Tuberculosis Interventions

Interventions for Tuberculosis Control and Elimination

2002

International Union Against Tuberculosis and Lung Disease

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Hans L Rieder

International Union Against Tuberculosis and Lung Disease

68, boulevard Saint Michel, 75006 Paris, France

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Editor

International Union Against Tuberculosis and Lung Disease (IUATLD), 68 boulevard Saint Michel, 75006 Paris, France

Author : H. L. Rieder

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Preface

This monograph adds a module to the series on the scientific basis of tuberculosis control (figure 1).[1] The International Tuberculosis Courses of the International Union Against Tuberculosis and Lung Disease (IUATLD) follow a logical sequence with these five modules. These courses are directed principally at managers of national tuberculosis control programs, largely in low-income countries.

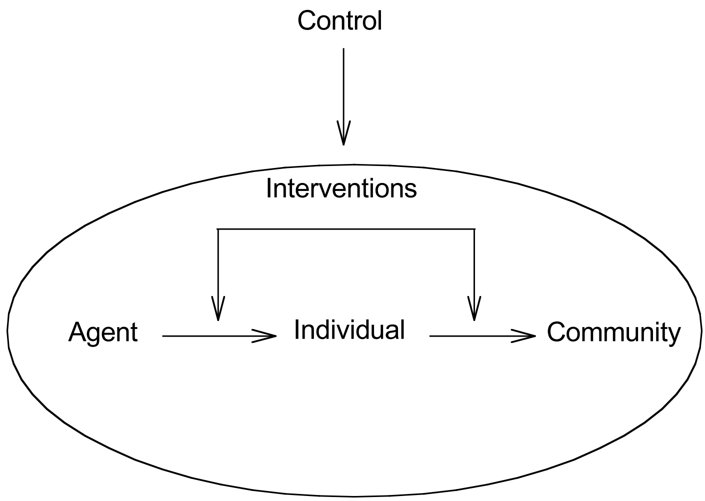

Figure 1. Modules and flow of teaching in the international tuberculosis courses of the IUATLD.[1]

The courses start with the bacteriologic basis of tuberculosis control, for which several documents are available.[2-6] In a second module, the effect of tubercle bacilli on the human host, the clinical presentation and diagnosis of tuberculosis is presented for which the book by Sir John Crofton and collaborators is used as background material.[7] Following this second module, the impact of tubercle bacilli on the community is presented, i.e., the epidemiologic basis of tuberculosis control.[1] Once these three facets – the agent, the individual, and the community – are understood, the various available interventions are discussed, and finally it needs to be specifically demonstrated how this knowledge can be integrated into the practice of a national tuberculosis control program.[8] The time allotted to each of these modules is determined by the requirements of the audience.

This monograph deals with the fourth module, interventions directed against *Mycobacterium tuberculosis* complex. There are numerous excellent reviews on the various available interventions. Often, they deal with one specific intervention. This monograph tries to assemble information about each available intervention and to weigh the role of each in current practice. Appendices provide additional information on current developments. The presentation should make it easy for the reader to select individual chapters of particular interest.

It is hoped that this module offers the review of currently available interventions that participants have been requesting since the inception of the IUATLD courses.

Paris, November 2001

Introduction

The aim of interventions in tuberculosis control or elimination strategies is to reduce or eliminate the adverse impact of epidemiological risk factors that promote the progression from one step to the next in the pathogenetically based model (figure 2).[9]

There are four principal interventions at our disposal to accomplish this task (figure 3):[10]

- Treatment of tuberculosis reduces the risk of death from tuberculosis, aims at restoring health and curing patients, and reduces the risk of transmission of tubercle bacilli in the community.

- Prophylactic treatment aims at preventing infection with *Mycobacterium tuberculosis* from occurring.

- Vaccination with Bacille Calmette-Guérin (BCG) before acquisition of infection with *M. tuberculosis* aims at priming the immune system, so that the risk of progression from sub-clinical, latent tuberculous infection to clinically overt tuberculosis is reduced should such infection be acquired.

- Preventive chemotherapy is treatment of sub-clinical, latent *Mycobacterium tuberculosis* populations in the human host, given to reduce the risk of progression to clinically overt tuberculosis.

The key to improving the epidemiologic situation is linked to the specifics of the transmission (incidence) and prevalence of infection with *M. tuberculosis.*[1] This has consequences for the role of the interventions.

The principal strategy aims at reducing the incidence infection with *M. tuberculosis*. A reduction in incidence of tuberculous infection is achieved by as swift as possible identification of potential transmitters of tubercle bacilli, i.e., the identification of persons with tuberculosis of the respiratory tract. Amongst these the most infectious are the patients with such a high bacillary load that the bacilli can be identified using sputum smear microscopy. While these patients account for only roughly half of all cases of pulmonary tuberculosis, they are the most potent sources of

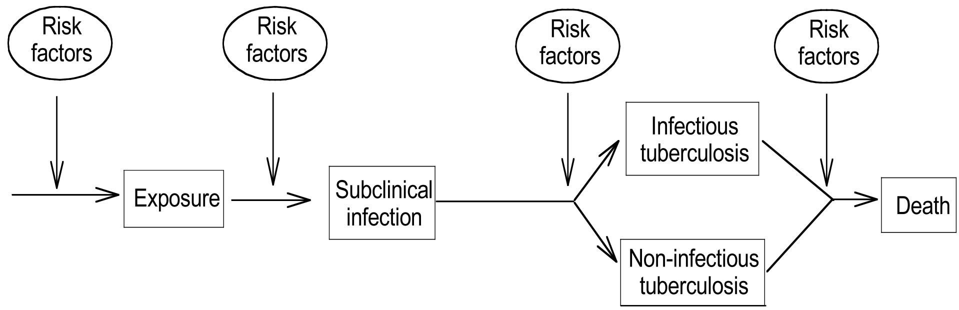

Figure 2. Pathogenetically-based model of the epidemiology of tuberculosis.[1] Reproduced from[9] by the permission of the publisher Urban & Vogel.

transmission (figure 4).[11] Once identified, they should be quickly and permanently rendered non-infectious through chemotherapy. In the terminology used in this monograph, this approach is called "tuberculosis control". Thus, tuberculosis control is the strategy aimed at reducing the incidence of tuberculous infection. This strategy also includes prophylactic treatment, defined as the provision of chemotherapy to persons exposed to, but not yet infected with *M. tuberculosis*.

The second strategy aims at reducing the prevalence infection with *M. tuberculosis*. Because *M. tuberculosis* probably survives in a large proportion of persons for years following acquisition, tuberculosis will continue to emerge from the pool of persons who are already infected. A strategy to reduce the prevalence of infection in the community will be designated "tuberculosis elimination strategy" in the context of this monograph. Tuberculous infection is highly prevalent in virtually every country's population, but varies demographically in important ways.[1] To be epidemiologically effective, preventive chemotherapy to reduce the prevalence of infection must target groups that are both easily identifiable and that potentially contribute a large fraction of future morbidity.

Vaccination with BCG varies somewhat from this concept, as it aims at reducing the risk of progression from infection to disease. Consequently, its effect is expected to be similar to that of the strategy to reduce the prevalence of infection.

The options available to address the tuberculosis problem in a community will first aim at reducing the incidence of tuberculous infection (case-finding and treatment of the most infectious cases, supplemented by prophylactic treatment of special populations). Where this has been achieved and maintained over a substantial period of time, a reduction of the prevalence of tuberculous infection by preventive chemotherapy must be considered as the next logical step. Vaccination with BCG will supplement tuberculosis control efforts, particularly in high-burden countries, mainly by reducing disability and death in young children.

In this monograph, the approach chosen to discuss the various interventions follows the sequence in the epidemiological model presented elsewhere (figure 2).[1,9] Interventions aim at reducing the impact of those risk factors recognized to promote the progression from one step to the next in the chain of events in the pathogenesis of tuberculosis (figure 3).[10]

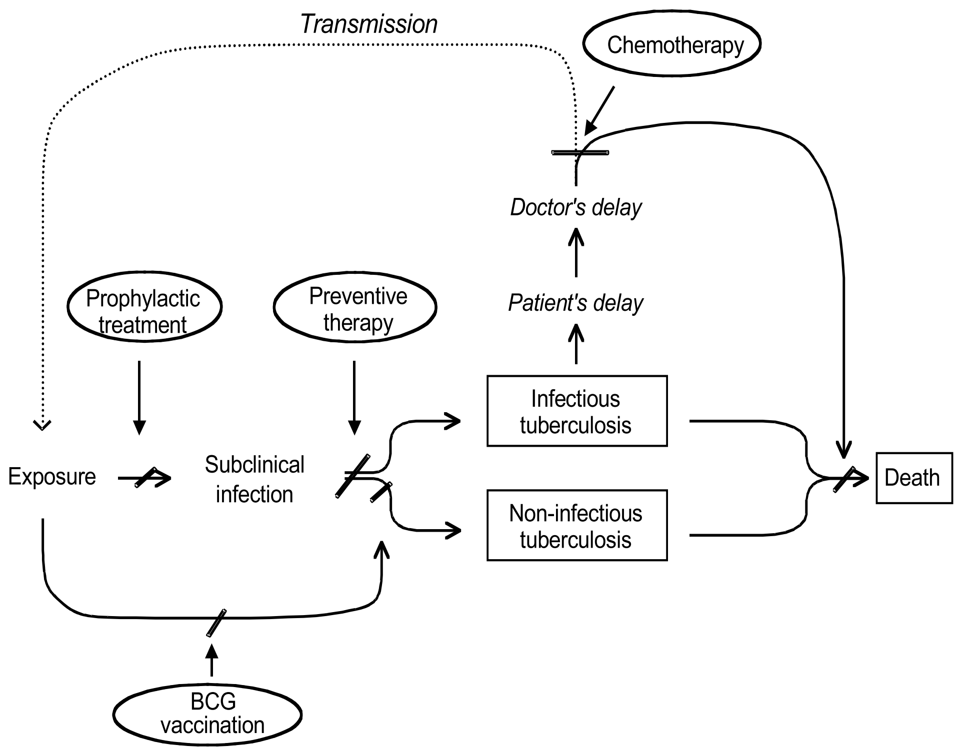

Figure 3. Model of interventions based on the epidemiology of tuberculosis. Reproduced from[10] by the permission of the publisher Marcel Dekker.

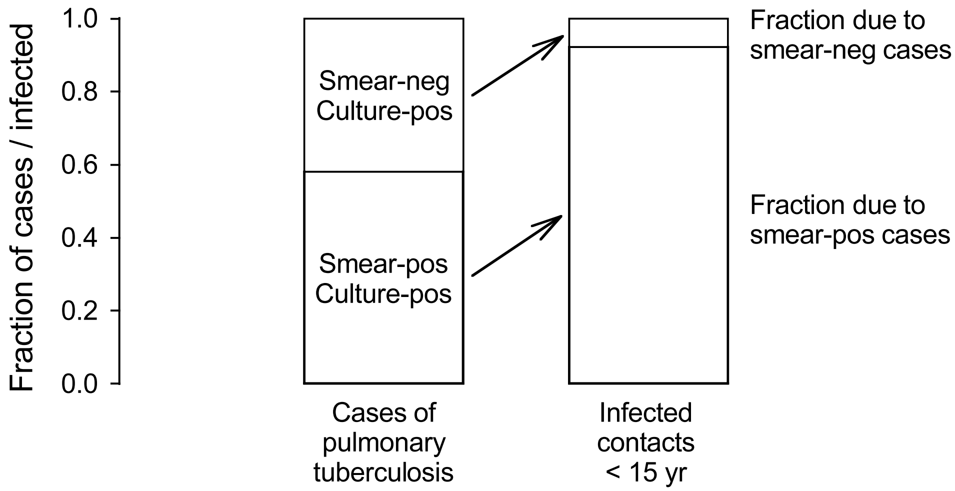

Figure 4. Sensitivity of sputum smear microscopy in identifying pulmonary tuberculosis among culture-confirmed cases and sensitivity of sputum smear microscopy in identifying transmitters of *M. tuberculosis.*[11]

Summary – the role of specific interventions

Chemotherapy

Chemotherapy of tuberculosis is universally indicated for all newly identified tuberculosis patients. No patient with newly diagnosed tuberculosis should be denied treatment.

Chemotherapy is the most powerful weapon in tuberculosis control. It carries individual benefit by reducing morbidity and fatality. It has epidemiologic impact by cutting the chain of transmission effectively if effective treatment leading to cure of individual patients can be assured.

A national tuberculosis program must choose and recommend efficacious, standardized treatment regimens and must ensure both that they are administered carefully to prevent emergence of drug resistance and the cure of the patient.

The limited armamentarium of available anti-tuberculosis medications imposes particular constraints on the use of the most efficacious drugs. Regimens and their administration should be designed to prevent the emergence of chronic excretors with incurable, multidrug-resistant tuberculosis. The following six drugs are currently on the essential drug list:

- ***Isoniazid*** is the cornerstone of every first-line regimen. It has the most potent early bactericidal activity of all known drugs. It rarely causes adverse drug events, the most important of which is hepatic injury, which may result in hepatitis in a small fraction of patients. It interacts with several medications, but the single most important is its enhancement of the effect of anti-epileptics.

- ***Rifampicin*** has unique relapse-preventing properties that allowed the duration of chemotherapy to be shortened to nine months or fewer. It is a superbly tolerated drug that may, however, complicate isoniazid-associated hepatitis, mainly by supporting cholestasis. Immunologically-linked events might be serious and life-threatening, but are very rare. Rifampicin interacts with a multitude of other medications: the most important interactions in practice are reduction of the efficacy of oral contraceptives and anti-retroviral medications, which preclude any such combination.

- ***Pyrazinamide*** also has particular relapse-preventing properties that have allowed the duration of required chemotherapy to be further reduced. In the currently recommended dosages, it is also a very well tolerated drug. Arthralgias are the most frequently reported adverse event that can be alleviated by the administration of acetylic salicylic acid or intermittent administration. There are no practically important interactions with other medications.

- ***Ethambutol***'s main purpose is to reduce the risk of emergence of resistance to isoniazid. It is a very well tolerated drug, and optic neuritis, its main adverse drug event, occurs infrequently with the currently recommended dosages. It does not interact with any other drug, but its absorption might be reduced if patients take certain antacids.

- ***Streptomycin*** might add bactericidal activity to a regimen in the intensive phase and may add additional protection against the emergence of drug resistance, particularly in patients receiving a re-treatment regimen. It is reasonably well tolerated by young patients, but its vestibulo-cochlear toxicity and hypersensitivity reactions make its prolonged use an unpleasant experience for many patients. The only potentially important interaction in daily practice is that its toxic effects are enhanced by some diuretics.

- ***Thioacetazone***'s main purpose is to reduce the risk of emergence of drug resistance to isoniazid and to reduce the risk of failure and relapse where there is resistance to the latter. More than any other drug it has the potential of multi-system adverse drug events. Among human immunodeficiency virus (HIV) infected patients, the most prominent is a muco-cutaneous syndrome that may progress to toxic epidermal necrolysis. This precludes its use in an increasing number of countries. No important interactions with other medications are known.

The treatment of previously untreated tuberculosis patients begins with the direct observation of intake of a four-drug regimen (isoniazid, rifampicin, pyrazinamide, and ethambutol, preferably in a fixed-dose combination tablet) during a two-month intensive phase. To facilitate the organization of directly observed therapy, treatment may be given thrice-weekly after a two-week to one-month daily phase. The continuation phase cannot usually be directly observed, thus a non-rifampicin-containing continuation phase of six months is the rule in most low-income countries. The continuation phase associates isoniazid plus ethambutol (or, increasingly rarely, isoniazid plus thioacetazone). These drugs are usually given in one-month supplies for self-administration. Where resources permit a directly observed continuation phase and second-line drugs in case of treatment failure, the continuation phase can be shortened to four months by giving isoniazid and rifampicin throughout. Twelve-month regimens based on isoniazid plus ethambutol or isoniazid plus thioacetazone, supplemented by streptomycin during the first two months, were efficacious in patients not infected with HIV, and have been widely used in the treatment of bacteriologically unconfirmed tuberculosis. Evidence is accumulating that these twelve-month regimens result in a high relapse rate in HIV-infected patients and are thus being phased out in an increasing number of countries.

Patients presenting again with tuberculosis after prior treatment are known to have an increased risk of harboring bacilli resistant to at least isoniazid. Patients whose first-line treatment regimen did not include rifampicin can be successfully treated with a re-treatment regimen of eight months duration, containing rifampicin throughout. Patients who fail (remain or become again bacteriologically positive) on a first-line regimen containing rifampicin throughout cannot usually be treated successfully with the above re-treatment regimen, and recourse to second-line drugs must necessarily be taken. In most high-burden countries, however, the resources required to appropriately treat all patients who need such a regimen are not available.

The immediate prospects for the development of new, high-quality drugs that would have nation-wide availability, be well tolerated, and affordable are slim for most high-burden countries. Consequently, the preservation of the activity of the currently available medications, particularly isoniazid, rifampicin, and pyrazinamide, must be accorded the highest priority. Directly observed therapy reduces the risk of acquisition of drug resistance and relapse, and is thus of both individual and public health benefit.

Prophylactic treatment

The evidence for the efficacy of prophylactic treatment in preventing acquisition of tuberculous infection among persons exposed to an infectious case is scant. However, the limited evidence would suggest that a child born into a household with an infectious tuberculosis patient only recently placed on chemotherapy should receive prophylactic treatment with isoniazid, continued for probably at least three months following cessation of relevant exposure. Should the bacteriologic response of the index case be poor (failing to convert sputum smears), prophylactic treatment should probably be prolonged (or adjusted where feasible if the index case has a drug-resistant strain).

Prophylactic treatment is an individual intervention primarily to protect the child without separation from the mother. No great epidemiologic or public health impact of this measure is to be anticipated.

Vaccination

Vaccination with BCG provides considerable protection against death from tuberculosis, and the development of disseminated and meningeal tuberculosis, particularly in infants. Neonatal BCG vaccination (or as early in life as possible) is thus indicated where tuberculosis is frequent, childhood tuberculosis rarely diagnosed, and adequate contact examinations rarely feasible. There is insufficient evidence to recommend vaccination beyond infancy, or re-vaccination.

BCG vaccination is an individual measure that is not expected to improve the epidemiologic situation in a country. It is of public health importance to the extent that it reduces disability and death from tuberculosis in the target population.

Preventive chemotherapy

Preventive chemotherapy using nine to twelve months of isoniazid is efficacious but operationally inefficient. In adults it carries the danger of monotherapy of clinically active tuberculosis which might not be recognized if mycobacterial culture facilities and chest radiography are not routinely available. This is of particular concern in HIV infected patients who would be most likely to benefit, because such patients frequently have active tuberculosis that cannot be identified on sputum smear microscopy alone.

The drug of choice is isoniazid, although shorter regimens based on rifampicin can be used where resources permit. Logistically and administratively easiest, and also of least concern for the development of drug resistance, is preventive chemotherapy for asymptomatic children under the age of five years who live in the household (not all of whom are necessarily infected) of a newly identified sputum smear-positive index case. It may be pragmatic to adjust the duration of isoniazid preventive chemotherapy in such cases to the length of treatment for the adult index case.

Preventive chemotherapy is an individual intervention, not shown to have as great an epidemiologic impact as chemotherapy of tuberculosis. Even if safeguards could be taken to prevent inadvertent monotherapy for patients with active tuberculosis, it remains an inefficient tool that reaches only a fraction of persons infected with *M. tuberculosis*.

1. Chemotherapy

The primary intervention must aim at reducing the incidence of infection with *M. tuberculosis.*[12] Subsequent events will reflect what happens if this primary prevention has not been properly applied. Efficacious and effective chemotherapy for patients transmitting tubercle bacilli is thus paramount to the success of a national tuberculosis program. The following major areas of concern are addressed in this chapter:

- The absolute prerequisite to effective chemotherapy is the availability of high-quality anti-tuberculosis drugs. With these drugs, optimum combination regimens have been identified. Regimens must be prescribed in a way that simultaneously prevents the emergence of resistant strains and cures the affected patient.

- Regimens suitable for use in national tuberculosis programs have been identified. The HIV epidemic has complicated tuberculosis control in general and chemotherapy in particular, and not all issues relating to treatment in the presence of HIV infection have yet been resolved.

- Administering chemotherapy through self-administered medication often gives poor results. Directly observed therapy, sometimes incorporating intermittent administration, increases the chances for a successful treatment outcome and has been shown to reduce the chance of emergence of drug resistant populations of bacilli.

- While the course of chemotherapy is uneventful in most patients and leads to complete restoration of health, some patients experience adverse drug events that need to be addressed without compromising the efficacy of treatment.

Essential drugs

There are six essential drugs that are active against *M. tuberculosis*: isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, and thioacetazone.[13] For each essential drug with activity against *M. tuberculosis*, a standard summary of the major aspects of interest is presented. These include, notably:

Discovery. A brief history of the discovery of the drug.

Activity, mechanism of action and resistance. Activity, mechanism of action, and mechanisms that allow *M. tuberculosis* to become resistant to anti-tuberculosis agents are intrinsically linked. In contrast to many other microorganisms, the susceptibility of virtually all wild strains of *M. tuberculosis* to the major anti-tuberculosis agents is identical. Any apparent variation in susceptibility is a misconception due to technical errors of the method used to demonstrate it. This means that an approach using the minimum inhibitory concentration (MIC) of the initial strain (in the absence of resistance) as a guide to treatment is theoretically invalid.

Pharmacokinetics. In treatment of tuberculosis (as in other diseases), concentration of the drug in the target organ determines whether the drug will have the desired effect or not. The maximum concentration that can be achieved is that which provides the highest concentration and the longest period the drug is above the MIC without being toxic.[14] There are four key pharmacokinetic parameters that are of particular interest (table 1):

- C_{max}: The maximum serum concentration of the drug that can be achieved;
- T_{max}: the point in time when the maximum serum concentration is achieved following administration of the drug;
- AUC: the area under the serum concentration-versus-time curve. This is an informative parameter that summarizes the overall avail-

Table 1. Pharmacokinetic parameters (rounded values) of essential anti-tuberculosis drugs.

