WHO/HTM/TB/2006.365

Ethambutol efficacy

and toxicity:

literature review and recommendations for daily and intermittent dosage in children

This review was produced by the Stop TB Department and the Department of Child and Adolescent Health and Development of the World Health Organization.

Contents

Abbreviations

AFB	acid-fast bacilli
C_{max}	maximum plasma concentration
CPM	capreomycin
CS	cycloserine
EBA	early bactericidal activity
EMB	ethambutol
ETH	ethionamide
FDC	fixed-dose combination
INH	isoniazid
KM	kanamycin
MIC	minimum inhibitory concentration
PSA	*p*-aminosalicylic acid
PZA	pyrazinamide
RMP	rifampicin
SM	streptomycin
T_{max}	time to reach C_{max}
TB	tuberculosis
THIO	thioacetazone
VEP	visual evoked potential
VIO	viomycin

In addition to the above abbreviations, used for convenience in the text of this review, there is a standard code for TB treatment regimens, which uses an abbreviation for each anti-TB drug. A regimen consists of two phases. The number in front of each phase represents the duration of that phase in months. A subscript number (e.g. $_3$) following a letter (drug abbreviation) is the number of doses per week of that drug. If there is no subscript number following a letter, treatment with that drug is daily. An alternative drug (or drugs) appears as a letter (or letters) in parentheses.

Example: 2 SHRZ/4 H_3R_3
The *initial phase* is 2 SHRZ. Duration of the initial phase is 2 months. Drug treatment is daily (no subscript numbers after the letters) with streptomycin (S), isoniazid (H), rifampicin (R) and pyrazinamide (Z).
The *continuation phase* is 4 H_3R_3. Duration of the continuation phase is 4 months , with isoniazid and rifampicin three times weekly (subscript number after the letters).

Foreword

A literature review commissioned by the Stop TB Department of World Health Organization was prompted by the varying recommendations in the literature, including WHO publications, with regard to the dose of ethambutol for the treatment of tuberculosis (TB) in children. Examples of WHO recommendations include the following:

- *WHO model list of essential medicines: 14th list, March 2005*, which recommends a daily dose of 15 mg/kg (without a range) and includes the advice that ethambutol should not be given to children under 5 years of age.

- *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*, 2005, issued by the Department of Child and Adolescent Health and Development, which recommends a daily dose of 20 mg/kg (range 15–25 mg/kg).

- *Treatment of tuberculosis: guidelines for national programmes*, 2003, issued by the Stop TB Department, which recommends a maximum dose of 15 mg/kg (without a range).

This document reviews the published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults and makes a recommendation for the dosage of EMB to be used in childhood that represents the best compromise between efficacy and toxicity.

Contributors

Lead author *(responsible for conducting the initial literature review)*

Peter Donald, Department of Paediatrics and Child Health, Faculty of Health Sciences, Stellenbosch University, Tygerberg, South Africa

Writing team *(responsible for drafting the document)*

Peter Donald, Dermot Maher, Stephan Maritz, Shamim Qazi

Members of subgroup on childhood TB[1] *(reviewed and endorsed the document)*

Valentina Aksenova, Hastings Tom Banda, Nulda Beyers, Gertrude Bita, Gunnar Bjune, Chifumbe Chintu, Mark Cotton, Olbeg Desinor, Peter Donald, Donald Enarson, Penny Enarson, Kristina Feja, Robert Gie (*Chairperson*), Steve Graham, Jan van den Hombergh, Dermot Maher (*Secretary*), Mamodikoe Makhene, Anna Mandalakas, Davide Manissero, Fatima Ribo March, Ezekiel Mupere, Philippa Musoke, Charles Mwansambo, Lisa Nelson, Kosuke Okada, Isadore-Evans Pazvakavambwa, Clydette Powell, Shamim Qazi, Nastiti N. Rahajoe, Mary Reichler, Annelies Van Rie, Clemax Sant'Anna, Simon Schaaf, Jane Schaller, Leslie Serchuk, Christine Sizemore, Asma El Sony, Jeff Starke, Hugo Vrakking, Martin Weber, Charles Wells

Acknowledgements

The librarians of the Medical Library of the Faculty of Health Sciences of Stellenbosch University provided valuable assistance with the literature search.

[1] Organized under the auspices of the DOTS Expansion Working Group (one of the seven working groups of the Global Partnership to Stop TB). Its goal is to reduce the global burden of mortality and morbidity caused by TB in children.

Summary

Introduction

Current recommendations by WHO and other bodies for the dosage of ethambutol (EMB) in children vary from a maximum daily dose of 15 mg/kg body weight daily (without a range) to daily doses of 15–20 mg/kg and of 20 mg/kg with a range of 15–25 mg/kg. This document reviews the published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults and makes a recommendation for the daily dose of EMB to be used in children. The conclusion also contains a recommendation for an intermittent dose.

Method

Using the key words ethambutol, childhood, tuberculosis, pharmacokinetics, bioavailability and toxicity, searches were conducted using Medline and PubMed. In addition extensive cross-references were sought from original papers, books and conference proceedings dating from 1961. When English summaries were available data were also extracted from papers in languages other than English.

Results

EMB has a clear dose-related efficacy that is best seen when it was given to adults alone, or in the company of only a single other drug; thus given together with isoniazid (INH) a dose of 15 mg/kg EMB gave better results than a dose of 6 mg/kg, and a dose of 25 mg/kg better results than 15 mg/kg. The occurrence of ocular toxicity in adults was also dose related and at doses of >50 mg/kg >40% of adults developed toxicity compared with 0–3% at a dose of 15 mg/kg/daily. Peak serum EMB concentrations in both children and adults increase in relation to dose, but are significantly lower in children than adults receiving the same mg/kg/body weight dose. In only 2 of 3811 children (0.05%) recorded as having received doses varying from 15 mg/kg to 30 mg/kg was EMB stopped for possible EMB ocular toxicity.

Conclusion

In view of the almost total lack of ocular toxicity in children of all ages receiving EMB at doses of from 15-30 mg/kg documented in this review it can be recommended that children of all ages can be given EMB in daily doses of 20 mg/kg (range 15–25 mg/kg) and three times weekly intermittent doses of 30 mg/kg body weight without undue concern.

1. Introduction

"Enough has been said to suggest that ethambutol is no competitor for isoniazid, but it might well be considered a companion drug and replacement for PAS. Two factors will determine this: cost and side reactions."

Aaron Chaves, 1966

In 1961 the Lederle Company announced the discovery of a new antituberculosis agent (Thomas et al., 1961): "In the course of screening randomly selected synthetic compounds, *N*,*N*'-diisopropylethylenediamine was found to protect mice from otherwise lethal infection with *Mycobacterium tuberculosis*, strain H37Rv." In vitro concentrations of 1–4 µg/ml inhibited the growth of *Mycobacterium tuberculosis* H37Rv; the new agent, ethambutol (EMB), was also shown to be effective in tuberculosis-infected guinea pigs. (Karlson, 1961). Unfortunately it was very soon apparent that this promising new agent was responsible for "toxic amblyopia" and this was found in 8 of 18 patients (44%) receiving 60–100 mg/kg body weight of the agent daily (Carr & Henkind, 1962). It was noted, however, that the "ocular disturbances improved on cessation of the drug".

More than 40 years later, EMB has an established place as a first-line antituberculosis agent, valued for the protection that it offers companion drugs against the development and consequences of drug resistance. Its use in adults is usually accompanied by the admonition that "Patients should be advised to discontinue treatment immediately and to report to a clinician if their sight or perception of colour deteriorates" (WHO, 2003). Because of the potentially serious nature of this complication there has been considerable reluctance to use EMB in young children, and most international and national guidelines recommend that EMB should not be given to children younger than 5 or 7 years of age. Nevertheless, there is a considerable body of published literature attesting to the use of EMB in young children; in only 2 of 3811 cases (0.05%) was EMB stopped because of fears of poorly documented ocular toxicity (see also Trébucq, 1997; Graham et al., 1998)

What is indisputable is that countries with a high tuberculosis burden are in desperate need of a drug such as EMB, with a low risk of toxicity, that can be given orally. The problem with EMB is that the one toxic complication to which it does give rise is not only potentially very serious, but is also impossible to detect satisfactorily in young children. This is particularly true in resource-limited countries – and it is precisely here that the need is greatest. In the presence of an escalating HIV/AIDS epidemic, the use of injections, as are needed with streptomycin for example, is now considered inadvisable, while thioacetazone has fallen into disrepute because of an unacceptably high incidence of toxic hypersensitivity reactions. Currently only five "first-line" antituberculosis agents are available for use. For many developing countries, if a fourth drug is needed in childhood, there is very little alternative to the use of EMB, and the only decision to be made is the dosage that should be used and whether use of the drug should be restricted to children over 7 years of age.

From the perspective of a tuberculosis control programme, most children have sputum (or gastric aspirate) smear-negative, paucibacillary forms of primary tuberculosis and can be successfully treated with a Category III regimen – INH, rifampicin (RMP) and pyrazinamide (PZA) in the initial phase). The number of children under 7 years of age with serious forms of tuberculosis needing Category I treatment (with four drugs, INH, RMP, PZA and EMB, in the initial phase) is relatively

small. Consequently, EMB is reserved for the minority of children with more extensive disease requiring Category I treatment and for children with drug-resistant tuberculosis, for whom the risks attached to the use of EMB can be better justified. However, a number of problems have been identified with regard to reliance upon RMP in the continuation phase in developing countries; these include the extra expense, the necessity of supervising treatment and the risk that the drug might be sold on the “black market” (Graham et al., 1998).

In addition to problems related to ocular toxicity, current recommendations by WHO and other bodies for the dose of EMB in children are not uniform and vary from a maximum dose of 15 mg/kg body weight daily (without a range) to daily doses of 15–20 mg/kg and of 20 mg/kg with a range of 15–25 mg/kg.

This document reviews the published evidence relating to the dosage, toxicity and pharmacokinetics of EMB in children and adults and makes recommendations for the daily dosage of EMB to be used in childhood and for an intermittent dose.

2. Methods

The key words ethambutol, childhood, tuberculosis, pharmacokinetics, bioavailability and toxicity were used in literature searches using Medline. In addition, extensive cross-references were sought from original papers, books and conference proceedings dating from 1961. When English summaries were available, data were also drawn from papers in languages other than English. The fragmentary data relating to children in some "adult" papers (e.g. Pilheu, 1970) often failed to provide useful information because the children's ages were not specified or the results were insufficiently documented. Many early articles did not attempt a statistical interpretation of results, leaving readers to draw their own conclusions. More often than not, authors were satisfied with recording "reversal of infectiousness".

In reviewing data relating to efficacy, particular attention was paid to the period before about 1970. It was during this period that EMB was often given either alone to drug-resistant patients or in combination with relatively weak drugs; it was therefore easier to discern a dose-related effect of EMB in these early reports than in later studies when very effective agents, especially RMP and PZA were introduced.

Separate sections are devoted to the efficacy of EMB in adults, toxicity of the drug in adults, efficacy and toxicity in childhood, and pharmacokinetics in adults and children; a further section reviews published recommendations on the use of EMB in children. For each of these sections, a corresponding annex summarizes the main points of each of the papers reviewed as they reflect on some facet of EMB; however, not all of the documents reviewed are referred to in the main body of the review. The annexes list the papers chronologically, while reference lists are organized alphabetically by author.

3. Results

3.1 Efficacy of ethambutol in adults

The value of the new drug was soon demonstrated in clinical trials inpatients with chronic drug-resistant tuberculosis and in new “initial” cases. patients. EMB was used with success In chronic drug-resistant disease, both as a sole agent in otherwise therapeutically destitute patients, and with available second-line agents. Early studies used very high doses of EMB, for example 50 mg/kg daily (Kass, 1965) or, later, 25 mg/kg throughout – subsequently reducing further, to 25 mg/kg for the first 2 months and 15 mg/kg daily thereafter (Bobrowitz & Gokulanathan, 1965). With this latter adaptation it was hoped to avoid the problem of ocular toxicity while maintaining clinical efficacy. Experience has shown, however, that no clinically effective dose is totally free from the danger of ocular toxicity.

At the closing of a large international conference to discuss the use of EMB, Dr Aaron Chaves, Director of Tuberculosis Clinics for the Department of Health of the City of New York stated, ”Enough has been said to suggest that ethambutol is no competitor for isoniazid, but it might well be considered a companion drug and replacement for PAS. Two factors will determine this: cost and side reactions.” (Anon., 1966). Subsequent events have borne out Dr Chaves’s words: in the doses necessitated by the occurrence of optic neuritis, EMB has come to be seen as a bacteriostatic agent, whose main function in modern regimens is protect companion drugs against resistance, particularly in the face of INH resistance. How well it fulfils this role at the doses currently recommended is a moot point.

In a variety of different liquid and solid media, the minimum inhibitory concentration (MIC) of EMB varies from 0.5 µg/ml to 2.0 µg/ml (Otten, 1988); in 7H12 BACTEC broth MIC varies from 0.95 to 3.8 µg/ml, and on 7H10 agar from 1.9 to 7.5 µg/ml (Suo et al., 1988). During in vitro experiments, EMB was less bactericidal than INH, RMP and streptomycin (SM) (Dickinson, Aber & Mitchison, 1977) and did not appear to influence the bactericidal activity of either INH or RMP when given with either of those drugs alone or with a combination (INH+RMP+EMB). However, as in clinical studies, it must be conceded that very much better in vitro bactericidal activity could be demonstrated at higher concentrations (10 µg/ml) and with longer exposure (Gangadharam et al., 1990)

During in vivo experiments with guinea-pigs, EMB alone failed to prevent disease progression and, again, did not appear to influence the bactericidal activity of INH or RMP (Dickinson & Mitchison, 1976). It was concluded that EMB was unlikely to contribute to the sterilization of tuberculosis lesions but might assist in the prevention of drug resistance. Clinical experience has tended to confirm these experimental findings.

In other in vitro experiments, the bactericidal activity of EMB, unlike that of RMP or INH, was the same at any concentration between 1.25 µg/ml and 5 µg/ml (Jenne & Beggs, 1973). Similar findings were reported by Kuck, Peets & Forbes (1963) and Hobby & Lenert (1972). The *duration* of exposure was considered to be more important at the relevant concentrations than the actual concentration. Should these findings be applicable in the clinical situation, it would provide some backing for the reliance on the lower doses of EMB currently in use.

The clearest picture of the potential value of EMB in the treatment of pulmonary tuberculosis is perhaps provided by early clinical studies during which the drug was used either alone or in the company of other relatively weak drugs. Thus, when EMB was given alone to otherwise therapeutically destitute patents with drug-resistant tuberculosis, culture conversion was achieved in 36–50% of individuals (Bobrowitz & Gokulanathan, 1965; Donomae & Yamamoto, 1966; Pyle et al., 1966; Gyselen et al., 1968; Tai & Chen, 1968). Failure was often accompanied by the emergence of EMB resistance, so confirming the antituberculosis activity of the drug. The study by Gyselen et al. (1968) provided the best view of future developments when "reversal of infectiousness" was achieved in 36% of patients receiving EMB alone, 58% of those receiving EMB together with another previously unused drug, but in 83% of those given EMB and the then new agent RMP.

Several early studies provide some evidence of a dose–effect relationship in reversal of infectiousness; examples include Donomae & Yamamoto (1966) (EMB 25 mg/kg compared with 12.5 mg/kg), Bobrowitz & Robins (1967) (25 mg/kg and then 15 mg/kg compared with 15 mg/kg throughout), and Doster et al. (1973) (15 mg/kg compared with 6 mg/kg). The efficacy of the doses used in these early studies is summarized in Table 1. A paper by Murray (1967) that included data from a study previously published by Ferebee et al. (1966) and subsequently published by Doster et al. (1973) provided evidence of a dose effect, with EMB (in combination with isoniazid) being more effective at 15 mg/kg than at 6 mg/kg.

Later drug trials concentrated increasingly upon the all-important aspect of sterilization of lesions reflected in the relapse rate and the ability of particular agents to support other agents in the regimen by preventing the development of drug resistance or the expansion of existing resistance.

In an assessment of the value of different agents in preventing the emergence of resistance in companion drugs, resistance to INH emerged in 4% of cases when EMB was combined with INH and resistance to RMP in 18% of cases when EMB was combined with RMP (summarized in Mitchison, 1984). EMB is thus considered to have only a moderate ability to protect companion drugs from resistance (Mitchison, 1985). In the presence of INH or SM resistance, EMB has in some studies appeared to contribute to a favourable outcome. Thus, in an evaluation of 6-month and 8-month regimens during which PZA could be compared with EMB, it was evident that the patients in the EMB series had a considerably higher relapse rate after either 6 or 8 months of treatment (Hong Kong Chest Service/ British Medical Research Council, 1979). However, among patients who had strains initially resistant to INH or SM, those receiving EMB had a more favourable response at the end of chemotherapy than those given the other regimens. These results were confirmed in other studies (Hong Kong Chest Service/British Medical Research Council, 1982). It should be noted that, in these studies, the EMB dose was 25 mg/kg during the intensive daily phase and 45 mg/kg during the intermittent continuation phase. The EMB dosages now used in adults – 15 and 30 mg/kg – are, respectively, 60% and 67% of the earlier doses.

In studies involving EMB at a dose of 25 mg/kg body weight, the early bactericidal activity (EBA) of the drug was substantial at 0.246, compared with 0.187 for RMP (Jindani et al., 1980). A later study (Botha et al., 1996) reported a similar EBA (0.245), also at a dose of 25 mg/kg. Since EBA reflects an agent's ability to kill the metabolically active bacilli in the walls of cavities, it might also reflect its capacity for

protecting companion drugs against resistance. In this respect, it should be noted that the EBA of EMB given at 15 mg/kg was found to be considerably lower (0.05), and this dose-related decline in activity, although seen in only a small number of patients (3), is cause for concern (Jindani et al., 1980).

In a recent evaluation of an EMB-containing regimen, EMB was used at daily doses of between 15 and 20 mg/kg body weight in most patients (Jindani, Nunn & Enarson, 2004). After a similar intensive phase of INH, RMP, PZA and EMB, patients received INH+RMP for 4 months or EMB+INH for 6 months. Disappointingly, although relapse occurred in only 1 (4%) of 23 patients who were resistant to INH at the start of therapy and who received INH+RMP in the continuation phase, 11(31%) of the 35 given EMB+INH in the continuation phase relapsed, confirming again the poor sterilizing action of EMB and its failure to protect the regimen from the consequences of INH resistance. It is not clear from the paper whether the use of EMB protected patients with INH resistance from the development of further resistance.

The evidence available from clinical trials in adults thus confirms that, at the dosages necessitated by the unacceptable levels of toxicity at higher dosages, EMB is at best bacteriostatic and, unless given for a longer period than is manageable in most tuberculosis control programmes has a limited influence upon the outcome in adult pulmonary tuberculosis.

3.2 Toxicity of ethambutol in adults

"It is necessary still to emphasize that the administration of potent drugs involves a 'calculated risk' where the presumptive benefit is balanced against the possibility of toxic effects and idiosyncrasies: but to calculate wisely it is necessary to know, as accurately as possible, what the risk may be in kind, degree and frequency; and the special condition which may increase or decrease the chance of injury…Full information will serve to protect in both ways: against the unjustified fear as well as against the risk of rashness."

T. Solman, 1953[1]

Several groups active during the early clinical assessment of EMB commented upon the difficulties encountered in assessing the development of ocular toxicity due to EMB (Ferebee, Doster & Murray, 1966; Bobrowitz & Robins, 1967; Doster et al., 1973). Even among patients who were not receiving EMB, changes in visual acuity were quite commonly documented, and in several clinical trials where the clinicians were blinded to the allocation of patients, ocular "toxicity" was recorded among the control groups. The possibility of toxicity would be sufficient to prompt careful clinicians to stop the drug; Ferebee, Doster & Murray (1966) referred to this as a "psychological" hazard.

Early studies of the use of EMB tended to be fairly precise in describing how toxicity was assessed; by contrast, some later studies either make no specific mention of ocular toxicity and its assessment, or carried out formal assessment only if patients presented with complaints of visual disturbances. Nevertheless, there is no doubt that the ocular toxicity of EMB is dose-related and that, although incidence declines as the dose declines, ocular toxicity has been encountered at all EMB doses in clinical use. There are case reports of confirmed cases of ocular toxicity occurring at an EMB dose of 15 mg/kg: the data (but not the case reports) are summarized in Table 2.

[1] Quoted in: Kass I (1965). Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of kanamycin, ethionamide and either cycloserine or pyrazinamide. *Tubercle*, 46:151–165.

Figure 1 illustrates the percentage of cases developing ocular toxicity in relation to EMB dose.

Disturbingly, more refined ophthalmological testing – by ophthalmologists – of patients receiving EMB has revealed more frequent abnormalities than is the case following a more superficial clinical evaluation (Yiannikas, Walsh & McLeod, 1983; Polak, Leys & van Lith, 1985; Joubert et al., 1986; Salmon, Carmichael & Welsh, 1987; De Palma et al., 1989). The importance of these abnormalities is uncertain, as is the potential for zinc deficiency to precipitate ocular toxicity in patients receiving EMB. At least one study found a considerably higher incidence of ocular toxicity among patients with low zinc concentrations (De Palma et al., 1989). In another study, Campbell & Elmes (1975) found no difference in the serum concentrations of copper or zinc after 2 months of treatment with EMB at 25 mg/kg. Children with tuberculosis, particularly those with HIV/AIDS, are very likely to be zinc-deficient (Ferguson at al., 1992; Roy, Kumar & Prasad, 1998).

3.3 Efficacy and toxicity of ethambutol in children

EMB has been used to treat tuberculosis almost in children as long as it has been used in adults. Its use has generally, but not always, been confined to children over 3 years of age, because of concern about the risk of ocular toxicity and the difficulty of assessing ocular function in young children. There are few, if any, totally satisfactory studies comparing the efficacy of EMB in children with that of other drugs. Many early papers record the absence of overt toxicity and express satisfaction about the availability of a drug to replace PAS, which was associated with considerable gastrointestinal discomfort and consequent patient resistance to its use.

In many studies of childhood tuberculosis, broad, subjective criteria, such as weight gain and general well-being, have been used to assess the success of a regimen – unlike adult studies, where sputum culture negativity can be used as an indisputable criterion of treatment success. Chest radiograph clearing has often been compared between regimens but, again, *statistical* comparisons are rare. Many cases of disease in childhood are also paucibacillary and a significant proportion of these would recover without any active treatment, especially in children aged 5–10 years. It is thus difficult to assess precisely the success of using EMB in children: reliance must be place on the evidence provided by adult studies to indicate the likely efficacy of EMB in children.

Convincing cases of EMB-induced ocular toxicity have not been reported in children (see Trébucq, 1997; Graham et al., 1998), although in two children EMB has been stopped as result of poorly documented eye problems (Mankodi et al., 1970; Medical Research Council Tuberculosis and Chest Diseases Unit, 1989). Several studies that carefully evaluated significant numbers of children receiving EMB at doses from 15 to 30 mg/kg body weight using sophisticated laboratory and clinical techniques have produced negative results (Chavarria et al., 1970; Scheffler, 1971; Nagy et al., 1980; Junnanond, Chotibut & Lawtiantong, 1983; Seth et al., 1991). In addition, Schmid (1981) mentions – almost in passing – the fact that he has treated 2634 children with EMB without any evidence of toxic ocular damage. Little credence can be given to cases of ocular toxicity reported in association with tuberculous meningitis, as the disease itself will frequently be responsible for the pathology described (Prachakvej & Subharngkahen, 1979; Ramachandran et al., 1986). Finally, as indicated elsewhere

in this document, it is possible that toxicity has not been encountered in children because of insufficient exposure to the drug – the serum EMB concentrations reached in children at the doses used are considerably lower than those reached in adults.

Experience with the use of EMB in children is summarized in Table 3. The papers listed in the table document a total of 3811 children who received EMB, only two of whom developed possible ocular toxicity.

3.4 Pharmacokinetics of ethambutol in adults and children

"The true maximum dose is the highest dose that a patient can tolerate, hopefully while achieving the desired therapeutic response."

