Tubercle* 1980; 61: 191–196.
90. Miller RR, Porter J, Greenblatt DJ. Clinical importance of the interaction of phenytoin and isoniazid. *Chest* 1979; 75: 356–358.
91. Grange GM, Winstanley PA, Davies PDO. Clinically significant drug interactions with antituberculosis agents. *Drugs Safety* 1994; 11: 242–251.
92. Girling DJ. The hepatic toxicity of antituberculosis regimens containing isonlazid, rifampicin and pyrazinamide. *Tubercle* 1978; 59: 13–32.
93. Skolnick JL, Stoler BS, Katz DB, Anderson WH. Rifampin, oral contraceptives, and pregnancy. *JAMA* 1976; 236: 1382.
94. Ormerod CP. Rifampicin and isoniazid prophylaxis for tuberculosis. *Arch Dis Child* 1998; 78: 169–171.
95. Girling DJ. The role of pyrazinamide in primary chemotherapy of pulmonary tuberculosis. *Tubercle* 1984; 65: 1–4.
96. Horsfall PAL, Plummer J. Double-blind controlled comparison of aspinin, allopurinol and placebo in the management of arthralgia during, pyrazinamide administration. *Tubercle* 1979; 610: 13–24.
97. Joint Tuberculosis Committee the British Society. Control and prevention of tuberculosis in the United Kingdom. Code of Practice 1994. *Thorax* 1994; 49: 1193–1200.
98. Leibold JE. The oculotoxicity of Ethambutol and its relation to dose. *NY Acad Sci* 1966; 135: 904–909.
99. Wilson WR, Wilkowski CJ, Wright AJ, *et al*. Treatment of streptomycin-susceptible and streptomycin-resistant enterococcal endocarditis. *Ann Intern Med* 1984; 100: 816–823.
100. Heifets LB, Lindholm-Levy PJ, Iseman MD. Rifabutin: minimal inhibitory and bactericidal concentrations for Mycobacterium tuberculosis. *Am Rev Respir Dis* 1988; 137: 719–721.
101. Hong Kong Chest Service/British Medical Research Council. A controlled study of rifabutin and an uncontrolled study of ofloxacin in the retreatment of patients with pulmonary tuberculosis resistant to isoniazid, streptomycin and rifampicin. *Tuberc Lung Dis* 1992; 73: 59–67.
102. Dhillon J, Dickinson M, Guy GA, *et al*. Activity of two long-acting rifamycins, rifapentine and FCE22807, in experimental murine tuberculosis. *Tuberc Lung Dis* 1992; 73: 116–123.
103. Berning SE, Madsen L, Iseman MD, Peloquin CA. Long-term safety of floxacin and ciprofloxacin in the treatment of mycobacterial infections. *Am J Respir Crit Care Med* 1995; 151: 2006–2009.
104. Dooley DP, Carpenter JL. Adjunctive corticosteroid therapy for tuberculosis: a critical reappraisal of the literature. *Clinical Infectious Diseases* 1997; 25: 872–887.
105. Strang JIG, Kakza HHS, Gibson DG, *et al*. Controlled trial of complete open drainage and prednisolone in the treatment of tuberculous pericardial effusion in Transkei. *Lancet* 1988; ii: 759–763.
106. Strang JIG, Kakza HHS, Gibson DG, *et al*. Controlled trial of prednisolone as adjuvant in the treatment of tuberculous constrictive pericarditis in Transkei. *Lancet* 1987; 11: 1418–1422.
107. Shaw PP, Wang SM, Tung SG, *et al*. Clinical analysts of 445 adult cases of tuberculosis meningitis. *Chinese J Tuberc Respir Dis* 1984; 3: 131–132.
108. Humphries MJ. The management of tuberculous meningitis. *Thorax* 1992; 47: 577–581.
109. Azeer AH, FitzGerald JM. Corticosteroids and tuberculosis: risk and use as adjunct therapy. *Tuberc Lung Dis* 1993; 74: 6–11.
110. Wright EC. Non-compliance- or how many aunts has Matilda. *Lancet* 1993; 342: 909–913.
111. Volmilk J, Gamer P. Systematic review of randomised controlled trials of strallegies to promote adherence to tuberculosis treatment. *BMJ* 1997; 315: 1403–1406.