Drug	Pharmacokinetic parameters in serum			
	C_{max} (mg/L)	T_{max} (h)	$AUC_{0-\infty}$ (mg × hr/L)	$\beta t_{1/2}$ (h)
Isoniazid	4	1-2	17	2-3
Rifampicin	14	1-3	71	2-4
Pyrazinamide (1,500 mg)	25-30	1.2	420	10
Streptomycin (1 g)	25-50	1-2		2-3
Ethambutol (25 mg/kg)	5	3	30	12
Thioacetazone (150 mg)	1.8	4		13

ability of the drug in the serum of the person to whom the drug is administered;

- $\beta t_{1/2}$: the serum elimination half-life (in hours) of the drug. It indicates the time required to reduce the blood serum (or plasma) concentration to half of its maximum value.

Dosage. This is the recommended dosage in the treatment of tuberculosis in daily or thrice-weekly treatment. Because neither WHO nor the IUATLD recommend twice-weekly treatment, the dosages recommended for such an administration schedule are not presented.

Adverse drug events. No drug is without side effects or adverse drug events. Four types of adverse drug events might be distinguished: [15] 1) toxic, 2) idiosyncratic, 3) hypersensitivity reactions, and 4) adverse drug events that cannot be classified into one of the three preceding groups. Toxic reactions are effects that will occur in the majority of patients at a given dose. Idiosyncrasy denotes an individual genetic defect that causes a qualitative abnormal response. [16] Hypersensitivity reactions are untoward immunologic reactions to a drug.

Interactions. Some drugs interact with other medications. Such interactions are listed here, to the extent known.

Isoniazid

Discovery. Isoniazid was synthesized in 1912 at the German University of Prague by Meyer and Mally (figure 5). [17] In 1952 it was independently re-discovered by the Bayer Laboratories in Germany, [18] Hoffmann-La Roche

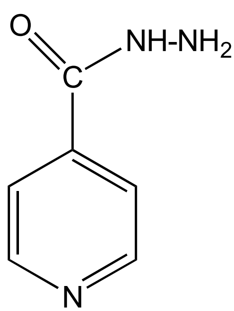

Figure 5. Chemical structure of isoniazid, synthesized by Meyer and Malley in 1912.[17]

Laboratories in Switzerland / United States,[19] and Squibb Laboratories in the United States,[20] without the knowledge of the other groups working on the drug.

Activity, mechanism of action and resistance. Isoniazid is only active against mycobacteria. Within the genus, its effect is mainly against *M. tuberculosis* complex and to a lesser extent against a few species of environmental mycobacteria, e.g., *M. kansasii*. The MIC of *M. tuberculosis* is 0.025 to 0.05 mg/L in broth and 0.1 to 0.2 mg/L in agar plates,[21-23] showing the uncertainty surrounding MIC determinations. Isoniazid has the most potent early bactericidal activity of all of the anti-tuberculosis drugs.[24-27] Adding other drugs will not increase this activity.[24,25] Thus, the rapid reduction in infectiousness observed following initiation of chemotherapy[28-30] is most likely attributable to a considerable extent to the bactericidal activity of isoniazid.

Early reports have suggested that the effect of isoniazid is on cell wall integrity. It was observed that acid-fastness was lost shortly after treatment with isoniazid.[31] Winder and Collins demonstrated that isoniazid inhibits the synthesis of mycolic acids.[32] Sacchettini and Blanchard[33] have traced the history of development in the understanding of the mechanisms of action of isoniazid. The next step in understanding was the direct correlation between isoniazid uptake, viability and mycolic acid biosynthesis.[34,35] A specific inhibitory effect was observed on the synthesis of saturated fatty acids greater than 26 carbons,[36] and the synthesis of monounsaturated long-chain fatty acids *in vivo.*[37] These and subsequent observations strongly implicated enzymatic steps in the elongation of fatty acids, and the biosynthesis of the very long fatty acyl chains of mycolic acids as the site of action of isoniazid.[33] Early studies by Middlebrook *et al.* and others noted the correlation between resistance and loss of catalase-peroxidase activity.[38-40] The molecular basis for these early observations has now been documented with the demonstration that isoniazid-resistant strains could be sensitized to the drug by transformation with the *M. tuberculosis katG*-encoded catalase peroxidase.[41,42] Additional evidence in support of the role of catalase-peroxidase stems from the observation that deletions and missense mutations within the *katG* gene are common in isoniazid-resistant clinical isolates of *M. tuberculosis.*[43,44]

The current concept classifies isoniazid as a pro-drug which requires the *katG* gene product for activation by the catalase,[33,45] targeting the last steps in mycolic acid synthesis.[46] While details of the mode of action still remain elusive,[47] the general mechanism of action is fairly well understood (figure 6).[46] Several mutations have been identified which confer resistance in *M. tuberculosis*. Important mutations are located on the *katG* gene,[41] and the *inhA* gene,[48] of which the latter is responsible for approximately 25% of clinical isolates that demonstrate resistance, generally associated with low-levels of resistance. Susceptibility to isoniazid is dependent on the presence of the catalase-peroxidase enzyme encoded by the *katG* gene.[44,49] Mutations in catalase-peroxidase lead to high-level isoniazid resistance.[41,50] The *ahpC* gene encodes the alkyl hydroperoxide reductase, and its absence leads to isoniazid resistance.[51] Approximately 60% to 70% of isoniazid resistant strains carry mutations in one of several genes involved in its activation from pro-drug (*katG* and possibly *ahpC*) or in the

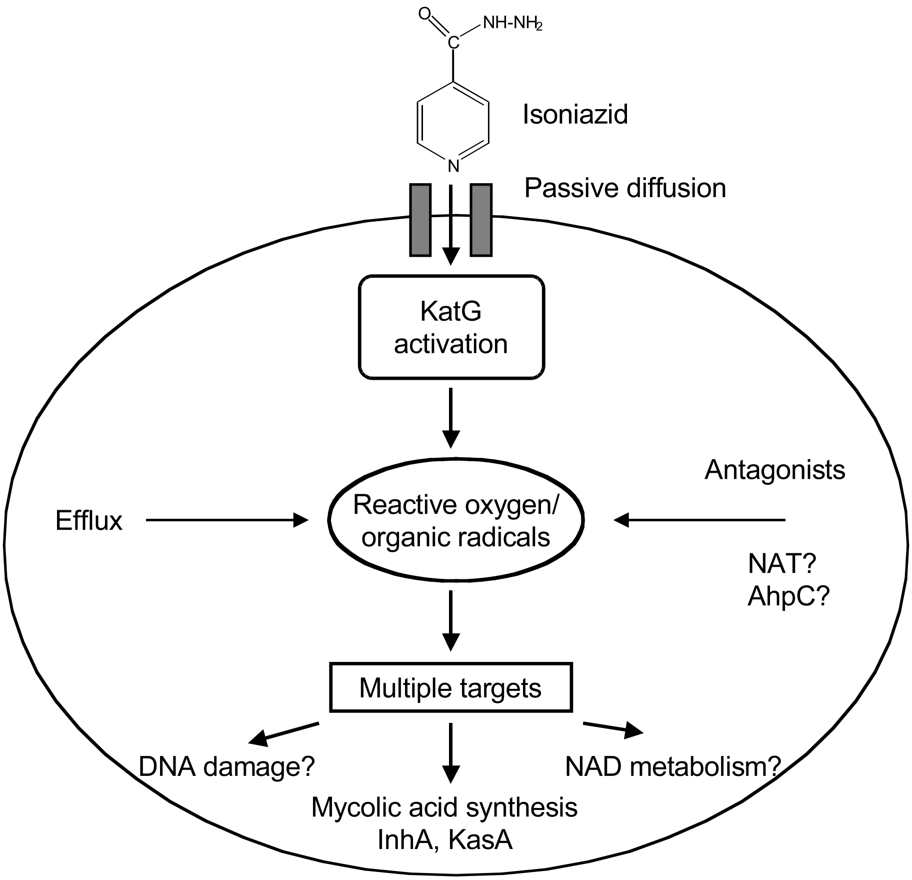

Figure 6. The proposed action of isoniazid. Reproduced from[46] by the permission of the publisher ASM Press.

drug target (*inhA*). However, the mechanism of resistance for one third of isoniazid-resistant strains remains to be elucidated.

The maximum proportion of isoniazid resistant mutants able to grow during isoniazid monotherapy of an isoniazid susceptible strain is estimated to be approximately 1 in 10^6.[52-54]

Pharmacokinetics. The serum concentrations achieved by administering 300 mg isoniazid (approximately 5 mg/kg body weight) are well above the MIC (figure 7).[55-57] The pharmacokinetics of isoniazid are influenced by

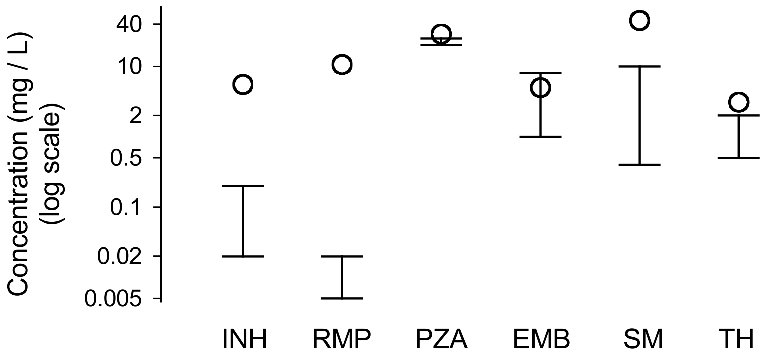

Figure 7. Maximum serum concentrations (hollow circles) and range of minimum inhibitory concentrations (lines) for isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), ethambutol (EMB), streptomycin (SM), and thioacetazone (TH).[55,56,180,182,301,422]

acetylator type (slow *versus* rapid),[55] food intake,[55] and age.[57] A comparative pharmacokinetic profile of isoniazid by type of food (fasting *versus* high-fat meal) is shown in figure 8.[55] The distribution volume of isoniazid diminishes with increasing age as shown in figure 9.[57] The elimination of isoniazid from serum is determined by the acetylator status of the individual.[58] There are three groups of acetylator types. Homozygous rapid activators are found in 40% of European and African populations and in most of those with a Mongolian ancestry. There is a heterozygous group with mutations in only one of the two alleles, and finally a homozygous group of slow inactivators with mutations in both alleles. The old "rapid inactivator group" from earlier publications consisted, in most populations, of a majority of heterozygous and a minority of homozygous rapid inactivators (Mitchison DA, personal written communication, May 22, 2001). The serum half-life, $\beta t_{1/2}$, in slow acetylators is about three hours following a dose of 5 mg/kg body weight, and about

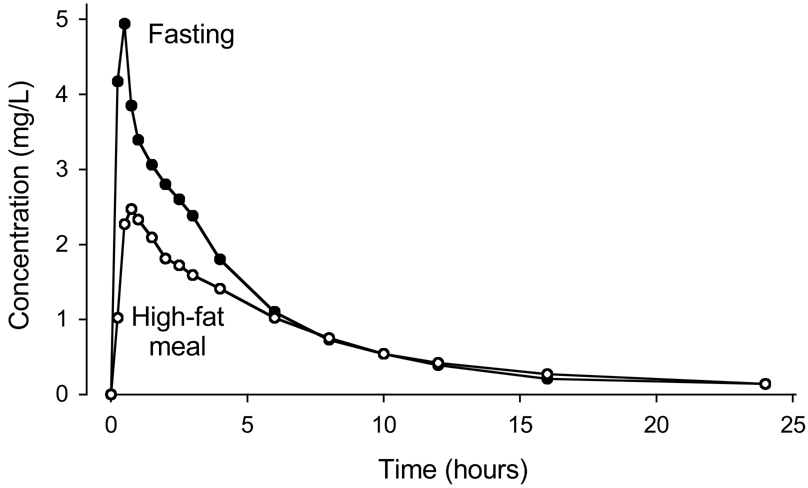

Figure 8. Pharmacokinetics of isoniazid following fasting and a high-fat meal.[55] Original data kindly provided by Charles A Peloquin.

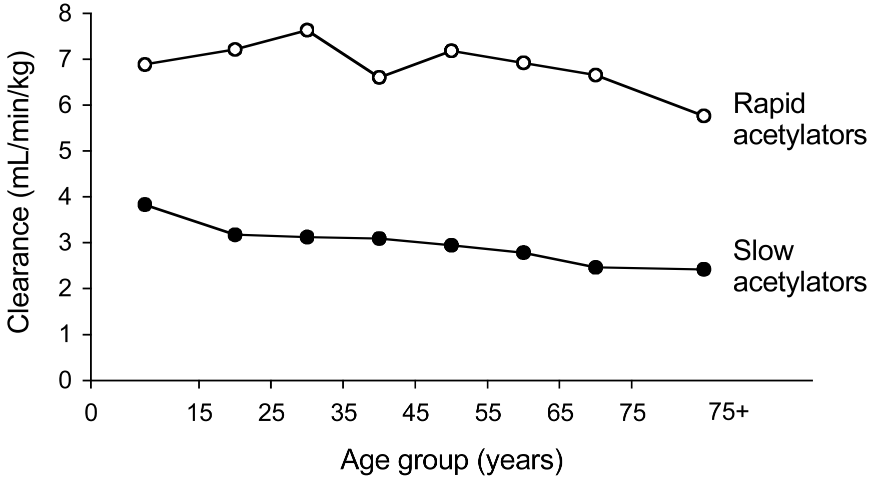

Figure 9. Clearance of isoniazid from serum, by acetylator type and age among tuberculosis patients.[57]

half as long for rapid acetylators.[59,60] The AUC is similarly affected by acetylator type which is approximately 14.2 mg/h/L in slow eliminators as compared to 2.3 mg/h/L in rapid eliminators.[60] The acetylator type is important for widely spaced intermittent therapy. It explains to a large extent why once-weekly therapy with isoniazid is particularly ineffective in rapid acetylators. For thrice-weekly treatment, the acetylator type is not important. Isoniazid also has excellent penetration into cerebrospinal fluid, although the peak concentrations achieved are much lower in rapid than in slow acetylators.[61]

Dosage. The recommended dosage of isoniazid is 5 mg/kg body weight (usually up to a maximum of 300 mg) in daily, and 10 mg/kg body weight in thrice-weekly treatment.[8,13]

Adverse drug events (table 2). Toxic reactions include peripheral neuropathy,[62] seizures,[62-68] and other central nervous system toxic reactions, such as hallucinosis,[69] psychosis,[70] memory loss,[71] optic neuropathy,[72] and pellagra.[73,74] Other toxic reactions from isoniazid include pyridoxine responsive anemia,[15,75,76] metabolic acidosis.[77] Pyridoxine is effective in both treatment and prevention of these reactions,[78-80] but pyridoxine non-responsive psychosis has also been reported.[81] In case of accidental or intentional overdose both charcoal treatment, if given early,[82,83] and hemodialysis[84] have proved useful.

Table 2. Summary of adverse reactions from isoniazid with estimated frequencies of occurrence. Note that these are estimates of frequencies which may vary across population groups.

Frequent ($\geqslant$ 5 per 100)	Common ($\geqslant$ 1 per 100 and < 5 per 100)	Infrequent ($\geqslant$ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
Liver enzyme elevations		Hepatitis Peripheral neuropathy Drug fever	Seizures Hallucinosis Psychosis Memory loss Optic neuropathy Pellagra Pyridoxine responsive anemia Metabolic acidosis Pyridoxine non-responsive psychosis Lupus erythematosus Hemolytic anemia Agranulocytosis Pure red cell aplasia Alopecia Asthma Dermatitis

Idiosyncratic reactions from isoniazid include lupus erythematosus,[85,86] rheumatic-like syndromes and various hematologic disorders, such as hemolytic anemia,[87] agranulocytosis,[88,89] pure red cell aplasia,[90-92] and other blood dyscrasias.[93] Other rare, probably idiosyncratic reactions, include alopecia.[94] These reactions are reported to subside promptly with withdrawal of the drug.[15]

Hypersensitivity reactions from isoniazid include drug fever,[95] asthma,[96,97] dermatitis,[98-100] and hepatitis.[77,101,102] Hepatotoxicity might be increased with the concomitant use of acetaminophen.[103-105]

Clinically, the most relevant and frequent adverse drug events from isoniazid are neuropathy and liver injury.

Routine use of pyridoxine (vitamin B6) for prevention of neuropathy is not indicated.[79] Preventive treatment with small dosages of pyridoxine (6 mg/day, not to exceed 10 to 15 mg[106,107]) is indicated for patients with increased requirements (e.g., during pregnancy), patients with nutritional deficiencies (alcoholics and aged patients), patients with a history of seizure disorder, and patients otherwise predisposed to the development of peripheral neuropathy, such as uremic patients or patients with diabetes.[79] Treatment of isoniazid-associated peripheral neuropathy (paresthesia) is with 100 to 200 mg pyridoxine per day.[79] It should be noted that there is antagonism between isoniazid and pyridoxine,[108] and thus the potential of inactivation of isoniazid with very high doses of pyridoxine. Therefore many clinicians prefer lower dosages (50 mg per day).

Liver enzyme elevations are frequent, but overt clinical hepatitis (with symptoms such as gastrointestinal distress, nausea, vomiting, and jaundice) occurs in less than five per cent of patients[109] and is age-dependent,[110-114] and may differ in frequency in different populations,[114] being virtually absent among, e.g., Filipinos,[115] and is increased in patients with pre-existent liver injury.[110] The hepatic damage caused by isoniazid is predominantly cytolysis.[116] The AUC for monoacetyl hydrazine, the putative precursor of the responsible agent, was greater in slow acetylators in a pharmacokinetic study, though the AUCs for acetyl isoniazid and diacetyl hydrazine were higher in rapid acetylators.[117] The association of differences in pharamcokinetics of isoniazid and its metabolites with hepatitis risk is poorly understood,[118] and has not been shown to be of great importance.[119] Indeed, evidence obtained from patients in Hong Kong and Singapore showed that elevated transaminase levels during treatment with isoniazid-containing regimens were no higher in rapid than in slow acetylators.[120-122] In the IUATLD trial on preventive chemotherapy with isoniazid in patients with fibrotic lesions,[123] the risk of hepatitis due to isoniazid alone could be assessed. Among patients receiving isoniazid for one year, the risk of hepatitis was 5.8 per 1,000 persons.[110] It increased from 2.8 per 1,000 for subjects aged less than 35 years to 7.7 per 1,000 for those aged 55 years or more, but risk was much lower in those without pre-existing liver damage (figure 10).[110] The hepatitis risk was highest in the first two months of treatment (figure 11). In a US Public Health Service survey, the hepati-

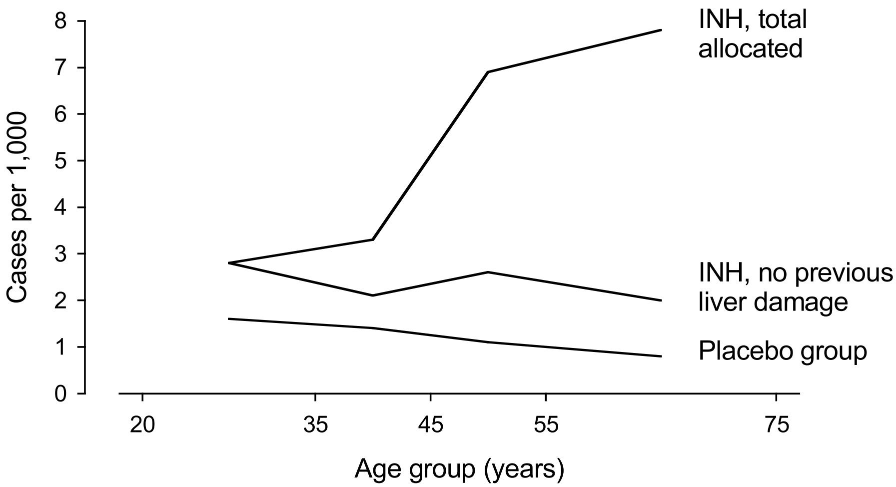

Figure 10. Hepatotoxicity from isoniazid during preventive therapy by age and pre-existing liver damage.[110]

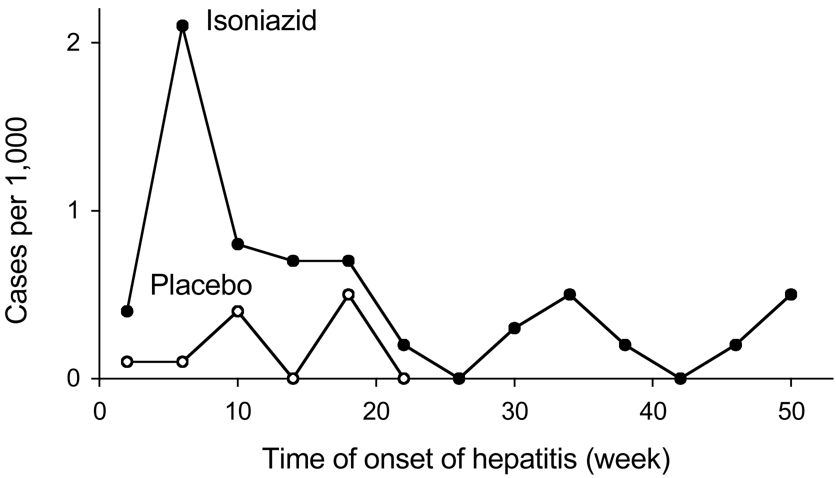

Figure 11. Hepatotoxicity from isoniazid during preventive therapy by length of exposure.[110]

tis risk per 1,000 subjects was zero for those aged less than 20 years, 2.4 for those aged 20 to 34 years, 9.2 for those aged 35 to 49 years, and 19.2 for those aged 50 to 64 years.[111] Isoniazid and rifampicin given together may potentiate the risk of hepatitis, and cases of hepatitis caused by the two drugs in combination have been reported.[124,125]

Patients abusing alcohol may be treated with isoniazid provided they do not display signs of overt alcoholic hepatitis. Careful clinical control, limitation of alcohol consumption and (where feasible) control of liver enzymes in such patients are recommended.

Interactions. Isoniazid is an inhibitor of oxidative and demethylation metabolism as well as other cytochrome P-450 dependent microsomal pathways.[126,127] It is also a monoamine and diamine oxidase inhibitor.[128,129] These properties bear on the various interactions that have been reported,[130] in that the most important interaction leads to a potentiation of the companion drug (opposite to the usual interactions seen with rifampicin).