Charles A. Peloquin (1998)

In early clinical pharmacology studies, serum concentrations of EMB were maximal "at about 2 hours" after dosing, and peak concentrations following daily doses of 50 and 25 mg/kg body weight were 10 and 5 µg/ml respectively. Serum concentrations were proportional to dose, less than 10% of the administered dose was present in the serum after 24 hours, and there was no evidence in the serum of accumulation of the drug over more than 3 months. Within 6 hours, 28% of an oral dose was excreted in the urine (Place & Thomas, 1963). Following a dose of 17 mg/kg, 2-hour serum level was 2 µg/ml. A daily peak of 5 µg/ml was shown to be highly effective in mice (Thomas, 1961) and monkeys (Schmidt, 1966). It was also noted that the response in monkeys was "dose-related over daily intakes of 12.5 to 100 mg/kg" and that, when EMB was given in combination with isoniazid, "serum levels of 0.6 to 2.0 µg of ethambutol per ml were associated with optimal benefits" (Schmidt, 1966).

Subsequent more sophisticated pharmacokinetic studies have tended to confirm these initial observations (Lee et al., 1977; Lee et al 1980; Peloquin et al., 1999; Zhu et al., 2004). According to these studies, most of the drug (approximately 80%) is excreted unchanged in the urine, the T_{max} tends to be somewhat delayed (between 2 and 4 hours) compared with that for other drugs, and C_{max} is lower following a meal than in fasting conditions (4.5 µg/ml compared with 3.8 µg/ml after 25 mg/kg EMB).

With the notable exception of the central nervous system, the tissue distribution of EMB is good; in several studies, tissue concentrations higher than serum or plasma levels have been found in both patients (Elliott et al., 1995) and experimental animals (Kelly, Kaleita & Eisner, 1981; Liss, Letourneau & Schepis, 1981). By contrast, two studies found that the concentration of EMB in abscess pus was considerably lower than in accompanying serum (Tuli, Kumar & Sen, 1977; Kumar, 1992).

There have been few studies of the pharmacokinetics of EMB in children and none in HIV-infected children. Serum concentrations in children receiving EMB doses varying from 15 to 35 mg/kg have been determined by Hussels & Otto (1971), Hussels, Kroening & Magdorf (1973), Benkert et al. (1974) and Zhu et al. (2004). All of these groups found that serum concentrations in children were lower than those in adults following similar doses (mg/kg) of EMB. Furthermore, Hussels and colleagues (Hussels & Otto, 1971; Hussels, Kroening & Magdorf, 1973) also found lower serum concentrations in younger children than in older children. Commenting on this, Schmid (1981) stated that it was his practice and that of his colleagues to use EMB in children at a dosage of 20 mg/kg, increasing this by 5 mg/kg for children under 5

years and reducing it by 5 mg/kg for those aged over 11 years. Taking into account the serum concentrations of EMB that they had documented, they would avoid toxicity by this means but achieve effective therapeutic concentrations (defined as >2 µg/ml) in the majority of children. Schmid stated that 2634 children had been treated with this regimen but that regular evaluation of the eyes has yielded no evidence of toxic damage ("toxischen Schädigungen").

Published maximum serum concentrations of EMB in adults and children determined by a variety of methods are set out in Tables 4 and 5 respectively, and the difference in the maximum concentrations in children and adults is illustrated in Figure 2. The serum concentrations reached in adults and children given similar doses of EMB are clearly different: for adults, $y = 0.1602*\text{dose}$, and for children, $y = 0.0906*\text{dose}$. The standard errors of the slope coefficients are, respectively, 0.005833 and 0.009080. This suggests that achievement serum concentrations equivalent to those reached in an adult given 15 mg/kg EMB might require a child's being given a dose of 25 mg/kg or higher.

Several factors that influence pharmacokinetics are subject to age-related variations – and these should be borne in mind in considering the above results. They include the ratio of extracellular to intracellular and total body water, biotransformation and elimination. The ratio of extracellular to intracellular and total body water falls throughout childhood, but most rapidly during the first 3 months of life. The liver is the most important organ for biotransformation and the ratio of liver volume to unit body weight declines throughout childhood and is twice as great at 1 year of age as at 14 years. Values for glomerular excretion increase fairly rapidly following birth and reach adult values between 2.5 and 5 months (Rylance et al., 1987; McCarver, 2004). The percentage of EMB excreted unchanged has been variously reported as 40–80% (Place et al., 1966) and 54–67% (Lee et al., 1977). It has also been speculated that the considerable variation in reported EMB absorption – and the somewhat delayed absorption – may be due to binding in the gastrointestinal tract (Lee et al., 1977). It is thus of interest that one of the most recent published studies of EMB pharmacokinetics in children found slow and incomplete absorption of EMB (Zhu et al., 2004).

3.5 Published recommendations for the use of ethambutol in children

Published recommendations for the use of EMB in children are summarized in Annex V and Table 6 and reflect those appearing in other contemporary literature. Thus, earlier recommendations advise 25 mg/kg for the first 2 months (or 8 weeks), followed by 15 mg/kg; later recommendations suggest 15 mg/kg throughout. Although the later recommendations reflect a more liberal approach to the use of EMB in younger children, this tends to be balanced by the use of "hedging" statements such as "…particular caution may be warranted" (Rieder 2002).

4. Conclusions

The published evidence indicates that the peak serum EMB concentrations achieved in children are significantly lower than those reached in adults receiving a similar dose (on a body weight basis) of EMB. Data also indicate that both the efficacy and the toxicity of EMB in adults are dose-related. At a daily dose of 15–20 mg/kg body weight in adults, EMB can be considered no more than bacteriostatic and will provide a measure of protection against the development of resistance to companion drugs and against the further expansion of existing resistance. Ocular toxicity can still occur in adults at a daily EMB dose of 15–20 mg/kg, but it is relatively rare and will usually occur only after several months of treatment. In a minority of cases, however, ocular toxicity can occur earlier in treatment.

All this evidence may unfortunately suggest that the reason that ocular toxicity has not been documented in children may be simply that children have not been given sufficiently high doses for EMB to be as clinically effective as it is in adults. Conversely, it may also imply that the currently recommended doses of EMB are unlikely to carry a serious risk of ocular toxicity to children and can probably be recommended for use in children of all ages. The proposal of Schmid (1981) – to use a dose of 20 mg/kg, reduced to 15 mg/kg in children over 11 years and increased to 25 mg/kg in children younger than 5 years – represented a compromise between efficacy and the smallest risk of toxicity. However, this would be a somewhat complicated regimen to use under the conditions of a tuberculosis control programme and considerably more data would be required to substantiate its value than are currently available.

In debating what dose of EMB children should receive several factors need to be taken into account:

- Should children to be exposed to the same serum concentrations of EMB as adults? Is it *necessary* for children to be exposed to the same serum concentrations as adults?

- If the same serum concentrations of EMB can be achieved in children as in adults (and this might mean a dose of 25–30 mg/kg of EMB in some instances), will children not then be liable to the same incidence of ocular toxicity as adults?

- At present it would appear that children receiving an EMB dose of 15 mg/kg will reach a peak serum concentration of slightly more than 1 µg/ml. As the sliding scale necessitated by the use of body weight bands dictates that dosages approach 20 mg/kg, it seems likely that the maximum serum concentration will approach a mean of 2 µg/ml. In the light of certain in vivo and in vitro experimental data, is this perhaps just sufficient to achieve the somewhat limited therapeutic aims for EMB in current regimens, i.e. the protection of companion drugs against resistance and the prevention of further resistance in the presence of existing resistance (especially to INH)?

Clearly, more studies are needed to provide data on the pharmacokinetics of EMB in children. Nevertheless, in view of the number of children, aged from under 1 year to 18 years, who have been treated with EMB at doses varying from 15 to 30 mg/kg/day without overt ocular toxicity (Table 5), this review supports a change to the recommended daily dose, to 20 mg/kg (range 15–25 mg/kg) body weight for children

of all ages. Increasing the EMB dose beyond this range to compensate for the deficiencies in serum concentrations that have been identified in children might increased the risk of EMB ocular toxicity. For intermittent treatment, recommended doses of 30 mg/kg (range 20–35 mg/kg) three times weekly or 45 mg/kg (range 40–50 mg/kg) twice weekly are proposed – as currently recommended for adults.

Just as with an adult patient, care should be taken to establish that a child does not suffer from renal disease as this could lead to exposure to unacceptably high serum concentrations of EMB. Should the use of EMB be necessitated by severe drug-resistant tuberculosis in a young child, it would also seem prudent, weighing up the relative dangers of toxicity versus efficacy and the danger of drug-resistant tuberculosis, to consider the use of higher daily doses (20–30 mg/kg) for a child of any age.

References

Anon. (1966). The future of ethambutol and capreomycin in the chemotherapy of tuberculosis. *Annals of the New York Academy of Sciences*, 135:1098–1118.

Acquinas M, Citron KM (1972). Rifampicin, ethambutol and capreomycin in pulmonary tuberculosis previously treated with both first and second line drugs: the results of 2 years' chemotherapy. *Tubercle*, 53:153–165.

Benkert K et al. (1974). Tagesprofile und Profilverlaufskontrollen von Ethambutol bei Kindern [Daily check and follow-up of use of ethambutol in children]. *Medizinische Klinik*, 69:1808–1813.

Bobrowitz ID (1966a). Ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:796–822.

Bobrowitz ID (1966b). Comparison of ethambutol-INH versus INH-PAS in original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Bobrowitz ID, Gokulanathan KS (1965). Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Bobrowitz ID, Robins DE (1967). Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 96:428–438.

Botha FJH et al. (1996). Early bactericidal activity of ethambutol, pyrazinamide and the fixed dose combination of isoniazid, rifampicin and pyrazinamide (Rifater) in patients with pulmonary tuberculosis. *South African Medical Journal*, 86:155–158.

Campbell IA, Elmes PC (1975). Ethambutol and the eye; zinc and copper. *Lancet*, 2: 711.

Carr RE, Henkind P (1962). Ocular manifestations of ethambutol. *Archives of Ophthalmology*, 67:566–571.

Chavarria AG et al. (1970). Evaluacion clinica del etambutol en 36 niños tuberculosos estudados durante cuatro años [Clinical evaluation of ethambutol in 36 tuberculous children studied for four years]. *Neumologia y Cirugia de Torax (Mexico)*, 31:39–47.

De Palma P et al. (1989). The incidence of optic neuropathy in 84 patients treated with ethambutol. *Metabolic, Pediatric, and Systemic Ophthalmology*, 12:80–82.

Dickinson JM, Mitchison DA (1976). Bactericidal activity in vitro and in the guinea pig of isoniazid, rifampicin and ethambutol. *Tubercle*, 57:251–258.

Dickinson JM, Aber VR, Mitchison DA (1977). Bactericidal activity of streptomycin, isoniazid, rifampin, ethambutol and pyrazinamide alone and in combination against *Mycobacterium tuberculosis*. *American Review of Respiratory Disease*, 116:627–635.

Donomae I, Yamamoto K (1966). Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Doster B et al. (1973). Ethambutol in the initial treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 107:177–190.

Elliott AM et al. (1995). Failure of drug penetration and the acquisition of drug resistance in chronic tuberculous empyema. *Tubercle and Lung Disease*, 76:463–467.

Ferebee SH, Doster BE, Murray FJ (1966). Ethambutol: a substitute for para-aminosalicylic acid in regimens for pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:910–920.

Ferguson EL et al. (1993). Zinc nutriture of preschool children living in two African countries. *Journal of Nutrition*, 123:1487–1496.

Gangadharam PR et al. (1990). The effects of exposure time, drug concentration, and temperature on the activity of ethambutol versus *Mycobacterium tuberculosis*. *American Review of Respiratory Disease*, 141:1478–1482.

Graham SM et al. (1998). Ethambutol in tuberculosis: time to reconsider? *Archives of Disease in Childhood*, 79:274–278.

Gyselen A et al. (1968). Rifampin and ethambutol in the retreatment of advanced pulmonary tuberculosis. *American Review of Respiratory Disease*, 98:933–943.

Hobby GI, Lenert TF (1972). Observations on the action of rifampin and ethambutol alone and in combination with other antituberculosis drugs. *American Review of Respiratory Disease*, 105:292–295.

Hong Kong Chest Service/ British Medical Research Council (1979). Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 60:201–210.

Hong Kong Chest Service/ British Medical Research Council (1982). Controlled trial of 4 three-times weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 63:89–98.

Hussels H, Otto HS (1971). Ethambutol-Serumkonzentrationen im Kindesalter [Serum ethambutol levels in childhood]. *Pneumonologie*, 145:392–396.

Hussels H, Kroening U, Magdorf K (1973). Ethambutol and rifampicin serum levels in children: second report on combined administration of ethambutol and rifampicin. *Pneumonologie*, 149:31–38.

Jenne JW, Beggs WH (1973). Correlation of in vitro and in vivo kinetics with clinical use of isoniazid, ethambutol and rifampin. *American Review of Respiratory Disease*, 107:1013–1021.

Jindani A, Nunn AJ, Enarson DA (2004). Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet*, 364:1244–1451.

Jindani A et al. (1980). The early bactericidal activity of drugs in patients with pulmonary tuberculosis. *American Review of Respiratory Disease*, 121:939–949.

Joubert PH et al. (1986). Subclinical impairment of colour vision in patients receiving ethambutol. *British Journal of Clinical Pharmacology*, 21:213–216.

Junnanond C, Chotibut S, Lawtiantong T (1983). Safety evaluation of ethambutol in children. *Journal of the Medical Association of Thailand*, 66:77–79.

Karlson AG (1961). Therapeutic effect of ethambutol (dextro-2,2'-(ethylenediimino)-di-1-butanol) on experimental tuberculosis in guinea pigs. *American Review of Respiratory Disease*, 84:902–904.

Kass I (1965). Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoamyloxythiosemicarbanilide. *Tubercle*, 46:166–177.

Kelly RG, Kaleita E, Eisner HJ (1981). Tissue distribution of (^{14}C)ethambutol in mice. *American Review of Respiratory Disease*, 123:689–690.

Kuck NA, Peets EA, Forbes M (1963). Modes of action of ethambutol on *Mycobacterium tuberculosis*, strain H37Rv. *American Review of Respiratory Disease*, 87:905–906.

Kumar K (1992). The penetration of drugs into the lesions of spinal tuberculosis. *International Orthopaedics*, 16:67–68.

Lee CS et al. (1977) Kinetics of oral ethambutol in the normal subject. *Clinical Pharmacology and Therapeutics*, 22:615–621.

Lee CS et al. (1980). Disposition kinetics of ethambutol in man. *Journal of Pharmacokinetics and Biopharmaceutics*, 8:335–346.

Liss RH, Letourneau RJ, Schepis JP (1981). Distribution of ethambutol in primate tissues and cells. *American Review of Respiratory Disease*, 123:529–532.

Mankodi NA et al. (1970). Ethambutol in unresponsive childhood tuberculosis. *Indian Pediatrics*, 7:202–211.

McCarver G (2004). Applicability of the principles of developmental pharmacology to the study of environmental toxicants. *Pediatrics*, 113:969–972.

Medical Research Council Tuberculosis and Chest Diseases Unit (1989). Management and outcome of chemotherapy for childhood tuberculosis. *Archives of Disease in Childhood*, 64:1004–1012.

Mehta DK, Ryan RSM, Hogerzeil H, eds (2004). *WHO model formulary 2004*. Geneva, World Health Organization.

Mitchison DA (1984). Drug resistance in mycobacteria. *British Medical Bulletin*, 40:84–90.

Mitchison DA (1985). The action of antituberculosis drugs in short-course chemotherapy. *Tubercle*, 66:219–225.

Murray FJ (1967). US Public Health Service experience with ethambutol. *International Congress of Chemotherapy, Vienna 1967*, 6:33–382.

Nagy A et al. (1980). Studiu privind toxitatea oculară a etambutolui [Study on ocular toxicity of ethambutol]. *Pneumoftizologia*, 29:163–166.

Otten H (1988). Ethambutol (EMB). In: Bartmann K, ed. *Antituberculosis drugs*. Berlin, Springer-Verlag:197–204.

Peloquin CA (1998). Serum concentrations of antimycobacterial drugs. *Chest*, 113:1154–1155.

Peloquin CA et al. (1999). Pharmacokinetics of ethambutol under fasting conditions with food and with antacids. *Antimicrobial Agents and Chemotherapy*, 43:568–572.

Pilheu J (1970). Ambulatory treatment of pulmonary tuberculosis with ethambutol-isoniazid. *Chest*, 58:497–500.

Place VA, Thomas JP (1963). Clinical pharmacology of ethambutol. *American Review of Respiratory Disease*, 87:901–904.

Place VA et al. Metabolic and special studies of ethambutol in normal volunteers and tuberculous patients. *Annals of the New York Academy of Sciences*, 135:775–795.

Polak CP, Leys M, van Lith GHM (1985). Blue-yellow colour vision changes as early symptoms of ethambutol oculotoxicity. *Ophthalmologica*, 191:223–226.

Prachakvej P, Subharngkahen I (1979). Visual loss from ethambutol. *Siriraj Hospital Gazette*, 31:908–912.

Pyle MM (1966). Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

Pyle MM et al. (1966). A four-year clinical investigation of ethambutol in initial and re-treatment cases of tuberculosis. *American Review of Respiratory Disease*, 93:428–441.

Ramachandran P et al. (1986). Three chemotherapy studies of tuberculous meningitis in children. *Tubercle*, 67:17–29.

Roy M, Kumar L, Prasad R (1998). Plasma zinc in Indian childhood tuberculosis: impact of antituberculosis therapy. *International Journal of Tuberculosis and Lung Disease*, 2:719–725.

Rylance G et al. (1987). Drug response determinants. In: Drugs for children. Copenhagen, World Health Organization Regional Office for Europe:7–19.

Salmon JF, Carmichael TR, Welsh NH (1987). Use of contrast sensitivity measurement in the detection of subclinical ethambutol toxic optic neuropathy. *British Journal of Ophthalmology*, 71:192–196.

Scheffler NK (1971). Augenuntersuchungen bei der Behandelung mit Ethambutol in zwei verscheidenen Dosierungen im Kindesalter [Eye examination of children treated with ethambutol under two different dosage schedules]. *Pneumonologie*, 145:396–400.

Schmid PC (1981). Ethambutol- und Rifampicin-verträglikeit und -dosierung im Kindesalter [Ethambutol and rifampicin tolerance and dosages in childhood]. *Pädiatrische Praxis*, 25:207–209.

Schmidt LH (1966). Studies on the antituberculosis activity of ethambutol in monkeys. *Annals of the New York Academy of Sciences*, 135:747–758.

Seth V et al. (1991) Visual evoked responses in tuberculous children on ethambutol treatment. *Indian Pediatrics*, 28:713–717.

Suo J et al. (1988). Minimal inhibitory concentrations of isoniazid, rifampin, ethambutol and streptomycin against *Mycobacterium tuberculosis* strains isolated before treatment of patients in Taiwan. *American Review of Respiratory Disease*, 138:999–1001.

Tai FH, Chen TC (1968). Studies on combined use of ethambutol and isoniazid in retreatment of drug-resistant cases of pulmonary tuberculosis. *Chinese Journal of Microbiology*, 1:84–91.

Thomas JP et al. (1961). A new synthetic compound with antituberculous activity in mice: ethambutol (dextro-2,2'-(ethylenediimino)-di-1-butanol). *American Review of Respiratory Disease*, 83:891–893.

Trébucq A (1997). Should ethambutol be recommended for routine treatment of tuberculosis in children? A review of the literature. *International Journal of Tuberculosis and Lung Disease*, 1:12–15.

Tuli SM, Kumar K, Sen PC (1977). Penetration of antitubercular drugs in clinical osteoarticular lesions. *Acta Orthopaedica Scandinavica*, 48:362–368.

WHO (2003). *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization (WHO/CDS/TB/2003.313).

WHO (2005). *Pocket book of hospital care for children: guidelines for the management of common illnesses with limited resources*. Geneva, World Health Organization.

Yiannikas C, Walsh JC, McLeod JG (1983). Visual evoked potentials in the detection of subclinical effects secondary to ethambutol. *Archives of Neurology*, 40:645–648.

Zhu M et al. (2004). Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

Table 1. Efficacy of daily doses of ethambutol in adults 1965–1973

Study [a]	Regimen [b]	EMB dose (mg/kg)	Duration of evaluation	Patients	Bacteriological efficacy [c]
Bobrowitz & Gokulanathan (1965)	EMB with CS/VIO or PZA	25 & 25/15	At least 4 months	28 re-treat	21 (75%)
	EMB alone	25		15 re-treat	2 (13%)
Kass (1965)	EMB+CPM with PZA/ETH/CS	50	At least 4 months	24 re-treat	24 (100%)
Ferebee, Doster & Murray (1966)	EMB+INH	6	20 weeks	131 initial	122 (93%)
Donomae & Yamamoto (1966)	EMB+INH	12.5	6 months	38 initial	30 (79%)
	EMB+INH	25	6 months	39 initial	38 (98%)
	EMB 1 g daily alone	20	6 months	49 re-treat	20 (41%)
	EMB 1 g alt. days alone	20	6 months	46 re-treat	12 (26%)
	EMB + other drugs	25/15	3 months	45 re-treat	28 (58%)
Pyle et al. (1966)	EMB+INH	20–30	3 months	26 initial	15 (58%)
	EMB+INH		6 months	23 initial	23(100%)
	EMB+INH+SM		3 months	55 initial	40 (69%)
	EMB+INH+SM		6 months	57 initial	57 (100%)
Corpe & Blalock (1966)	EMB+ETH+KM	25	>6 months	118 re-treat	83 (70%)
Bobrowitz & Robins (1967)	EMB+INH	25/15	>4 months	89 initial	71 (95%)
	EMB+INH	15	>4 months	85 initial	54 (89%)
	INH+PAS	–	>4 months	74 initial	42 (82%)
Gyselen et al. (1968)	EMB alone	25/15	20-121 weeks	14 re-treat	5 (36%)
	EMB + other drugs	25/15	29-123 weeks	19 re-treat	11 (58%)
	EMB+RMP	25/15	20-70 weeks	12 re-treat	10 (83%)
Tai & Chen (1968)	EMB+INH	25/15	1 year	100 re-treat	45 (46%)
Pilheu (1970)	EMB+INH	25/15	1 year	145 initial	141 (97%)
Doster et al. (1973)	EMB+INH	6	20 weeks	91 initial	80 (88%) [d]
		15		114 initial	105 (91%)

[a] Summaries of the papers cited appear in Annex I.
[b] CPM = capreomycin, CS = cycloserine, EMB = ethambutol, ETH = ethionamide, INH = isoniazid, KM = kanamycin, PAS = *p*-aminosalicylic acid, PZA = pyrazinamide, RMP = rifampicin, SM = streptomycin, VIO = viomycin
[c] Bacteriological efficacy refers to sputum culture-negativity usually after 4 months, but sometimes 6 months
[d] 8 of the 11 EMB 6 mg/kg failures, but none of the 9 EMB 15 mg/kg, were resistant to INH.