Scombroid fishes (such as mackerel, tuna and salmon) have a high histidin content which is converted to histamine by bacteria, if improperly refrigerated. Eating such fish while taking isoniazid may lead to the typical signs of scombroid fish poisoning, with erythematous and urticarial rash, facial flushing, diarrhea, palpitations, headache, nausea, paresthesias, abdominal cramps, and dizziness.[131-134] It may progress to bronchospasm and hypotensison.

Certain types of cheeses rich in monoamines may also lead to hypersensitivity reactions.[135-138] With wine, such reactions have also been reported.[128]

Effects of isoniazid potentiated: para-aminosalicylic acid,[139] insulin,[140] carbamazepine,[141] valproic acid (a single report, usually the effect is the opposite),[142] theophylline.[143]

Effects of isoniazid opposed: prednisolone,[59] ketoconazole.[144] After intake of ethanol, most is metabolized to acetaldehyde in the liver. Acetaldehyde appears to form acetaldehyde-adducts with isoniazid *in vitro*, and thus may lower its bioavailability, but the adduct itself may increase the toxicity of either drug.[145]

Effect of drug potentiated by isoniazid:

- acetominophen hepatotoxicity is increased by isoniazid;[103,104]

- anti-coagulants such as warfarin;[146]

- anti-epileptics such as phenobarbital, diphenylhydantoin,[147] and phenytoin,[148,149] carbamazepine,[150-153] ethosuximide,[154] epanutin,[155] and valproic acid;[142,156,157]

- anti-neoplastics such as vincristine;[158]

- benzodiazepines which are oxidatively metabolized (not through glucorination),[159] such as diazepam[160] and triazolam;[161]

- haloperidol[162] and tricyclic anti-depressants;[163]

- theophylline.[143,164] The effect on theophylline pharmacokinetics might be such that even in combination with rifampicin (which has the opposite effect), theophylline clearance might be lowered, requiring a lower dose of theophylline in patients simultaneously treated with isoniazid and rifampicin.[165]

Because of its monoamine oxidase inhibiting activity, isoniazid may potentiate the effect of monamine oxidase inhibitor anti-depressants,[166,167] meperidine[168] and levodopa.[169]

Effects of drug opposed by isoniazid: enflurane,[170] cyclosporine[155] (disputed).

Rifampicin

Discovery. In 1957, a *Streptomyces* strain, designated strain ME / 83, later named *Streptomyces mediterranei* was isolated in the Lepetit Research Laboratories from a soil sample collected at a pine arboretum near Saint Raphaël, France.[171,172] From this strain several rifamycins, whose structure was elucidated by Oppolzer and collaborators,[173] were isolated. By reduction of one of these, rifamycin S and rifamycin SV were obtained. Rifamycin SV was only effective parenterally, as it was not absorbed to a significant degree when administered orally. Further chemical modification led to an orally active substance, rifampicin (figure 12).[174]

Activity, mechanism of action and resistance. The minimum inhibitory concentration of rifampicin for *M. tuberculosis* is about 0.25 mg/L in broth

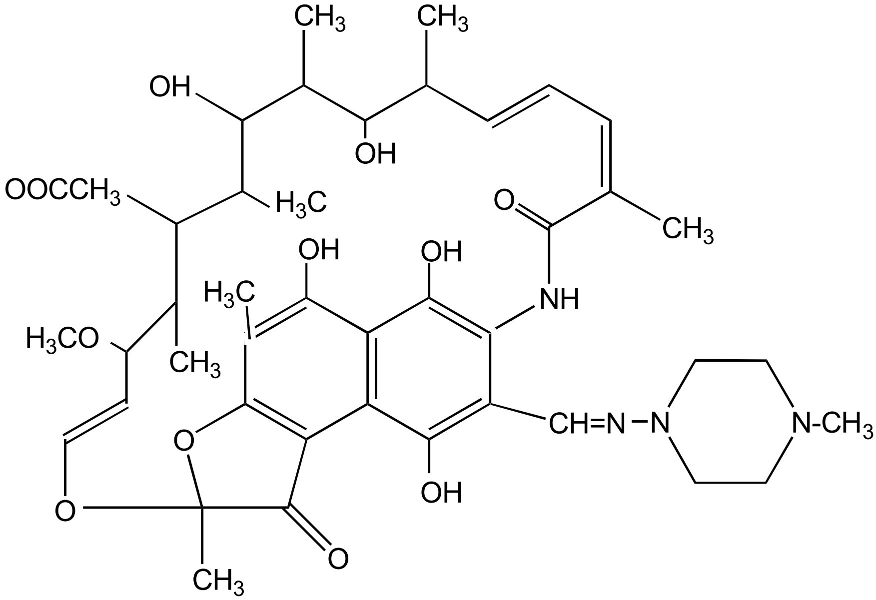

Figure 12. Chemical structure of rifampicin, isolated and semi-synthesized by Maggi and collaborators in 1966.[174]

and 0.5 mg/L in agar.[21-23] Rifampicin is active against a wide range of micro-organisms including *M. leprae*, *S. aureus*, *N. meningitidis*, and *L. pneumophila*.

Rifampicin, like all naphthalenic ansamycins (the class to which rifampicin belongs), is a specific inhibitor of DNA-dependent RNA polymerase.[175]

Rifampicin acts by interfering with the synthesis of mRNA by binding to the RNA polymerase.[176] Mycobacteria develop resistance to rifampicin by mutations in a defined region for the RNA polymerase subunit β. Mutations in the *rpoB* gene of *M. tuberculosis* are responsible for most of the resistance.[177] Mutations have been found in more than 97% of resistant isolates.[178,179]

The maximum proportion of rifampicin-resistant mutants able to grow during rifampicin monotherapy of an isoniazid-susceptible strain is estimated to be approximately 1 in 10^8.[53]

Pharmacokinetics. After oral administration of rifampicin on an empty stomach, the absorption is rapid and practically complete.[180] With a dose of 8.1 (± 0.7) mg/kg body weight, a peak level of 6.3 (± 0.5) mg/L is achieved 3.2 hours after oral administration. After oral intake of 600 mg rifampicin, a peak level of 12 to 14 mg/L is achieved after one to three hours (figure 13).[181,182] The AUC (between 0 and 12 hours) is 36 mg/L/hr, and the half-life is estimated to be 4.7 (± 1.9) hours,[183] but has been found to be shorter in three studies (3.8 to 4.1 hours) after a single dose of 10 mg/kg body weight.[175] A drug-concentration – time profile is shown in figure 49.[175] Rifampicin is excreted unchanged in urine and bile and is also metabolized. Its major metabolite, desacetyl-rifampicin, is excreted principally in bile, but also in urine.[184] It appears that there are differences between men and women in the blood levels achieved, with women achieving significantly higher levels than men, a difference not explained by differences in body weight.[185] The pharmacokinetics of rifampicin are influenced by meals,[186,187] but depend on the type of constituents. Carbohydrates and proteins seem to have virtually no influence, while a fatty meal reduces serum concentrations considerably, as shown in four groups of 35 patients each (figure 14).[188] The major differences in pharmacokinetics following a meal include a reduced total amount absorbed (area under the curve) and delayed achievement of peak serum levels.[175]

Tissue penetration of rifampicin is excellent into cavity linings, lung parenchyma and kidneys, with levels above the serum levels (figure 15).[175] Levels below the serum levels but well above the minimum inhibitory concentration are achieved in pyogenic bone lesions and the pleura. Critical

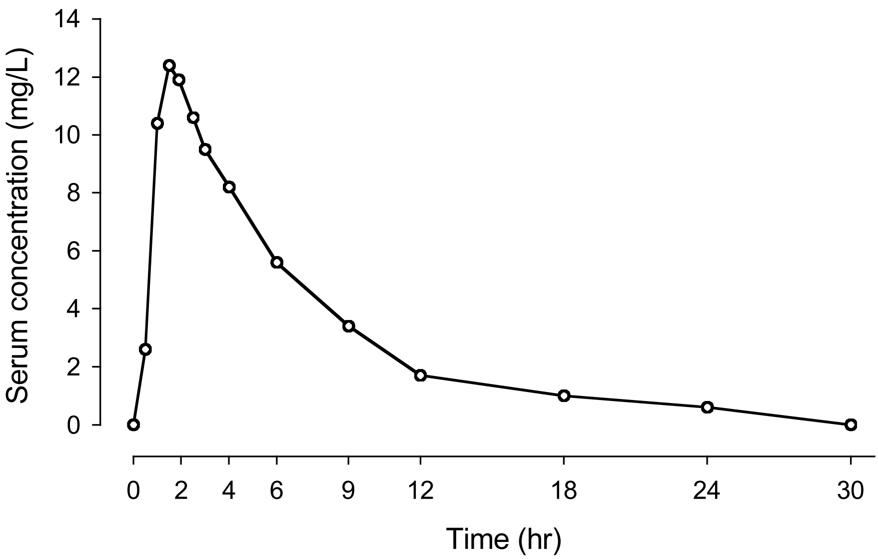

Figure 13. Pharmacokinetics of rifampicin in healthy volunteers. Reproduced from[181] by the permission of the publisher ASM Press.

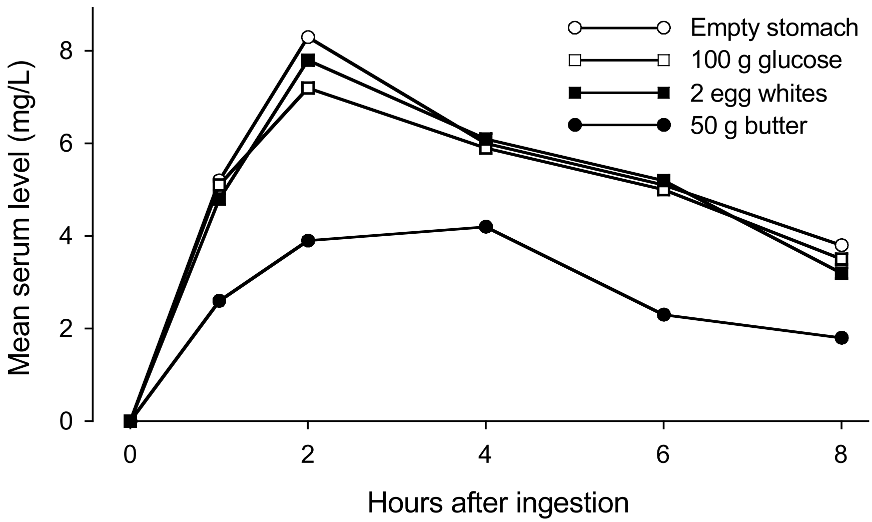

Figure 14. Pharmacokinetics of rifampicin following meals compared to fasting. Reproduced from[188] by the permission of the publisher Churchill Livingstone.

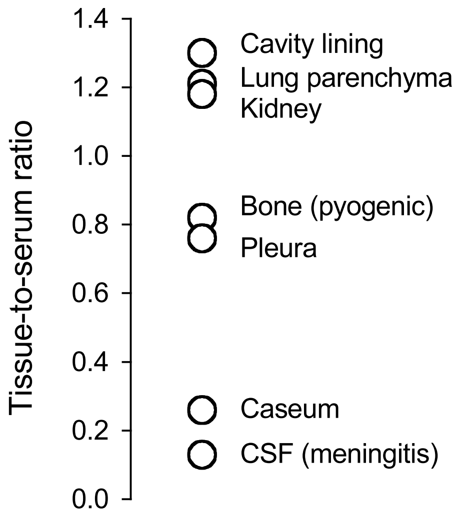

Figure 15. Tissue penetration of rifampicin with tissue-to-serum ratios.[175]

concentrations close to the minimum inhibitory concentration were measured in caseum and cerebrospinal fluid in meningitis.

The cerebrospinal fluid to plasma concentration level ratio is between 0.52 and 1.17 over 12 hours in the experimental (healthy) rabbit model.[189] In comparative studies, mean peak rifampicin concentrations in the cerebrospinal fluid of patients with tuberculous meningitis of 2.4 mg/L were obtained six hours after administration of 600 mg rifampicin, while a delayed mean peak of only 0.81 mg/L was reached nine hours after drug ingestion in normal subjects.[175]

The quality of rifampicin is very susceptible to the manufacturing process. The same amount on a weight basis can lead to markedly reduced bioavailability if the particle size in the manufacturing process or the excipient are changed.[190] A particularly critical issue in the manufacture of rifampicin is its crystalline structure, which might be affected during the mixing process (particularly if there is a failure to properly control temperature and the grinding process), especially in fixed-dose combination preparations.[191-193]

Dosage. The recommended dosage of rifampicin is 10 mg/kg body weight in daily treatment.[13] The recommended dosage in thrice-weekly treatment is the same as the daily dosage, because an increased frequency of a flu-like syndrome has been observed with intermittent treatment at higher dosages.[194]

Adverse drug events (table 3). Serum bilirubin levels increase above normal values with the usual dosage of rifampicin on the first day of treatment, but normalize within two weeks (figure 16).[195,196] The most frequent hepatic abnormality caused by rifampicin is cholestasis. Rifampicin induces isoniazid hydrolase, leading to increased formation of hydrazine, a finding that could explain the increased hepatotoxicity observed in patients receiving both rifampicin and isoniazid (figure 17).[124,197,198] Hepatitis as a result of combination therapy with rifampicin and isoniazid is the most important adverse drug event in adults[120,194,199,200] and occurs also in children, albeit less frequently.[109,201-203] Patients with HIV infection appear to be at particularly high risk of hepatotoxicity.[204-206] Whether hepatitis B HBsAg carriers are at increased risk appears to be equivocal.[207,208] In contrast, hepatitis C carriers appear to be at greatly increased risk of drug-induced hepatitis.[206]

Rifampicin has been reported to cause acute interstitial nephritis[209] and glomerulonephritis.[210]

Hypersensitivity reactions are infrequent or rare, and include pruritus,[211] and rarely severe muco-cutaneous toxicity, such as toxic epidermal necrolysis,[212-214] particularly in HIV-infected patients.[215,216]

Rifampicin may cause menstrual disturbances such as oligomenorrhea and amenorrhea.[217] Anaphylactic shock has been reported among HIV-infected patients.[218,219]

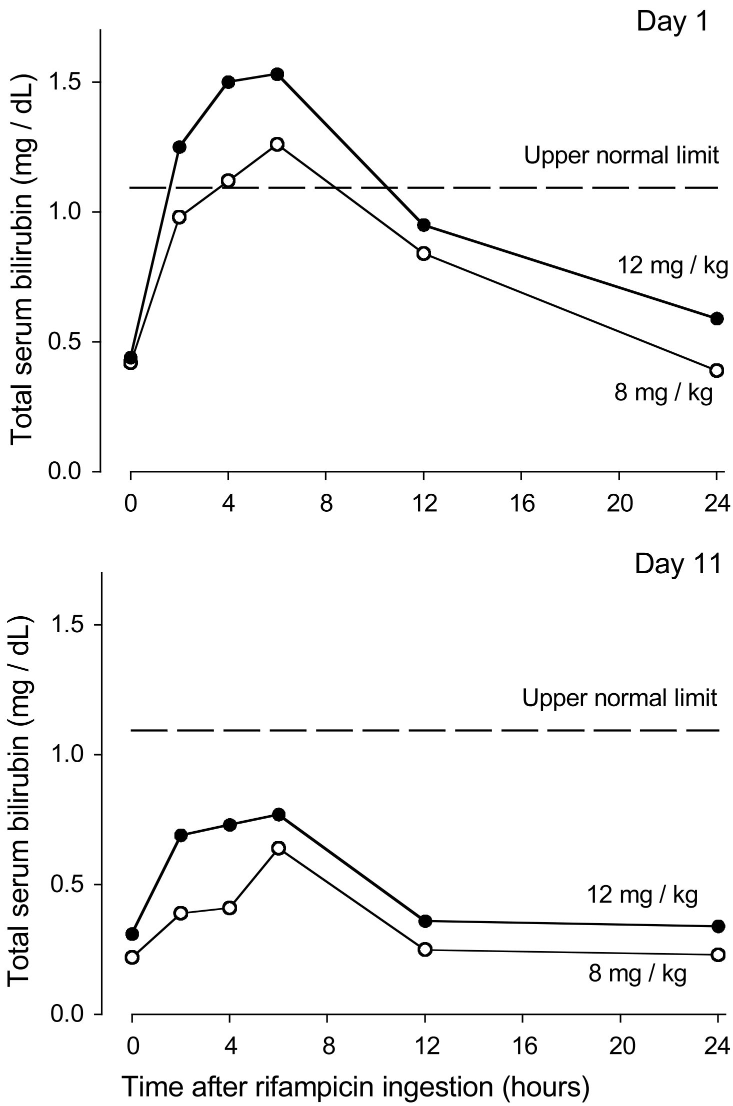

Figure 16. Total serum bilirubin levels in adults with normal liver function after ingestion of rifampicin at the beginning of treatment and after two weeks. Reproduced from[195] by the permission of the publisher Monaldi Archives for Chest Disease.

Among hematologic abnormalities, rifampicin has been reported to cause leukopenia,[220] hemolytic crisis,[221] and thrombocytopenia,[222] the latter being perhaps one of the more frequent adverse drug events.

Rifampicin reduces pruritus in patients with primary biliary cirrhosis, similar to the effect of phenobarbitone.[223]

Table 3. Summary of adverse reactions from rifampicin with estimated frequencies of occurrence. Note that these are estimates of frequencies which may vary across population groups.

Frequent (⩾ 5 per 100)	Common (⩾ 1 per 100 and < 5 per 100)	Infrequent (⩾ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
Bilirubin elevations in the beginning of treatment		Hepatitis	Interstitial nephritis
Orange discoloration of urine and tears*		Pruritus	Glomerulonephritis
Liver enzyme elevations		Flu syndrome	Renal failure
		Drug fever	Toxic epidermal necrolysis
			Oligomenorrhea
			Amenorrhea
			Anaphylactic shock
			Neutropenia
			Leukopenia
			Hemolytic anemia
			Pseudomembranous colitis
			Eosinophilic colitis
			Lupus erythematosus
			Myopathy

* Not an adverse drug event, but a normal occurrence that might cause anxiety in patients.

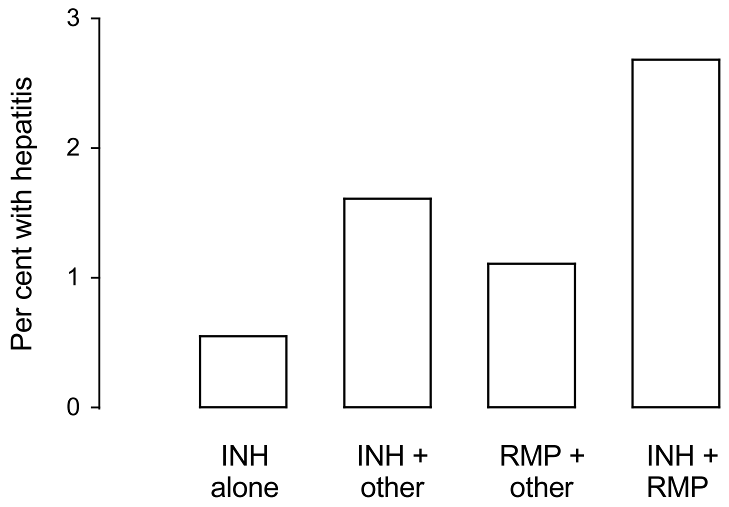

Figure 17. Hepatitis frequency following isoniazid alone or in combination with rifampicin.[198]

Rifampicin may rarely cause pseudomembranous colitis[224,225] and eosinophilc colitis.[226]

Rifampicin has also been reported to induce lupus erythematosus.[227]

Rifampicin has also been reported to cause myopathy.[228]

With intermittent therapy, when higher doses than the now-recommended daily dose equivalent have been used, a "flu" syndrome has frequently been reported.[194,229] Also shortness of breath, hemolytic anemia, and renal failure usually occur only if rifampicin is given intermittently.[194]

Although not an adverse drug event, it should be noted that rifampicin leads to orange discoloration of urine and tears,[230] and may permanently damage soft contact lenses.[231] Intoxication leads to the "red man syndrome".[232-234]

Interactions. Rifampicin is an inducer of several enzymes in the cytochrome P-450 system,[235] leading to numerous interactions with multiple drugs. This action leads most frequently to faster elimination and lower concentrations of the companion drug, an effect opposite to that seen with the most common isoniazid interactions.

No important interactions between rifampicin and other anti-tuberculosis drugs have been found, with the exception of para-aminosalicylic acid preparations[139] containing a bentonite excipient.[175] Rifampicin reduces the incidence of pyrazinamide-associated arthralgia, not by increasing pyrazinamide elimination, but presumably through increased excretion of uric acid.[236] Numerous interactions with other medications have been described,[140,237-240] as detailed below.

Effect of rifampicin potentiated: Cotrimoxazole.[241] A pharmacokinetic study reported an inhibitory effect of the anti-retroviral indinavir on the metabolism of rifampicin.[242]

Effect of rifampicin opposed: No drug has been identified yet that opposes the action of rifampicin.

Effect of drug potentiated by rifampicin: Acetominophen hepatic failure and encephalopathy as a result of suspected potentiation by rifampicin has been reported.[105]

Effect of drug opposed by rifampicin:

- anti-arrhythmics such as quinidine,[243, 244] phenytoin,[148] and lorcainide;[245]

- anti-asthmatics such as theophylline.[246-248] The effect on theophylline pharmacokinetics might be opposed if rifampicin is given in combination with isoniazid (which has the opposite effect), so that theophylline clearance might be lowered, requiring a lower dose of theophylline in patients simultaneously treated with isoniazid and rifampicin;[165]

- anti-coagulants such as acenocoumarol,[249,250] phenprocoumon,[251,252] and warfarin;[253-257]

- anti-diabetics such as tolbutamide,[258,259] glidazide[260] or, to a lesser extent, glimeripide[261] and glyburide;[262]

- anti-fungals such as the imidazol derivatives fluconazol[263,263] and ketoconazol;[144]

- anti-malarials such as hydroxychloroquine[264] and quinine[265] and mefloquine;[266]

- antimicrobial agents such as chloramphenicol;[267]

- anti-retroviral agents such as protease inhibitors (saquinavir, ritonavir, indinavir, nelfinavir),[268,269] nevirapine (inconsistent),[270] and other antiviral agents such as zidovudine;[271,272]

- barbiturates such as hexobarbital;[259]

- benzodiazepins such as diazepam;[273]

- beta-blockers such as propranolol;[274]

- calcium blockers or antagonists such as verapamil[275-277] and nifedipine;[278]

- cardiac glycosides such as digoxin;[244,279,280]

- haloperidol;[162]

- hormones such as oral contraceptives,[281] gluococorticoids,[282,283], insulin,[284,285], and thyroxine;[286]

- immunosuppressants such as azathioprine,[140] cyclosporin,[287-290] and tacrolimus;[291]

- opioids;[292-294]
- vitamin K[295], vitamin D metabolism;[296]
- sulphasalazine.[297]

Pyrazinamide

Discovery. Following up on the anti-tuberculosis activity of nicotinamide (a vitamin B_3 precursor), further experimentation led to the synthesis of pyrazinamide by Kushner at the Lederle Laboratories, communicated in 1952 (figure 18)[298] and by Solotorovski at the Merck laboratories in the same year.[299] The synthesis of pyrazinoic acid, the active metabolite of pyrazinamide, had already been patented in 1934.[300]

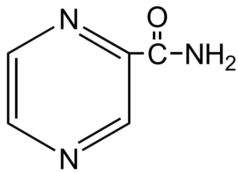

Figure 18. Chemical structure of pyrazinamide, synthesized by Kushner and collaborators in 1952.[298]

Activity, mechanism of action and resistance. Pyrazinamide is only active against mycobacteria, and among the genus, mycobacteria other than *M. tuberculosis* (including *M. bovis*) are naturally resistant.[301] It was recognized early on that pyrazinamide acts only in an acid environment.[302] The active derivative of pyrazinamide is pyrazinoic acid, which is preferentially accumulated in an acidic pH.[303] Pyrazinamide itself is not active against intracellularly growing *M. tuberculosis*:[304] only the accumulation of pyrazinoic acid through the action of the amidase pyrazinamidase by susceptible *M. tuberculosis* leads to its intracellular bactericidal action.[305]

The presence of both a functional pyrazinamidase and pyrazinamide transport system into *M. tuberculosis* have been postulated as prerequisites for drug susceptibility.[306] Relatively little is known about the actual drug target, although the NAD metabolic pathway has been postulated as one of the potential targets.[307]

Mutations in *pncA*, a gene encoding pyrazinamidase, cause resistance to pyrazinamide.[308,309] Resistance against pyrazinamide appears to develop rapidly if given as a single effective agent.[310] *M. bovis* is naturally resistant to pyrazinamide.[311]

Pharmacokinetics. After oral intake of 1500 mg of pyrazinamide, a peak level of 25 to 30 mg/L is achieved after one to one and a half hours (figure 19).[181] Pyrazinamide has one of the best penetrations into cerebrospinal fluid among the anti-tuberculosis medications.[312,313] About four per cent of pyrazinamide is excreted unchanged in urine and about 30% as pyrazinoic acid.[314] It is only slightly influenced by ingestion of antacids, but with a fatty meal T_{max} is delayed and C_{max} slightly lowered, although these effects are unlikely to bear clinical relevance.[315] Absorption of pyrazinamide is not influenced by food intake.

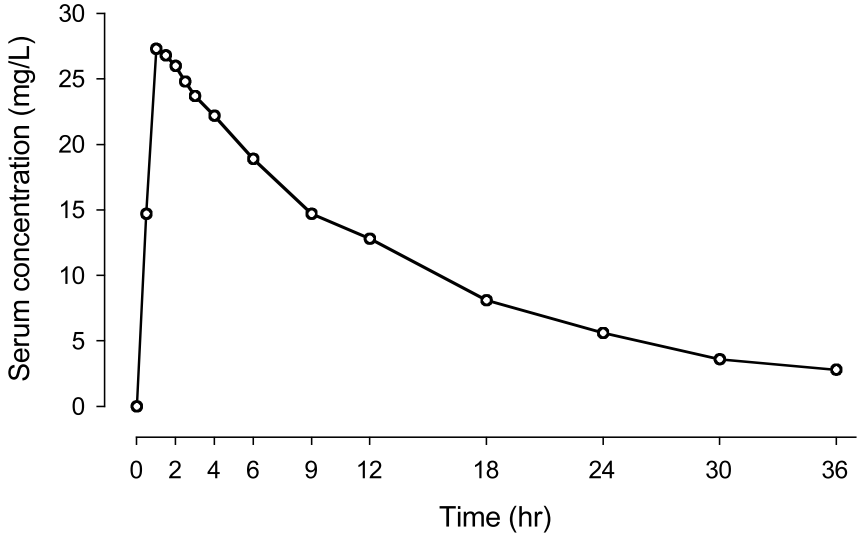

Figure 19. Pharmacokinetics of pyrazinamide in healthy volunteers. Reproduced from[181] by the permission of the publisher ASM Press.

Dosage. The dosages of pyrazinamide have varied greatly since its introduction. In early periods, the usual dosage was around 40 to 50 mg/kg body weight[316,317] and up to eight grams were given per day.[310] Such dosages frequently resulted in hepatotoxicity[317] and its early withdrawal from chemotherapy regimens. The current recommendations are to give 25 mg/kg body weight per day.[8,13]

Adverse drug events (table 4). The two major adverse drug events of pyrazinamide are hepatotoxicity[115,120,200,310,317-324] and interference with the metabolism of purine. The latter leads to decreased excretion and accumulation of uric acid, occasionally accompanied by gout-like arthralgia.[310,325,326] The suppressive effect of pyrazinoic acid on uric acid excretion is maximal for

Table 4. Summary of adverse reactions from pyrazinamide with estimated frequencies of occurrence. Note that these are estimates of frequencies which may vary across population groups.

Frequent (⩾ 5 per 100)	Common (⩾ 1 per 100 and < 5 per 100)	Infrequent (⩾ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
Arthralgias	Nausea	Hepatitis Rash Nausea	Sideroblastic anemia Lupus erythematosus Convulsions Photodermatitis

24 hours.[327] Thus, uric acid retention could be reduced by intermittent administration.

Relatively frequent events include rash[200,328,329] and nausea.[200] Rarer adverse drug events include sideroblastic anemia,[75,93] lupus erythematosus,[330] convulsions,[331] and photodermatitis.[332]

Interactions

Effect of pyrazinamide potentiated: Allopurinol increases plasma concentrations of pyrazinoic acid which is directly responsible for the inhibition of renal urate secretion.[333] Therefore, pyrazinamide-induced arthralgias are unresponsive to allopurinol.

Effect of pyrazinamide opposed: A potentially serious interaction may exist with zidovudin, with combination treatment leading to barely detectable pyrazinamide levels.[334] However, these findings have not been confirmed.

Effect of drug potentiated by pyrazinamide: None identified.

Effect of drug opposed by pyrazinamide: Pyrazinamide might antagonistically affect the action of medications that have a uricosuric effect such as acetylic salicylic acid, ascorbic acid, probenecid, and iodine containing radiocontrast offering preparations.[335,336]

Ethambutol

Discovery. The synthesis of ethambutol (figure 20) was reported in 1961.[337] Its excellent activity *in vitro* and *in vivo* against *M. tuberculosis* was reported in the same year.[338-340]

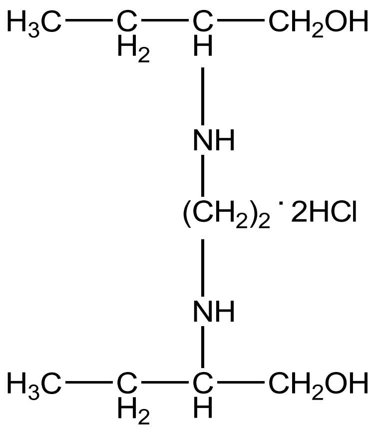

Figure 20. Chemical structure of ethambutol, reported by Thomas and collaborators in 1961.[337]

Activity, mechanism of action and resistance. Ethambutol is only active against mycobacteria.[340] Ethambutol is bactericidal on both extracellular and intracellular tubercle bacilli.[341] The MIC of ethambutol for *M. tuberculosis* is about 0.95 to 7.5 mg/L in broth and 1.9 to 7.5 mg/L on agar.[21,23]

Ethambutol specifically inhibits biosynthesis of the mycobacterial cell wall.[46] It acts on the biosynthesis of arabinogalactan, the major polysaccharide of the mycobacterial cell wall.[342] It inhibits the polymerization of cell wall arabinogalactan and of lipoarabinomannan.[343,344] It indirectly inhibits mycolic acid synthesis (by limiting the availability of arabinan for the mycolic acids to attach to)[345] and triggers a cascade of changes in the lipid metabolism of mycobacteria, leading to the disaggregation of bacteria clumps into smaller clusters.[346] It appears to be able to break down the "exclusion barrier" located in the *M. avium* cell wall and thus significantly enables the activity of other drugs, both intracellularly and extracellularly.[347,348]

The maximum proportion of ethambutol-resistant mutants able to grow during ethambutol monotherapy of an isoniazid-susceptible strain is estimated to be approximately 1 in 10^8.[53]

Pharmacokinetics. The absorption of ethambutol is rapid. Following a dosage of 25 mg/kg body weight, a peak serum concentration of 4 to 5 mg/L is achieved approximately two to four hours after administration (figure 21).[349,350] The drug is not extensively metabolized. Roughly 80% of ethambutol is eliminated by glomerular filtration and tubular secretion.[349-351]

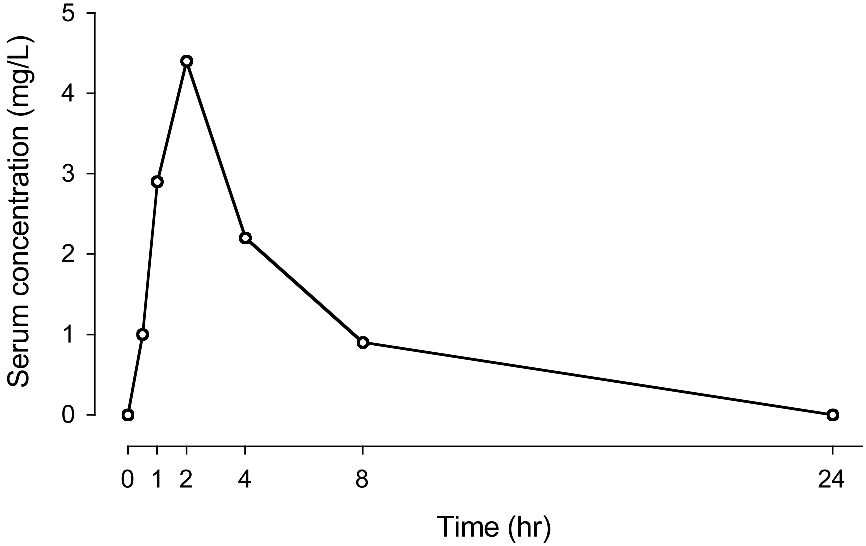

Figure 21. Pharmacokinetics of ethambutol in healthy volunteers. Reproduced from[349] by the permission of the publisher American Thoracic Society at the American Lung Association.

Ethambutol penetrates tissues rapidly and in high concentrations, including lung, liver and kidney in experimental tuberculosis.[352,353] It has poor penetration into cerebrospinal fluid and brain.[352] Renal failure decreases body clearance and increases serum half-life, and dose adjustment in such patients is mandatory.[354] High-fat meals alter the pharmacokinetics of ethambutol somewhat, but probably not importantly.[355]

Dosage. Although 15 mg/kg body weight in the continuation phase and 25 mg/kg body weight in the intensive phase have been recommended,[356] international consensus recommends 15 mg/kg (range 15 to 20 mg/kg) throughout[8,13] to obviate operational difficulties in changing the dosage and to further reduce toxicity.

Adverse drug events (table 5). The most important adverse drug event of ethambutol is ocular toxicity, first reported in 1962,[357] and followed by numerous accounts.[358-376] It is postulated that many instances of ethambutol's ocular toxicity might be explained by its binding to zinc or copper.[152,377] Two types of ocular toxicity (optic neuropathy) from ethambutol have been described.[372,378] The more common form is a noninflammatory axial fiber disease involving central fibers of the optic nerve.[378] Patients with central or axial toxicity have reduced visual acuity, central scotoma,

Table 5. Summary of adverse reactions from ethambutol with estimated frequencies of occurrence. Note that these are estimates of frequencies, which may vary across population groups.

Frequent (⩾ 5 per 100)	Common (⩾ 1 per 100 and < 5 per 100)	Infrequent (⩾ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
		Retrobulbar neuritis Periaxial ocular toxicity	Aplastic anemia Eosinophilic pneumonia Thrompocytopenia Hyperuricemia

and loss of ability to see green (reported as white or gray). The ability to see red, which has been reported as pink, has occasionally been affected. Those with periaxal toxicity have a defect in the peripheral isopters of their field of vision, with little or no decrease in visual acuity and normal red-green color discrimination. The optic discs and the fundi appeared normal in both types of toxicity. The incidence of ocular toxicity is dose dependent.[372,379] The chance of visual recovery appears to be related to the total dose administered and the initial degree of loss of vision.[370] It has been recommended not to use ethambutol in children too young for objective tests for visual acuity.[363] There is, however, no evidence that children are particularly prone to ocular toxicity,[380] and ethambutol may thus be used in children. However, as children might be less likely to report ocular toxicity, particular caution may be warranted. Ocular toxicity is usually reversible upon cessation of ethambutol administration, but recovery might be protracted.[368] Compared to the frequency of fatal outcome resulting from anti-tuberculosis medication, the occurrence of blindness from ethambutol is rare.[367]

Ethambutol may cause aplastic anemia,[367] but this is exceedingly rare. Ethambutol is a rare cause of pulmonary infiltrates with eosinophilia,[381] rash,[367,382] exacerbation of lupus erythematosus,[330] thrombocytopenia[383] and hyperuricemia.[384]

Interactions

Effect of ethambutol potentiated: Although listed in some text books, ethionamide and isoniazid have not been conclusively shown to increase ethambutol ocular toxicity.

Effect of ethambutol opposed: Aluminum-magnesium antacid reduces ethambutol resorption, and lowers and delays, respectively, C_{max} and T_{max}.[355]

Effect of drug potentiated by ethambutol: None identified.

Effect of drug opposed by ethambutol: None identified.

Streptomycin

Discovery. Selman A Waksman isolated *Actinomyces griseus* from soil in 1916,[385] later termed *Streptomyces griseus*.[386] In 1939, Waksman's research group started an extensive study of substances produced by soil organisms which destroyed other soil organisms (termed antibiotics by Waksman).[387] The first antibiotic isolated from an *Actinomyces* species was actinomycin in 1940.[386] In 1942, streptothricin was isolated.[386] In September 1943 *Streptomyces griseus* was re-identified.[388] and the isolation of streptomycin was reported in January 1944 (figure 22).[389] It is noteworthy that the original table presenting the antimicrobial activity of streptomycin accorded a single, inconspicuous line to its effect on *M. tuberculosis* and this finding found no mention in the text (figure 23).[390] But in the same year Schatz and Waksman published a paper devoted particularly to the action of streptomycin on *M. tuberculosis*.[391] In 1952, Waksman received the Nobel Prize for Physiology or Medicine.[386,387]

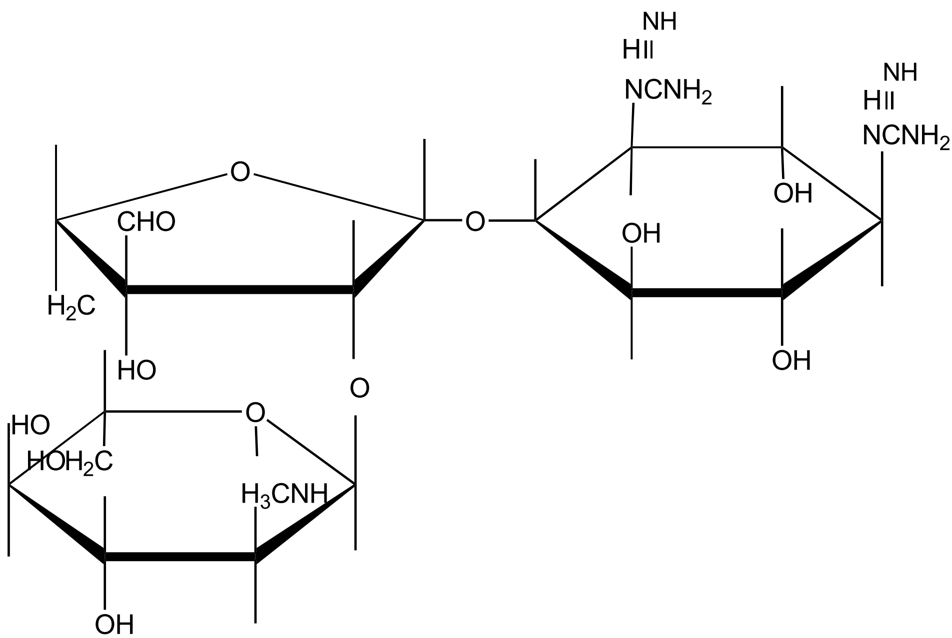

Figure 22. Chemical structure of streptomycin, isolated by Schatz, Bugie, and Waksman and reported in 1944.[390]

TABLE III.
Comparative Bacteriostatic Spectra of Streptomycin and Streptothricin.
On basis of crude, ash-free dry material.

		Units of activity per gram ash-free dry material	
Organism	Gram stain	Streptomycin x 1000	Streptothricin x 1000
B. subtilis O	+	125	500
B. mycoides O	+	250	< 3
B. mycoides 317-911	+	20	< 3
B. cereus	+	30	< 3
B. mesentericus	+	15	–
B. megatherium	+	100	150
S. aureus	+	15	200
S. lutea	+	100	150
M. phlei	+	100	50
M. tuberculosis	+	30	–
Phytomonas pruni	–	100	400
Listerella	–	10	–
Shigella gallinarum	–	–	150
E. coli	–	25	100
S. marcescens	–	25	5
A. aerogenes	–	10	50
P. vulgaris	–	10	50
S. aertycke	–	2.5	–
S. schottmülleri	–	–	50
Ps. fluorescens	–	2	< 3
Ps. aeruginosa	–	1	< 3
Cl. butylicum	–	3	< 3

Figure 23. Original table published when the isolation of streptomycin was reported. Reproduced from[389] by the permission of the publisher Society for Experimental Biology and Medicine.

Activity, mechanism of action and resistance. Streptomycin has a broad-spectrum activity against many gram-positive and gram-negative microorganisms and against various species of mycobacteria. Its effect on *M. tuberculosis in vitro* and in the guinea pig was reported as early as December 1944,[392] and a preliminary report on its usefulness in the treatment of tuberculosis in man in September 1945 by Feldman and Hinshaw,[393,394] followed by a more extensive report in 1946.[395] The MIC of *M. tuberculosis* is 0.25 to 2.0 mg/L.[21,56] It had been surmised that streptomycin is active only against extracellularly growing tubercle bacilli, but this notion has not been borne out by experiments which have demonstrated its activity against bacilli residing inside macrophages as well.[396]

Streptomycin inhibits protein synthesis of *M. tuberculosis*. Streptomycin acts on ribosomes and causes misreading of the genetic code, inhibition of translation of mRNA, and aberrant proofreading.[397]

It was demonstrated a half century ago that a strain may contain different variants with different levels of susceptibility (or resistance) to streptomycin.[398] Interestingly, problems with molecular techniques to properly identify clinically relevant resistance led some authors to conclude that the seemingly outdated use of drug-containing media described in these early reports[398] may again become a valid procedure.[399] Resistance results from a limited number of missense mutations in the *rrs* gene (16S rRNA) or in the *rpsL* gene (ribosomal protein S12).[400]

The maximum proportion of streptomycin resistant mutants able to grow during streptomycin monotherapy of an isoniazid susceptible strain is estimated to be approximately 1 in 10^8.[53]

Pharmacokinetics. Streptomycin is not at all, or only insignificantly, absorbed from the gut and its administration is parenteral. Following intramuscular administration, resorption is rapid and maximum serum concentrations are achieved within one to two hours (figure 24).[183,401] Streptomycin, like all aminoglycosides, is excreted by glomerular filtration. When kid-

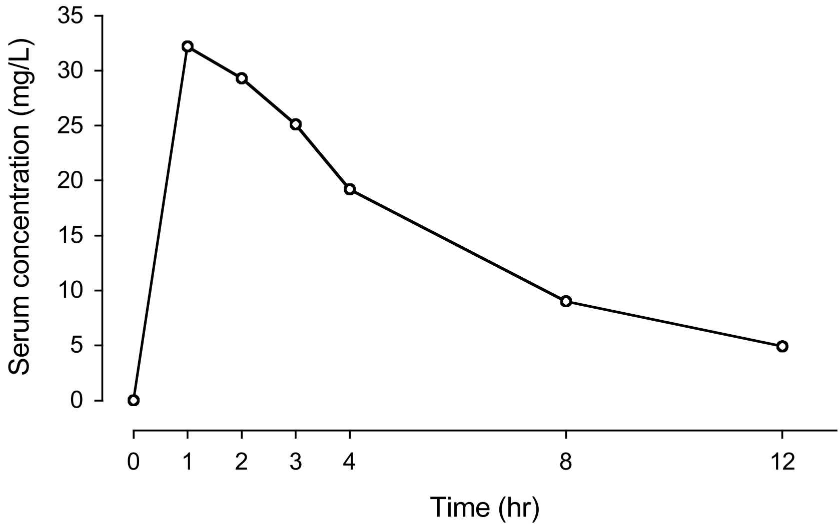

Figure 24. Pharmacokinetics of streptomycin in tuberculosis patients. Reproduced from[183] by the permission of the publisher American Thoracic Society at the American Lung Association.

ney function is impaired, the dosage must be adjusted, as excretion is exclusively renal.[56] Streptomycin has a limited ability to penetrate membranes, resulting in low concentrations of cerebrospinal fluid.[402]

Dosage. After large doses (up to three grams daily were given in the early trials[395]) toxicity was frequent and dosage reductions were sought that would not compromise efficacy.[403] The current recommendation is to give 15 mg/kg body weight (range 12 to 18),[8, 13] with a usual maximal dose of one gram in adults. The dosage is reduced in elderly patients. It has to be administered parenterally, usually by intramuscular injection, but intravenous application is preferred by some because of higher peak but lower trough levels.[404]

Adverse drug events (table 6). The main adverse effect of streptomycin is vestibulo-cochlear toxicity, which is usually[323,403,405] but not always, dose-dependent.[406] Hypersensitivity reactions are also relatively frequent and important,[56] not only in patients, but also in health care personnel administering the medication.[407] Because of its penetration into amniotic fluid and its ototoxic effect on the fetus,[408] streptomycin should never be administered to pregnant women.[56] Streptomycin may cause neuromuscular blockade,[409] not reversed by neostigmine.[410]

Table 6. Summary of adverse reactions from streptomycin with estimated frequencies of occurrence. Note that these are estimates of frequencies, which may vary across population groups.