Table 2. Incidence of optic neuritis following use of ethambutol in adults in daily regimens

Authors [a]	Daily ethambutol dosage, mg/kg							
	≤ 15	15–20	20	20–30	25/15	25	35–50	≥ 50
	Incidence of optic neuritis							
Carr & Henkind (1962)								8/18 (44%)
Bobrowitz & Gokulanathan (1965)					0/17	2/18 (11%)		
Kass (1965)								9/60(15%)
Place, Peets & Buyske (1966)	0/4					2/16 (13%)		3/7 (43%)
Corpe & Blalock (1966)						0/118		
Pyle (1966)				4/130 (3%)			2/6 (33%)	
Donomae & Yamamoto (1966)	0/46		1/49 (2%)			2/46 (4%)		
Leibold (1966)				2/59 (3%)			11/59 (19%)	
Ferebee, Doster & Murray (1966)	4/271 (2%)							
Bobrowitz (1966b) } Bobrowitz & Robins (1967) }	1/85 (1%)				1/89 (1%)			
Tai (1968)					1/100 (1%)			
Adel (1969)					10/78 (13%) [b]			
Citron (1969)						2/34 (6%)		
Horsfall (1969)					3/68 (4%)			
Radenbach (1969)					6/300 (2%)			
Wäre (1969)					2/113 (2%)			
Pilheu (1970)					0/145			
Roussos & Tsolkas (1970)	4/250 (2%)							
Schütz (1970)					0/31			
Tiburtius (1970)					9/300 (3%)			
Lees et al. (1971)					1/72 (1%)			

Authors [a]	Daily ethambutol dosage, mg/kg							
	≤ 15	15–20	20	20–30	25/15	25	35–50	≥ 50
	Incidence of optic neuritis							
Acquinas & Citron (1972)					2/36 (6%)			
Br. Med. Res. Council (1973)	3/118 (3%)							
Somner et al. (1973)					0/26			
Barron, Tepper & Iovine (1974)					3/304 (1%)			
HK TB Treatment Service, Brompton Hosp., Br. Med. Res. Council (1974)					2/107 (2%)			
Br. Thoracic & TB Assoc. (1975)						0/169		
Br. Thoracic & TB Assoc. (1981)						0/341		
TB Res. Centre Madras (1981)	2/120 (2%)							
HK Chest Service, Br. Med. Res. Council (1981)					0/239			
De Palma et al. (1989): Zn >1 µg/ml Zn <0.7 µg/ml						3/53 (6%) 5/31 (16%)		
TB Research Centre (1997)	0/305							
Jindani et al. (2004)		4/1355 (0.3%)						
Griffiths et al. (2005)					8/139 (6%)			

[a] Summaries of the papers cited appear in Annex II.
[b] In 6 of these cases the development of optic neuritis was accompanied by a deterioration in renal function.

Table 3. The occurrence of ocular toxicity associated with the use of ethambutol in children

Authors [a]	No.	Age (y)	Daily EMB dose	Treatment duration (m)	Comments on toxicity
Chavarria et al. (1967)	15	2–16	25 mg/kg	12–24	"…nor were there any manifestations of toxicity"
Del Principe, Caione & Zamparelli (1968)	58	1–12	30 mg/kg for 3 m then 15–20 mg/kg for 3 m	6	EMB was "…always well tolerated"
Chavarria et al. (1970)	36	0.3–16	25 mg/kg for 1 m then 15 mg/kg	2–6	"We have never observed toxicity during 4 years of use of ethambutol"
Mankodi et al. (1970)	16	3–12	25 mg/kg for 3 m then 15 mg/kg	8–18	"In one child there was minimal edema of the optic disc after 7 months of therapy; however there were no visual symptoms." Treatment was stopped for 4 months and reintroduced without complication.
Patwardhan, Bhatia & Merchant (1970)	20	0.5–5	25 mg/kg	12	"…no toxic effects were noted"
Schmid (1970)	80	1–6	25 mg/kg	3–4	"No changes… in the eyes (visus or fundus) were observed"
Simon (1970)	49	?	15 mg/kg	3	"Dose: 15 mg/kg, because children cannot sufficiently describe secondary effects"
Pilheu (1970)	34	?	15 mg/kg	12	"Periodic…complete ophthalmological examinations…" No visual abnormalities noted
Mérida de León (1971)	20	3–13	25 mg/kg for 2 m then 15 mg/kg	8–12	None: "…no aparición de daño en el campo visual" [no evidence of visual field deficit]
Scheffler (1971)	60	3.5–15	25 mg/kg for 3 m then 15–20 mg/kg	6 (average)	"Temporary disturbance of vision during the administration of ethambutol in two cases was not connected with the use of ethambutol and disappeared without interruption of the treatment."
Dingley & Sehgal (1974)	54	2–14	25 mg/kg for 2 m then 15 mg/kg for 4 m	6	"…no ophthalmologic abnormalities were detected in the patients treated with ethambutol"
Benkert et al. (1974)	26	3–14	15–25 mg/kg	–	"No side effect was caused in any case"
Bhatia & Merchant (1975)	54	0.2–5	25 mg/kg for 3 m then 15 mg/kg for 12 m	15	"No untoward effects were seen in our series of children given ethambutol for 6–18 months"

| Authors [a] | No. | Age (y) | Daily EMB dose | Treatment duration (m) | Comments on toxicity |

Authors [a]	No.	Age (y)	Daily EMB dose	Treatment duration (m)	Comments on toxicity
Schmid (1981)	2634	3–14	15–25 mg/kg	6	"…keine Komplikationen und keine toxischen Schädigungen beobacht. Trotzdem halten wir regelmäßige Visuskontrollen (Geschtsfeld, Farbshen, Augenhintergrund) fürangezeicht" [no complications and no toxic damage observed. However, regular visual testing continues (visual field, colour discrimination and fundoscopy)]
Gramer, Jeschke & Krieglstein (1982)	6	9–16	20 mg/kg	9	"Visual acuity, visual field and mean retinal threshold of the central field revealed no significant changes with increasing cumulative ethambutol doses up to 166 g"
Junnanond, Chotibut & Lawtiantong (1983)	27	5.5–15	20 mg/kg	2–24	"In this study there were no abnormal ocular changes in any of the patients"
Fox, quoted by Ramachandran et al. (1986)	45	1–15	15–20 mg/kg	9–18	"There was no evidence from any of the assessments in any patient of ocular toxicity due to ethambutol"
Med. Res.Council TB & Chest Diseases Unit (1989)	151	<1–14	6–12 mg/kg 13–17 mg/kg 18–30 mg/kg	21/32 (66%) 61/76 (80%) 33/43 (77%)	"In this survey…only one possible case of ocular toxicity was reported in 151 children receiving the drug, many in doses higher than those recommended and for a longer period"
Mir et al. (1990)	11	Mean 8	15–25 mg/kg	2	"Only one of the children had to discontinue therapy for a pyrazinamide intoleration"
Seth et al. (1991)	47	3–13	20 mg/kg	12	"…children do not seem to be at greater risk for developing ethambutol induced optic damage as compared to adults….provided appropriate dosage schedules are adhered to"
Singh et al. (1992)	104	0.75–18	15 mg/kg	12–14	"The protocol of chemotherapy… produced satisfactory results without any side effect…"
Palme et al. (2002)	250	0–14	15–25 mg/kg	2–12	"…we found no case of impaired vision associated with ethambutol therapy…"
Zhu et al. (2004)	14	0.2–17	13–26 mg/kg		Transient blurred vision in 1 child. Treatment continued

[a] Summaries of the papers cited appear in Annex III.

Table 4. Mean peak serum concentrations of ethambutol in relation to dose in adults

Authors♣	No. of patients	Dose (mg/kg)	Peak serum conc. (µg/ml)
Place & Thomas (1963)	10	50	10
	10	25	5
	2	17	2
Bobrowitz & Gokulanathan (1965)	64	25	4.1
	46	15	2.6
Peets et al. (1965)	3	25	5
Gómez-Pimienta et al. (1966)	7	20	3.4
Donomae & Yamamoto (1966)	40	25	4.4
		12.5	1.2
Place et al. (1966)	10	4	0.67
	10	8	1.4
	10	12.5	2.0
	10	25	4.0
	10	50	8.5
Horsfall (1969)	25	25	4.1
Eule & Werner (1970)	10	25	4
		50	8
		75	11
Lee et al. (1977)	6	15	4.01
Israili, Rogers & El-Attar (1987)			
1st day	17	12.5	3.7
days 4–7	17	12.5	5
Kumar (1992)	10	25	8.2
			6.4
Schall et al. (1995)	20	7.5 [b]	1.45
Peloquin et al. (1999)			
fasting	14	25 [b]	4.5
non-fasting	14	25 [b]	3.8
Zhu et al. (2004)	38	19	2.11
	18	20	2.06
	16	18 [b]	3.21

[a] Summaries of the papers quoted appear in Annex IV.
[b] Healthy volunteers.

Table 5. Mean peak serum concentrations of ethambutol in relation to dose in children

Authors [a]	No. of patients	EMB dose (mg/kg)	Age (years)	Peak serum conc. (µg/ml)
Hussels & Otto (1971)	6	15	2–5	1.2
	6	15	6–9	1.1
	7	15	10–14	0.9
	4	25	2–5	2.0
	7	25	6–9	1.5
	8	25	10–14	2.8
Hussels, Kroening & Magdorf (1973)	5	35	2–5	1.5
	9	35	6–9	2.3
	14	35	10–14	3.0
	5	35 [b]	2–5	2.5
	9	35 [b]	6–9	2.5
	14	35 [b]	10–14	6.3
Benkert et al. (1974)	4	15	3–6	0.9
	4	15	7–10	2.0
	5	15	11–14	1.8
	5	25	3–6	3.0
	5	25	7–10	2.6
	3	25	11–14	3.5
Zhu et al. 2004	14	Mean 16	Mean 5.4	0.78

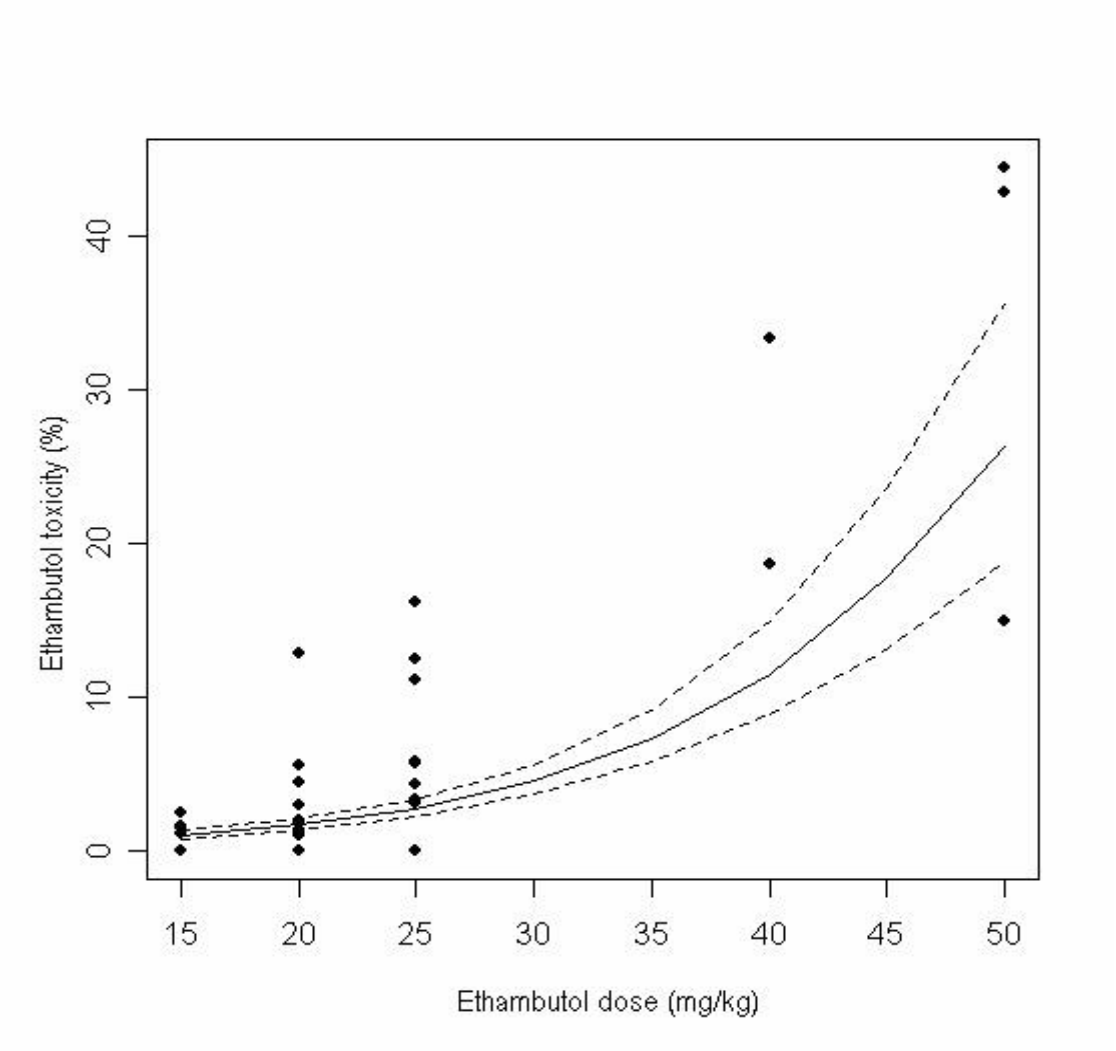
[a] Summaries of the papers quoted appear in Annex III.
[b] Given with rifampicin, 10 mg/kg body weight.

Table 6. Published recommendations for ethambutol dosage in children

Authors [a]	EMB daily dosage	EMB intermittent treatment	Comments
Horne (1990)	25 mg/kg for 2 m then 15 mg/kg	30 mg/kg 3 times/week or 45 mg/kg twice a week	"Ethambutol is best avoided in children too young for objective eye tests…"
Chaulet et al. (1992)	25 mg/kg for 8 wk then 15 mg/kg	–	"… most pediatricians are reluctant to prescribe ethambutol in children under 12"
American Thoracic Society (1994)	15–20 mg/kg	–	"Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<8 years of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely."
Starke & Correa (1995)	15–25 mg/kg	50 mg/kg twice a week	"Although ethambutol has not been used extensively in young children, ophthalmological toxicity in children has not been reported with an ethambutol dosage of 15 mg/kg/day and the drug may be used carefully."
British Thoracic Society (1998)	15 mg/kg	30 mg/kg 3 times/week 50 mg/kg twice a week	"Because of the possible (but rare) toxic effects of ethambutol on the eye, it is recommended that visual acuity should be tested by Snellen chart before it is first prescribed. The drug should only be used in patients who have reasonable visual acuity and who are able to appreciate and report visual symptoms or changes in vision… In small children and in those with language difficulties, ethambutol should be used where appropriate…"
American Academy of Pediatrics (2000)	15–25 mg/kg	50 mg/kg twice a week	"…use of ethambutol in young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits."
Rieder (2002)	15 mg/kg (15–20 mg/kg)	–	"It has been recommended not to use ethambutol in children too young for objective tests for visual acuity. There is, however, no evidence that children are particularly prone to ocular toxicity, and ethambutol may thus be used in children. However, as children might be less likely to report ocular toxicity, particular caution may be warranted."
WHO (2003)	15 mg/kg (15–20 mg/kg)	–	"There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages."
Mehta, Ryan & Hogerzeil (2004)	15 mg/kg	–	"Contraindications: optic neuritis; children under 5 years – unable to report symptomatic visual disturbances."
WHO (2005)	20 mg/kg (15–25 mg/kg)	30 mg/kg (25–35 mg/kg) 3 times/week	

[a] Summaries of the papers quoted appear in Annex V.

Figure 1. Ocular toxicity and dose of ethambutol [a]

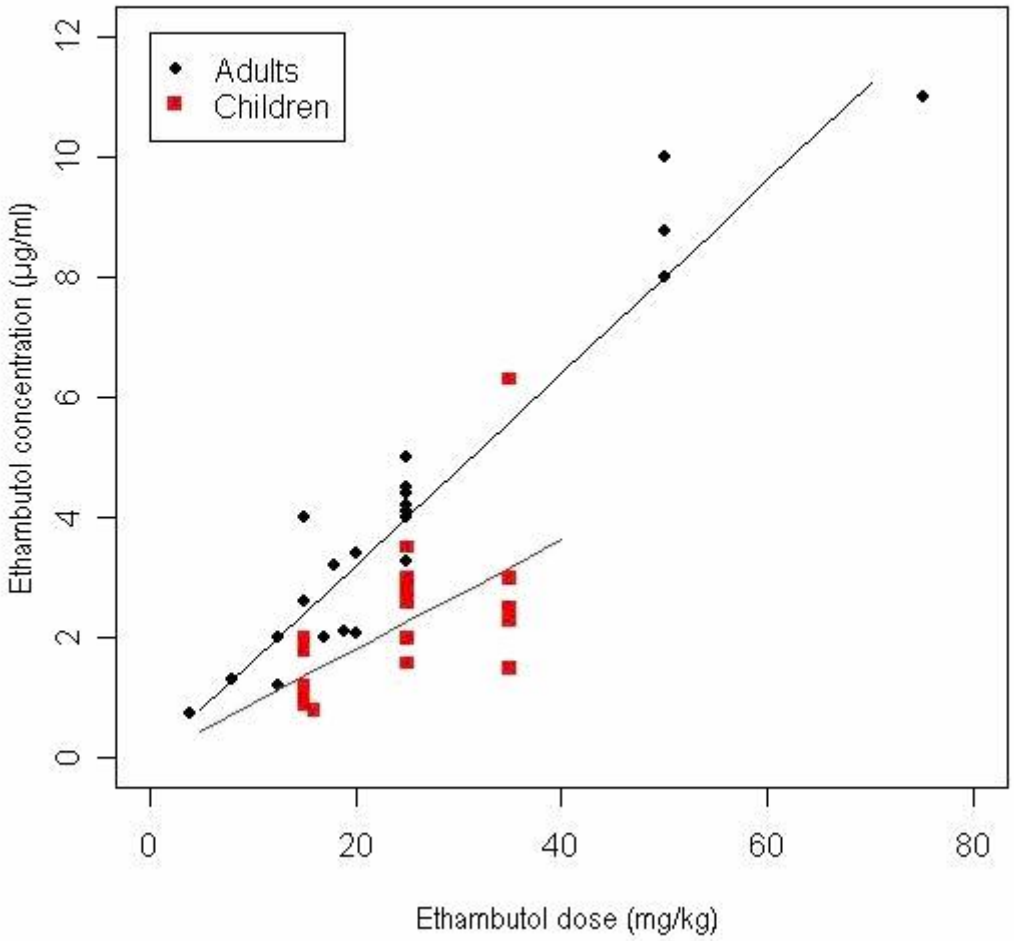


[a] Data are derived from papers discussed in Annex II and listed in Table 2 .

y = exp(–6.0599 + 0.1006*dose) / (1+ exp(–6.0599 + 0.1006*dose))

The broken lines represent the 95% confidence interval limits.

Figure 2. Ethambutol serum concentration in adults and children [a]



[a] Data are derived from papers discussed in Appendices III and IV and listed in Tables 4 and 5.

The two lines are: adults $y = 0.1602*\text{dose}$, and children $y = 0.0906*\text{dose}$.
The standard errors of the two slope coefficients are, respectively, 0.005833 and 0.009080.
The difference between the slopes is clearly significant.

Annex I

Efficacy of ethambutol in adults

- **Bobrowitz ID, Gokulanathan KS (1965)**. Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Sixty four patients evaluated. EMB dose 25 mg/kg; later 25 mg/kg for first 60 days, then 15 mg/kg. Interim analysis of results in patients who had received more than 4 months of treatment. Seventeen patients received EMB alone; 15 of these received more than 4 months of treatment. Of these 15, 6 (40%) became culture-negative but 4 became positive again. Data on emergence of EMB resistance were incomplete, but resistance emerged in 6 of the cases on EMB alone. Of 28 patients receiving combined treatment for at least 4 months, 21 (75%) became and remained culture-negative.

- **Kass I (1965)**. Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoamyloxythiosemicarbanilide. *Tubercle*, 46:166–177.

Thirty patients received EMB 50 mg/kg daily, given in 2 equal doses of 25 mg/kg, accompanied by capreomycin (CPM). Twenty-four patients, treated for at least 4 months, became culture-negative. After 120 days of treatment, 22 (92%) remained culture negative.

- **Ferebee SH, Doster BE, Murray FJ (1966)**. Ethambutol: a substitute for para-aminosalicylic acid in regimens for pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:910–920.

Four regimens were compared: two alternating regimens that were given to patients with more serious cavitating disease, plus INH+PAS and INH+EMB. EMB dose was 6 mg/kg.

SM+PZA / INH+PAS	147 patients
SM+PZA / INH+EMB	140 patients
INH+PAS	148 patients
INH+EMB	131 patients

There was no difference between the two alternating regimens with regard to bacteriological change; at the end of 24 weeks only 1 patient in each group was culture-positive. After 20 weeks, 9 (7%) patients on the INH+EMB regimen remained culture-positive; 7 of these had cultures resistant to INH but not to EMB. Only 2 (1%) patients on the INH+PAS regimen were culture-positive after 20 weeks. The EMB-containing regimens were considered to be as effective as the PAS regimens in the "reversal of infectiousness" in extensive cavitary disease. In patients with less serious disease, the regimen of INH+EMB 6 mg/kg was not as effective as INH+PAS: not only did more patients remain culture-positive, but most were resistant to INH – indicating a failure of EMB at 6 mg/kg to protect INH against resistance. No statistical evaluation is provided.

- **Bobrowitz ID (1966b)**. Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

  Bobrowitz ID, Robins DE (1967). Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 96:428–438.

These two papers deal with the same group of patients: 174 cases (89 in group 1, 85 in group II) receiving EMB, and 74 cases in group III who received INH and PAS.

			Sputum-negative at 4 months
I	INH+EMB (25 mg/kg 60 days, then 15 mg/kg)	89 patients	94.6%
II	INH+EMB (15 mg/kg throughout)	85 patients	88.5%
III	INH+PAS	74 patients	82.3%

Not all patients were followed up beyond (or even to) completion of treatment. No statistical analysis is provided, but the data might suggest little difference between EMB at 15 mg/kg throughout and EMB at 25 and subsequently 15 mg/kg.

- **Donomae I, Yamamoto K (1966)**. Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Initial treatment cases	No. of patients	Reversal of infectiousness at 6 months
1. EMB 25 mg/kg + INH	46	38/39 (97.6%)
2. EMB 12.5 mg/kg + INH	46	30/38 (78.9%)
3. PAS+INH	46	32/36 (88.8%)

(Difference between groups 1 & 2, p = .02)

Results suggest that, in respect of bactericidal activity, EMB is decidedly better at 25 mg/kg than at 12.5 mg/kg. It is also of interest that the EMB dose of 12.5 mg/kg probably provides serum concentrations approaching those that would be reached in children given EMB at 15 mg/kg.

Re-treatment cases	No of patients	Reversal of infectiousness at 6 months
A. EMB alone		
A1. EMB 1 g daily	49	20/47 (42.5%)
A2. EMB 1 g on alternate days	46	12/42 (28.6%)
A3. Conventional treatment	46	13/41 (31.7%)

Again a definite dose effect is seen

EMB resistance at 5–6 months was 58.3% in group A1 and 38.4% in group A2; the lower incidence of resistance in group A2 may again suggest less bactericidal activity at the lower dose.

B. EMB + INH + other drugs (KM, CS, ETH)		
EMB 25/15 mg/kg	45	28/36 (77.8% at 3 months)

- **Pyle MM (1966)**. Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

  Pyle MM et al. (1966). A four-year clinical investigation of ethambutol in initial and re-treatment cases of tuberculosis. *American Review of Respiratory Disease*, 93:428–441.

In management of re-treatment cases, EMB dose ranged from 15 to 50 mg/kg, but the “usual dose” was 25 mg/kg. After 6 months of treatment, 12 (50%) of 24 re-treatment cases were culture-negative.

In the following table, doses of EMB used in management of initial (i.e. previously untreated) cases were 20–30 mg/kg.

EMB-containing regimens in initial treatment	No of patients	Reversal of infectiousness	
		3 months	6 months
EMB+INH	23	15/26 (57.5%)	23/23 (100%)
EMB+INH+SM	57	40/55 (68.9%)	57/57 (100%)

- **Corpe RF, Blalock FA (1966)**. Multi-drug therapy including ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:823–830.

EMB was used at 25 mg/kg in a basic regimen together with INH and ETH; 118 patients were evaluated. Three consecutive months with two negative sputum cultures were required to demonstrate reversal of infectiousness. Of the 118 patients, 100 achieved reversal of infectiousness, of whom 17 later relapsed; conversion was maintained in 83/118 (70.3%).

- **Murray FJ (1967)**. US Public Health Service experience with ethambutol. *International Congress of Chemotherapy, Vienna*, 6:33–382.

The data in this transcript of a congress presentation are almost certainly an expansion of those presented by Ferebee, Doster & Murray (1966) in the paper quoted above. (The data were finally published by Doster et al. in 1973.[3]). Murray presents data from patients treated with INH/EMB at an EMB dose of 6 mg/kg (222) or 15 mg/kg (62) compared with the PAS/INH combination. Data are presented in the form of a figure. Up to 12 weeks of treatment the percentage of patients achieving culture negativity is identical in the INH/PAS and INH/EMB groups. At 12 weeks, however, patients treated with INH/EMB at an EMB dose of 6 mg/kg start to fail, while the percentage of patients given INH/EMB at an EMB dose of 15 mg/kg and reaching culture negativity continues to increase and match that for patients given INH/PAS. Although no details are given, this provides fairly convincing evidence of a dose effect, EMB (in combination with INH) being more effective at 15 mg/kg than at 6 mg/kg.

Further details are provided by Doster et al. (1973). With the PAS regimen, only 3.3% of patients showed bacteriological failure at the 20th week compared with 12.1% of those on low-dose EMB (6 mg/kg). Furthermore, 8 of 11 low-dose EMB failures had bacilli resistant to INH. With an EMB dose of 15 mg/kg**,** 7.9% of patients were bacteriologically positive at 20 weeks compared with 5.4% of PAS patients. Equally significantly, none of the 9 patients who were given INH/EMB 15 mg/kg and who were still culture-positive had cultures resistant to INH. Although it is the microbiological results that are of primary interest, it should be noted that radiological improvement was noted in 72% of the patients receiving EMB at 6 mg/kg and in 80% of those receiving 15 mg/kg.

This trial is relevant to the debate about paediatric dosages of EMB, in that the serum concentrations achieved in adults given EMB at 6 mg/kg may be similar to those reached in children given 15 mg/kg.

- **Gyselen A et al (1968)**. Rifampin and ethambutol in the retreatment of advanced pulmonary tuberculosis. *American Review of Respiratory Disease*, 98:933–943.

EMB was given to three groups of advanced re-treatment patients at 25 mg/kg/day for 60 days and thereafter at 15 mg/kg; patients were followed up for periods of 20–123 weeks:

I 14 patients received EMB alone
II 19 patients received EMB and another previously unused drug (CPM, ETH, CS, VIO, THIO)
III 12 patients received EMB+RMP.

		Reversal of infectiousness
I	9 became sputum culture-negative but 4 later relapsed	5 (36%)
II	16 became sputum culture-negative but 5 later relapsed	11 (58%)
III	11 became sputum culture-negative but 1 later relapsed	10 (83%)

- **Tai F-H, Chen T-C (1968)**. Studies on combined use of ethambutol and isoniazid in retreatment of drug-resistant cases of pulmonary tuberculosis. *Chinese Journal of Microbiology*, 1:84–91.

EMB combined with INH was used in the re-treatment of 100 drug-resistant patients, 98 of whom completed 1 year of treatment. Dose was 25 mg/kg for 2 months and 15 mg/kg thereafter. Because EMB was combined with INH, patients were receiving virtual monotherapy with EMB; nonetheless, of the 98 patients who completed 1 year's therapy, 45 (46%) were culture-negative, while the remainder were either persistently culture-positive or relapsed again after conversion.

[3] Doster B et al. (1973). Ethambutol in the initial treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 107:177–190.

- **Mitchison DA, Dickinson JM (1971)**. Laboratory aspects of intermittent drug therapy. *Postgraduate Medical Journal*, 47:737–741.

Aspects of intermittent therapy were studied in guinea-pigs. In the case of RMP and EMB (at a concentration of 10 µg/ml), but not INH, pulsed therapy with higher doses of the drugs increased the bactericidal effect, suggesting that these two drugs might be well suited to use in intermittent therapy.

- **Schütz I (1971)**. Problematik der Ethambutol-Dosierung (Difficulties of ethambutol dosage]. *Pneumonologie*, 145:389–392.

Discussion of the use of EMB in the treatment of pulmonary TB followed by relapse. EMB was given at 15 or 20 mg/kg/day, with INH and SM, to 6 patients who relapsed. Three patients relapsed with resistance to INH and/or SM, suggesting that EMB at that dose was unable to protect the companion drugs; by contrast, 2 patients receiving 25 mg/kg EMB relapsed with EMB-resistant organisms.

- **Pilheu J (1970)**. Ambulatory treatment of pulmonary tuberculosis with ethambutol-isoniazid. *Chest*, 58:497–500.

EMB and INH were given for 12 months to 145 patients, including 34 children (ages unspecified), from several South American countries. EMB was given at 25 mg/kg for 2 months and then at 15 mg/kg; children were given 15 mg/kg. One child died; of the remaining 144 patients, 141 (97.3%) achieved culture negativity by the end of the 12 months of treatment. Culture negativity was defined as three negative sputum cultures.

- **Hong Kong Tuberculosis Treatment Services/Brompton Hospital/British Medical Research Council (1974)**. A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis. *Tubercle*, 55:1–27. (See also *Tubercle*, 1975, 56:179–189.)

Daily regimen		Favourable response at 18 months
ER7	EMB 25 mg/kg for 2 months then 15 mg/kg	87% of 91 patients
Intermittent regimens		
ER2	EMB 45 mg/kg	79% of 84 patients
ER1	EMB 90 mg/kg	81% of 53 patients
ER7/ER1	EMB 25 mg/kg and then 90 mg/kg	87% of 62 patients
Control regimen		
ETH+PZA+CS		88% of 68 patients

There is thus some indication that the regimens intermittent from the start were less successful than those with a daily intensive phase. Of 48 patients who failed bacteriologically on the RMP regimens, all except 6 had RMP-resistant strains, again suggesting the inability of EMB to protect a companion drug at the doses used.

- **Hong Kong Chest Service/British Medical Research Council (1978)**. Controlled clinical trial of 6-month and 9-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 60:201–210. (See also *American Review of Respiratory Disease*, 1978, 118:219–227.)

Four regimens given for 6 months (8 months in the case of those with an intermittent continuation phase) were evaluated. The EMB dose was 25 mg/kg when given daily and 45 mg/kg when given intermittently (twice weekly). All but 1 of 680 patients with fully drug-sensitive bacilli at the start of treatment had a favourable response at the end of chemotherapy. However, the relapse rate for EMB regimens was considerably higher (43% of 21 patients after 6 months' treatment, 29% of 24 patients after 8 months) than for the other regimens, and even higher in those patients with initially INH- or SM-resistant organisms. Among the 10 patients with initial resistance to INH or SM, none who received EMB developed further resistance to RMP compared with 2 of 9 patients who received PZA.

6-month regimens	No. of patients	Relapse at end of 24 months
6SHR	143	8 (6%)
2SHRZ; $4[SHZ]_2$	87	6 (7%)
2SHRE; $4[SHE]_2$	84	19 (23%)
$4[SHRZ]_3$; $4[SHZ]_2$	71	14 (6%)
8-month regimens		
2SHRZ; $6[SHZ]_2$	87	3 (3%)
2SHRE; $6[SHE]_2$	84	8 (10%)
$4[SHRZ]_3$;$6[SHZ]_2$	83	1 (1%)

This study provided further evidence that EMB failed to promote sterilization of lesions although it probably did contribute to the prevention of further drug resistance.

- **Tuberculosis Research Centre, Madras (1981)**. Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis – a controlled trial of four regimens. *Tubercle*, 61:13–29. (See also *Tubercle*, 1982, 63:89–98 for a report of the results at 24 months.)

A controlled randomized trial of four regimens of intermittent therapy with INH and EMB in pulmonary TB. EMB was unable to compensate for the deficiencies in isoniazid in the group of rapid inactivators, particularly in the intermittent regimens. There was some evidence that as the interval between doses was increased the efficacy of INH declined, while that of EMB increased.

Regimen	No. of patients	Dose of EMB	5-year favourable response	Relapse
EH	107	15 mg/kg	83%	15% of 54
E_2H_2	101	45 mg/kg	63%	26% of 38
E_1H_2	107	90 mg/kg	63%	33% of 43
E_1H_1	109	90 mg/kg	33%	54% of 37

- **Babu Swai O et al. (1988)**. Controlled trial of a regimen of two durations for the treatment of isoniazid-resistant pulmonary tuberculosis. *Tubercle*, 69:5–14.

Patients with INH resistance or INH and SM resistance were evaluated; of 306 entered in the study, 226 were finally analysed. Two regimens were evaluated: an 8-week intensive phase of SM, PZA RMP and EMB was followed by RMP and EMB daily for 4 months or 7 months. The dose of EMB was 25 mg/kg daily for the first 8 weeks and 15 mg/kg daily thereafter.

Relapse rates were low in both series: up to 30 months' follow-up, relapse occurred in 4% of those receiving 6-month treatment and in 3% of those receiving 9-month treatment. Among patients with resistance to both SM and INH, 3/14 (21%) in the 6-month series relapsed, but 0/20 in the 9-month series.

- **Tuberculosis Research Centre (1997)**. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1:509–517.

In this randomized study 1203 patients were assigned to three possible regimens: EMB dose was 600 mg daily or 1200 mg twice weekly. Patients' mean body weight was 40 kg, indicating an EMB dose of 15 mg/kg. Thus, for a body weight of 50 kg, EMB dose was approximately 12 mg/kg daily or 24 mg/kg twice weekly; for a body weight of 45 kg, EMB dose was 13.3 mg/kg daily or 27 mg/kg twice weekly.

Regimen		Drug-susceptible: unfavourable response to treatment
I	$2EHRZ_7/6EH_7$	11/305 (3.6%)
II	$2EHRZ_2/4EHR_2$	1/263 (0.4%)
III	$2HRZ_2/4HR_2$	24/257 (9.3%)

Of the 36 patients with initially drug-sensitive organisms who had an unfavourable response, 24 (67%) developed resistance to one or more drugs. Of these 24, 21 (88%) had received regimen III, which did not contain EMB, which suggests that the presence of EMB in the regimens *did* protect against the emergence of drug resistance. In contrast, among the 74 patients with organisms initially resistant to INH who responded badly, 23 (31%) developed resistance to RMP, so that the presence of EMB in the regimens did *not* appear to protect against the development of MDR.

Regimen		Isoniazid-resistant: unfavourable response to treatment or relapse
I	EHRZ7/6EH	22/94 (23.4%)
II	2EHRZ2/4EHR2	23/59 (40%)
III	2HRZ2/4HR2	50/74 (68%)

This paper gave rise to considerable debate on the ability of EMB to offer adequate protection against the development of further drug resistance in the presence of a significant incidence of INH resistance in a community (see Long & Scalini, 1999, 2000; Matthew & Santha 2000).

- **Jindani A, Nunn AJ, Enarson DA (2004)**. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet*, 364:1244–1251.

This recent study provides further evidence of the likely efficacy of EMB in doses close to those that might be used in children. An intensive 2-month phase of daily INH, RMP, PZA and SM followed by 6 months of INH and thioacetazone was introduced by the IUATLD and promoted by WHO, "…to reduce the probability of promoting additional drug resistance in any patient with organisms already resistant to either isoniazid or rifampicin". With the advent of the HIV pandemic, the potentially fatal toxic effects of thioacetazone and the potential for the spread of HIV infection through the use of an injectable agent such as SM led to EMB replacing both SM and thioacetazone in this regimen. Three regimens were evaluated in 1355 patients randomly assigned to treatment groups:

Regimen	Culture-neg. at 2 months	Unfavourable outcome at 18 months
2EHRZ/6HE (424 patients)	86%	36/346 (10%)
2$[EHRZ]_3$/6HE (433 patients)	77%	48/351 (14%)
2EHRZ/4HR (404 patients)	83%	17/347 (5%)

Daily EMB dose ranged from 15.4 to 24 mg/kg for patients weighing <40 kg, and from 14.5 to 20 mg/kg for patients weighing 40–55 kg; for patients weighing >55 kg the dose was 21.8 mg/kg and decreased with increasing body weight. Most patients fell in the 40–55 kg group and thus received 14.5–20 mg/kg EMB daily.

Among patients with organisms resistant to INH, unfavourable outcomes occurred as follows:

2EHRZ/6HE	5/13 (38%)
2$[EHRZ]_3$/6HE	6/22 (27%)
2EHRZ/4HR	1/23 (4%)
(p = 0.02)	

These results suggest very strongly that EMB in the doses used did not contribute to improving the outcome in the presence of INH resistance; however, there is no information on the development of further resistance among the patients who did relapse.

References

Babu Swai O et al. (1988). Controlled trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. *Tubercle*, 69:5–14.

Bobrowitz ID (1966b). Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Bobrowitz ID, Gokulanathan KS (1965). Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Bobrowitz ID, Robins DE (1967). Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 96:428–438.

Corpe RF, Blalock FA (1966). Multi-drug therapy including ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:823–830.

Donomae I, Yamamoto K (1966). Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Ferebee SH, Doster BE, Murray FJ (1966). Ethambutol: a substitute for para-aminosalicylic acid in regimens for pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:910–920.

Gyselen A et al. (1968). Rifampin and ethambutol in the retreatment of advanced pulmonary tuberculosis. *American Review of Respiratory Disease*, 98:933–943.

Hong Kong Chest Service/British Medical Research Council (1979). Controlled clinical trial of 6-month and 9-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 60:201–210.

Hong Kong Tuberculosis Treatment Services/Brompton Hospital/British Medical Research Council (1974). A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis. *Tubercle*, 55:1–27.

Jindani A, Nunn AJ, Enarson DA (2004). Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet*, 364:1244–1251.

Kass I (1965). Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoammyloxythiosemicarbanilide. *Tubercle*, 46:166–177.

Long R, Scalini M (1999). Is the treatment of WHO Category 1 tuberculosis with 2HRZE/6HE a defensible practice? *International Journal of Tuberculosis and Lung Disease*, 3:747–748.

Long R, Scalini M (2000). More on the question of optimal chemotherapy in the presence of isoniazid resistance. *International Journal of Tuberculosis and Lung Disease*, 4:890–894.

Matthew R, Santha T (2000). The treatment of WHO Category 1 tuberculosis with 2 HRZE/6HE is indeed defensible. *International Journal of Tuberculosis and Lung Disease*, 4: 795.

Mitchison DA, Dickinson JM (1971). Laboratory aspects of intermittent drug therapy. *Postgraduate Medical Journal*, 47:737–741.

Murray FJ (1967). US Public Health Service experience with ethambutol. *International Congress of Chemotherapy, Vienna*, 6: 33–382.

Pilheu J (1970). Ambulatory treatment of pulmonary tuberculosis with ethambutol-isoniazid. *Chest*, 58:497–500.

Pyle MM (1966). Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

Pyle MM et al. (1966). A four-year clinical investigation of ethambutol in initial and re-treatment cases of tuberculosis. *Annals of the New York Academy of Sciences*, 93:428–441.

Schütz I (1971). Problematik der Ethambutol-Dosierung [Difficulties with ethambutol dosage]. *Pneumonologie*, 145:189–392.

Tai F-H, Chen T-C (1968). Studies on combined use of ethambutol and isoniazid in retreatment of drug-resistant cases of pulmonary tuberculosis. *Chinese Journal of Microbiology*, 1:84–91.

Tuberculosis Research Centre, Madras (1981). Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis – a controlled trial of four regimens. *Tubercle*, 61:13–29.

Tuberculosis Research Centre (1997). A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*,1:509–517.

Annex II

Toxicity of ethambutol in adults

- **Carr RE, Henkind P (1962)**. Ocular manifestations of ethambutol. *Archives of Ophthalmology*, 67:566–571.

In this first report of eye complications following the use of EMB, 18 patients throughout USA received EMB at doses of 60–100 mg/kg. Of these, 8 (44%) developed either severe or mild toxic amblyopia. There is a detailed description of one case; of note with relevance to later reports is the description of retinal changes associated with the severe manifestations – definite bilateral papillitis, hyperaemic discs, flame-shaped haemorrhages. Some later papers state that no objective anatomical abnormalities are associated with EMB optic neuritis.

- **Bobrowitz ID, Gokulanathan KS (1965)**. Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Of 64 re-treatment patients, 17 were given EMB alone and 47 EMB combined with other drugs. Dose was 25 mg/kg throughout in 18 patients; 46 patients received 25 mg/kg for 60 days and 15 mg/kg thereafter. Optical evaluation – visual acuity, visual fields and colour discrimination – was carried out before treatment. Frequency and manner of evaluation during treatment are not specified.

Ocular toxicity in was noted in 2 (11%) of 18 patients given 25 mg/kg throughout, one in 7th month and one in 9th month of therapy.

(The continuation of this study is reported in Bobrowitz ID (1966a). Ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:796–822. The same group of 18 patients who received 25 mg/kg throughout, but the 25 mg/kg followed by 15 mg/kg group now included 117 patients with no visual toxicity.)

There is an interesting discussion of the vagaries of assessing visual acuity with Snellen charts about 15% of patients developed a “2 line” deficit, which normalized without stopping treatment.

- **Kass I (1965)**. Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoamyloxythiosemicarbanilide. *Tubercle*, 46:166–177.

EMB 50 mg/kg was given to 60 patients (as 25 mg/kg twice daily). Ocular toxicity was noted in 9 (15%) after an “average” of 151 (26–317)days. No details of ophthalmological evaluation are given.

- **Place VA, Peets EA, Buyske DA (1966)**. Metabolic and special studies of ethambutol in normal volunteers and tuberculous patients. *Annals of the New York Academy of Sciences*, 135:775–795.

Regimen	No. of patients	Ocular toxicity
EMB 50 mg/kg	7	3 (43%) after 3½, 17 (?) and 27 months
EMB 25 mg/kg	16	2 (13%) after 4 and 7½ months
EMB 15 mg/kg	4	0

- **Corpe RF, Blalock FA (1966)**. Multi-drug therapy including ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:823–830.

EMB was given at 25 mg/kg in a basic regimen together with INH&ETH to 118 patients. No toxicity was said to have been experienced, *but* ” Ethambutol was temporarily discontinued because of amblyopia or symptoms referable to the eyes in six patients. As soon as the situation had been evaluated and lack of drug toxicity established, ethambutol was reinstated and continued as

prescribed. Ethambutol was discontinued permanently in four patients, early in the study, because of amblyopia [which] represented a careful approach."

- **Pyle MM (1966)**. Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

149 patients were treated with ethambutol for more than 3 months, as follows:

EMB dosage	No. of patients	Ocular toxicity
40–50 mg/kg	6	2 (33%)
20–30 mg/kg	30	4 (3%)
15–20 mg/kg	13	0

Similar data are reported in: Pyle MM et al. (1966). A four-year clinical investigation of ethambutol in initial and re-treatment cases of tuberculosis. *American Review of Respiratory Disease*, 93:428–441. That article lists 3 cases of ocular toxicity at EMB doses of 20–30 mg/kg, occurring at 4, 4.5 and 10 months after the start of treatment.

- **Donomae I, Yamamoto K (1966)**. Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Visual acuity and colour discrimination were evaluated every 2–4 weeks and visual fields monthly. Initial treatment, or treatment of new cases, was with one of three regimens – two of INH+EMB and one of INH+PAS:

Regimen	No. of patients	Ocular toxicity	Duration of treatment
INH+EMB 25 mg/kg	46	2 (4%)	3 & 4 months
INH+EMB 12.5 mg/kg	46	0	
Re-treatment:			
EMB 1 g daily	49	1 (2%)	1 month
EMB 1 g alternate days (Dose approximately 20 mg/kg.)	46	0	

- **Leibold JE (1966)**. The ocular toxicity of ethambutol and its relation to dose. *Annals of the New York Academy of Sciences*, 135:904–909.

Eyes were examined before treatment and every 2 weeks thereafter for visual acuity, colour discrimination and visual fields. Two groups of patients were treated as follows:

EMB dosage	No. of patients	Ocular toxicity
High, >35 mg/kg	59	11 (19%)
Low, <30 mg/kg	59	2 (3%)

In the low-dosage, group ocular toxicity developed at a dose of 20 mg/kg after 139 days and at 24 mg/kg after 235 days.

- **Ferebee SH, Doster BE, Murray FJ (1966)**. Ethambutol: a substitute for para-aminosalicylic acid in regimens for pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:910–920.

All patients received a Snellen eye test every 2 weeks during treatment. EMB dose was 6 mg/kg; four regimens were compared:

Regimen	No. of patients	Ocular toxicity
SM+PZA/INH+PAS	147	2 (1%)
SM+PZA/INH+EMB	140	2 (1%)
INH+PAS	148	4 (3%)
INH+EMB	131	2 (2%)

The authors commented: “Changes of equal frequency and similar magnitude in visual acuity were observed in PAS patients without concern, but when the patient was receiving ethambutol, the changes were attributed to the drug.”

- **Bobrowitz ID (1966b)**. Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Three regimens were evaluated:

Regimen		No. of patients	Ocular toxicity
I	INH+EMB 25 mg/kg for 60 days then 15 mg/kg	63	1 (2%)
II	INH+EMB 15 mg/kg throughout	55	0
III	INH+PAS	51	0

Loss of one, two or more lines in reading of Snellen chart is discussed: “In our study about one-quarter of the patients showed a reading loss of one line according to the readings of the Snellen eye chart.”

- **Bobrowitz ID, Robins DE (1967)**. Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 96:428–438.

Patients as in Bobrowitz (1966) above but now numbering 174 cases. Another case of possible ocular toxicity was noted in Group II.

Regimen		No. of patients	Ocular toxicity
I	INH+EMB 25 mg/kg for 60 days then 15 mg/kg	89	1 (1%), 4th month
II	INH+EMB 15 mg/kg throughout	85	1 (1%), 13th month
III	INH+PAS	74	0

- **Filippone C, Barnabè R, Bonanni R (1968)**. Osservazioni oftalmologiche in corso di terapia con etambutolo [Ophthalmological findings in the course of ethambutol therapy]. *Minerva Oftalmologica*, 10:38–41.

[In Italian with a brief English summary.] EMB was used in 15 chronic pulmonary TB cases at a dosage of 25 mg/kg for 4 months; No subjective or objective signs of impairment were noted, apart from slight, but constant, decreases in electroretinogram B-wave amplitude.

- **Tai FH, Chen TC (1968)**. Studies on combined use of ethambutol and isoniazid in retreatment of drug-resistant cases of pulmonary tuberculosis. *Chinese Journal of Microbiology*, 1:84–91.

EMB combined with INH was used in the re-treatment of 100 drug-resistant patients at a dose of 25 mg/kg for first 2 months and 15 mg/kg thereafter. One case (1%) of ocular toxicity. ”Reduced vision and color discrimination noted after two and half months.” Medication was stopped only in the ninth month of treatment, after which the vision and colour discrimination improved.

As EMB was combined with INH these patients were receiving virtual monotherapy with EMB. Nonetheless, of the 98 patients who completed one year’s therapy 38% were persistently culture-negative.

- **Adel A (1969)**. Ophthalmological side-effects of ethambutol. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl.):55–58.

Ophthalmological toxicity was observed among 78 adult patients aged 36–74 (mean 60) years treated in Finland with EMB at 25 mg/kg daily and later 15 mg/kg daily. In 10 (13%) cases, side-effects were noted, appearing within 2–12 (mean 5.4) months. In 6 cases in whom side-effects were noted, there was also a deterioration in renal function.

- **Citron KM (1969)**. Ethambutol: a review with special reference to ocular toxicity. *Tubercle*, 50(Suppl.):22–36.

Ocular toxicity was recorded in 2 (6%) of 34 patients given EMB at 25 mg/kg.

- **Horsfall PAL (1969)**. Ethambutol in the retreatment of chronic pulmonary tuberculosis. *Far East Medical Journal*, 7:213–218.

EMB was used in the re-treatment of 68 patients, at a dosage of 25 mg/kg daily for 60 days and 15 mg/kg daily thereafter, together with various combinations of INH, streptomycin, capreomycin, viomycin and other drugs. Where EMB was functioning virtually alone, approximately 33% of patients had sputum conversion. When three drugs were used, this figure rose to 50%. Significant reduction in visual acuity was experienced by 3 patients (4%). EMB serum concentrations were measured by an agar diffusion method with *M. smegmatis* as the test organism. Measurements were done 3 hours after dosing with 25 mg/kg; concentrations were 1.97–6.67 (mean 4.1) µg/ml.