Frequent ($\geqslant$ 5 per 100)	Common ($\geqslant$ 1 per 100 and < 5 per 100)	Infrequent ($\geqslant$ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
Vestibular toxicity	Cochlear toxicity Hypersensitivity reactions	Renal damage	Neuromuscular blockade

Interactions

Effect of streptomycin potentiated: Ototoxicity of streptomycin is increased by diuretics such as furosemide[411] and ethacrynic acid.[412]

Effect of streptomycin opposed: None identified.

Effect of drug potentiated by streptomycin: Like other aminoglycosides, streptomycin has a neuromuscular blocking effect[413] and may lead to prolonged respiratory depression following curare-like drugs, such as pancuronium,[414] succinylcholine or tubocuronium[415] or non-depolarizing relaxants such as diallyl-nortroxiferine.[416]

Effect of drug opposed by streptomycin: None identified.

Thioacetazone

Discovery. Freund and Schander synthesized benzaldehyde-semicarbazone in 1896 and 1902, respectively.[417,418] From this basic compound, derivatives with anti-tuberculosis properties were later developed. After investigations on sulphonamides had revealed that thiazoles and thiodiazole derivatives exerted some activity against mycobacteria,[419] Domagk and collaborators at the Bayer Laboratories synthesized a new class of drugs, the thiosemicarbazones, of which thioacetazone (figure 25) was shown to be active against tubercle bacilli.[420]

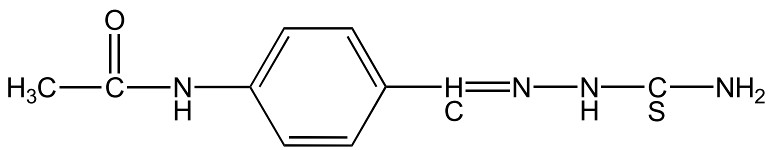

Figure 25. Chemical structure of thioacetazone, synthesized by Domagk and collaborators in 1946.[420]

Among the numerous derivatives of semicarbazones, three have found particular activity against *M. tuberculosis*:[421]

p-acetylamino-benzaldehyde-semicarbazone;

p-methoxy-benzaldehyde-semicarbazone;

p-ethylsulfone-benzaldehyde-semicarbazone.

Of these, p-acetylamino-benzaldehyde-semicarbazone, tested under the name TB I, now known as thioacetazone, became the most widely used semicarbazone.

Activity, mechanism of action and resistance. Thiosemicarbazones, including thioacetazone, are active only against mycobacteria, and favorable *in vitro* and *in vivo* results against *M. tuberculosis* were published in 1949.[419] The observed *in vitro* susceptibility of *M. tuberculosis* varies considerably, depending on the technique of susceptibility testing and the origin of the strain.[422] An observation made in a comparison of tubercle bacilli isolated from India and in the United Kingdom showed that Indian strains were considerably less susceptible to thioacetazone than strains from the United Kingdom.[423] This geographic variation was subsequently confirmed.[424-427] The susceptibility of strains may vary even within the same country.[428] The correlation between *in vitro* and *in vivo* results is often very poor.[429]

The mode of action of thioacetazone has not been elucidated,[430] although it has been shown that thioacetazone forms copper complex salts and it has been postulated that these might represent the effective compound.[431]

There is partial cross-resistance between thioacetazone and ethionamide.[422]

Pharmacokinetics. Thioacetazone is rapidly absorbed and maximum serum concentrations are achieved about four hours (range two to six hours) after ingestion,[432-434] and is eliminated from serum almost completely within 24 hours (figure 26).[434]

Dosage. The currently recommended dosage of thioacetazone is 2.5 mg/kg body weight per day.[13] Only daily treatment is recommended.

Adverse drug events (table 7). Thioacetazone frequently causes adverse drug events,[435-438] which occur in up to 40% of patients. The most fre-

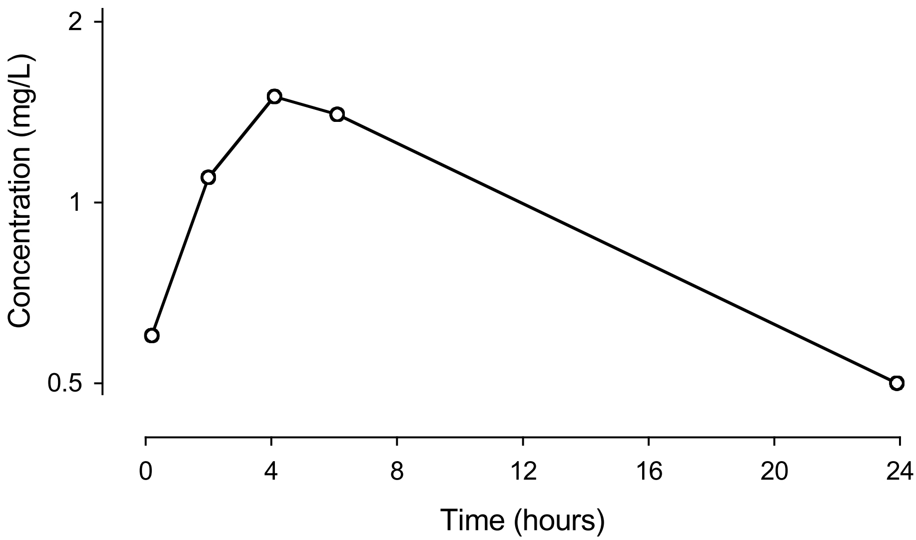

Figure 26. Pharmacokinetics of thioacetazone in healthy volunteers.[434]

quent adverse drug events are gastrointestinal (weight loss, nausea, vomiting),[421] central nervous system,[421] and cutaneous adverse drug events.[435] An international investigation in 13 countries into adverse drug events due to thioacetazone was coordinated by the British Medical Research Council.[439] The frequency of adverse drug events in that study was 21% compared to eight per cent of patients who were not receiving thioacetazone. More than half of the adverse drug events were mild. The study confirmed earlier observations that gastrointestinal and neurologic adverse drug events (headache, blurred vision, perioral numbness, mental symptoms, and peripheral nerve symptoms) were the most frequent, followed by cutaneous adverse drug events. Two out of 1,000 patients developed agranulocytosis.[439] The frequency of adverse cutaneous reactions varied in different populations. Differences in nutrition may be a contributor to this observation as, for example, consumption of cheese and fish appear to increase the risk of cutaneous and neurologic adverse drug events.[440]

It was recognized relatively early that patients with HIV infection have increased susceptibility to developing toxic epidermal necrolysis when given sulfur-containing medications such as sulfadoxine[441] or sulfamethoxazole.[442] The causal relationship between the occurrence of cutaneous adverse reactions and the use of thioacetazone has been elegantly demonstrated (figure 27).[443] Reactions may present as pruritus without rash, rash without epidermolysis, and most seriously as toxic epidermal necrolysis.[444] The latter has a case fatality rate of 20% to 30%, depending on the selection of cases (figure 28). Both reactions and deaths occur relatively early in the course of administration, with more than half occur-

Table 7. Summary of adverse reactions from thioacetazone with estimated frequencies of occurrence. Note that these are estimates of frequencies, which may vary across population groups.

Frequent (⩾ 5 per 100)	Common (⩾ 1 per 100 and < 5 per 100)	Infrequent (⩾ 1 per 1,000 and < 1 per 100)	Rare (< 1 per 1,000)
Weight loss Nausea Vomiting Itching Mental disturbances Headache Blurred vision Perioral numbness	Toxic epidermal necrolysis (in HIV) infected patients)	Toxic epidermal necrolysis (in non HIV) infected patients)	Agranulocytosis

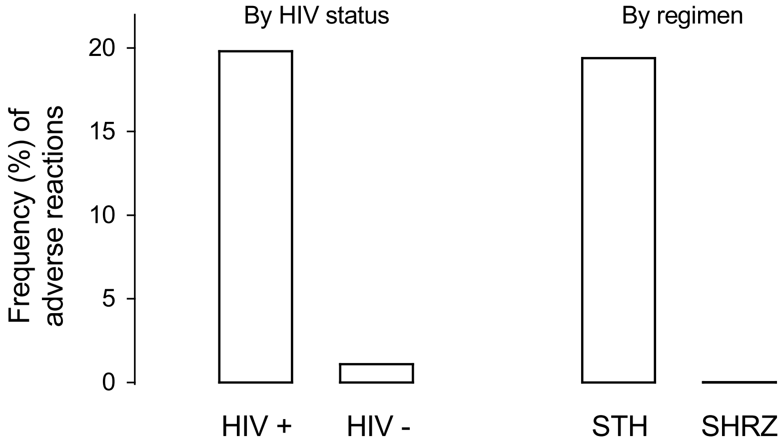

Figure 27. Demonstration of the causal relation between cutaneous adverse reaction and thioacetazone, by HIV status and regimen.[443]

ring within the first three weeks of treatment (figure 29) (Tanzania National Tuberculosis / Leprosy Programme, IUATLD, unpublished data). Numerous accounts have now been published that confirm the potential seriousness of the utilization of thioacetazone in HIV infected tuberculosis patients.[445-448] While most adverse reactions are toxic effects, cutaneous adverse reactions appear to be largely idiosyncratic, and are not influenced by reducing the dosage.[421]

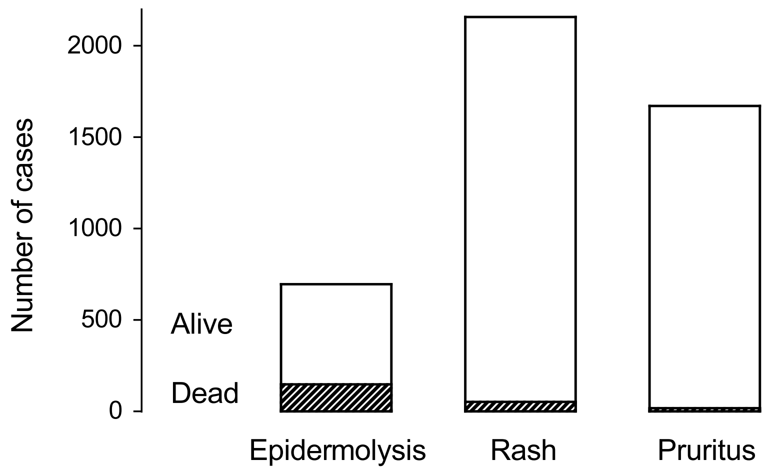

Figure 28. Adverse cutaneous reactions and deaths associated with the use of thioacetazone, by severity of reaction. Tanzania National Tuberculosis / Leprosy Programme and IUATLD, unpublished data.

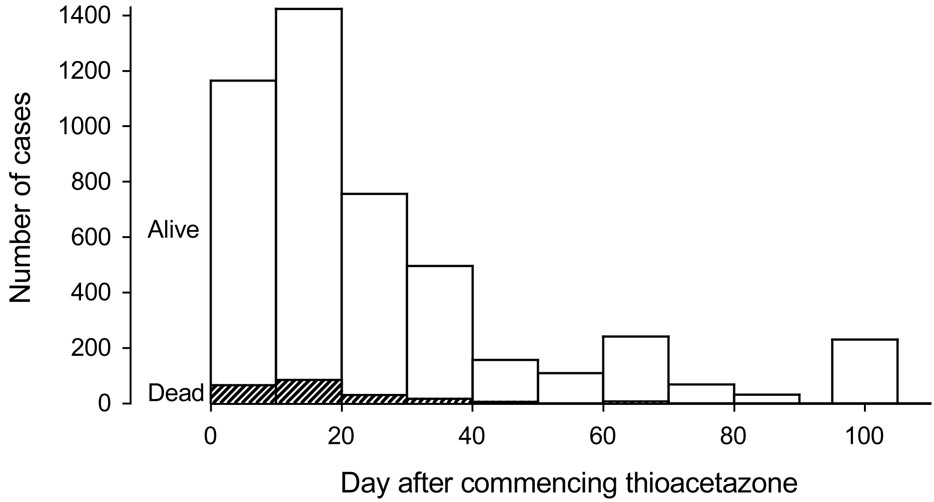

Figure 29. Adverse cutaneous reactions and deaths associated with the use of thioacetazone, by duration of thioacetazone intake. Tanzania National Tuberculosis / Leprosy Programme and IUATLD, unpublished data.

Because of this strong association, thioacetazone should never be given to patients known to be HIV infected.[13] It is also sensible policy to relinquish its use in countries where the HIV prevalence among tuberculosis patients is known to be high.[449,450]

Interactions. Interactions between thioacetazone and other medications are not known.

Fixed-dose combinations

Tuberculosis needs to be treated with multiple drugs. It is thus not surprising that efforts have been undertaken to develop so called fixed-dose combinations. Fixed-dose combinations simplify treatment, minimize prescription errors, and simplify supply management.[191,451] As fixed-dose combinations containing rifampicin may be particularly prone to posing difficulties in assuring bioavailability, specific requirements have been outlined to ensure their quality.[452,453]

The dosages of the individual components in a fixed-dose combination are of critical importance to prevent both over- and under-dosage. The WHO recommends the dosages per tablet as summarized in table 8.[454,455]

Table 8. Fixed-dose combinations (FDC) of antituberculosis drugs and dosages of individual drugs as recommended by WHO.[454]

FDC per tablet	For daily use (mg drug)	For three-times weekly use (mg drug)
{TH}	150 T + 300 H	
	50 T + 100 H *	–
{EH}	400 E + 150 H	–
{RH}	300 R + 150 H	–
	150 R + 75 H	150 R + 150 H
	60 R + 30 H *	60 R + 60 H
{RHZ}	150 R + 75 H + 400 Z	150 R + 150 H + 500 Z
	60 R + 30 H + 150 Z *	–
{RHZE}	150 R + 75 H + 400 Z + 275 E	–

* For pediatric use
Abbreviations: T = thioacetazone; H = isoniazid; E = ethambutol; R = rifampicin; Z = pyrazinamide.

Fixed-dose combinations will guarantee that drugs cannot be taken separately. They thus reduce the potential of acquisition of drug resistance. However, prescription errors or selective use of the number of tablets by the patient may lead to sub-inhibitory concentrations of all drugs. The need for direct observation of drug intake is thus not obviated with their introduction into national programs.

Principal prerequisites for an efficacious anti-tuberculosis drug

It is general practice to define the action of antimicrobial agents as “bacteriostatic” or “bactericidal”. This terminology might not be that useful in describing the activity of anti-tuberculosis medications. Mitchison has proposed the utility of defining three prerequisites for an anti-tuberculosis drug (table 9):[456]

- Early bactericidal activity;
- Sterilizing activity;
- Ability to prevent emergence of resistance to the companion drug.

Table 9. Grading of activities of anti-tuberculosis drugs. Reproduced from [456] by the permission of the publisher Churchill Livingstone.

Extent of activity	Prevention of resistance	Early bactericidal	Sterilizing
High	isoniazid	isoniazid	rifampicin
	rifampicin		pyrazinamide
		ethambutol	
	ethambutol	rifampicin	isoniazid
	streptomycin		
		streptomycin	streptomycin
	pyrazinamide	pyrazinamide	thioacetazone
Low	thioacetazone	thioacetazone	ethambutol

Early bactericidal activity

Early bactericidal activity is defined as the ability of the drug to kill tubercle bacilli in the first few days of treatment.[24,25,456] In a study measuring sputum colony counts in newly diagnosed tuberculosis patients treated with a multitude of monotherapy and multidrug therapy regimens during the first two weeks of treatment, no other drug or drug combination was superior to isoniazid alone in the first two days of treatment (figures 30 and 31).[24,25] This high early bactericidal activity of isoniazid was subsequently confirmed.[26,457] It is likely that the rapid reduction in infectiousness seen in

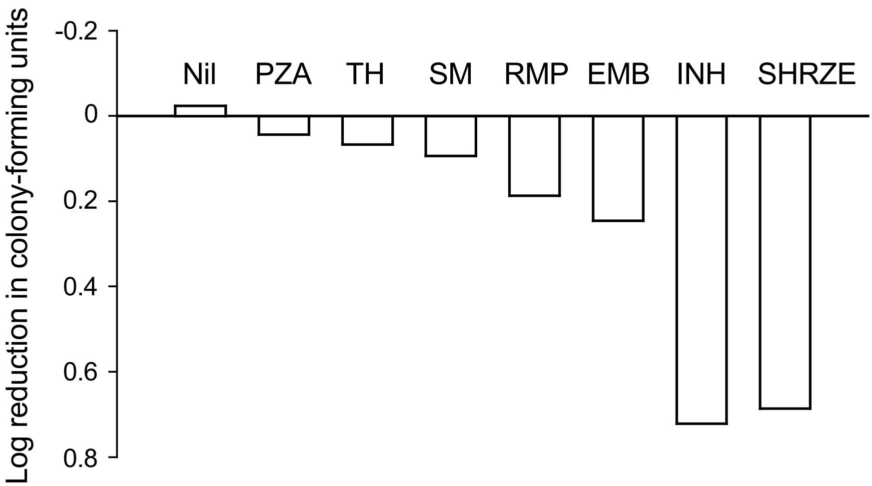

Figure 30. Early, two-day bactericidal activity of anti-tuberculosis drugs, measured as the reduction in colony-forming units in sputum.[24]

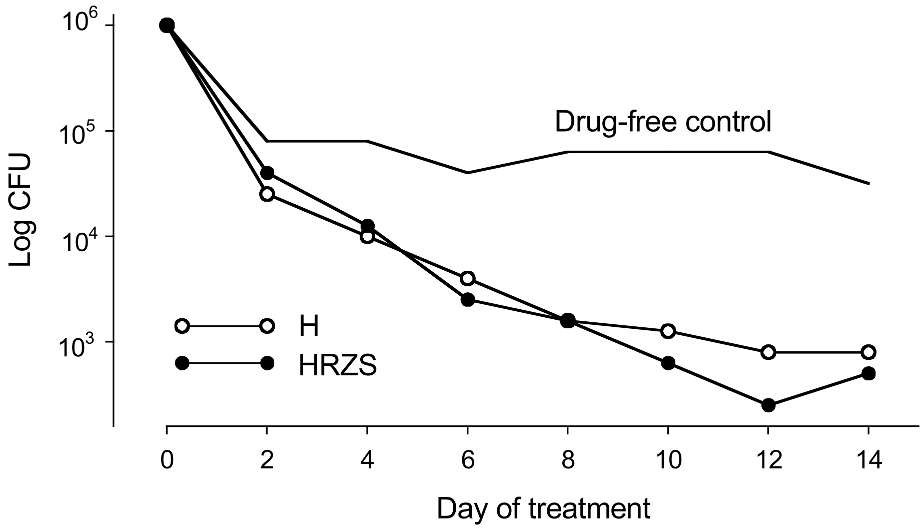

Figure 31. Bactericidal activity of isoniazid compared to a four-drug combination therapy over the first two weeks of treatment.[25]

tuberculosis patients once placed on chemotherapy[29,30,458,459] is largely due to the use of isoniazid.

Sterilizing activity

Sterilizing activity is defined as the ability to remove so called "persisters", once the large bulk of rapidly growing organisms has been killed. A model presented by Grosset clarifies these two major components of chemotherapy (figure 32).[460] Inability to destroy rapidly growing bacilli, located largely extracellularly, leads to treatment failure, while inability to eradicate persisters leads to relapse subsequent to treatment completion. Persisters are bacilli that have a lower metabolic activity and thus replicate much more slowly than bacilli found in cavity linings. It was postulated that the efficacy of rifampicin as a sterilizing agent was due to its activity on special populations.[461] This was tested in an experiment reproducing conditions appropriate for high and low metabolism of tubercle bacilli, respectively, using temperature control as the means.[462] At body temperature, there was only slightly higher activity of rifampicin over isoniazid during a seven-day period. If pulsed temperature elevation was applied for only one hour per day to increase metabolism, rifampicin was considerably more active than isoniazid (figure 33).[462]

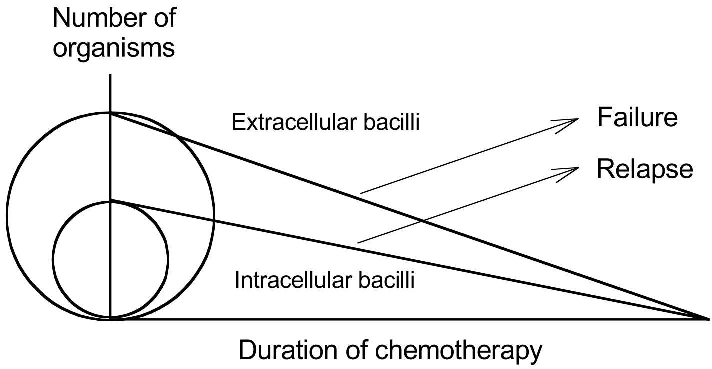

Figure 32. Schematic presentation demonstrating the mechanisms for treatment failure and disease relapse. Reproduced from[460] by the permission of the publisher Excerpta Medica.

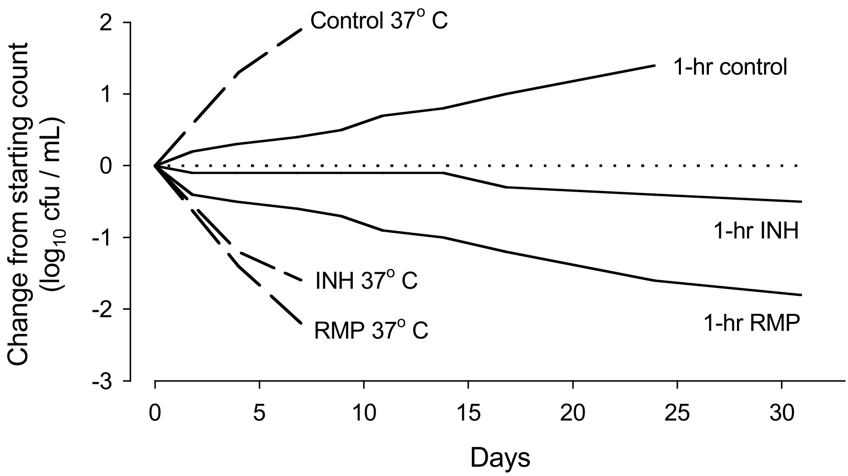

Figure 33. Comparative activity of isoniazid and rifampicin in experiments mimicking high and low metabolic activity. Reproduced from[462] by the permission of the publisher American Thoracic Society at the American Lung Association.