- **Radenbach KL (1969)**. Results of clinical studies with capreomycin, ethambutol and rifampicin in the Heckeshorn Hospital, Berlin. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl): 43–53.

"Painstaking examinations were performed before treatment, every 2 weeks during the first 12 weeks of treatment and every 4 weeks thereafter." EMB dosage was 25 mg/kg daily for 12 weeks and 15 mg/kg thereafter.

Hospital	No. of patients	Ocular toxicity
Heckeshorn	157	3 (2%), 7th, 10th and 16th weeks
Havelhöhe	143	3 (2%), 7th, 10th and 11th weeks

- **Wäre M et al. (1969)**. Clinical experience of the retreatment of drug-resistant pulmonary tuberculosis with rifampicin combined with ethambutol and capreomycin. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl.):59–63.

This paper describes the incidence of side-effects in 113 patients treated with regimens of rifampicin, capreomycin and EMB. All the patients received EMB at 25 mg/kg daily for 2–3 months and 15 mg/kg thereafter.

One patient developed "mild ocular toxicity in the 3rd month of treatment"; the patient's vision improved when EMB was stopped and no further problems were encountered when EMB was continued at 15 mg/kg/day. Another patient received 25 mg/kg and developed ocular toxicity after 12 months of this treatment.

- **IUAT Committee on Treatment 1969 (1970)**. Report of Dr Farga. *Bulletin of the International Union against Tuberculosis*, 44:8.

Report of a meeting of the IUAT Committee. Investigation of ethambutol toxicity discussed. Dr Eule presented results that appear in a subsequent publication (see Eule et al. (1973) below) Results were also presented by Dr Farga: among 111 patients treated with EMB 50 mg/kg three times a week, 1 (1%) case of ocular toxicity was encountered. Few details are given.

- **Pilheu J (1970)**. Ambulatory treatment of pulmonary tuberculosis with ethambutol-isoniazid. *Chest*, 58:497–500.

EMB was given at 25 mg/kg for 2 months and at 15 mg/kg thereafter to 145 patients; 34 children were given EMB at 15 mg/kg. “Periodic.….complete ophthalmologic examinations…” were performed. No visual abnormalities were noted.

- **Roussos T, Tsolkas A** (1970). The toxicity of Myambutol on the human eye. *Annals of Ophthalmology*, 2:578–580.

250 patients were given EMB at 15 mg/kg daily for periods of 4–8 months. There was monthly examination of visual acuity and visual field and evaluation of colour sense, plus “meticulous fundoscopic examination”. Changes were observed in 4 (2%) patients after 48 days, 70 days, 4 months and 7 months of EMB treatment.

- **Schütz I, Radenbach KL, Bartmann K (1970)**. The combination of ethambutol, capreomycin and a third drug in chronic pulmonary tuberculosis with bacterial polyresistance. *Antibiotics and Chemotherapy*, 16:43–58.

After treatment of 31 patients with “chronic, far advanced, progressive, open, cavitary pulmonary tuberculosis” with EMB at 25 mg/kg daily for 12 weeks and then 15 mg/kg, together with capreomycin and a third drug, “…visual disturbances failed to appear…”

- **Tamai A (1970)**. Ocular toxicity of ethambutol: a clinical investigation conducted from May 1965 to December 1969. *Yonago Acta Medica*, 14:61–69.

A case report of ocular toxicity arising after 2 months of treatment with EMB at a dose of 20 mg/kg is accompanied by a long table giving the incidence of toxicity in a number of other studies. Some of these studies are listed above, but most are in Japanese and thus not readily accessible to the author of this review. In Tamai’s experience “…the administration of the d-form of ethambutol in 1243 cases caused suspected ocular disturbance in 83 cases or 6.7%, and definite disturbance in 42 cases or 3.4%….” The dose of EMB, however, is not specified and no other details are given.

- **Tiburtius H (1970)**. The undesired side-effects of Myambutol. *Antibiotics and Chemotherapy*, 16:298–301.

In what was probably a continuation of Radenbach’s 1969 study (see above), 300 patients were admitted to Heckeshorn and Havelhöhe Hospitals in Berlin: there was “regular eye check up during the course of Myambutol therapy”. Daily EMB dose was 25 mg/kg for 6–12 weeks and 15–20 mg/kg thereafter.

Ocular toxicity was noted in 9 (3%) of 300 patients; for 5 patients, onset is noted on days 46, 56, 60, 74 and 105 of therapy. Ages are given as males 5–77 years and females 7–78 years: some children were thus included in the study but they are not further identified.

- **Bowen DI, Vaterlaws AL (1971)**. Toxic amblyopia due to ethambutol in a case of drug resistant pulmonary tuberculosis. *British Journal of Diseases of the Chest*, 65:105–110.

Case report of toxic neuropathy in an adult following EMB given at 25 mg/kg for 5 months. Treatment continued, at 700 mg EMB, because of MDR tuberculosis but ocular defects progressed; all treatment was then stopped. There was some recovery but visual field defects persisted.

- **Lees AW et al. (1971)**. Toxicity from rifampicin plus isoniazid and rifampicin plus ethambutol therapy. *Tubercle*, 52:182–190.

Visual acuity was evaluated before treatment and at monthly intervals thereafter; 72 patients were given rifampicin (600 mg), with EMB at 25 mg/kg for 2 months and 15 mg/kg thereafter. Ocular toxicity

occurred in 1 patients (1%) after 3 months. Visual acuity subsequently returned almost to normal but colour discrimination remained impaired.

- **Acquinas M, Citron KM (1972)**. Rifampicin, ethambutol and capreomycin in pulmonary tuberculosis previously treated with both first and second line drugs: the results of 2 years chemotherapy. *Tubercle*, 53:153–165.

"Visual function was investigated by monthly visual acuity tests." EMB was given at 25 mg/kg for 6 months and thereafter at 15 mg/kg to 36 patients. Ocular toxicity was noted in 2 patients (6%) after the 26th week and diagnosed as "severe eye toxicity". One patient had a haemorrhagic retinopathy and visual acuity was still poor 18 months later. "Possible…. toxicity" was noted in 2 other patients.

- **Orou F, Sideroff G, Schabel F (1972)**. Frequenzuntersuchung von Opticuserkrankungen im Rahmen der Myambutol-Behandelung [Studies on the occurrence of optic nerve diseases in the course of Myambutol therapy]. *Klinische Monatsblatter fur Augenheilkunde*, 161:601–603.

[In German with a short English summary.] The eyes of 208 patients receiving EMB were evaluated. In 9 (4.33%) there was retrobulbar neuritis. "The critical dose for Myambutol appears to be in the region of 25 mg/kg body weight." Of 48 patients who received EMB at 15 mg/kg none developed optic neuritis. Optic neuritis developed in 8 (5%) of 161 patients given 25 mg/kg and in 1 (14%) of 7 patients between 30 and 40 mg/kg.

- **Reimers D (1972)**. Irreversible Augenschäden durch Ethambutol. Vorläufige Mitteilung [Irreversible eye damage caused by ethambutol. Preliminary report]. *Praxis der Pneumologie vereinigt mit Der Tuberkulosearzt*, 26:445–449.

A report of a 64-year-old woman receiving EMB 23–25 mg/kg who developed severe bilateral axial type lesions after 7 months of treatment. The lesions were irreversible.

- **British Medical Research Council (1973)**. Co-operative controlled trial of a standard regimen of streptomycin, PAS and isoniazid and three alternative regimens of chemotherapy in Britain. *Tubercle*, 54:99–129.

Patients were randomized to one of four groups:

P series: SM+INH+PAS months 1–3, then daily INH+PAS months 4–12
E series: SM+INH+EMB months 1–3, then daily INH+EMB months 4–12
R series: SM+INH+RMP months 1–3, then daily INH+RMP months 4–12
S_2H_2 series: SM+INH+PAS months 1–3, then twice weekly INH+SM months 4–12

EMB dosage was 15 mg/kg throughout. Visual acuity, colour vision, central and peripheral fields of vision were evaluated pretreatment and at 3, 6 and 12 months in the E series and the P series (as a control); examiner was unaware of randomization. Results were evaluated by an independent assessor. Four patients were considered to have "…mild presymptomatic optic atrophy"; this included 1 patient receiving PAS.

No. of patients	Ocular toxicity
P series: 126	1 (1%)
E series: 118	3 (3%)

- **Doster B et al. (1973)**. Ethambutol in the initial treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 107:177–190.

Four US Public Health Service trials are described:

Trial I: 20-week regimens of INH+PAS and INH+EMB 6 mg/kg
Trial II: 20-week regimens of INH+PAS and INH+EMB 15 mg/kg

Trial III: SM+PZA alternated with INH+PAS
SM+PZA alternated with INH+EMB 6 mg/kg
SM+INH+PZA
Trial IV: SM+EMB 15 mg/kg alternated with INH+PAS
SM+PZA alternated with INH+EMB 15 mg/kg
SM+INH+EMB 15 mg/kg

Visual acuity was evaluated with Snellen charts before the trial and at 4-weekly intervals during treatment. The problems caused by minor abnormalities in visual acuity are discussed at length.

Treatment	Ocular toxicity
No EMB	8.3%
EMB 6 mg/kg (12 weeks)	11.7%
EMB 6 mg/kg (20 weeks)	10.3%
EMB 15 mg/kg (12 weeks)	6.1%
EMB 15 mg/kg (10–24 weeks)	3.2%

"The true toxicity of EMB was unlikely to vary this widely among institutions; it seems more probable that differences reflected varying interpretations of the manufacturer's warnings, or what might be called *the toxicity of the package insert*." Because of the doubts expressed about these results they have not been included in Table 2 or used in the construction of Figure 1

- **Eule H et al. (1973)**. Double blind study of the toxicity of different doses of ethambutol given in an intermittent treatment regimen of streptomycin, isoniazid and ethambutol. *Bulletin of the International Union against Tuberculosis*, 48:106–109.

EMB was given in three intermittent regimens of 52 weeks' duration, with different doses in the continuation phase:

I	63 patients	SM+INH+EMB 25 mg/kg daily for 6 weeks, then SM+INH+EMB 25 mg/kg twice weekly
II	60 patients	SM+INH+EMB 25 mg/kg daily for 6 weeks, then SM+INH+EMB 50 mg/kg twice weekly
III	61 patients	SM+INH+EMB 25 mg/kg daily for 6 weeks, then SM+INH+EMB 75 mg/kg twice weekly

Ocular toxicity occurred in 2 patients (3%) in regimen III, with symptoms being noted in the 16th week of treatment. Details of ophthalmological evaluation not noted.

- **Fraga H et al. (1973)**. A controlled comparison of three intermittent regimens after an initial period of daily drugs, in the retreatment of pulmonary tuberculosis (progress report). *Bulletin of the International Union against Tuberculosis*, 48:116–118.

Three regimens compared (unspecified methodology) – first two lasted 50 weeks, the third 40 weeks:

RMP+EMB 25 mg/kg for 8 weeks, then unsupervised intermittent twice weekly RMP+EMB 50 mg/kg
RMP+EMB 25 mg/kg for 8 weeks, then supervised intermittent twice weekly RMP+EMB 50 mg/kg
RMP+EMB 25 mg/kg for 8 weeks, then supervised intermittent twice weekly RMP+EMB 25 mg/kg

"Ocular toxicity was not registered in any case."

- **Somner AR et al. (1973)**. Drug resistant pulmonary tuberculosis treated with ethambutol and rifampicin in north east England. *Tubercle*, 54:141–145.

26 patients with advanced drug-resistant pulmonary TB were treated with RMP and EMB at 25 mg/kg for 2 months then 15 mg/kg for 2 years. No ocular toxicity was noted. The authors contrast the dose of EMB in this study with that used by Acquinas & Citron (1972) in Hong Kong (see above). The methodology for ophthalmological assessment is not given.

- **Barron GJ, Tepper L, Iovine G (1974)**. Ocular toxicity from ethambutol. *American Journal of Ophthalmology*, 77:256–260.

304 patients were give EMB at 25 mg/kg for 60 days, then 15 mg/kg. There were 3 cases (1%) of ocular toxicity at 2, 3 and 16 months. The cases that occurred at 2 months and 3 months were in fact receiving EMB at 15 mg/kg.

- **Hong Kong Tuberculosis Treatment Services/Brompton Hospital/British Medical Research Council (1974)**. A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis. *Tubercle*, 55:1–27.

Daily regimen:
ER7 EMB at 25 mg/kg for 2 months, then 15mg/kg in 107 patients

Ocular toxicity was noted in 2 patients (2%) at 7 months and 8 months

Intermittent regimens:
ER2 EMB at 45 mg/kg
ER1 EMB at 90 mg/kg
ER7/ER1 EMB 25 at mg/kg, then 90 mg/kg

No ocular toxicity was noted with intermittent regimens. However, the authors comment, "Ophthalmological examinations were undertaken *if indicated*; patients were fully assessed before the trial to provide a baseline."

- **British Thoracic and Tuberculosis Association (1975)**. Short-course chemotherapy in pulmonary tuberculosis. *Lancet*, 1:119–124.

Patients with pulmonary TB received EMB2+INH+RMP for 6 months (68 patients) or 12 months (101 patients). EMB was given at 25 mg/kg for 2 months. No ocular toxicity was noted, but methodology of evaluation is not specified.

- **Derka H (1975)**. Besteht Korrelation zwischen der Höhe der Myambutoldosis und der Häufigkeit der Neuritis Nervi optici? [Is there a correlation between Myambutol dosage and occurrence of optic neuritis?] *Ophthalmologica*, 171:123–131.

The author analyses 16 publications giving details of EMB dose (15–60 mg/kg) and the occurrence of ocular toxicity, and establishes a relationship between dose and toxicity.

- **National Research Institute for Tuberculosis, Poland: Second Department of Tuberculosis and Respiratory Diseases Study Centre, Lódz (1976)**. A comparative study of daily followed by twice or once-weekly regimens of ethambutol and rifampicin in retreatment of patients with tuberculosis: second report. *Tubercle*, 57:105–113. (See also *Tubercle*, 1975, 56:1–26.)

329 patients with INH-resistant TB were subjected to "regular optic evaluation". Treatment regimens were 600 mg RMP + EMB 25 mg/kg daily for 12 weeks, then RMP 600 mg (82 patients) or 1200 mg + EMB 50 mg/kg once or twice weekly for 12 (82 patients), 18 (82 patients) or 24 months (83 patients). Of the 161 patients who proceeded to the twice weekly intermittent regimen and completed at least 1 year of treatment, only 1 (0.6%) developed ocular toxicity; none of the patients on the once weekly intermittent regimen developed toxicity.

- **Hong Kong Chest Service/British Medical Research Council (1979)**. Controlled clinical trial of 6-month and 9-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 60:201210. (See also *American Review of Respiratory Disease*, 1978, 118:219–227.

Four regimens were evaluated:
6SHR
2SHRZ; 4 or 8$[SHZ]_2$
2SHRE; 4 or 8$[SHE]_2$
4$[SHRZ]_3$; 4 or 8$[SHZ]_2$

Doses of EMB were 25 mg/kg daily and 45 mg/kg twice weekly. There is no specific mention of evaluation for occurrence of ocular toxicity, the main focus being the development of any immune response to intermittent RMP.

- **Kuming BS, Braude L (1979)**. Anterior optic neuritis caused by ethambutol toxicity. *South African Medical Journal*, 55:4.

Report of 1 case of EMB toxicity in a man with a bilateral nephrectomy. In February 1977 he received treatment for TB, including EMB, but developed scotoma and blurred vision. EMB was stopped and his vision recovered. In March 1978 he was again treated with EMB; 14 days he was noted as having a history of decreasing visual acuity over 4 days, i.e. ocular toxicity developed 10 days after EMB was started. Fundi showed subretinal oedema and scattered flame-shaped haemorrhages. Vision normalized over 10 days after stopping EMB.

- **British Thoracic Association (1981)**. A controlled trial of six months chemotherapy in pulmonary tuberculosis. *British Journal of Diseases of the Chest*, 75:141–153.

EMB was given at 25 mg/kg for 2 months only, followed by 4 months (EHRZ6) or 7 months (EHR9) of further treatment. "No patient developed visual symptoms."

Regimen	No. of patients	Ocular toxicity
EHRZ6	164	0
EHR9	177	0

- **Tuberculosis Research Centre, Madras (1981)**. Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis- a controlled trial of four regimens. *Tubercle*, 61:13–19.

Details of ophthalmological evaluation not given. Four regimens were evaluated in 474 patients:

EH EMB 15 mg/kg + INH given daily
E_2H_2 EMB 45 mg/kg INH, twice weekly
E_1H_2 EMB 90 mg/kg once weekly + INH twice weekly
E_1H_2 EMB 90 mg/kg once weekly + INH once weekly

	No. of patients	Ocular toxicity
EH	120	2 (2%)
E_2H_2	120	2 (2%)
E_1H_2	123	1 (1%)
E_1H_1	121	1 (1%)

- **Hong Kong Chest Service/British Medical Research Council (1981)**. Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. *Lancet*, 1:171–174.

Four 6-month intermittent (three times weekly) regimens were evaluated and compared with a daily regimen: $HRSZE_3$, $HRSE_3$, $HRZE_3$ and $HRSZ_3$. EMB dose was 25 mg/kg for 2 months and 15 mg/kg daily or 30 mg/kg when intermittent. A fifth regimen – $HRZE_7$ – was given daily. Of 1207 patients entered in the studies, 3 were withdrawn because of transient visual changes; these were 2/146 (1%) on $HRZSE_3$, and 1/156 (1%) on $HRSE_3$. As the same intermittent dose of EMB (30 mg/kg) was given throughout, the number of patients withdrawn could also be stated as 3/725 (0.5%).

- **Bonnet I, Woeherle R (1982)**. Ethambutol – nevrite optique aiguë bilaterale severe – lente recuperation en 2 ans [Ethambutol – severe bilateral acute optic neuritis – slow recovery over 2 years]. *Bulletin des Sociétés d'Ophtalmologie de France*, 82:909–910.

Case report of EMB toxicity in a 47-year-old woman with tuberculous meningitis given EMB at 15 mg/kg.

- **Yiannikas C, Walsh JC, McLeod JG (1983)**. Visual evoked potentials in the detection of subclinical effects secondary to ethambutol. *Archives of Neurology*, 40:645–648.

Pattern-reversal visual-evoked potentials (VEPs) to monocular whole-field stimulation were recorded before starting EMB treatment in 14 patients and again at 1 month and 3 months. VEPs changed in 6 patients, reverting to normal in 3 cases after EMB was stopped. EMB dosages in these patients were 16, 17, 18, 20, 21 and 25 mg/kg. These disturbing results suggest that, even when no clinical abnormalities are found, underlying changes have occurred.

Karnik AM, Al-Shamali MA, Fenech FF (1985). A case of ocular toxicity to ethambutol- an idiosyncratic reaction. *Postgraduate Medical Journal*, 61:811–813.

Case report of onset of optic neuritis within 3 days of starting EMB treatment at 15 mg/kg. Bitemporal hemianopia was found, but colour vision remained intact, suggesting that this might have been an idiosyncratic reaction to EMB.

- **Polak CP, Leys M, van Lith GHM (1985)**. Blue-yellow colour vision changes as early symptoms of ethambutol oculotoxicity. *Ophthalmologica*, 191:223–226.

This study attempts to define sensitive parameters for the early detection of toxic changes caused by EMB in 19 patients receiving EMB at 15 mg/kg/day. Patients were extensively tested – as soon as possible after starting treatment and at 3-monthly intervals over 2 years. In 7 patients (37%) there was progressive deterioration of visual acuity during the follow-up period on treatment. In 2/19 (11%) patients central and paracentral scotomata were found and attributed to EMB. Colour vision abnormalities were found in 12 patients on the first examination. Major blue-yellow errors were found *before* treatment in 15 (64%) eyes of 12 patients – and in 12 (21%) eyes of a group of 28 healthy volunteers (p = 0.001). The percentage of abnormalities attributed to EMB in this study is disconcertingly high and, despite statistical significance, begs questions about its precise implications. If the caution recommended by the authors were exercised under programme conditions, almost no patients would receive EMB. Perhaps sufficiently rigorous investigation would show that almost all patients receiving EMB manifest some subtle change in function.

- **Chatterjee VKK et al. (1986)**. Ocular toxicity following ethambutol in standard dosage. *British Journal of Diseases of the Chest*, 80:288–291.

A case report of very rapid (3 days) onset of ocular toxicity associated with EMB at 15 mg/kg, which led to irreversible blindness.

- **Citron KM, Thomas GO (1986)**. Ocular toxicity from ethambutol. *Thorax*, 41:737–739.

An editorial reviewing the use of EMB and its association with ocular toxicity and tabulating occurrence of toxicity in a number of studies. It is claimed that only 10 cases of toxicity occurred among 2184 patients, yet several of the cited references make no mention of any ocular function testing (for example, Algerian Working Group et al., 1984 (reference 8), Hong Kong and British Medical Research Council, 1980 (reference 9), and Hong Kong Chest Service/British Medical Research Council, 1983 (reference 11), plus reference 14 (British Thoracic Association, 1982) which is discussed in the text). These data may be available from other sources, but do not appear in the cited papers.

- **Joubert PH et al. (1986)**. Subclinical impairment of colour vision in patients receiving ethambutol. *British Journal of Clinical Pharmacology*, 21:213–216.

Colour discrimination was evaluated by Farnsworth-Munsell 100-hue test in 54 patients receiving EMB at 15 mg/kg (14.7 ± 4.0) for 49 (± 40) days and compared with that in 50 patients not receiving EMB. The EMB group showed significantly more errors than controls along the deuteran axis; those taking EMB for more than 2 months had significantly more abnormalities along the tritan axis. Disturbingly, results suggest that subclinical abnormalities are common in patients receiving EMB.

- **Jimenez-Lucho VE, del Busto R, Odel J (1987)**. Isoniazid and ethambutol as a cause of optic neuropathy. *European Journal of Respiratory Diseases*, 71:42–45.

A case report documenting EMB ocular toxicity in which INH also played a role – the neuropathy subsided only when INH was stopped. EMB was given at 15 mg/kg and first symptoms were noted after 7 months of treatment.

- **Salmon JF, Carmichael TR, Welsh NH (1987)**. Use of contrast sensitivity measurement in the detection of subclinical ethambutol toxic optic neuropathy. *British Journal of Ophthalmology*, 71:192–196.

Subclinical EMB toxicity was evaluated by testing contrast sensitivity with Arden grating plates – similarly to Joubert et al. (1986) and Yiannikas, Walsh & McLeod (1983), cited above. Significantly more patients on EMB had abnormal scores than those not receiving EMB. Loss of contrast sensitivity may reflect “subclinical toxic optic neuropathy”.

- **Kahana LM (1987)**. Toxic ocular effects of ethambutol. *Canadian Medical Association Journal*, 137:213–216.

Four case reports of EMB ocular toxicity:

EMB dosage	Duration of treatment at onset of toxicity
15 mg/kg	12 months; this patient suffered from renal TB
15 mg/kg	13 months
25 mg/kg for 2months, then 15 mg/kg	10 months
25 mg/kg	4 months

- **Smith JL (1987)**. Should ethambutol be barred? *Journal of Clinical Neuro-ophthalmology*, 7:84–86.

Editorial comment with details of 5 patients, including 3 with renal TB, who experienced ocular toxicity following the use of EMB.

Diagnosis	EMB dose	Treatment duration before onset of toxicity
Renal TB	14 mg/kg	6 months
Renal TB	21 mg/kg 60 days, then 12.5 mg/kg	3 months
Pulmonary TB	18mg/kg	9 months
Renal TB	24 mg/kg	6 months
Pulmonary TB	25 mg/kg	4 months

Renal disease was an obvious precipitating cause in 3 of these cases.

- **De Palma P et al. (1989)**. The incidence of optic neuropathy in 84 patients treated with ethambutol. *Metabolic, Pediatric, and Systemic Ophthalmology*, 12:80–82.

Incidence of ocular toxicity was evaluated in 84 patients by follow-up of visual acuity, colour vision (Farnsworth 100-hue test) and visual field. EMB dose was 25 mg/kg/day. Plasma zinc concentrations were determined and were >1 µg/ml in 53 patients and <0.7 µg/ml in 31**.** Follow-up evaluation was

monthly in the first group and 2-weekly in the second. Of patients with plasma Zn >1 µg/ml, 3 (6%) developed one or more visual abnormalities at 1 month and 2 months of treatment. Among those with plasma Zn <0.7 µg/ml, 5 patients (16%) had one or more visual abnormality presenting at 2, 4, 6 and 10 weeks.

	Test:		
Plasma Zn (*n*)	Farnsworth	Visual acuity	Visual field
>1 µg/ml (53)	3	2	1
<0.7 µg/ml (31)	5	3	–

- **Schild HS, Fox BC (1991)**. Rapid-onset reversible ocular toxicity from ethambutol therapy. *American Journal of Medicine*, 90:404–406.

Case report of toxicity arising within 2 days of starting therapy with EMB, 1700 g for a 70-kg patient, i.e. approximately 25 mg/kg.

- **Babu Swai O et al. (1988)**. Controlled trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. *Tubercle*, 69:5–14.

Patients with INH resistance or INH and SM resistance were evaluated. Of 306 patients entered in the study, 226 were finally analysed. Two regimens were evaluated: an 8-week intensive phase of SM, PZA, RMP and EMB was followed by RMP and EMB daily for 4 months or 7 months. The dose of EMB was 25 mg/kg daily for the 8 weeks and 15 mg/kg daily thereafter. Ophthalmological examinations were not performed routinely but cases of suspected ethambutol toxicity were seen by the provincial physician. “No ocular toxicity was reported though the centers were expressly advised to refer any patients with visual problems during chemotherapy to the provincial physician.”

- **Russo PA, Chaglasian MA (1994)**. Toxic optic neuropathy associated with ethambutol: implications for current therapy. *Journal of the American Optometric Association*, 65:332–338.

Case report of ocular toxicity: EMB was given at 16 mg/kg for 5 months before appearance of first symptoms. There was a history of renal failure and hypertension. There were complaints of visual symptoms for 4 months before EMB was stopped. Toxic optic neuropathy with advanced optic atrophy was found.

Tuberculosis Research Centre (1997). A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1:509–517.

In a randomized study, 1203 patients were assigned to three possible regimens. EMB was given in a dose of 600 mg daily or 1200 mg twice weekly. Assuming a body weight of 50 kg this is a daily dose of approximately 12 mg/kg or a twice-weekly dose of 24 mg/kg; for a body weight of 45 kg, doses were 13.3 mg/kg daily or 27 mg/kg twice weekly.

Regimen	No. of patients
I $EHRZ_7/6EH_7$	305
II $2EHRZ_2/4EHR_2$	263
III $2HRZ_2/4HR_2$	257

“Detailed examination by an ophthalmologist was carried out at 2 months and the end of treatment for all patients, and at any time during chemotherapy if indicated.” “….ocular toxicity attributable to ethambutol did not occur in this study.”

- **Goyal JL, De S, Singh NP, Bhatia A (2003)**. Evaluation of visual functions in patients on ethambutol therapy for tuberculosis: a prospective study. *Journal of Communicable Diseases*, 35:230–243.

The results of a very careful prospective evaluation of ocular toxicity in 30 newly-diagnosed adult TB patients receiving EMB were compared with results in a similar group of patients not receiving EMB. EMB ocular toxicity was found in 3 patients (10%). Unfortunately the authors give neither the dose of EMB that the patients received nor the duration of therapy before toxicity supervened.

- **Jindani A, Nunn AJ, Enarson DA (2004)**. Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet*, 364:1244–1251.

Three regimens were evaluated in 1355 patients randomly assigned to receive :

2EHRZ/6HE 456 patients
2$[EHRZ]_3$/6HE 466 patients
2EHRZ/4HR 433 patients

EMB dose in patients <40 kg body weight ranged from 15.4 to 24 mg/kg/day and for patients 40–55 kg from 14.5 to 20 mg/kg; for patients >55kg the dose was 21.8 mg/kg, and decreasing with increasing body weight. Most patients fell in the 40–55 kg group body weight. The precise method of optic evaluation is not specified, but the authors state “Loss of visual acuity led to the termination of ethambutol from the allocated regimens in four patients.” That is, incidence was 4/1355 (0.3%).

- **Griffith DE** et al. (2005). Ethambutol ocular toxicity in treatment regimens for *Mycobacterium avium* complex lung disease. *American Journal of Respiratory and Critical Care Medicine*, 172:250–253.

229 patients being treated for *M. avium* complex disease between 1996 and 2000 were prospectively enrolled in this study. Mean age was 63.8 ± 13.6 years; EMB was given either daily at 25 mg/kg for 2 months and 15 mg/kg thereafter (139 patients) or twice weekly at 25 mg/kg (90 patients). Total weekly dose of EMB for those on daily treatment was 175 mg/kg for 2 months and 105 mg/kg thereafter; for those on intermittent therapy it was 75 mg/kg throughout.

Ocular toxicity, confirmed by an ophthalmologist, developed in 8 patients (6%) on daily therapy. These patients had received a mean EMB dose of 17.8 ± 4.2 mg/kg (range 14–24 mg/kg/day) for a mean duration of 6.7 ± 5.8 months at the time that toxicity developed. None of the patients on intermittent treatment developed toxicity. In all patients with ocular toxicity, vision returned to normal after EMB was stopped. In contrast to previous studies, no case of toxicity was detected during routine visits to an ophthalmologist. Visual symptoms preceded any decrease in visual acuity or change in colour discrimination.

This study provides one of the more accurate quantifications of the relationship between exposure to EMB and the occurrence of toxicity, suggesting very strongly that the total weekly dose was related to the development of toxicity. Although the mean period before toxicity developed was 6.7 months, the range was wide at 1–16 months.

References

Acquinas M, Citron KM (1972). Rifampicin, ethambutol and capreomycin in pulmonary tuberculosis previously treated with both first and second line drugs: the results of 2 years chemotherapy. *Tubercle*, 53:153–165.

Adel A (1969). Ophthalmological side-effects of ethambutol. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl.):55–58.

Babu Swai O et al. (1988). Controlled trial of a regimen of two durations for the treatment of isoniazid resistant pulmonary tuberculosis. *Tubercle*, 69:5–14.

Barron GJ, Tepper L, Iovine G (1974). Ocular toxicity from ethambutol. *American Journal of Ophthalmology*, 77:256–260.

Bobrowitz ID (1966a). Ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:796–822.

Bobrowitz ID (1966b). Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Bobrowitz ID, Gokulanathan KS (1965). Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Bobrowitz ID, Robins DE (1967). Ethambutol-isoniazid versus PAS-isoniazid in original treatment of pulmonary tuberculosis *American Review of Respiratory Disease*, 96:428–438.

Bonnet I, Woeherle R (1982). Ethambutol – nevrite optique aiguë bilaterale severe – lente recuperation en 2 ans [Ethambutol – severe bilateral acute optic neuritis – slow recovery over 2 years]. *Bulletin des Sociétés d'Ophtalmologie de France*, 82:909–910.

Bowen DI, Vaterlaws AL (1971). Toxic amblyopia due to ethambutol in a case of drug-resistant pulmonary tuberculosis. *British Journal of Diseases of the Chest*, 65:105–110.

British Medical Research Council (1973). Co-operative controlled trial of a standard regimen of streptomycin, PAS and isoniazid and three alternative regimens of chemotherapy in Britain. *Tubercle*, 54:99–129.

British Thoracic and Tuberculosis Association (1975). Short-course chemotherapy in pulmonary tuberculosis. *Lancet*, 1:119–124.

British Thoracic Association (1981). A controlled trial of six months chemotherapy in pulmonary tuberculosis. *British Journal of Diseases of the Chest*, 75:141–153.

Campbell IA, Elmes PC (1975). Ethambutol and the eye; zinc and copper. *Lancet*, 2:711.

Carr RE, Henkind P (1962). Ocular manifestations of ethambutol. *Archives of Ophthalmology*, 67:566–571.

Chatterjee VKK et al. (1986). Ocular toxicity following ethambutol in standard dosage. *British Journal of Diseases of the Chest*, 80:288–291.

Citron KM (1969). Ethambutol: a review with special reference to ocular toxicity. *Tubercle*, 50(Suppl.):22–36.

Corpe RF, Blalock FA (1966). Multi-drug therapy including ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:823–830.

De Palma P et al. (1989). The incidence of optic neuropathy in 84 patients treated with ethambutol. *Metabolic, Pediatric, and Systemic Ophthalmology*, 12:80–82.

Derka H (1975). Besteht Korrelation zwischen der Höhe der Myambutoldosis und der Häufigkeit der Neuritis Nervi optici? [Is there a correlation between Myambutol dosage and occurrence of optic neuritis?] *Ophthalmologica*, 171:123–131.

Donomae I, Yamamoto K (1966). Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Doster B et al. (1973) Ethambutol in the initial treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 107:177–190.

Eule H et al. (1973). Double blind study of the toxicity of different doses of ethambutol given in an intermittent treatment regimen of streptomycin, isoniazid and ethambutol. *Bulletin of the International Union against Tuberculosis*, 48:106–109.

Farga H et al. (1973) A controlled comparison of three intermittent regimens after an initial period of daily drugs in the retreatment of pulmonary tuberculosis (progress report). *Bulletin of the International Union against Tuberculosis*, 48:116–118.

Ferebee SH, Doster BE, Murray FJ (1966). Ethambutol: a substitute for para-aminosalicylic acid in regimens for pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:910–920.

Filippone C, Barnabè R, Bonanni R (1968). Osservazioni oftalmologiche in corso di terapia con etambutolo [Ophthalmological findings in the course of ethambutol therapy]. *Minerva Oftalmologica*, 10:38–41.

Goyal JL, De S, Singh NP, Bhatia A (2003). Evaluation of visual functions in patients on ethambutol therapy for tuberculosis: a prospective study. *Journal of Communicable Diseases*, 35:230–243.

Griffith DE et al. (2005). Ethambutol ocular toxicity in treatment regimens for *Mycobacterium avium* complex lung disease. *American Journal of Respiratory and Critical Care Medicine*, 172:250–253.

Hong Kong Tuberculosis Treatment Services/Brompton Hospital/British Medical Research Council (1974). A controlled clinical trial of daily and intermittent regimens of rifampicin plus ethambutol in the retreatment of patients with pulmonary tuberculosis. *Tubercle*, 55:1–27.

Hong Kong Chest Service/British Medical Research Council (1979). Controlled clinical trial of 6-month and 9-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 60:201–210.

Hong Kong Chest Service/British Medical Research Council (1981). Controlled trial of four thrice-weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. *Lancet*, 1:171–174.

Horsfall PAL (1969). Ethambutol in the retreatment of chronic pulmonary tuberculosis. *Far East Medical Journal*, 7:213–218.

IUAT Committee on Treatment 1969 (1970). Report of Dr Farga. *Bulletin of the International Union against Tuberculosis*, 44:8.

Jimenez-Lucho VE, del Busto R, Odel J (1987). Isoniazid and ethambutol as a cause of optic neuropathy. *European Journal of Respiratory Diseases*, 71:42–45.

Jindani A, Nunn AJ, Enarson DA (2004). Two 8-month regimens of chemotherapy for treatment of newly diagnosed pulmonary tuberculosis: international multicentre randomized trial. *Lancet*, 364:1244–1251.

Joubert PH et al. (1986) Subclinical impairment of colour vision in patients receiving ethambutol. *British Journal of Clinical Pharmacology*, 21:213–216.

Kahana LM (1987). Toxic ocular effects of ethambutol. *Canadian Medical Association Journal*, 137:213–216.

Karnik AM, Al-Shamali MA, Fenech FF (1985). A case of ocular toxicity to ethambutol – an idiosyncratic reaction. *Postgraduate Medical Journal*, 61:811–813.

Kass I (1965). Chemotherapy regimens used in retreatment of pulmonary tuberculosis. Part II. Observations on the efficacy of combinations of ethambutol, capreomycin and companion drugs, including 4-4 diisoamyloxythiosemicarbanilide. *Tubercle*, 46:166–177.

Kuming BS, Braude L (1979). Anterior optic neuritis caused by ethambutol toxicity. *South African Medical Journal*, 55:4.

Leibold JE (1966). The ocular toxicity of ethambutol and its relation to dose. *Annals of the New York Academy of Sciences*, 135:904–909.

Lees AW et al. (1971). Toxicity from rifampicin plus isoniazid and rifampicin plus ethambutol therapy. *Tubercle*, 52:182–190.

National Research Institute for Tuberculosis, Poland: Second Department of Tuberculosis and Respiratory Diseases Study Centre, Lódz (1976). A comparative study of daily followed by twice or once-weekly regimens of ethambutol and rifampicin in retreatment of patients with tuberculosis: second report. *Tubercle*, 57:105–113.

Orou F, Sideroff G, Schabel F (1972). Frequenzuntersuchung von Opticuserkrankungen im Rahmen der Myambutol-Behandelung [Studies on the occurrence of optic nerve diseases in the course of Myambutol therapy]. *Klinische Monatsblatter fur Augenheilkunde*, 161:601–603.

Pilheu J (1970). Ambulatory treatment of pulmonary tuberculosis with ethambutol-isoniazid. *Chest*, 58:497–500.

Polak CP, Leys M, van Lith GHM (1985). Blue-yellow colour vision changes as early symptoms of ethambutol oculotoxicity. *Ophthalmologica*, 191:223–226.

Pyle MM (1966). Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

Radenbach KL (1969). Results of clinical studies with capreomycin, ethambutol and rifampicin in the Heckeshorn Hospital, Berlin. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl.):43–53.

Reimers D (1972). Irreversible Augenschäden durch Ethambutol [Irreversible eye damage caused by ethambutol. Preliminary report]. *Praxis der Pneumologie vereinigt mit Der Tuberkulosearzt*, 26:445–449.

Russo PA, Chaglasian MA (1994). Toxic optic neuropathy associated with ethambutol: implications for current therapy. *Journal of the American Optometric Association*, 65:332–338.

Roussos T, Tsolkas A (1970). The toxicity of Myambutol on the human eye. *Annals of Ophthalmology*, 2:578–580.

Salmon JF, Carmichael TR, Welsh NH (1987). Use of contrast sensitivity measurement in the detection of subclinical ethambutol toxic optic neuropathy. *British Journal of Ophthalmology*, 71:192–196.

Schild HS, Fox BC (1991). Rapid-onset reversible ocular toxicity from ethambutol therapy. *American Journal of Medicine*, 90:404–406.

Schütz I, Radenbach KL, Bartmann K (1970). The combination of ethambutol, capreomycin and a third drug in chronic pulmonary tuberculosis with bacterial polyresistance. *Antibiotics and Chemotherapy*, 16:43–58.

Smith JL (1987). Should ethambutol be barred? *Journal of Clinical Neuro-ophthalmology*, 7:84–86.

Somner AR et al. (1973) Drug resistant pulmonary tuberculosis treated with ethambutol and rifampicin in north east England. *Tubercle*, 54:141–145.

Tai FH, Chen TC (1968). Studies on combined use of ethambutol and isoniazid in retreatment of drug-resistant cases of pulmonary tuberculosis. *Chinese Journal of Microbiology*, 1:84–91.

Tamai A (1970). Ocular toxicity of ethambutol: a clinical investigation conducted from May 1965 to December 1969. *Yonago Acta Medica*, 14:61–69.

Tiburtius H (1970). The undesired side-effects of Myambutol. *Antibiotics and Chemotherapy*, 16:298–301.

Tuberculosis Research Centre, Madras (1981). Ethambutol plus isoniazid for the treatment of pulmonary tuberculosis – a controlled trial of four regimens. *Tubercle*, 61:13–19.

Tuberculosis Research Centre (1997). A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1:509–517.

Wäre M et al. (1969). Clinical experience of the retreatment of drug-resistant pulmonary tuberculosis with rifampicin combined with ethambutol and capreomycin. *Scandinavian Journal of Respiratory Diseases*, 69(Suppl.):59–63.

Yiannikas C, Walsh JC, McLeod JG (1983). Visual evoked potentials in the detection of subclinical effects secondary to ethambutol. *Archives of Neurology*, 40:645–648.

Annex III

Efficacy and toxicity of ethambutol in childhood

- **Chavarria AG et al. (1967)**. El ethambutol asociado a isoniacida en el tratamiento de la tuberculosis en el niño [Ethambutol and isoniazid in the treatment of childhood tuberculosis]. *Revista Mexicana de Pediatria*, 36:194–200.

[In Spanish with a short English summary.] Fifteen children aged 1–15 years were treated with EMB at 25 mg/kg/day for 12–24 months. "…nor were there manifestations of toxicity."

- **Del Principe A, Caione C, Zamparelli F (1968)**. Prime applicazioni dell'etambutolo nella terapia della tuberculosi infantile [Preliminary use of ethambutol in the treatment of tuberculosis in children]. *Annali dell'Istituto "Carlo Forlanini"*, 28:42–73.

[In Italian with a short English summary.] EMB either alone or in combination with other agents was used in the treatment of 58 children. In 27 children EMB was used alone, in 11 EMB was combined with INH and in the remainder EMB was used with other antituberculosis agents. EMB dose was 25 mg/kg for 3 months and then 15 mg/kg, but given three times daily.

Treatment of primary TB alone was considered "very satisfying". Better results were obtained with INH+EMB, and EMB in combination with other drugs was also "very efficacious" against resistant bacilli. Ocular toxicity is discussed, but there do not appear to have been any cases of ocular toxicity. "EMB…was always well tolerated."

- **Chavarria AG et al. (1970)**. Evaluacion clinica del etambutol en 36 niños tuberculosos estudados durante cuatro años [Clinical evaluation of ethambutol in 36 children with tuberculosis followed up for four years]. *Neumologia y Cirugia de Torax (Mexico)*, 31:39–47.

[In Spanish with a short English summary.] EMB+INH+SM was given to 36 children aged 4 months to 16 years, with pulmonary and extrapulmonary TB; 23 had been treated previously with INH+PAS+SM with "poor results." EMB dose was 25 mg/kg daily for the first month (?), then 15 mg/kg, given at 12=hourly intervals. "The results using ethambutol were excellent in 85% and poor in 15%. In the last group it was necessary to associate capreomycin or ethionamide. We have never observed toxicity during 4 years of use of ethambutol." The method of evaluation for ocular toxicity, however, is not clear.

- **Mankodi NA et al. (1970)**. Ethambutol in unresponsive childhood tuberculosis. *Indian Pediatrics*, 7:202–211.

EMB was used in 16 children, aged 3–12 years, with "advanced tuberculosis" who had already been treated for 6–24 months "without manifest improvement". AFB were isolated from 11 of 13 children with pulmonary disease. EMB was given at 25 mg/kg for 3 months and then at 15 mg/kg for 8–18 months.

"The clinical improvement has been a notable feature in all the children except two." "The children were closely observed for manifestations of toxicity." In one 11-year-old child, "minimal edema" of the optic disc was noted after 7 months of therapy. EMB was stopped for 4 months, the oedema subsided and EMB was reintroduced without any further problem.

- **Patwardhan P, Bhatia M, Merchant SM (1970)**. Ethambutol in primary childhood tuberculosis. *Indian Pediatrics*, 7:194–201.

Sixty children, aged 6 months to 5 years, received one of three regimens: INH alone (25), INH+SM (15) or INH+EMB (20). In the discussion it is stated: "In our series though the drug was given for a

minimum of 1 year no toxic effects were noted." Ocular toxicity is discussed as a possible complication of EMB, but not specifically referred to in the results.

- **Schmid PC (1970)**. Discussion on Myambutol (ethambutol). *Antibiotics and Chemotherapy*, 16:305–315.

In discussion following a symposium: "So far we have treated 80 children aged from one to six years with Myambutol. It was applied in combination with INH for three to four months." "It is necessary to give 25 mg/kg body weight daily." "No changes ….in the eyes (visus and fundus) were observed."

The children referred to are probably included in the 2634 described in Schmid (1981) below. In the same discussion, K. Simon describes experience with 49 cases of primary TB (ages unspecified) treated with EMB at 15 mg/kg: "Secondary effects were not observed."

- **Hussels H, Otto HS (1971)**. Ethambutol-Serumkonzentrationen im Kindesalter [Serum ethambutol levels in childhood]. *Pneumonologie*, 145:392–396.

Serum EMB concentrations were determined following 2 different dosages of EMB in children 2–5, 5–9 and 10–14 years of age. Determinations were carried out by a microbiological method at 0, 1, 2, 4, 7 and 24 hours after dosing. Maximum values were found at either 2 or 4 hours:

	Maximum concentration, µg/ml (no.)	
Age	15 mg/kg	25 mg/kg
2–5 years	1.2 (6)	2.0 (4)
6–9 years	1.1 (6)	1.5 (7)
10–14 years	0.9 (?)	2.8 (8)

The authors comment that drugs in children, particularly younger children, should be dosed according to body surface area and not body weight, because of the larger extravascular fluid compartment and faster metabolism in children. Only in children 10–14 years receiving 25 mg/kg EMB was a mean EMB concentration of >2 µg/ml reached.

- **Mérida de León JC (1971)**. Tratamiento de la tuberculosis pulmonar con isoniacida y jarabe de Myambutol en niños [Treatment of childhood pulmonary tuberculosis with isoniazid and ethambutol syrup]. *Revisita del Collegio Medico de Guatemala*, 22:48–55.

[In Spanish with no English abstract or summary.] EMB was given to 20 children aged 3–13 years at 25 mg/kg for 2 months and then at 15 mg/kg for a total of 8–12 months.

Ocular evaluation "une vez inicio del tratamiento, una intermedia y una al final" [at the start, in the middle, and at the end of treatment]. No toxicity is noted. The paper includes a number of Spanish references to EMB use, but gives names of authors only without dates or journal names.

- **Scheffler NK (1971)**. Augenuntersuchungen bei der Behandelung mit Ethambutol in zwei verscheidenen Dosierungen im Kindesalter [Eye examination of children treated with ethambutol under two different dosage schedules]. *Pneumonologie*, 145:396–400.

Sixty children aged 3½–15 years were treated with EMB – either 25 mg/kg for 3 months and then 15 mg/kg, or 25 mg/kg for 3 months and then 20 mg/kg – for 2–12 (mean 6**)** months. There was ocular evaluation before treatment and 4-weekly thereafter in all children 6 years and older.

Temporary visual disturbance was noted in 2 children, but this resolved without stopping EMB. The author remarks on the difficulty of evaluating children up to 5 years of age.

- **Hussels H, Kroening U, Magdorf K (1973)**. Ethambutol and rifampicin serum levels in children: second report on the combined administration of ethambutol and rifampicin. *Pneumonologie*, 149:31–38.

In a further study by Hussels et al. (see Hussels et al., 1971, above), serum EMB was again determined by a microbiological method. Two evaluations are presented; in the first EMB was administered alone at a dose of 35 mg/kg, and in the second EMB was given at 10 mg/kg together with RMP. The children were again grouped in three age ranges: 2 to <6 years, 6 to <10 and 10 to 14 years.

This study aimed to achieve serum EMB concentrations in excess of 2.0 µg/ml – a value derived from the study of Pyle et al (1967) in which the MIC against *M. tuberculosis* isolated from patients before treatment was given as 2.0 µg/ml. The authors evaluated EMB given with RMP following the findings of Boman et al (1970) of higher concentrations of PAS when the drug was given in conjunction with RMP.