Ability to prevent emergence of resistance to the companion drug

Prevention of the emergence of drug resistance is defined as the ability of a drug to prevent selection of mutants resistant to the companion drug. Not every anti-tuberculosis drug has the same ability to prevent emergence of resistance against a companion drug in clinical practice (figure 34).[463]

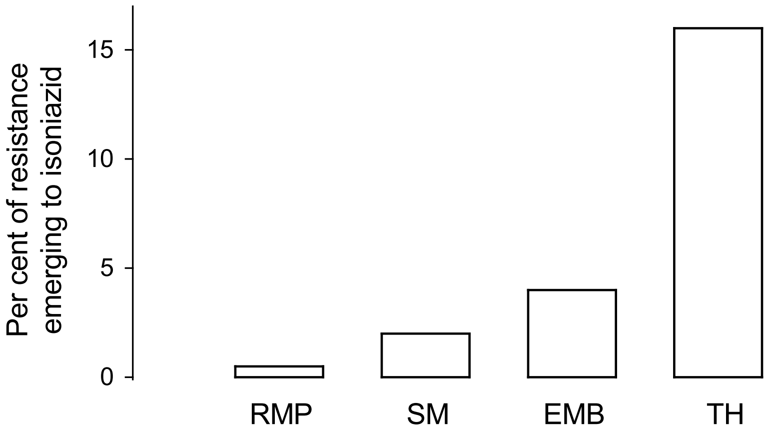

Figure 34. Ability of an anti-tuberculosis drug to prevent as a companion drug the emergence of isoniazid resistance.[463]

In summary, each anti-tuberculosis medication can be assigned a grading scale according to these three properties (table 9).[456] This explains the reason for the high efficacy of chemotherapy regimens incorporating isoniazid, rifampicin, and pyrazinamide.

Emergence of anti-tuberculosis drug resistance

The most convincing evidence for the mechanism of emergence of clinically significant drug resistance is effective or functional monotherapy. This and related mechanisms are discussed in some detail.

There are several mechanisms by which tubercle bacilli may acquire resistance:[464]

- Effective or functional monotherapy;
- Monotherapy during sterilization of special populations;
- Differences in bactericidal activity;
- Sub-inhibitory concentrations;
- Differences in post-antibiotic lag phase.

Effective or functional monotherapy

The first clinical trial in tuberculosis was by necessity limited to the first drug developed against tuberculosis, streptomycin. In the trial conducted by the British Medical Research Council, a total of 109 patients were admitted to the streptomycin arm.[465] Serial susceptibility testing results were available among 41 of these patients, 35 of whom acquired streptomycin resistance (figure 35). As the testing interval between susceptible and resistant cultures varied to a considerable extent among individual patients, the point in time when resistance emerged cannot be known precisely. For this reason, the event was estimated to have occurred at the mid-point between the time the last susceptible and the first resistant culture was obtained. Resistance had already started to emerge after three weeks of treatment. By the time a patient had received two months of streptomycin monotherapy, the probability that drug resistance had been acquired exceeded 60%.

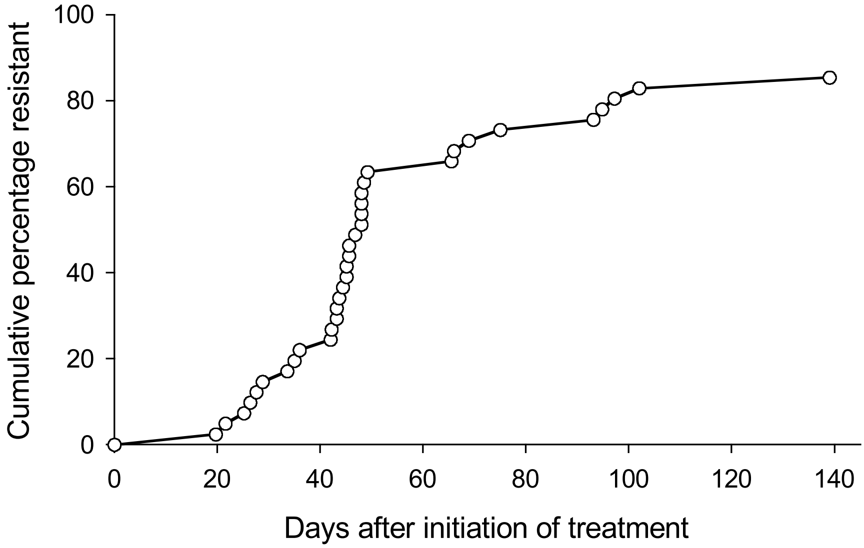

Figure 35. Emergence of streptomycin resistance during monotherapy in the British Medical Research Council trial.[465]

The explanation for this phenomenon is that among the many susceptible bacilli present in cavitary disease, spontaneous mutations occur at a given probability for each drug that convey resistance to that drug. The bacterial populations found in cavitary lesions obtained from resected lung tissue of patients were of the order of 10^7 to 10^9 bacilli, whereas those found in caseous foci did not exceed 10^2 to 10^4 bacilli.[466] It has been experimentally demonstrated that it is selection of these mutants rather than adaptation to the medication.[467] In a cavitary lesion containing 10^8 organisms, there will be around 10^2 isoniazid resistant mutants (i.e., one in a million) with the opportunity to replicate and become the dominant strain while the susceptible organisms are being killed off (figure 36).[468,469]

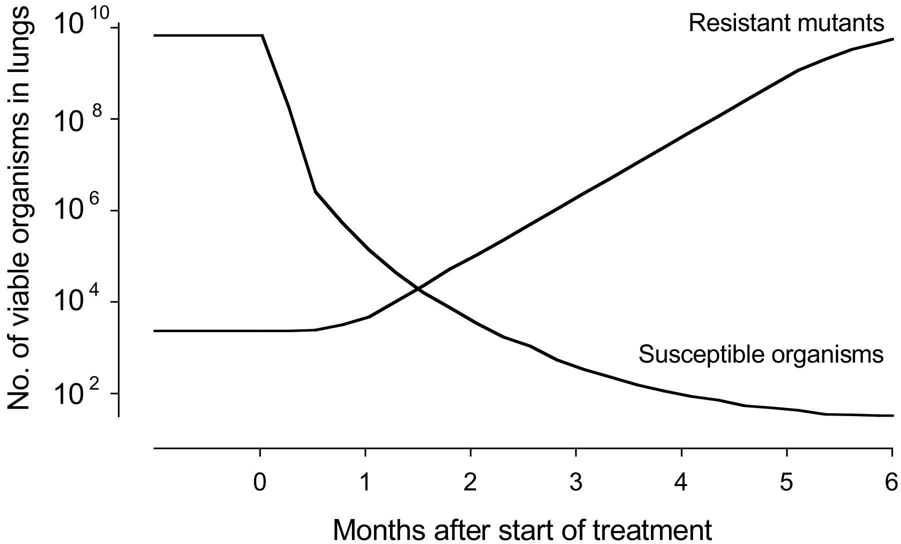

Figure 36. Diagrammatic presentation of the emergence of resistance to isoniazid during isoniazid monotherapy. Reproduced from[469] by the permission of the publisher Churchill Livingstone and the author.

Monotherapy during sterilization of special populations

Not all drugs work equally well on all bacillary sub-populations. These sub-populations are exemplified in figure 37.[456] None of the drugs works on the "dormant" or "latent"[470] sub-population. Other specific sub-populations are the target of some drugs, such as pyrazinamide, which is active only in an acid environment. If, for instance, a patient with an initially isoniazid-resistant strain receives isoniazid, pyrazinamide, and ethambutol, the sub-population hypothesis would suggest that the patient's large bulk of rapidly metabolizing organisms is treated with ethambutol monotherapy. As there will be effective monotherapy in these special populations, resistant mutants should have a survival benefit.[464]

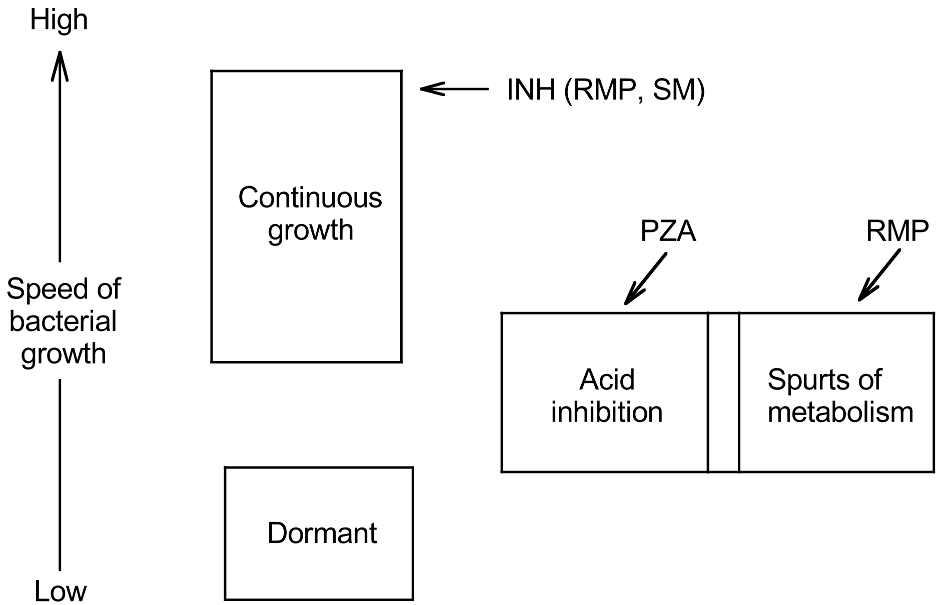

Figure 37. Special population hypothesis, indicating those bacterial populations at the start which are killed by the various drugs. Reproduced from[456] by the permission of the publisher Churchill Livingstone.

Differences in bactericidal activity

Isoniazid has the highest early bactericidal activity of all of the anti-tuberculosis drugs. Thus, isoniazid-resistant mutants may have a selection advantage over a two-day period. This is not usually relevant, as this advantage is overcome over the ensuing period. However, should it happen that treatment is stopped after two days and subsequently resumed for another two-day period, the proportion of isoniazid-resistant mutants will have increased at the end of each cycle (figure 38).[464]

Sub-inhibitory concentrations

Whenever sub-inhibitory concentrations of a drug A are being taken, growth of bacilli susceptible to drug A will be mildly suppressed and their natural re-growth retarded if it is stopped. This does not apply to mutants resistant to drug A. They will not be affected at all by drug A but only by other drugs given simultaneously (figure 39).[464] The mutants resistant to drug A will thus have a selective advantage. This might not be an uncommon scenario as the number of tablets required to be ingested (including

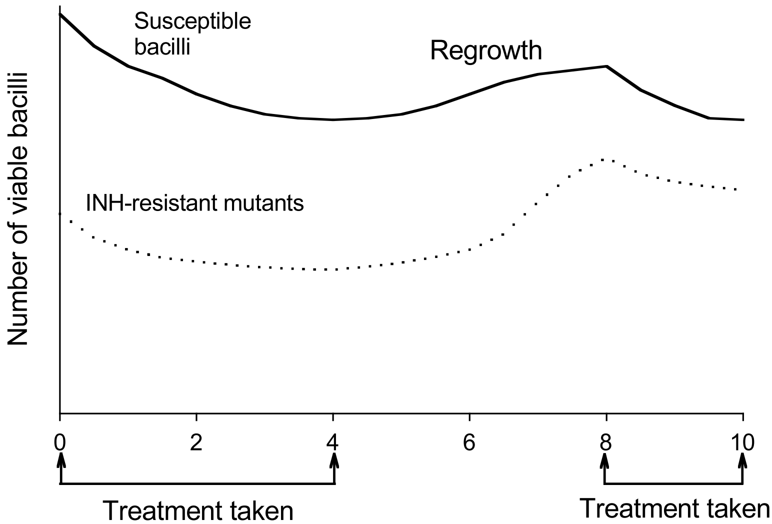

Figure 38. Bactericidal effects during two successive initial two-day phases of treatment with isoniazid and rifampicin. Reproduced from[464] by the permission of the publisher International Union Against Tuberculosis and Lung Disease.

fixed-dose combination tablets) is large, and during self-administration patients might be tempted to take some but not all of the tablets. Mitchison[464] points out that this mechanism would be most effective for

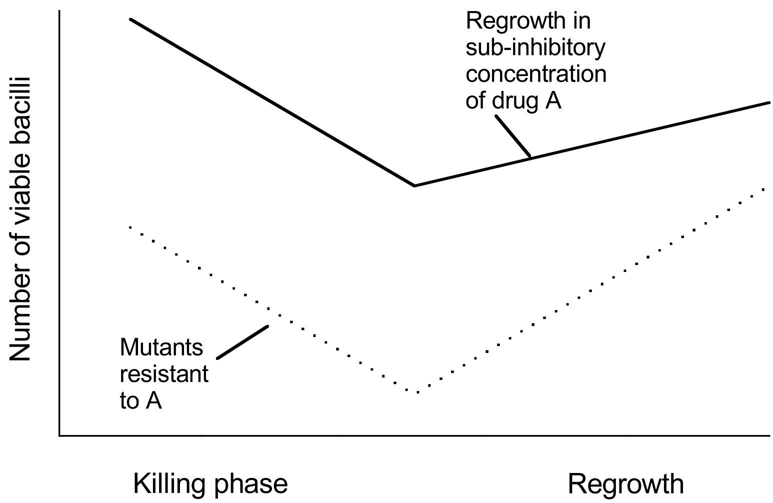

Figure 39. Sub-inhibitory concentrations of anti-tuberculosis drugs during regrowth. Reproduced from[464] by the permission of the publisher International Union Against Tuberculosis and Lung Disease.

drugs with a high therapeutic margin such as isoniazid, as the effective half-life at sub-inhibitory concentrations would persist longer than that of other drugs.[471] The difference in pharmacokinetics of the drugs given together (in a combination tablet or in separate preparations) may be such that after several hours only one of the drugs is still active, leading to functional monotherapy. Sub-inhibitory concentrations of one or more drugs may be observed in patients with impaired gastrointestinal absorption.

Differences in post-antibiotic effect (lag phase)

When drugs are stopped, the length of time it takes bacilli to restart growth (post-antibiotic lag phase) differs for different anti-tuberculosis medications (figure 40).[472] Thus, for example, mutants resistant to drug A (with a long lag phase) are killed by drug B (with a short lag phase). Mutants resistant to drug A will thus start re-growth earlier when both drugs are stopped and obtain a selective advantage at the end of the cycle (figure 41).[464]

Clinical trials in the treatment of pulmonary tuberculosis

Since the discovery of streptomycin, clinical trials with anti-tuberculosis medications in various combinations have been carried out throughout the world to ascertain the shortest possible and best tolerated efficacious treatment regimens. The standard approach for studying a new drug or drug

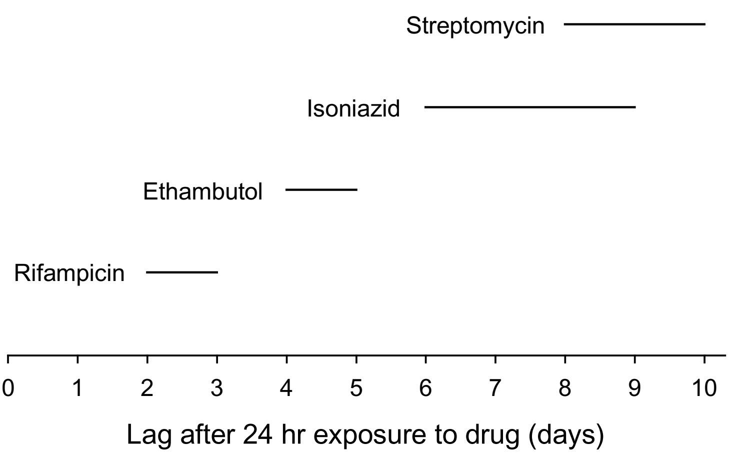

Figure 40. Post-antibiotic effects with *M. tuberculosis* lag periods before re-commencement of growth after exposure in 7H10 medium.[472]

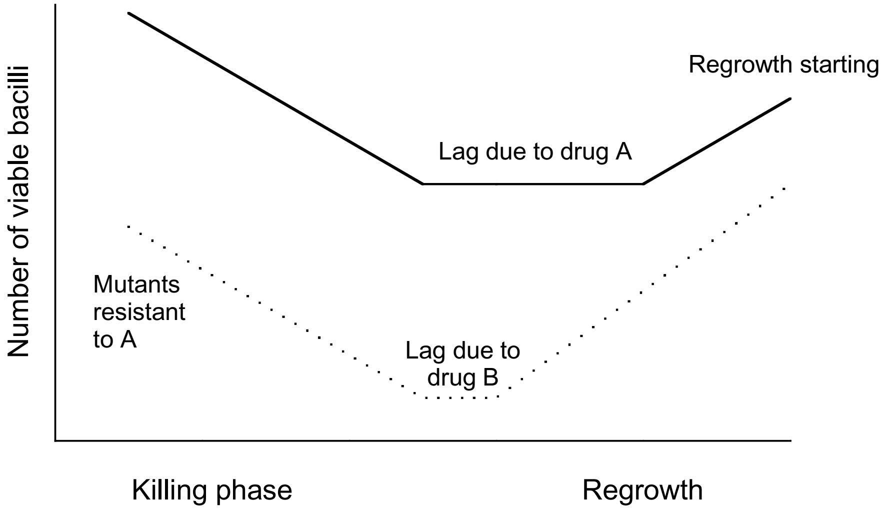

Figure 41. Bacteriopausal effects during regrowth of *M. tuberculosis.* Reproduced from[464] by the permission of the publisher International Union Against Tuberculosis and Lung Disease.

combination is the randomized controlled clinical trial, whereby a group of patients is randomly assigned to the new regimen (experimental arm) or to the standard regimen (control arm). The element of randomization to reduce selection bias was actually first introduced in tuberculosis, with the first streptomycin trial of the British Medical Research Council.[465,473,474]

Clinical trials have been conducted all over the world by different organizations and institutions. However, there can be little doubt that the leading role in the development of modern chemotherapy against tuberculosis was taken by the British Medical Research Council and its collaborators throughout the world,[122,475] and by the United States Public Health Service and the United States Veterans Administration.[476]

While the efficacy of anti-tuberculosis treatment was fully appreciated, it is noteworthy that tuberculosis was for a long time not considered to be curable; temporary remission and prevention of emergence of resistance were the primary objectives for a long time. This is particularly surprising as it had been shown already in the 1950s that tuberculosis is curable using appropriate combination therapy.[477,478]

In the following, only the highlights leading up to modern chemotherapy are summarized. For a more detailed account, the comprehensive review by Fox and collaborators from the British Medical Research

Council[122] or the individual trials conducted by the US Public Health Service[319,479-491] might be consulted.

Streptomycin monotherapy

Shortly after the discovery of streptomycin, clinical trials with streptomycin monotherapy were conducted in Great Britain[465] and the United States.[492] It was noted in these trials that case fatality from tuberculosis was considerably reduced. However, it was also seen that patients improved over the first few months and subsequently deteriorated, in many cases due to acquisition of streptomycin resistance. Among survivors, sputum conversion did not much differ between those receiving streptomycin and those not (figure 42).[492] The insoluble problem was the selection of resistant strains. While toxicity could be reduced by lowering the dosage and spacing administration more widely, the problem of bacterial resistance was not resolved.[493] The streptomycin trials impacted considerably on research for the next 20 years, which largely concentrated on methods of preventing the emergence of drug resistance.

Streptomycin plus para-aminosalicylic acid

The introduction of para-aminosalicylic acid into the armamentarium allowed combination therapy to be used. In a study of the British Medical Research

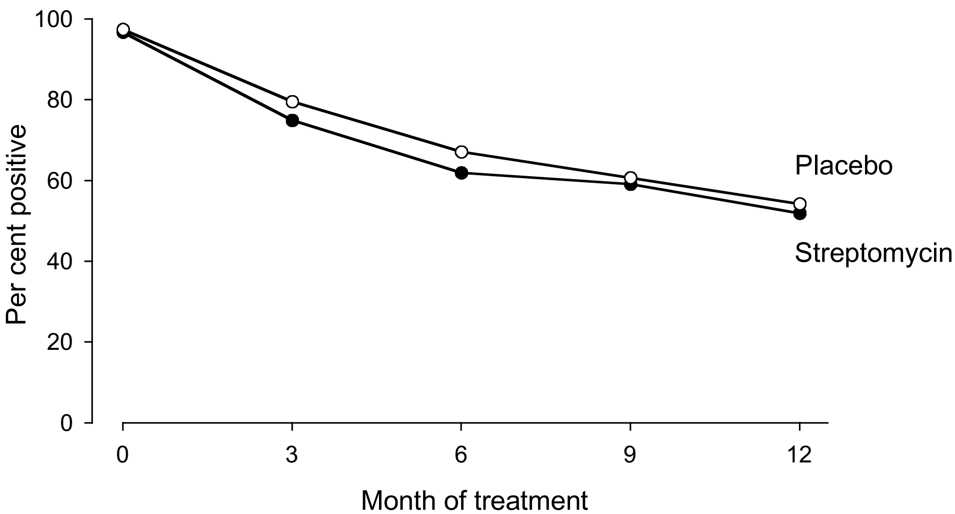

Figure 42. Sputum culture conversion among patients receiving streptomycin compared to placebo.[492]

Council, streptomycin monotherapy, para-aminosalicylic acid monotherapy and chemotherapy with both drugs combined was carried out.[494,495] It was demonstrated unequivocally, and for the first time, that combined chemotherapy reduced the risk of acquisition of resistance. Similarly, a clinical trial in Denver, Colorado, USA showed that the combination of streptomycin and para-aminosalicylic acid overcame the emergence of resistance, in contrast to monotherapy with either one (figure 43).[493]

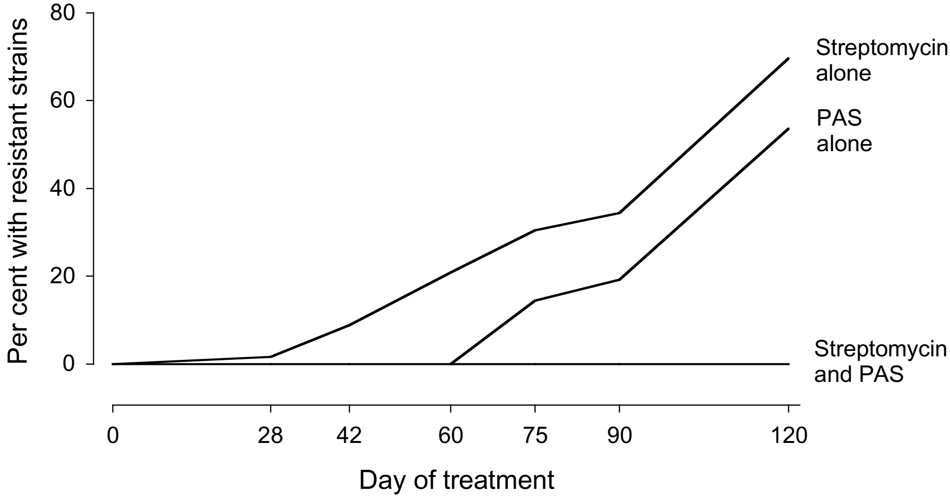

Figure 43. Emergence of resistance to streptomycin and/or para-aminosalicylic acid given alone or in combination. Reproduced from[493] by the permission of the publisher American Thoracic Society at the American Lung Association.