		Maximum concentration, µg/ml (no.)	
Age	No. of children	EMB alone	EMB+RMP
2–<6 years	8	1.5	2.5
6–<10 years	11	2.3	2.5
10–14 years	9	3.0	6.3

As can be seen from the table, higher EMB concentrations were indeed found when EMB was given with RMP. However, there was a "wide distribution of individual serum concentrations" such that " the differences between the mean values of ethambutol serum levels after administration of ethambutol alone and in combination with rifampicin did not prove to be statistically significant." Almost incidentally, it is perhaps noteworthy that RMP concentrations when RMP was given with EMB were lower than when RMP was given alone.

- **Dingley HB, Sehgal KL (1974)**. Treatment of pulmonary tuberculosis in children – a controlled study. *Indian Pediatrics*, 11:289–295.

Four regimens were compared in 280 children aged 1½–14 years treated for 6 months in hospital. EMB dose was 25 mg/kg for 2 months and 15 mg/kg thereafter. "Ophthalmological examination for children in the group who were given ethambutol."

Regimen		No. of children
I	EMB+INH	54
II	THIO+INH	50
III	PAS+INH	48
IV	SM+INH	57

"…no ophthalmological abnormalities were detected in the patients treated with ethambutol." It is stated that "…better and quicker results are obtained when ethambutol is combined with INH", but no statistical evaluation was carried out.

- **Benkert K et al. (1974)**. Tagesprofile und Profilverlaufskontrollen von Ethambutol bei Kindern [Daily check and follow-up of use of ethambutol in children]. *Medizinische Klinik*, 69:1808–1813.

Specific microbiological methodology was used to determine EMB plasma concentrations in 26 **c**hildren, aged 3–14 years, 13 receiving 15 mg/kg and 13 receiving 25 mg/kg EMB. "No side effect was caused in any case."

Age	2-hour serum concentration (µg/ml)	
	EMB 15 mg/kg (no.)	EMB 25 mg/kg (no.)
3–6 years	0.9 (4)	3.0 (5)
7–10 years	2.0 (4)	2.6 (5)
11-14 years	1.8 (5)	3.5 (3)

- **Bhatia MP, Merchant SM** (1975)**.** Comparative study of antitubercular drugs in the management of primary complex. *Indian Pediatrics*, 12:1197–1203.

Three regimens containing EMB/INH were evaluated:

54 children received EMB as a single oral dose of 25 mg/kg for 10–12 weeks and 15 mg/kg thereafter, up to a minimum of 1 year.
33 children received EMB as a single oral dose of 25 mg/kg for 3 months. INH was given for 1 year.
18 children received EMB as a single oral dose of 25 mg/kg for 3 months. INH was given for 3 months.

“No untoward reactions were observed….” There is no specific mention of ocular toxicity.

- **Prachakvej P, Subharngkahen I (1979)**. Visual loss from ethambutol. *Siriraj Hospital Gazette*, 31:908–912.

The author of this review was unable to read this article, but deduces from the tables, which contain phrases in English, and from other reviews that it deals with the use of EMB in children with tuberculous meningitis, some of whom, not unexpectedly, had disorders of ocular function.

- **Nagy A et al. (1980)**. Studiu privind toxitatea oculară a etambutolui [Study of the ocular toxicity of ethambutol]. *Revista de igiena, bacteriologie, virusologie, parazitologie, epidemiologie, pneumoftiziologie. Pneumoftiziologia*, 29:163–166.

The study included 30 children aged 4–5 years who received EMB 25 mg/kg twice weekly. Ophthalmological evaluation before treatment and again 3 and 6 months after the start of treatment included visual acuity, visual field, “chromatic sense” and pupil reflexes. “No case of toxic ocular manifestations was recorded.” However, the children received a relatively low total dose of EMB.

- **Schmid PC (1981)**. Ethambutol- und Rifampicin-verträglikeit und -dosierung im Kindesalter [Ethambutol and rifampicin tolerance and dosages in childhood]. *Pädiatrische Praxis*, 25:207–209.

This literature review and details of personal experience with regard to EMB dosing in children were provided in response to a reader’s question. Taking into account blood concentrations achieved by doses with EMB doses of 15 mg/kg and 25 mg/kg in children aged 3–6, 7–10 and 11–14 years, the author suggests a dose of 20 mg/kg as appropriate. However, because children should be dosed according to body surface area, and taking into account the more rapid metabolism in children, this dose should be adjusted upwards by 5 mg/kg in infants and toddlers and downwards by 5 mg/kg in children older than 11 years. Using this approach, 2634 children were treated without complications or toxic effects: “…keine Komplikationen und keine toxischen Schädigungen beobachtet.”

- **Gramer RE, Jeschke R, Krieglstein GK (1982)**. Zur computergeseuerten Gesichtsfeldkontrolle bei Kindern mit Ethambutol-Medikation [Computerized perimetry in children treated with ethambutol]. *Klinische Pädiatrie*, 194:52–55.

Computerized perimetry of the central visual field (visual acuity, visual field and mean retinal threshold of the central field) was used to assess ocular toxicity in 6 children aged 9–16 years receiving EMB at 20 mg/kg. Patients were assessed every 7 weeks; no abnormalities were detected.

- **Junnanond C, Chotibut S, Lawtiantong T (1983)**. Safety evaluation of ethambutol in children. *Journal of the Medical Association of Thailand*, 66:77–79.

Twenty-seven children aged 5½–15 years received EMB at 20 mg/kg for periods of 2–24 months. Ophthalmological evaluation was performed before treatment, at 1-month intervals for the first 6 months and at three-month intervals thereafter until treatment completion. Two children, aged 7 and 10 years, complained of blurred vision and diplopia during the fourth and fifth months of treatment, but ocular examination revealed nothing and treatment was continued without any deleterious effect.

- **Ramachandran P et al. (1986)**. Three chemotherapy studies of tuberculous meningitis in children. *Tubercle*, 67:17–29.

Three regimens for the treatment of tuberculous meningitis were studied in 180 children aged 1–12 years (53% of children < 3 years of age). EMB was given at 17.5 mg/kg for 6 – 10 months during the continuation phase.

Sixteen patients developed pallor of the optic discs (5 while on EMB); 6 died before completing treatment but the remaining 10 recovered vision and optic findings returned to normal. Another 12 patients developed optic atrophy with blindness (7 while receiving EMB): 5 died and the remainder continued to have optic atrophy and blindness.

Four patients developed cortical blindness during the first month of treatment, before the start of EMB treatment. In 3/9 patients who developed ocular complications while on EMB, the drug was stopped although the authors believed that the complications were due to the disease, not to EMB.

The paper quotes Professor Wallace Fox with respect to 45 Korean children aged 1–15 years who were treated for 9 or 18 months with EMB at 15–25 mg/kg for spinal TB. The children were assessed monthly for visual acuity, colour vision, visual field and macular threshold, but there was no evidence of EMB toxicity.

- **Medical Research Council Tuberculosis and Chest Diseases Unit (1989)**. Management and outcome of chemotherapy for childhood tuberculosis. *Archives of Disease in Childhood*, 64:1004–1012

This paper reviews the management of TB and outcome among children diagnosed in England and Wales during 1983. Of the 151 children, 30% were aged <5 years, 25% were 5–9 years old and 46% were 10–14 years. EMB was given at more than 17 mg/kg to 28% of children; 18% were treated for more than 3 months. One child (1%) developed possible ocular toxicity. No details of the case are given.

- **Mir ES et al. (1990)** Tratamiento de seis meses en tuberculosis pulmonar infantil. Revision de 11 casos [Six months' treatment of childhood pulmonary tuberculosis. Review of 11 cases]. *Anales espanoles de pediatria*, 32:303–306. (Spanish with English abstract.)

This paper reviews the 6-month short-course management of childhood pulmonary tuberculosis in 11 children. The regimen included EMB at 15–25 mg/kg for 2 months. Treatment was stopped in 1 child because of pyrazinamide intolerance, but ocular toxicity is not specifically mentioned in the summary.

- **Singh SB et al. (1992)**. Osteoarticular tuberculosis in children. *Indian Pediatrics*, 29:1133–1137.

In a study of 104 cases of osteoarticular TB in children, mean age 7.3 years, EMB was given at 15 mg/kg for an average of 12 months. The regimen "…produced satisfactory results without any side effect…" Evaluation of the eyes is not specifically mentioned.

- **Seth V et al. (1991)**. Visual evoked responses in tuberculous children on ethambutol treatment. *Indian Pediatrics*, 28:713–717.

EMB was given at 20 mg/kg to 47 children aged 3–13 years. Visual evoked responses were evaluated before treatment, after 2, 4, 6, 9 and 12 months of treatment and again 3–6 months after treatment ended. No signs of optic toxicity were noted at any point.

- **Palme IB et al. (2002)**. Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. *Pediatric Infectious Disease Journal*, 21:1053–1061.

A prospective cohort study of the treatment of children with TB was conducted from the main children's hospital in Addis Ababa, Ethiopia, from December 1995 to January 1997. At least 250 of the more than 500 patients were given EMB at 15–25 mg/kg daily. " In line with a recent review by Graham et al. (1998), we found no case of impaired vision associated with ethambutol therapy…" There is no

indication of whether or how ocular function was assessed or whether results relied on parental observation or complaints by the older children.

- **Zhu M et al. (2004)**. Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

EMB pharmacokinetics studied in three groups:

A. 38 adult patients, studied on 49 occasions.
B. 18 adult patients studied by sparse blood sampling on 48 study dates.
C. 14 children studied on 20 occasions. Median age of the children was 5.4 years (range 0.2–17) and the median dose of EMB was 16 mg/kg (range 13–26 mg/kg). No adverse reactions were observed in the children, 9 of whom were under 6 years of age.

Group (no.)	EMB dose (mg/kg)	C_{max} (µg/ml)
Adults (38)	19 (10–27)	2.11 (0.99–5.50)
Adults (18)	20 (10–27)	2.06 (0.48–4.51)
Children (14)	16 (13–26)	0.78 (0.0–3.56)

Findings were similar to those of Hussels et al. (1971, 1973); very erratic absorption of EMB in children was noted.

References

Benkert K et al. (1974). Tagesprofile und Profilverlaufskontrollen von Ethambutol bei Kindern [Daily check and follow-up of use of ethambutol in children]. *Medizinische Klinik*, 69:1808–1813.

Bhatia MP, Merchant SM (1975). Comparative study of antitubercular drugs in the management of primary complex. *Indian Pediatrics*, 12:1197–1203.

Boman G et al. (1970). Pharmacokinetische und genetische Gesigspunkte über den Metabolismus von Isoniazid, p-Aminosalicylsäure und Rifampicin [Pharmacokinetic and genetic aspects of the metabolism of isoniazid, *p*-aminosalicylic acid and rifampicin]. *Pneumonologie*, 2(Suppl.):15–20.

Chavarria AG et al. (1967). El etambutol asociado a isoniacida en el tratamiento de la tuberculosis en el niño [Ethambutol and isoniazid for the treatment of childhood tuberculosis]. *Revista Mexicana de Pediatria*, 36:194–200.

Chavarria AG et al. (1970). Evaluacion clinica del etambutol en 36 niños tuberculosos estudados durante cuatro años [Four-year clinical evaluation of ethambutol in 36 children with tuberculosis]. *Neumologia y Cirugia de Torax (Mexico)*, 31:39–47.

Del Principe A, Caione C, Zamparelli F (1968). Prime applicazioni dell'etambutolo nella terapia della tuberculosi infantile [Preliminary use of ethambutol in the treatment of tuberculosis in children]. *Annali Dell'Istituto "Carlo Forlanini"*, 28:42–73.

Dingley HB, Sehgal KL (1974). Treatment of pulmonary tuberculosis in children – a controlled study. *Indian Pediatrics*, 11:289–295.

Graham SM et al. (1998). Ethambutol in tuberculosis: time to reconsider? *Archives of Disease in Childhood*, 79:274–278.

Gramer RE, Jeschke R, Krieglstein GK (1982). Zur computergeseuerten Gesichtsfeldkontrolle bei Kindern mit Ethambutol-Medikation [Computerized perimetry in children treated with ethambutol]. *Klinische Pädiatrie*, 194:52–55.

Hussels H, Otto HS (1971). Ethambutol-serumkonzentrationen im Kindesalter [Serum ethambutol levels in childhood]. *Pneumonologie*, 145:392–396.

Hussels H, Kroening U, Magdorf K (1973). Ethambutol and rifampicin serum levels in children: second report on combined administration of ethambutol and rifampicin. *Pneumologie*, 149:31–38.

Junnanond C, Chotibut S, Lawtiantong T (1983). Safety evaluation of ethambutol in children. *Journal of the Medical Association of Thailand*, 66:77–79.

Mankodi NA et al. (1970) Ethambutol in unresponsive childhood tuberculosis. *Indian Pediatrics*, 7:202–211.

Medical Research Council Tuberculosis and Chest Diseases Unit (1989). Management and outcome of chemotherapy for childhood tuberculosis. *Archives of Disease in Childhood*, 64:1004–1012.

Mérida de León JC (1971). Tratamiento de la tuberculosis pulmonar con isoniacida y jarabe de Myambutol en niños [Treatment of pulmonary tuberculosis with isoniazid and Myambutol syrup]. *Revisita del Collegio Medico de Guatemala*, 22:48–55.

Mir ES et al. (1990). Tratamiento de seis meses en tuberculosis pulmonar infantil. Revision de 11 casos [Six months' treatment of pulmonary tuberculosis in children]. *Anales espanoles de pediatria*, 32:303–306.

Nagy A et al. (1980). Studiu privind toxitatea oculară a etambutolui [Study of the ocular toxicity of ethambutol]. *Revista de igiena, bacteriologie, virusologie, parazitologie, epidemiologie, pneumoftiziologie. Pneumoftiziologia*, 29:163–166.

Palme IB et al. (2002). Impact of human immunodeficiency virus 1 infection on clinical presentation, treatment outcome and survival in a cohort of Ethiopian children with tuberculosis. *Pediatric Infectious Disease Journal*, 21:1053–1061.

Patwardhan P, Bhatia M, Merchant SM (1970). Ethambutol in primary childhood tuberculosis. *Indian Pediatrics*, 7:194–201.

Prachakvej P, Subharngkahen I (1979). Visual loss from ethambutol. *Siriraj Hospital Gazette*, 31:908–912.

Ramachandran P et al. (1986). Three chemotherapy studies of tuberculous meningitis in children. *Tubercle*, 67:17–29.

Scheffler NK (1971). Augenuntersuchungen bei der behandelung mit ethambutol in zwei verscheidenen Dosierungen im Kindesalter [Eye examination of children treated with ethambutol under two different dosage schedules]. *Pneumonologie*, 145:396–400.

Schmid PC (1970). Discussion on Myambutol (ethambutol). *Antibiotica et Chemotherapia*, 16:305–315.

Schmid PC (1981). Ethambutol- und Rifampicin-verträglikeit und -dosierung im Kindesalter [Ethambutol and rifampicin tolerance and dosages in childhood]. *Pädiatrische Praxis*, 25:207–209.

Seth V et al. (1991). Visual evoked responses in tuberculous children on ethambutol treatment. *Indian Pediatrics*, 28:713–717.

Singh SB et al. (1992). Osteoarticular tuberculosis in children. *Indian Pediatrics*, 29:1133–1137.

Zhu M et al. (2004) Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

Annex IV

Pharmacokinetics of ethambutol in adults and children

A. Adults

- **Place VA, Thomas JP (1963)**. Clinical pharmacology of ethambutol. *American Review of Respiratory Disease*, 87:901–904.

Serum EMB concentrations in 10 normal subjects given a single oral dose of EMB were determined by microbiologically by an agar diffusion technique using *M. smegmatis.* Serum concentrations were maximal at about 2 hours.

Dose	Peak serum concentration
50 mg/kg	10 µg/ml
25 mg/kg	5 µg/ml
17 mg/ml	2 µg/ml

"…in humans a 25 mg/kg dose of ethambutol produced a peak serum concentration of 5 µg/ml. A daily peak of this magnitude was associated with 90 to 100 per cent protection of mice and monkeys…."

A total daily EMB dose of 50 mg/kg body weight was also administered as three doses of 17 mg/kg given at 0, 4 and 8 hours. "Serum concentrations ranging from 1–4 µg/ml resulted." The actual figures are not given, but it is evident from the figure that the 2-hour concentration after the first dose is very close to 2 µg/ml and the 4-hour concentration is approximately 1.2 µg/ml

- **Peets EA et al. (1965)**. The absorption, excretion, and metabolic fate of ethambutol in man. *American Review of Respiratory Disease*, 91:51–58.

Three patients were studied; EMB was given orally at 25 mg/kg or IV at 10 mg. Radiolabelled compound was used with "…countercurrent distribution and paper chromatography…"

"Following the oral administration of 25 mg per kilogram of body weight to 3 patients, the peak concentrations of drug in the plasma occurred at about four hours, the average peak being 5 µg of ethambutol equivalents per milliliter of plasma…"

"…little, if any, ethambutol accumulates in the tissues, from 90 to 94 per cent of the administered radioactivity having been recovered from the urine and the feces."

- **Bobrowitz ID, Gokulanathan KS (1965)**. Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

The 64 patients evaluated were given EMB at 25mg/kg; later, 25 mg/kg for the first 60 days and then 15 mg/kg. "Blood levels" were determined 2, 4 and 8 hours after the morning dose on the first day of treatment, one day a week during the first month of therapy and one day a month thereafter. Later, blood levels were obtained 3 hours after the morning dose. The method for determining blood concentrations is not stated but was probably, as above, microbiological using agar seeded with *M. smegmatis*.

"The blood levels of EMB taken at 2, 4 and 8 hours showed peaks at 2 hours or at 4 hours…" " The average of all the blood levels in individual patients showed a variation from a low of 2.1 µg/ml to a high of 6.2 µg/ml….the general average blood level for EMB in all of the patients on 25 mg/kg was 4.1 µg/ml." (It is not stated whether this average reflects all of the values or only the peak values.)

For 3-hour values in the group given EMB at 15 mg/kg later in therapy, it is stated that: "the general average EMB blood level in this group was 2.6 µg/ml." Values ranged from 0.5 µg/ml to 5.6 µg/ml. Most patients had values below 3.0 µg/ml.

- **Bobrowitz ID (1966a)**. Ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:796–822.

In an extension of the above data, values are given for 3 hours. After an EMB dose of **25 mg/kg,** the serum concentration was 3.9 µg/ml; after a dose of 15 mg/kg the average serum concentration was 2.58 µg/ml.

- **Bobrowitz ID (1966b)**. Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Three regimens were studied in 169 patients:

I. INH+EMB 25 mg/kg and then 15 mg/kg
II. INH+EMB 15 mg/kg
III. INH+PAS

"Blood levels" were obtained 3 hours after dose at 2, 4 and 8 weeks and 6 months.

Regimen I: Average blood levels at 2, 4 and 8 weeks were 3.0, 3.6, 3.2 µg/ml respectively and at 6 months 1.6 µg/ml.

Regimen II: Average blood levels at 2, 4 and 8 weeks and 6 months were 1.9, 1.9, 2.0 and 1.8 µg/ml.

- **Gómez-Pimienta JL et al. (1966)**. Retreatment of pulmonary tuberculosis with ethambutol. *Annals of the New York Academy of Sciences*, 135:882–889.

Serum concentrations were determined at 2 hours in 7 patients receiving EMB at 20 mg/kg; a biological method was used. Concentrations varied from 2 to 4 µg/ml, with an average of approximately 3.4 µg/ml**.**

- **Donomae I, Yamamoto K (1966)**. Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Serum EMB levels were determined by bioassay in approximately 40 patients; the number of patients is not given in the text but was deduced from data points in figures.

In patients given EMB at 25 mg/kg, serum concentrations averaged 4.4 µg/ml at 2 hours and 4.1 µg/ml at 4 hours. For patients given 12.5 mg/kg, values were 1.2 µg/ml and 1.0 µg/ml.

- **Pyle MM (1966)**. Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

Chemical assay was used to determine serum concentration 3 hours after medication in 110 cases given EMB at a dose between 20 and 30 mg/kg. "…the patient's serum concentration usually varies between 3 and 5 µg per milliliter." More precise details are not given.

- **Pyle MM et al. (1966)**. A four year investigation of ethambutol in initial and retreatment cases of tuberculosis. *American Review of Respiratory Disease*, 93:428–441.

Reports a smaller data set of the above patients. Serum concentrations determined 3 hours after medication in 90 patients receiving EMB at 20–30 mg/kg were 3–5 µg/ml. Again, more precise details are not given

- **Place VA et al. (1966)**. Metabolic and special studies of ethambutol in normal volunteers and tuberculous patients. *Annals of the New York Academy of Sciences*, 135:775–795.

The data recorded were similar to those in the two above articles, but with a wider range of EMB doses were used. Doses of 4, 8, 12.5, 25 and 50 mg/kg gave peak serum concentrations of approximately 0.67, 1.3, 2.0, 4.2 and 8.75 µg/ml.

- **Schmidt LH (1966)**. Studies on the antituberculosis activity of ethambutol in monkeys. *Annals of the New York Academy of Sciences*, 135:747–758.

The efficacy of different doses of EMB and isoniazid and the relationship of blood concentration to efficacy were studied in rhesus monkeys. Blood was drawn 2 and 6 hours after dosing.

Reviewing the results of these experiments, the author stated: ”Hence, correlation of therapeutic achievements with the levels of ethambutol suggests that in a combination regimen, **o**ne need maintain a serum ethambutol concentration no greater than 1 to 2 µg/ per ml in order to achieve maximum benefit.”

- **Horsfall PAL (1969)**. Ethambutol in the retreatment of chronic pulmonary tuberculosis. *Far East Medical Journal*, 7:213–218.

EMB was given at 25 mg/kg daily for 60 days, and at 15 mg/kg daily thereafter, in various combinations with isoniazid, streptomycin, capreomycin, viomycin and other drugs. Where EMB was functioning virtually alone, sputum conversion occurred in approximately one-third of patients; when three drugs were used, this rose to 50%.

EMB serum concentrations were also measured by an agar diffusion method with *M. smegmatis* as the test organism; measurements were done 3 hours after dosing with 25 mg/kg. Concentrations ranged from 1.97 to 6.67 µg/ml with a mean of 4.1 µg/ml.

- **Eule H, Werner E (1970)**. Ethambutol-serumspiegel bei unterscheidlicher Dosierung; Vergleich von vier verscheidenen Bestimmungsmethoden Mit 4 Abbildungen [Ethambutol levels in diverse dosage: comparison of four different determination methods]. *Zeitschrift für Erkrankungen der Atmungsorgane mit Folia bronchologica*, 133:443–448.

Four different methods of determining concentrations of ethambutol were evaluated; one method was chemical and the other three microbiological with different organisms. Values were determined after EMB doses of 25, 50 and 75 mg/kg in 10 individuals**.** Results are shown in the form of a figure: 2-hour concentrations after 25, 50 and 75 mg/kg were approximately 4, 8 and 11 µg/ml respectively.

- **Dume T, Wagner CI, Wetzels E (1971)**. Zur pharmakokinetik von Ethambutol bei gesunden und Patienten mit terminaler Nierinsuffizienz [Pharmacokinetics of ethambutol in healthy individuals and in patients with terminal renal failure]. *Deutsche Medizinische Wochenschrift*, 96:1430–1431.

Chemical methodology was used to determine serum concentrations of EMB in healthy volunteers given a dose of 25 mg/kg EMB, with the aim of evaluating the metabolism in renal failure. Mean C_{max} was 2 µg/ml.

- **Lee CS et al. (1977)**. Kinetics of oral ethambutol in the normal subject. *Clinical Pharmacology and Therapeutics*, 22:615–621.

Six normal adult volunteers received EMB orally – as tablets or solution – at 15mg/kg. Mean peak concentration at a mean 2.83 (2.0–4.0) hours after tablets was 4.01 (3.25–5.62) µg/ml and at 1.91 (1.5–2.5) hours after solution 4.45 (3.35–6.00) µg/ml.

- **Tuli SM, Kumar K, Sen PC (1977)**. Penetration of antitubercular drugs in clinical osteoarticular lesions. *Acta Orthopaedica Scandinavica*, 48:362–368.