Streptomycin plus para-aminosalicylic acid plus isoniazid

It appears that the logical step following the introduction of isoniazid, namely to compare the efficacy of streptomycin, para-aminosalicylic acid, and isoniazid with a control arm of streptomycin plus para-aminosalicylic acid, was never subjected to a formal randomized clinical trial, either by the US Public Health Service or by the British Medical Research Council. This is particularly astonishing, as this triple combination therapy must be considered the breakthrough in tuberculosis treatment because it introduced the certainty of consistently curing tuberculosis patients with an initially fully susceptible strain.

It is furthermore a curiosity in the history of medicine that the curative results of this combination therapy were not even accorded a full-length article. The experiences in Edinburgh of Sir John Crofton and collaborators were relegated to the correspondence section of the *American Review of Tuberculosis* (figure 44).[477] The efficacy of this approach seemed convincing, although a randomized trial would surely have been indicated to remove any lingering doubts about biased selection and ascertainment. A subsequent study of the British Medical Research Council, begun in 1956, added a streptomycin supplement until susceptibility to PAS was demon-

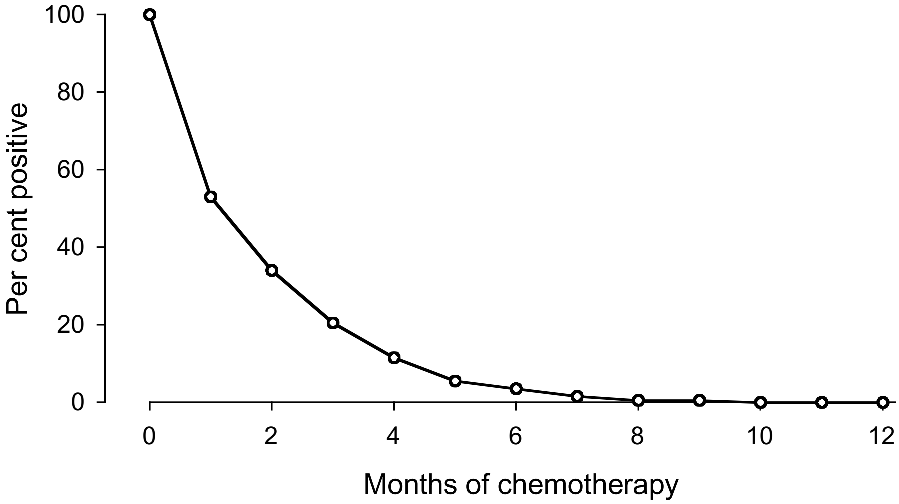

Figure 44. Sputum culture conversion in patients with pulmonary tuberculosis due to susceptible organsisms, with triple therapy consisting of streptomycin, para-aminosalicylic acid, and isoniazid. Reproduced from[477] by the permission of the publisher American Thoracic Society at the American Lung Association.

strated.[496] This indicates that the importance of a resistance-preventing component in the intensive phase was not yet fully appreciated. In the report on US Public Health Service trial 4, it was explicitly stated that there was no advantage of using all three drugs in cases of recent origin.[482] In US Public Health Service trial 3, a comparison of the combination streptomycin plus isoniazid with streptomycin plus PAS was made; it demonstrated the superior ability of the isoniazid-containing regimen to induce culture conversion (figure 45).[481] However, the difference between a regimen of streptomycin plus para-aminosalicylic acid plus isoniazid versus streptomycin plus para-aminosalicylic acid was not ascertained.

Nevertheless, common sense prevailed and by the end of the 1950s, the regimen that had been used in Edinburgh became, at least in the United

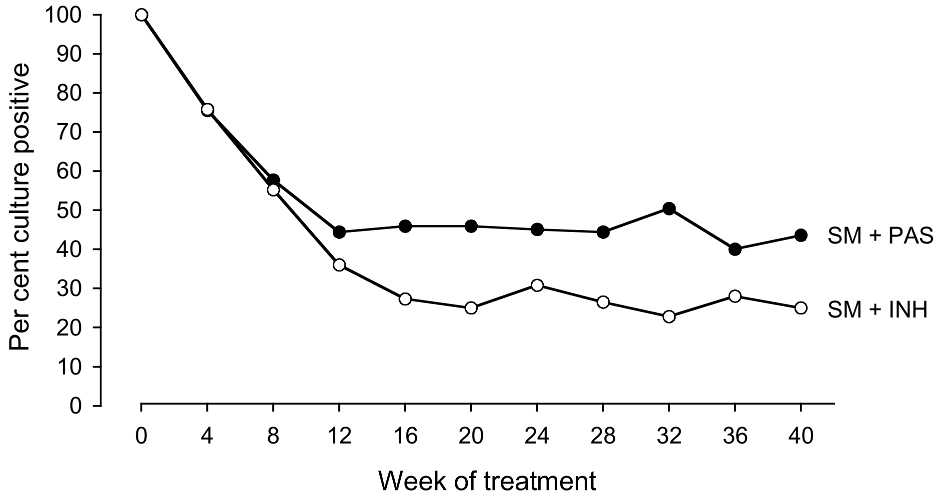

Figure 45. Sputum culture conversion among patients treated with streptomycin and para-aminosalicylic acid compared to streptomycin and isoniazid.[481]

Kingdom, standard practice[497] following a trial by the British Medical Research Council demonstrating faster conversion, fewer bacteriologic failures and relapses.[496,498] The WHO considered it one of the major regimens for low-income countries.[499] It took many years for experts of other countries to be convinced of its importance, and that only after an international comparative clinical trial.[500]

Isoniazid plus ethambutol

Because of the frequency of side effects associated with para-aminosalicylic acid, ethambutol appeared an attractive alternative. The US Public Health Service trial 16 showed that sputum conversion was indistinguishable in patients receiving, in addition to isoniazid, ethambutol in lieu of para-aminosalicylic acid (figure 46), although there was a marked reduction in the occurrence of adverse drug events.[484]

Neither the US Public Health Service nor the British Medical Research Council studied a 12-month regimen with isoniazid and ethambutol throughout, supplemented by streptomycin in the intensive phase, although this regimen has been widely used in low-income countries where thioacetazone has been abandoned.

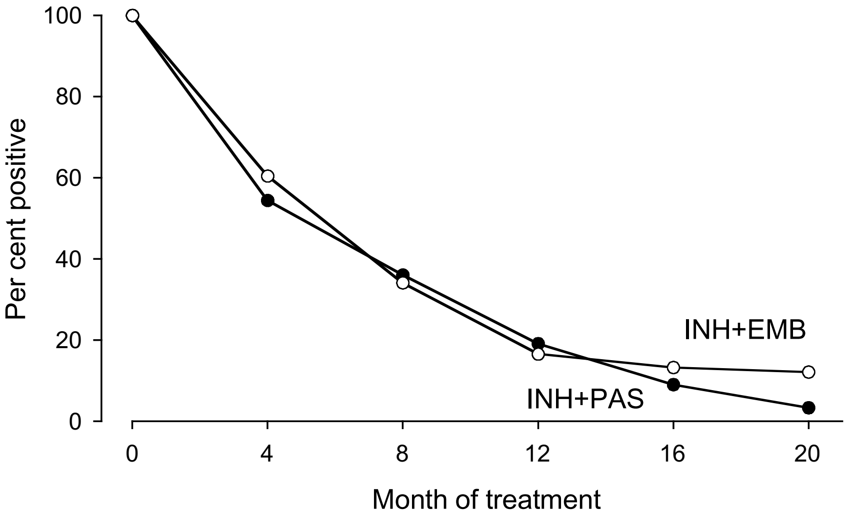

Figure 46. Sputum conversion among patients receiving isoniazid and para-amino-salicylic acid compared to isoniazid and ethambutol.[484]

Isoniazid plus thioacetazone

In East Africa, a comparison of 12-month regimens was carried out with isoniazid plus thioacetazone throughout, one arm containing streptomycin during the first two months and another arm without streptomycin.[501] It was demonstrated that the two-month supplement of streptomycin contributed to a higher cumulative conversion rate (figure 47).

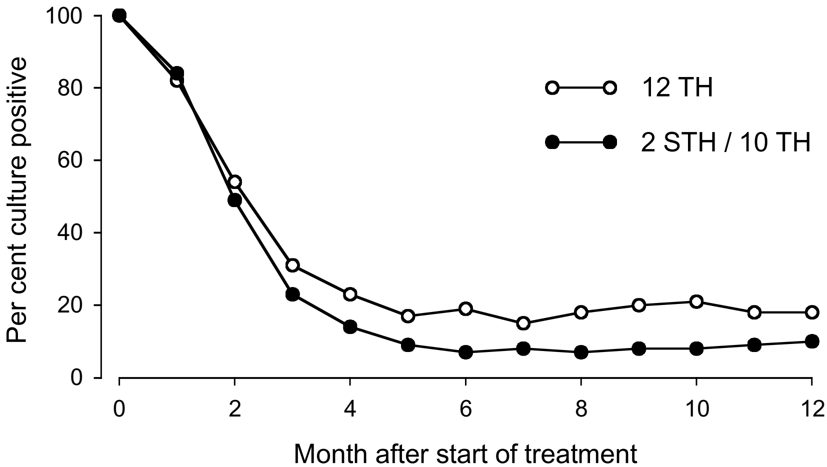

Figure 47. Effect on culture conversion of adding two months of streptomycin to a 12-month regimen of isoniazid and thioacetazone.[501]

Thioacetazone replaced para-aminosalicylic acid very rapidly throughout English-speaking sub-Saharan Africa because of the better tolerance and important cost savings.

Isoniazid plus rifampicin

With the introduction of rifampicin, a more rapid conversion was demonstrated when it replaced streptomycin (figure 48).[487] This was, however, not the main progress made with rifampicin-containing chemotherapy. In a trial in France, rifampicin-containing regimens were tested in three different durations of chemotherapy: six, nine, and 12 months.[502,503] It was demonstrated that nine months of isoniazid plus rifampicin, supplemented by either ethambutol or streptomycin during the first three months, was the optimum duration,[502] and the relapse rate during a remarkable mean follow-up time of 101 months with this regimen was only two out of 85 patients.[503]

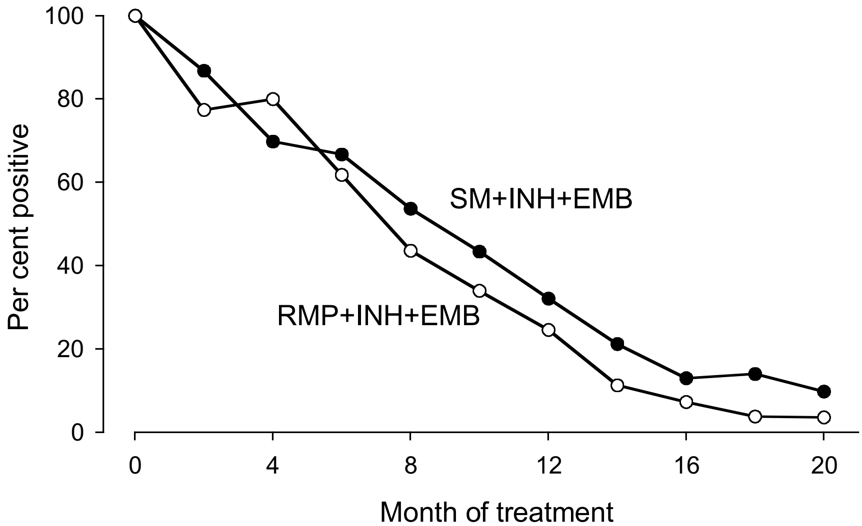

Figure 48. Effect of replacing streptomycin by rifampicin on culture conversion.[487]

The use of rifampicin provided curative treatment of less than one year's duration, and the term "short-course chemotherapy" became the brand name of this new successful strategy.[504]

Isoniazid plus rifampicin plus pyrazinamide (plus a fourth drug)

Despite its remarkable efficacy in experimental models,[505,506] pyrazinamide was not retained in routine chemotherapy because of its hepatotoxicity.

Based on evidence that the addition of pyrazinamide hastened sputum conversion, a series of studies was designed by the British Medical Research Council. In 1970, it was demonstrated for the first time that the inclusion of rifampicin and pyrazinamide in a regimen of isoniazid and streptomycin substantially reduced the subsequent risk of relapse.[122]

A multitude of clinical trials was designed and carried out by the British Medical Research Council with regimens containing, as a minimum, isoniazid, rifampicin, and pyrazinamide in the intensive phase, virtually always supplemented by streptomycin during this period.[122] Two studies in East Africa were critical for future research into this combination.[507,508] In these trials it was observed that regimens containing pyrazinamide but not rifampicin were almost as effective as those containing rifampicin. Furthermore, there was later evidence that both drugs given in the regimen were more effective than one alone.[122] These studies laid the basis for modern treatment.

The consistent finding in these studies was that the four drugs were optimally given for a two-month intensive phase, followed either by four months of rifampicin plus isoniazid or six months of a combination of drugs not containing rifampicin (the continuation phase).

The role of the fourth drug (streptomycin or ethambutol) is unclear as few studies have evaluated it,[491,509] but most likely it has a minor role in patients with a strain that is fully susceptible at the outset.[122] A recommendation to drop the fourth drug in patients with sputum smear-negative tuberculosis seems to have no evidence base. Patients with paucibacillary disease may require a shorter duration of treatment (see below); however, dropping the fourth drug in the intensive phase may not be justified as it may lead to functional monotherapy with rifampicin in lesions with a low pH among patients with a strain that is initially resistant to isoniazid (pyrazinamide not being active in such lesions).

Rifampicin-containing continuation phase

A regimen consisting of a two-month intensive phase with isoniazid, rifampicin, pyrazinamide, and streptomycin, followed by a four-month continuation phase with isoniazid plus rifampicin, all given daily, was first evaluated in Singapore.[510-512] The high efficacy of this regimen was confirmed in the United Kingdom, and was equally effective if streptomycin was replaced by ethambutol.[513-515] It has become the standard regimen for patients with fully susceptible organisms in most industrialized countries. Shorter durations have been put on trial,[516,517] but the frequency of relapse makes it impossible to reduce the minimum duration of six months. In the United States, US Public Health Service trial 21 evaluated the same regimen, but without the supplement of ethambutol or streptomycin (except for those with a high probability of initial resistance) in the intensive phase and showed it to be efficacious.[490,491] However, given the possibility of drug resistance among new cases of tuberculosis in many locations, the recommendation for a four-drug initial treatment is preferred, at least in areas where drug resistance is frequent or unknown. In the United Kingdom, a four-drug intensive phase is always recommended.[518] The IUATLD and WHO also recommend a four-drug intensive phase in new sputum smear-positive cases of pulmonary tuberculosis and other severe cases of tuberculosis where this regimen is being used.[8,13]

Non-rifampicin-containing continuation phase

Current options for a non-rifampicin-containing continuation phase are isoniazid plus thioacetazone or isoniazid plus ethambutol.

A four-drug, two-month intensive phase followed by six months of isoniazid plus thioacetazone has been found to be highly efficacious in East Africa.[519,520]

No critical evaluation of an ethambutol-containing continuation phase has been carried out extensively. One trial in India evaluated the effectiveness of a fully unsupervised eight-month regimen with isoniazid and ethambutol throughout, supplemented by rifampicin and pyrazinamide in the two-month intensive phase.[521,522] The entire treatment was self-administered and compared to a six-month regimen using rifampicin throughout, given twice-weekly, and at least partially supervised. The results during chemotherapy were encouraging with the eight-month regimen. Four per cent had an unfavorable response during chemotherapy and five per cent relapsed; the relapse rate was only half that in the directly observed control arms.

Intermittent regimens

To facilitate directly observed therapy, various intermittent regimens have been studied extensively.[122,521] In Chennai (formerly Madras), India, all parameters were superior in patients receiving twice-weekly isoniazid plus para-aminosalicylic acid, supplemented by streptomycin during the intensive phase, as compared with patients receiving once-weekly isoniazid plus para-aminosalicylic acid for self-administered treatment.[523] This study represented a major advance in research aiming at improving adherence with intermittent regimens.[498]

The majority of the trials have evaluated six-month regimens, with rifampicin throughout, each dose given under direct observation. In Denver, Colorado, USA, for instance, a regimen with daily treatment given for just the first two weeks, followed by twice weekly adminstration for the remainder of the course, was highly successful,[524] and similar studies have been conducted in Poland.[509,525]

Intermittent regimens have been shown to be as (or almost as) efficacious as daily regimens, and greatly facilitate direct observation of drug-intake. A potential problem with intermittent regimens is that errors resulting from missing one dose may have greater impact than missing a single dose in a daily regimen. This might be further compounded if the fourth drug in the intensive phase is omitted. In a controlled clinical trial in India with a twice-weekly regimen, bacteriologic sputum conversion was inferior if ethambutol was omitted (figure 49).[521] Twice-weekly regimens might also be inferior even if all drugs are being taken in populations where a large proportion of patients acetylates isoniazid rapidly, as such patients generally have inferior results in widely spaced drug administration.[122] Thus, while regimens for both twice-weekly and thrice-weekly application have been studied, the only intermittent regimens WHO recommends are thrice-weekly regimens.[13]

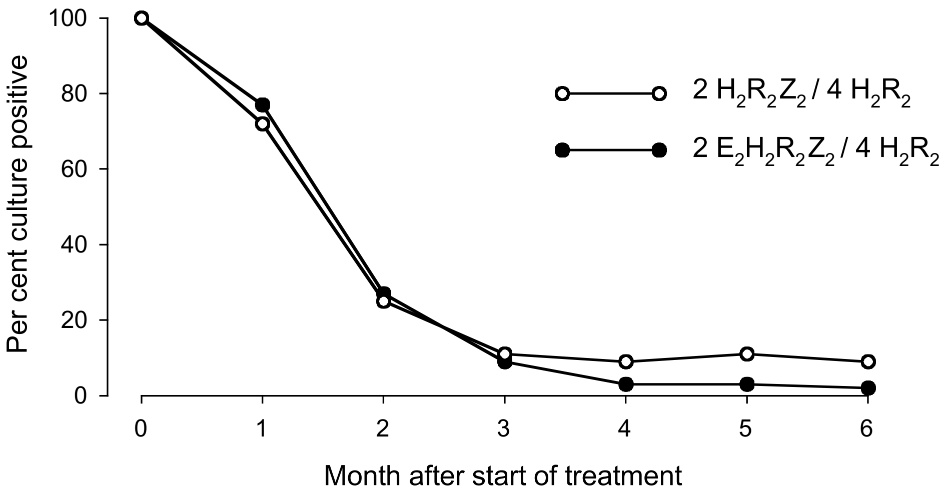

Figure 49. Effect of adding a fourth drug (ethambutol) during the first two months to a rifampicin throughout regimen on culture conversion.[521]

Not all drugs are equally suitable for intermittent use. Thioacetazone, for example, is not suitable for intermittent use.[526] Furthermore, intermittent treatment is indicated only to facilitate directly observed therapy, not for self-administered treatment. Thus, unless a rifampicin-containing continuation phase is selected, the principal issue is the efficacy of the use of intermittent therapy during the intensive phase of treatment.

Remarkably little is known about the efficacy of intermittent use during an intensive phase containing four medications, followed by a self-administered continuation phase that does not contain rifampicin. Concerns have been raised that an eight-month regimen with an intermittent intensive phase from the outset may be inferior in HIV-infected patients.[527] To facilitate directly observed therapy in national programs, these are critical issues that need urgent attention.

Treatment regimens of less than six months' duration

Regimens of four months' duration (containing rifampicin throughout) for bacteriologically confirmed pulmonary tuberculosis have been studied in Singapore, but yielded unacceptably high relapse rates.[510-512]

A regimen of four and a half months duration for bacteriologically (sputum smear and culture) confirmed pulmonary tuberculosis has been studied in Agra, India.[516,517] In this trial, four drugs (isoniazid, rifampicin, pyrazinamide, and streptomycin) were given for a total of three months, followed by one and a half month of isoniazid plus rifampicin, all given daily. All but one of the 65 patients enrolled were eligible for and followed up for relapse, and only one patient relapsed during the two-year follow-up period.[517] Despite the seeming efficacy of this four and a half-month regimen, confirmatory studies have not become available, the regimen has never been accepted by the medical community, and the credibility of the result of the study was actually challenged.[528]

Among patients with repeatedly negative sputum smears, shorter regimens have been investigated.[122] If the initial culture was negative (but radiologically the disease was considered to be active) or positive, relapse rates were three per cent or less with a three-month or a four-month regimen, respectively.[529] However, in routine practice even countries involved in these trials have abandoned the practice of treating patients with newly diagnosed (but bacteriologically unconfirmed) pulmonary tuberculosis for less than six months.