Penetration of EMB into joints and cold abscesses was evaluated. Concentrations in joints similar to serum concentrations were found, but concentrations in cold abscesses were one-half to one-third those in serum. After a dose of 25 mg/kg, EMB concentration was 4.51 µg/ml in serum and 3.51 µg/ml in joints; in the case of cold abscesses, mean serum concentration was 10.17 µg/ml and abscess concentration 3.21 µg/ml. However, this latter serum concentration is unusually high and not in keeping with any other published data; for this reason it has not been incorporated in Table 4 or Figure 2 of the present review.

- **Lee CS et al. (1980)**. Disposition kinetics of ethambutol in man. *Journal of Pharmacokinetics and Biopharmaceutics*, 8:335–346.

In this study, EMB was administered by constant flow IV infusion to 6 healthy volunteers. Perhaps the most important clinical finding was the confirmation that EMB excretion was largely renal: a mean 0.79 (0.75–0.84) of the dose was excreted unchanged in the urine. The authors concluded that EMB followed multicompartment kinetics after IV dosing.

- **Liss RH, Letourneau RJ, Schepis JP (1981)**. Distribution of ethambutol in primate tissues and cells. *American Review of Respiratory Disease*, 123:529–532.

The distribution of radiolabelled EMB in squirrel monkeys was studied following a single oral dose of 25 mg/kg. Tissue distribution and concentration of EMB were then studied by radioautography, radiochemical and microbiological methods.

With the exception of the brain and spinal cord, EMB was widely distributed in most tissues, including the lung, and localized within pulmonary alveolar and axillary lymph node macrophages. These findings are in keeping with studies that show a poor penetration of EMB into the cerebrospinal fluid. The concentrations in the lung tissues were markedly higher than in corresponding plasma samples.

- **Israili ZH, Rogers CM, El-Attar H (1987)**. Pharmacokinetics of antituberculosis drugs in patients. *Journal of Clinical Pharmacotherapeutics*, 27:78–83.

The pharmacokinetics of INH, RMP and EMB were evaluated in 26 middle-aged male tuberculosis patients. EMB was always analysed in combination with INH and RMP. EMB was `determined by electron-capture, gas chromatography, and a gas chromatographic, mass spectrometric method. Determinations were done on day 1 or days 4–7. The daily dose of EMB was 12.5 mg/kg (± 1.6 mg/kg).

As in previous studies, EMB concentrations reached a maximum 1–4 hours after dosing and declined biexponentially. At day 1, mean C_{max} was 3.7 (± 2.4) µg/ml; after 4–7 days the mean value was 5.0 (± 4.2) µg/ml. In one patient who was given the daily total EMB dose in two doses, C_{max} was 1.2–1.5 µg/ml.

- **Kumar K (1992)**. The penetration of drugs into the lesions of spinal tuberculosis. *International Orthopaedics*, 16:67–68.

Concentrations of EMB in blood and spinal pus were measured by “chemical assay” at the start of treatment and after 3–5 months. There was no change in the concentrations in the lesions. Ten patients aged 15–37 years were studied. Mean serum concentration of EMB 3 hours after administration of a 25 mg/kg dose was 8.2 µg/ml at the start of treatment and 6.4 µg/ml after 3–5 months; in the psoas pus concentrations were 2.9 and 4.6 µg/ml respectively.

- **Schall R et al. (1995)**. Relative bioavailability of rifampicin, isoniazid and ethambutol from a combination tablet vs. concomitant administration of a capsule containing rifampicin and a tablet containing isoniazid and ethambutol. *Arzneimittelforschung*, 11:1236–139.

EMB concentrations in healthy volunteers, mean body weight 80 kg, were analysed by gas chromatography with a view to comparing the bioavailability of EMB in combination tablets with that of a standard preparation; the EMB dose was 600 mg (7.5 mg/kg). C_{max} for the reference preparation was 1.43 µg/ml (SD 1.29) compared with 1.49 µg/ml (SD 1.31) for the FDC. In this healthy population, T_{max} for the two preparations was 3.5 and 3.75 hours respectively.

- **Elliott AM et al. (1995)**. Failure of drug penetration and the acquisition of drug resistance in chronic tuberculous empyema. *Tubercle and Lung Disease*, 76:463–467.

The concentration of antituberculosis drugs was determined in the pleural fluid of a patient with tuberculous empyaema who developed INH resistance while receiving INH, RMP, EMB (20 mg/kg) and ofloxacin. Serum C_{max} of EMB in the serum (approximately 1.6 µg/ml) was 19% lower than that in empyaema fluid (approximately 1.9 µg/ml).

- **Peloquin CA et al. (1999)**. Pharmacokinetics of ethambutol under fasting conditions with food and with antacids. *Antimicrobial Agents and Chemotherapy*, 43:568–572.

The pharmacokinetics of EMB given at a dose of 25 mg/kg were studied in 14 healthy female and male volunteers. Fasting conditions resulted in a C_{max} of 4.5 (± 1.0) µg/ml. Following antacids, C_{max} was 3.3 (± 0.5) µg/ml, and after a high-fat meal the value was 3.8 (± 0.8) µg/ml. As in previous studies, the T_{max} tended to be greater than 2 hours, varying from 2.46 and 2.50 hours under fasting conditions to 2.93 hours after antacids and 3.21 hours after a high-fat meal.

- **Zhu M et al. (2004)**. Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

EMB pharmacokinetics were studied in three groups:

1. 38 adult patients, studied on 49 occasions
2. 18 adult patients, studied by sparse blood sampling on 48 study dates
3. 14 children studied on 20 occasions: median age was 5.4 years (range 0.2–17), median EMB dose was 16 mg/kg (range 13–26), and no adverse reactions were observed in the children, 9 of whom were aged less than 6 years.

Group (no.)	Median EMB dose (mg/kg)	C_{max} (µg/ml)
Adults (38)	19 (10–27)	2.11 (0.99–5.50)
Adults (18)	20 (10–27)	2.06 (0.48–4.51)
Children (14)	16 (13–26)	0.78 (0.0–3.56)

Very erratic absorption of EMB was noted in children.

B. Children

- **Hussels H, Otto HS (1971)**. Ethambutol-Serumkonzentrationen im Kindesalter [Serum ethambutol levels in childhood]. *Pneumonologie*, 145:392–396.

EMB serum concentrations were determined following 2 doses of INH in 18 children divided into three groups: 2–5, 6–9 and 10–14 years of age. A microbiological method was used and concentrations were determined at 0, 1, 2, 4, 7 and 24 hours after dosing. Maximum concentrations occurred at either 2 or 4 hours:

	Maximum concentration, µg/ml (no.)	
Age	EMB 15 mg/kg	EMB 25 mg/kg

2–5 years	1.2 (6)	2.0 (4)
6–9 years	1.1 (6)	1.5 (7)
10–14 years	0.9 (7)	2.8 (8)

The authors comment that drugs in children, particularly younger children, should be dosed according to body surface area and not body weight, because of the larger extravascular fluid compartment and faster metabolism in children. Only in children aged 10–14 years receiving EMB at 25 mg/kg was a mean serum concentration of >2 µg/ml reached.

- **Hussels H, Kroening U, Magdorf K (1973)**. Ethambutol and rifampicin serum levels in children: second report on the combined administration of ethambutol and rifampicin. *Pneumonologie*, 149:31–38.

In a further study by Hussels et al. (see Hussels et al., 1971, above), serum EMB was again determined by a microbiological method. Two evaluations are presented; in the first EMB was administered alone at a dose of 35 mg/kg, and in the second EMB was given at 10 mg/kg together with RMP. The children were again grouped in three age ranges: 2 to <6 years, 6 to <10 and 10 to 14 years.

This study aimed to achieve serum EMB concentrations in excess of 2.0 µg/ml – a value derived from the study of Pyle et al (1967) in which the MIC against *M. tuberculosis* isolated from patients before treatment was given as 2.0 µg/ml. The authors evaluated EMB given with RMP following the findings of Boman et al (1970) of higher concentrations of PAS when the drug was given in conjunction with RMP.

		Maximum concentration, µg/ml (no.)	
Age	No. of children	EMB alone	EMB+RMP
2–<6 years	8	1.5	2.5
6–<10 years	11	2.3	2.5
10–14 years	9	3.0	6.3

As can be seen from the table, higher EMB concentrations were indeed found when EMB was given with RMP. However, there was a “wide distribution of individual serum concentrations” such that ” the differences between the mean values of ethambutol serum levels after administration of ethambutol alone and in combination with rifampicin did not prove to be statistically significant.” Almost incidentally, it is perhaps noteworthy that RMP concentrations when given with EMB were lower than when RMP was given alone.

- **Benkert K et al. (1974)**. Tagesprofile und Profilverlaufskontrollen von Ethambutol bei Kindern [Plasma levels of ethambutol in children]. *Medizinische Klinik*, 69:1808–1813.

Specific microbiological methodology was used to determine 2-hour plasma EMB concentrations in 26 children, aged 3–14 years, 13 receiving EMB at 15 mg/kg and 13 EMB at 25 mg/kg.

	2-hour plasma concentration (µg/ml)	
Age	EMB 15 mg/kg (no.)	EMB 25 mg/kg (no.)
3–6 years	0.9 (4)	3.0 (5)
7–10 years	2.0 (4)	2.6 (5)
11–14 years	1.8 (5)	3.5 (3)

- **Zhu M et al. (2004)**. Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

EMB pharmacokinetics were studied in three groups:

1. 38 adult patients, studied on 49 occasions
2. 18 adult patients, studied by sparse blood sampling on 48 study dates

3. 14 children studied on 20 occasions: median age was 5.4 years (range 0.2–17), median EMB dose was 16 mg/kg (range 13–26), and no adverse reactions were observed in the children, 9 of whom were aged less than 6 years.

Group (no.)	Median EMB dose (mg/kg)	C_{max} (µg/ml)
Adults (38)	19 (10–27)	2.11 (0.99–5.50)
Adults (18)	20 (10–27)	2.06 (0.48–4.51)
Children (14)	16 (13–26)	0.78 (0.0–3.56)

Very erratic absorption of EMB was noted in children.

References

Benkert K et al. (1974). Tagesprofile und Profilverlaufskontrollen von Ethambutol bei Kindern [Plasma levels of ethambutol in children]. *Medizinische Klinik*, 69:1808–1813.

Bobrowitz ID (1966a). Ethambutol in the retreatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:796–822.

Bobrowitz ID (1966b). Comparison of ethambutol-INH versus INH-PAS in the original treatment of pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:921–939.

Bobrowitz ID, Gokulanathan KS (1965). Ethambutol in the retreatment of pulmonary tuberculosis. *Diseases of the Chest*, 48:239–250.

Boman G et al. (1970). Pharmacokinetische und genetische Gesigspunkte über den Metabolismus von Isoniazid, p-Aminosalicylsäure und Rifampicin [Pharmacokinetic and genetic aspects of the metabolism of ethambutol, *p*-aminosalicylic acid and rifampicin]. *Pneumonologie*, 2(Suppl.):15–20.

Donomae I, Yamamoto K (1966). Clinical evaluation of ethambutol in pulmonary tuberculosis. *Annals of the New York Academy of Sciences*, 135:849–881.

Dume T, Wagner CI, Wetzels E (1971**)**. Zur pharmakokinetik von Ethambutol bei gesunden und Patienten mit terminaler Nierinsuffizienz [Pharmacokinetics of ethambutol in healthy individuals and in patients with terminal renal failure]. *Deutsche Medizinische Wochenschrift*, 96:1430–1431.

Elliott AM et al. (1995) Failure of drug penetration and the acquisition of drug resistance in chronic tuberculous empyema. *Tubercle and Lung Disease*, 76:463–467.

Eule H, Werner E (1970). Ethambutol-serumspiegel bei unterscheidlicher Dosierung; Vergleich von vier verscheidenen Bestimmungsmethoden Mit 4 Abbildungen [Ethambutol levels in diverse dosage: comparison of four different determination methods]. *Zeitschrift für Erkrankungen der Atmungsorgane mit Folia bronchologica*, 133:443–448.

Gómez-Pimienta JL et al. (1966). Retreatment of pulmonary tuberculosis with ethambutol. *Annals of the New York Academy of Sciences*, 135:882–889.

Horsfall PAL (1969). Ethambutol in the retreatment of chronic pulmonary tuberculosis. *Far East Medical Journal*, 7:213–218.

Hussels H, Otto HS (1971). Ethambutol-Serumkonzentrationen im Kindesalter [Serum ethambutol levels in childhood]. *Pneumonologie*, 145:392–396.

Hussels H, Kroening U, Magdorf K (1973). Ethambutol and rifampicin serum levels in children: second report on the combined administration of ethambutol and rifampicin. *Pneumologie*, 149:31–38.

Israili ZH, Rogers CM, El-Attar H (1987). Pharmacokinetics of antituberculosis drugs in patients. *Journal of Clinical Pharmacotherapeutics*, 27:78–83.

Kumar K (1992). The penetration of drugs into the lesions of spinal tuberculosis. *International Orthopaedics*, 16:67–68.

Lee CS et al. (1977). Kinetics of oral ethambutol in the normal subject. *Clinical Pharmacology and Therapeutics*, 22:615–621.

Lee CS et al. (1980). Disposition kinetics of ethambutol in man. *Journal of Pharmacokinetics and Biopharmaceutics*, 8:335–346.

Liss RH, Letourneau RJ, Schepis JP (1981). Distribution of ethambutol in primate tissues and cells. *American Review of Respiratory Disease*, 123:529–532.

Peets EA et al. (1965). The absorption, excretion, and metabolic fate of ethambutol in man. *American Review of Respiratory Disease*, 91:51–58.

Peloquin CA et al. (1999). Pharmacokinetics of ethambutol under fasting conditions with food and with antacids. *Antimicrobial Agents and Chemotherapy*, 43:568–572.

Place VA, Thomas JP (1963). Clinical pharmacology of ethambutol. *American Review of Respiratory Disease*, 87:901–904.

Place VA et al. (1966). Metabolic and special studies of ethambutol in normal volunteers and tuberculous patients. *Annals of the New York Academy of Sciences*, 135:775–795.

Pyle MM (1966). Ethambutol in the retreatment and primary treatment of tuberculosis: a four-year clinical investigation. *Annals of the New York Academy of Sciences*, 135:835–845.

Pyle MM et al. (1966) A four year investigation of ethambutol in initial and retreatment cases of tuberculosis. *American Review of Respiratory Disease*, 93:428–441.

Schall R et al. (1995). Relative bioavailability of rifampicin, isoniazid and ethambutol from a combination tablet vs. concomitant administration of a capsule containing rifampicin and a tablet containing isoniazid and ethambutol. *Arzneimittelforschung*, 11:1236–1239.

Schmidt LH (1966). Studies on the antituberculosis activity of ethambutol in monkeys. *Annals of the New York Academy of Sciences*, 135:747–758.

Tuli SM, Kumar K, Sen PC (1977). Penetration of antitubercular drugs in clinical osteoarticular lesions. *Acta Orthopaedica Scandinavica*, 48:362–368.

Zhu M et al. (2004). Pharmacokinetics of ethambutol in children and adults with tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 8:1360–1367.

Annex V

Published recommendations for the use of ethambutol in children

- **Horne NW (1990)**. Drugs used in chemotherapy. In: *Modern drug treatment of tuberculosis*, 7th ed. London, Chest , Heart and Stroke Association.

"In short term chemotherapy for the newly diagnosed patient ethambutol is used as a companion drug to rifampicin and isoniazid, the dose being 25 mg/kg body weight for 2 months and then 15 mg/kg. Only very rarely indeed is the lower dose of 15 mg/kg responsible for adverse effects. The dose in intermittent regimens is 30 mg/kg three times weekly or 45 mg/kg twice weekly." (pp.16–19).

"…A pretreatment record of visual acuity should be made by the Snellen test. For those who cannot read, Cambridge low contrast vision tests may prove a useful alternative…."

"The patient should be told that ethambutol may affect vision and that drugs should be stopped immediately should vision become impaired…"

"Ethambutol is best avoided in children too young for objective eye tests…"

"It is probably unwise to prescribe ethambutol for young children because of the difficulty in identifying early loss of visual acuity in them. If it is absolutely necessary to use this drug, special test cards, Mary Sheridan Stycar vision tests, are available for children from seven years of age downwards to those about one year old."

- **Chaulet P, Mazouni M-S, Ait Khaled N (1992)**. Treatment of tuberculosis in children. In: Chaulet P et al., eds. *Children in the tropics. Childhood tuberculosis, still with us*. Paris, International Children's Centre:196–197.

Referring to EMB: "Its main drawback is its toxicity when administered at high doses (25 mg/kg) for several months: the resulting retrobulbar optic neuritis is easy to detect in adults but cannot be detected at an early stage in children. The first sign of such optic neuritis is the inability to discriminate between colours, a fact which is difficult to discern in children. For this reason most paediatricians are reluctant to prescribe ethambutol in children under 12. Recommended dose of ethambutol is 25 mg/kg of body weight during the first eight weeks of treatment, and 15 mg per kg of body weight thereafter."

- **American Thoracic Society (1994)**. Treatment of tuberculosis and tuberculosis infection in adults and children. *American Journal of Respiratory and Critical Care Medicine*, 149:1359–1374.

"In children who are too young for assessment of visual acuity and red-green color discrimination, ethambutol should be used with particular caution; consideration should be given to the use of possible alternative drugs."

In Table 2, the recommended daily EMB dosage is 15–20 mg/kg for adults and children with a footnote: "Ethambutol is generally not recommended for children whose visual acuity cannot be monitored (<8 yr of age). However, ethambutol should be considered for all children with organisms resistant to other drugs when susceptibility to ethambutol has been demonstrated or susceptibility is likely."

It is also noted: "Because it is difficult to monitor for ocular toxicity from ethambutol, this agent is less useful in young children." (p. 1368, point 5).

On p. 1362 it is stated: "With doses of 15 mg/kg the peak concentration is approximately 4 µg/ml." There is in fact only one publication (Lee et al., 1977) that gives values this high after a dose of 15 mg/kg and the values in children at this dose definitely appear to be lower.

- **Starke JR, Correa AG (1995)**. Management of mycobacterial infection and disease in children. *Pediatric Infectious Disease Journal*, 14:455–470.

"Although ethambutol has not been used extensively in young children, ophthalmological toxicity in children has not been reported with an ethambutol dosage of 15 mg/kg/day and the drug may be used carefully. As soon as isoniazid and rifampin susceptibility is established or considered likely the fourth drug can be discontinued."

The daily dose of ethambutol recommended in this review is 15–25 mg/kg and that for twice weekly therapy 50 mg/kg.

- **Joint Tuberculosis Committee of the British Thoracic Society (1998)**. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, 53:536–548.

Recommended EMB doses are 15 mg/kg daily, 30 mg/kg three times weekly, and 45 mg/kg twice weekly.

Under the heading *Special precautions and pretreatment screening* (p. 541), the following statement appears: "Because of the possible (but rare) toxic effects of ethambutol on the eye, it is recommended that visual acuity should be tested by Snellen chart before it is first prescribed. The drug should only be used in patients who have reasonable visual acuity and who are able to appreciate and report visual symptoms or changes in vision. The notes should record that the patient has been told to stop the drug *immediately* if such symptoms occur, and to report to the physician. The general practitioner should be informed of this. In small children and in those with language difficulties ethambutol should be used where appropriate, with the above advice given to parents or other family members."

- **American Academy of Pediatrics (2000)**. Tuberculosis In: *Report of the Committee on Infectious Diseases*, 25th ed. Elk Grove Village, IL.

"At 15 mg/kg per day ethambutol is bacteriostatic only, and its primary therapeutic role is to prevent emergence of drug-resistant organisms. A dose of 25 mg/kg per day is necessary for bactericidal activity. Since ethambutol may cause reversible optic neuritis, recipients should be monitored monthly for visual acuity, visual fields, and red-green color discrimination. Because cooperation is essential for performance of these tests, use of ethambutol in young children whose visual acuity cannot be monitored requires careful consideration of risks and benefits."

Table 3.67 gives the recommended daily dose of ethambutol as 15–25 mg/kg per day and 50 mg/kg per dose for twice-weekly therapy.

- **Rieder HL (2002)**. *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Disease.

"Although 15 mg/kg body weight in the continuation phase and 25 mg/kg body weight in the intensive phase have been recommended, international consensus recommends 15 mg/kg (range 15 to 20 mg/kg**)** throughout to obviate operational difficulties in changing the dosage and to further reduce toxicity." (p. 39)

"It has been recommended not to use ethambutol in children too young for objective tests for visual acuity. There is, however, no evidence that children are particularly prone to ocular toxicity, and ethambutol may thus be used in children. However, as children might be less likely to report ocular toxicity, particular caution may be warranted." (p. 40)

- **WHO (2003)**. *Treatment of tuberculosis: guidelines for national programmes*. Geneva, World Health Organization (WHO/CDS/TB/2003.313).

"Ethambutol and thioacetazone are used in association with more powerful drugs to prevent the emergence of resistant bacilli." (p. 27, section 4.3). Table 4.1 (p. 28)gives the recommended dosage and dose range for ethambutol as 15 mg/kg/day (15–20).

" It is now recommended that ethambutol be included as a fourth drug during the initial phase of treatment for most patients with smear-negative PTB and EPTB. Ethambutol may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients known to be infected with fully drug-susceptible bacilli, and young children with primary TB." (p. 31, section 4.4).

In reference to the replacement of thioacetazone with EMB: "It has been replaced by ethambutol. There has been understandable caution with the use of ethambutol in children too young to report early visual deterioration, but ethambutol has been safely used in infants and young children at recommended dosages." (p. 64, section 8.4).

In the same section it is conceded that children may require different dosages from adults: "…there are important differences between children and adults that may affect drug choice and dosage. Recommended dosages are based on research in adults and yet metabolism of drugs varies with age. The effectiveness of the recommendation of EH for the maintenance or continuation phase has never been studied in children, whereas RH has proven efficacy."

- **Mehta DK, Ryan RSM, Hogerzeil H, eds (2004)**. *WHO model formulary.* Geneva, World Health Organization.

Recommended dose of ethambutol in children is 15 mg/kg daily. One of the contraindications listed is "children under 5 years – unable to report symptomatic visual disturbances".

- **WHO (2005)**. *Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources*. Geneva, World Health Organization.

Appendix 2 gives the following EMB dosages/regimens, advising that dosage be calculated on the basis of body weight:

Daily dose: 20 mg/kg (range 15–25 mg/kg)
Intermittent dose: 30 mg/kg three times/week mg/kg (range 25–35 mg/kg)

References

American Academy of Pediatrics (2000**)**. Tuberculosis In: *Report of the Committee on Infectious Diseases*, 25th ed. Elk Grove Village, IL.

American Thoracic Society (1994). Treatment of tuberculosis and tuberculosis infection in adults and children. *American Journal of Respiratory and Critical Care Medicine*, 149:1359–1374.

Chaulet P, Mazouni M-S, Ait Khaled N (1992). Treatment of tuberculosis in children. In: Chaulet P et al., eds. *Children in the tropics. Childhood tuberculosis, still with us.* Paris, International Children's Centre, 196–197.

Horne NW (1990**)**. Drugs used in chemotherapy. In: *Modern drug treatment of tuberculosis*, 7th ed. London, Chest , Heart and Stroke Association.

Joint Tuberculosis Committee of the British Thoracic Society (1998). Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, 53:536–548.

Lee CS et al. (1977). Kinetics of oral ethambutol in the normal subject. *Clinical pharmacology and therapeutics*, 22:615–621.

Mehta DK, Ryan RSM, Hogerzeil H, eds (2004). *WHO model formulary.* Geneva, World Health Organization.

Rieder HL (2002). *Interventions for tuberculosis control and elimination*. Paris, International Union Against Tuberculosis and Lung Disease.

Starke JR, Correa AG (1995). Management of mycobacterial infection and disease in children. *Pediatric Infectious Disease Journal*, 14:455–470.

WHO (2003). *Treatment of tuberculosis: guidelines for national programmes*. Geneva, World Health Organization (WHO/CDS/TB/2003.313).

WHO (2005). *Pocket book of hospital care for children. Guidelines for the management of common illnesses with limited resources*. Geneva, World Health Organization.