Currently, regimens shorter than six months duration are not recommended by WHO for bacteriologically unconfirmed tuberculosis. A principal consideration is the prevailing uncertainty about the quality of bacteriologic examinations (sputum smear microscopy) in many national tuberculosis programs.

Clinical trials in extrapulmonary tuberculosis

Two forms of extrapulmonary tuberculosis have been studied in well-designed clinical trials: tuberculosis of peripheral lymph nodes and tuberculosis of the spine. The treatment of tuberculosis of the central nervous system has been subject to numerous investigations, but because of the small cases in each study, the certainty about the optimum treatment is limited.

Tuberculosis of peripheral lymph nodes

In many populations, tuberculosis of peripheral lymph nodes (particularly cervical and axillary) is the most frequent extrapulmonary manifestation of tuberculosis.[530] While in the past, in milk-consuming cultures, tuberculosis of peripheral lymph nodes may frequently have been caused by *M. bovis,* particularly in children, it is now almost universally caused by *M. tuberculosis,*[531] it is found in all age groups, but with a predilection for the young[532,533] and for females.[530]

It appears that treatment of lymphatic tuberculosis was long considered to be a surgical domain, due to a misunderstanding of it as a localized disease process. This concept was demonstrated to be erroneous in a retrospective study conducted among cases diagnosed between 1965 and 1973 in the United Kingdom.[534]

A prospective study of the treatment of tuberculosis of peripheral lymph nodes was carried out in the United Kingdom, comparing two 18-month regimens, one with isoniazid plus ethambutol, the other with isoniazid plus rifampicin throughout, and both supplemented by streptomycin during the first two months.[476] No difference in treatment results between the two groups was found.

In a second prospective study, conducted by the British Thoracic Society, an 18-month regimen was compared with a nine-month regimen.[535,536] Both regimens were based on isoniazid plus rifampicin throughout and supplemented by ethambutol during a two-month intensive phase. No difference in treatment outcome was identified between the two regimens.

In a third prospective study in the United Kingdom, various regimens using isoniazid plus rifampicin throughout were compared.[537] The control regimen was the same as the nine-month regimen in the British Thoracic Society. One of the experimental regimens had the same duration, but ethambutol was replaced by pyrazinamide. The second experimental arm received the same regimen as the first, but for only six months. No differences among the three regimens were found.

A review of published materials concludes that a six-month regimen similar to that used in pulmonary tuberculosis is also adequate for treatment of tuberculosis of peripheral lymph nodes.[538]

It was noted in the British trials that tuberculosis of peripheral lymph nodes does not always appear to respond clinically to treatment, and treatment may be declared a failure on clinical grounds. Cultures from nodes that were newly developing during treatment or from abscesses from newly draining nodes subsequent to treatment completion remained bacteriologically sterile. It has been postulated that the phenomenon is caused by an immunologic response to tuberculo-protein.[535]

Tuberculosis of the spine

Tuberculosis of the spine is one of the most important extrapulmonary forms of tuberculosis both in terms of relative frequency and the substantial potential of permanent disability. It has been estimated that more than half of all osteoarticular manifestations of tuberculosis in India affect the spine.[539]

Before the advent of anti-tuberculosis chemotherapy, treatment consisted of bed-rest, improvement of the patient's nutritional status, and, in some cases, posterior spinal fusion.[540]

In the 1950s and early 1960s, two extreme positions marked the divergence of opinions about the appropriate approach to the treatment of tuberculosis of the spine. In Nigeria, successful treatment with chemotherapy alone was reported.[541,542] In Hong Kong, excellent results were reported with anterior spinal fusion.[543-546]

It was against this background that the British Medical Research Council planned[539,547,548] and conducted a series of controlled clinical trials, resulting in 14 scientific reports.[549-562]

The trials were conducted in Hong Kong, India, Korea, and Zimbabwe. All trials evaluated the role of chemotherapy and various operative and non-operative surgical procedures. Chemotherapy lasted from six to 18 months at various points in time. The most recent trial established that a regimen of six months' duration with isoniazid plus rifampicin throughout was as effective as any other regimen.[562] It was concluded that outpatient chemotherapy with standard short-course chemotherapy based on isoniazid, rifampicin, and pyrazinamide should be the main management of uncomplicated spinal tuberculosis.[561]

It is likely, based on the results of these studies, that a regimen that is effective for pulmonary tuberculosis should be equally effective for the treatment of tuberculosis of the spine.

Tuberculosis of the central nervous system

Tuberculous meningitis is the most important central nervous system manifestation of tuberculosis. The optimum treatment of tuberculous meningitis is not known, and recommendations are based on the pharmacokinetic properties of the medications and, to a large extent, on inference and common sense.

The blood-brain barrier poses particular problems for the choice of the right drug combinations as penetration into the cerebrospinal fluid and its ratio to serum concentrations varies widely among the various anti-tuberculosis drugs.

The key issue is the extent of plasma binding of the drug, as probably only the unbound portion penetrates into the central nervous system, thus explaining the differences between isoniazid and pyrazinamide on one hand, and rifampicin on the other.

Isoniazid is recognized as a drug with excellent penetration into cerebrospinal fluid.[61,563]

Rifampicin, in contrast to isoniazid, has very poor penetration into cerebrospinal fluid,[563] but seems to appear in higher concentrations at the beginning of treatment, in the phase where the meninges are inflamed.[564,565] However, because tuberculosis is not a localized disease, the use of rifampicin is beneficial for the treatment of lesions other than those in the central nervous system that may be simultaneously present.

Pyrazinamide has excellent penetration into cerebrospinal fluid.[563]

Ethambutol penetrates poorly into normal or uninflamed meninges, but penetrates fairly well into inflamed meninges.[565-568]

Streptomycin penetrates relatively poorly into cerebrospinal fluid.[563]

Among the thioamides, ethionamide has been found to have high penetration into cerebrospinal fluid.[565,568-570]

Based on these pharmacokinetic properties and other considerations, it has been recommended that treatment for suspected or confirmed tuberculous meningitis should begin with a two-month intensive phase incorporating isoniazid, rifampicin, and pyrazinamide plus streptomycin.[571] The optimum duration of the continuation phase is not known, but based on limited information[572] a continuation phase associating isoniazid and rifampicin for a duration of at least seven months has been advocated.[563] This regimen may pose problems in patients with an isoniazid-resistant strain because of the unpredictable concentrations of rifampicin. Where available, ethionamide might provide a less well tolerated alternative in such a case.[570,573]

Influence of HIV infection on the choice of a regimen

Among tuberculosis patients with HIV infection, two major issues need to be addressed.

The first concerns the initial observations made by clinicians when treating HIV-infected patients with anti-tuberculosis drugs: tolerance of the medications was poorer than in patients without HIV infection.

A second issue concerns the efficacy of the regimens usually prescribed. Patients with HIV infection may suffer from diarrhea, which may, through its lowering of drug serum concentrations, adversely compromise the efficacy of the regimen, favoring the emergence of resistance and subsequent relapse.

Adverse drug events

Adverse drug events occur much more frequently among HIV-infected tuberculosis patients. In particular, cutaneous hypersensitivity reactions are frequent. These have mostly been attributable to thioacetazone,[443,445,447,574-577] and to a lesser extent to streptomycin,[575] rifampicin,[215,216,578] and isoniazid.[578]

The frequent and sometimes fatal cutaneous adverse drug events among HIV-infected tuberculosis patients due to thioacetazone preclude its use in patients known to be HIV-infected.[8,13] It is best replaced with ethambutol.

An increased frequency of non-cutaneous adverse drug events (hepatotoxicity, gastrointestinal disturbances, thrombocytopenia) to isoniazid[578, 579] and rifampicin has been reported.[578-580]

Anti-retroviral therapy poses particular problems because of interactions with rifampicin that preclude simultaneous use of the two regimens.

Treatment efficacy

As enteropathy is a frequent occurrence in HIV-infected patients, anti-tuberculosis medications might be less well absorbed,[581] thus leading to treatment failure, relapse[582] or acquisition of drug resistance.[583] Pharmacokinetic studies among patients with AIDS in various centers in Puerto Rico and the USA have demonstrated that serum peak concentrations, particularly of rifampicin and ethambutol, were frequently lower than expected.[334] However, malabsorption of anti-tuberculosis medications does not seem to be a major issue in most HIV-infected patients.[584,585]

Sputum conversion is rapid, and even faster among HIV-positive than HIV-negative patients (figure 50).[586] However, concern has been expressed

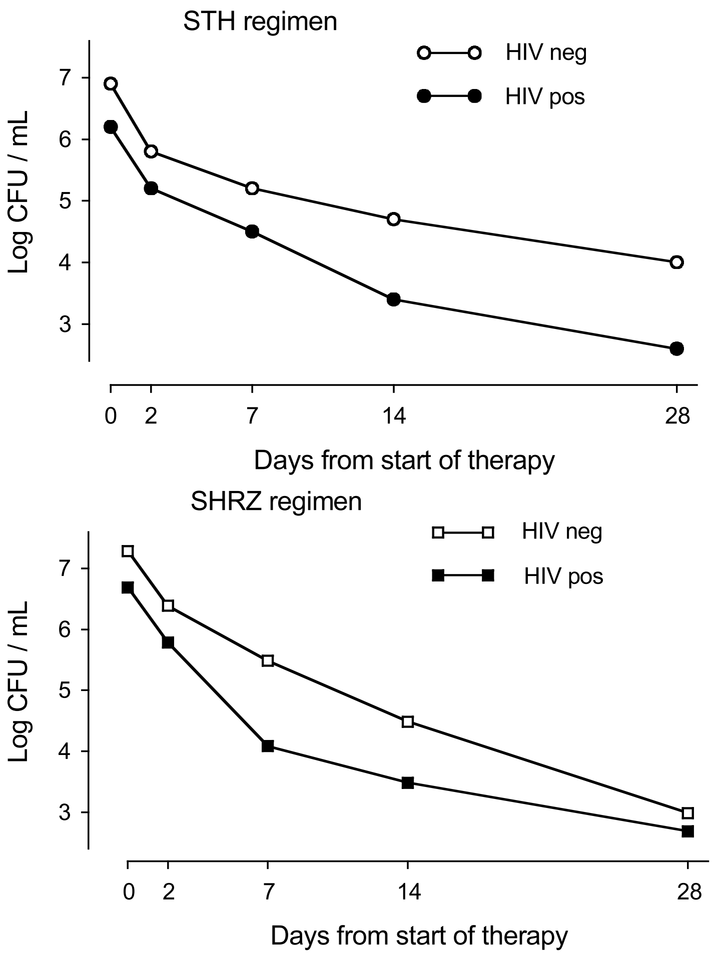

Figure 50. Bacteriologic response to chemotherapy among HIV-negative and -positive patients, by treatment regimen.[586]

that the sputum bacillary load may not reflect the underlying number of bacilli a patient harbors, and thus there might be a need for prolonged treatment.[587]

Regimens of six to nine months duration containing rifampicin throughout have been highly efficacious in terms of both low frequency of bacteriologic failure[576] and relapse.[579,588,589] Eight-month regimens give acceptable results in the field.[590] In contrast, 12-month regimens that do not incorporate any rifampicin have shown a high frequency of failures[591,592] and relapse.[591,593,594]

If antiretroviral therapy is given simultaneously with treatment for tuberculosis, paradoxical responses have been reported with worsening of the clinical presentation, assumed to be an immunologic response.[595] Antiretroviral drugs such as protease inhibitors (saquinavir, indinavir, ritonavir, and nelfinadvir) and non-nucleoside reverse transcriptase inhibitors (nevirapine, delaviridine, and efavirenz) have substantive interactions with rifamycins.[596] Rifampicin will reduce the blood concentrations of protease inhibitors. The efficacy of the latter will thus be reduced when concommitantly administered with rifampicin. The interaction with nucleoside reverse transcriptase inhibitors (zidovudine, didanosine, zalcitabine, stavudine, and lamivudine) is probably not clinically relevant.[596]

The US Public Health Service conducted study 22, comparing the efficacy of once-weekly isoniazid plus rifapentine with twice-weekly isoniazid plus rifampicin in a four-month continuation phase following a four-drug, two-month intensive phase.[597] Among 61 patients with concomitant HIV infection, none experienced treatment failure. However, three of the 31 patients on the rifampicin-containing continuation phase relapsed, all with fully susceptible organisms, but five of the 30 patients on the rifapentine regimen relapsed, four of whom had acquired rifamycin resistance. Obviously, isoniazid as a companion drug in once-weekly treatment is inadequate, and patients effectively received rifapentine monotherapy. There is indeed cause for concern that, by analogy, HIV-infected patients with initial isoniazid resistance may acquire unnoticed (no apparent failure during treatment) rifampicin resistance if treated with this drug in the continuation phase.[598] Nevertheless, the reasons for acquisition of rifamycin resistance in this study have not yet been fully elucidated, and there are indications that it is attributable to an inadequate dosage of rifapentine.

Relapse following cessation of chemotherapy appears to be more frequent among HIV-infected compared to HIV-non-infected individuals,[594,599] and post-treatment preventive chemotherapy with isoniazid appears to reduce that risk.[599]

Influence of isoniazid resistance on the choice of a regimen

Isoniazid is a key drug in the treatment of tuberculosis and its inclusion in every first-line regimen is the standard of care. Pre-existing initial resistance to isoniazid might be conducive to the development of additional resistance, particularly if treatment organization is poor, as the data from the WHO/IUATLD global surveillance project on drug resistance seem to suggest (figure 51).[600]

Patients with initial isoniazid resistance who are given a four-drug intensive phase for two months, followed by isoniazid and thioacetazone in the continuation phase, fail more frequently than patients with fully susceptible organisms.[519,601] Such patients can be re-treated effectively with a regimen containing rifampicin plus ethambutol throughout, supplemented by pyrazinamide during the first three months, and additionally by streptomycin during the first two months.[8,13,602-604]

It is not very well known how effective such a re-treatment regimen is if there is additional ethambutol resistance. The extent to which such functional rifampicin monotherapy in the continuation phase of the re-treat-

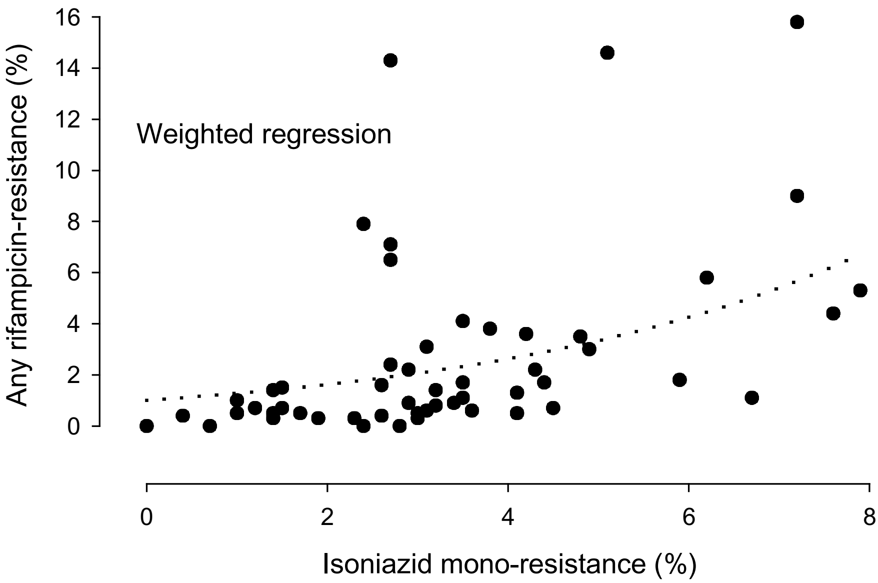

Figure 51. Correlation between isoniazid mono-resistance and any rifampicin resistance among never treated patients. Ecological analysis from the Global Project on Surveillance of Anti-tuberculosis Drug Resistance.[600]

ment regimen is efficacious and not causing drug resistance in HIV-infected patients remains to be seen.[598]

Influence of isoniazid plus rifampicin resistance on the choice of a regimen

Patients with multidrug-resistant tuberculosis (bacilli resistant to at least isoniazid and rifampicin) are only rarely expected to be cured solely using the six essential drugs. Under program conditions treatment outcome with the standard WHO recommended re-treatment regimen is poor if there is multidrug resistance.[605] Barring spontaneous remission, such patients are incurable and frequently become chronic excretors of bacilli in countries where only the essential drugs are available for use.

Drugs other than the six essential drugs are of lower efficacy, much more costly, and in the majority of cases, much less well tolerated.[606-608] It is also not yet known which treatment strategy is best. Proposals for treating multidrug-resistant tuberculosis include the utilization of a standard regimen or an individualized approach based on susceptibility testing.[609] There have been no randomized controlled clinical trials to evaluate these regimens and insufficient experience has been accumulated to make firm recommendations at this point in time.

Strategic considerations, indications, and recommendations for the choice of treatment regimens in a national tuberculosis control program

The number of possible errors can be minimized by the systematic, country-wide use of standard regimens. Recommended standard treatment regimens are based on clinical efficacy trials in terms of dosage, mode of administration, and duration of treatment. Deviations from standard treatment regimens are indicated only in the case of adverse drug events, for patients presenting with pre-existing medical conditions that require a modification of the regimen, or in the presence of suspected or confirmed resistance to one or more drugs.

Both WHO and the IUATLD recommend standard treatment regimens which vary according to the category of the patient.[13] The three categories are:[8]

- Patients with sputum smear-positive tuberculosis or severe extrapulmonary tuberculosis never treated before for as much as one month;
- Patients with other forms of tuberculosis (sputum smear-negative and extrapulmonary) never treated before for as much as one month;
- Patients with sputum smear-positive tuberculosis treated previously for one month or more (return after treatment failure, return after default, and relapse).

No specific recommendations have been made on how to deal with patients with continued bacteriologically active disease following a full re-treatment course (chronic excretors).

A primary objective of any tuberculosis control program must be to limit to the largest possible extent the emergence of organisms resistant to the available medications. This is a guiding principle for any chemotherapy, but it is particularly crucial in tuberculosis control, because the armamentarium of drugs is limited and the prospects in the near future for new, affordable drugs with an efficacy comparable to that of isoniazid, rifampicin or pyrazinamide are slim for most low-income countries.

Choice of first-line regimen

First-line regimens of six to eight months duration are the most efficacious available. All are based on a four-drug initial intensive phase. Whether a four-month (with rifampicin) or a six-month continuation phase (without rifampicin) is selected depends on the availability of resources for drugs and personnel, and considerations about the fall-back (re-treatment) regimen, particularly in the case of treatment failure. Twelve-month regimens (without rifampicin) have been widely used for bacteriologically unconfirmed disease, but their efficacy in HIV-infected patients appears to be inferior to the shorter, but more intensive alternatives.

The continuation phase in the eight-month regimen consists of six months of isoniazid plus thioacetazone. A frequently chosen alternative to thioacetazone is ethambutol. This change potentially weakens the re-treatment regimen (functional rifampicin monotherapy in the continuation phase). This increases the risk of development of multidrug resistance. The IUATLD therefore recommends the addition of pyrazinamide throughout the re-treatment regimen[8] when ethambutol has been used in the continuation phase of initial treatment.

Many countries have moved towards a first-line regimen which contains rifampicin throughout. Patients truly failing on such a regimen have a high probability of initial multidrug resistance (or initial isoniazid resistance and acquired rifampicin resistance). The re-treatment regimen recommended by the IUATLD and WHO is highly unlikely to cure such a patient, and additionally carries the risk of acquisition of ethambutol resistance. It is not clear whether re-treatment incorporating both ethambutol and pyrazinamide in the continuation phase will overcome this problem. Given the relative weakness of these two drugs, there is a risk of losing both. This has been termed the "amplifier effect" (a new term for an old phenomenon, successive acquisition of additional drug resistance) and has been observed to occur in an outbreak in urban Peru.[610,611] It has not been observed in other settings where a non-rifampicin-containing continuation phase is routine in the first-line regimen.[612]

8-month regimens

The eight-month regimen evaluated in East Africa (a directly observed four-drug, two-month intensive phase followed by six months of self-administered isoniazid plus thioacetazone) has become the principal treatment regimen for previously untreated smear-positive pulmonary tuberculosis in IUATLD collaborative programs.[8,604] Programs basing their chemotherapy on this regimen are using a highly cost-effective intervention.[613]

Replacement of streptomycin by ethambutol in the intensive phase did not adversely affect adherence to directly observed therapy in a study conducted in large urban settings in Tanzania,[614] and gave similar treatment outcome under routine conditions in Madagascar, although the proportion of failures was somewhat higher than in the streptomycin group.[615] It also yielded good results in Benin.[616]

It is likely that replacement of thioacetazone by ethambutol is equally effective, as demonstrated in a clinical trial in India in a patient population with a low prevalence of HIV infection.[521,522] When thioacetazone cannot be used because of a high prevalence of HIV infection, its replacement by ethambutol is therefore often recommended.[8]

6-month regimens

The shortest treatment regimen of proven efficacy for bacteriologically confirmed tuberculosis consists of six months of isoniazid plus rifampicin, supplemented by pyrazinamide plus either streptomycin or ethambutol during the first two months. This has been convincingly demonstrated where all medications were taken daily throughout the course of treatment.[122] In Poland, a study with this regimen, with the continuation phase given twice weekly, led to neither failures nor relapses.[525] Similar good results were obtained with the same regimen in Singapore, with the continuation given thrice weekly.[617]

Most industrialized countries have adopted this regimen, given daily in the intensive phase and daily or intermittent in the continuation phase, as their regimen of choice for patients without a history of prior treatment.

12-month regimens

The best documented 12-month regimen currently used in low-income countries consists of 12 months of isoniazid plus thioacetazone, supplemented by streptomycin during the first two months.[122] This regimen has been widely used in IUATLD collaborative programs in patients without a prior history of treatment. Amongst these, it is given for cases with positive sputum smears who cannot receive a directly observed rifampicin-containing intensive phase and for the majority of patients whose sputum smears are negative or who have extrapulmonary tuberculosis which is not life-threatening.

In Uganda, the frequency of adverse drug events and survival as the main outcomes of interest were compared for the above 12-month regimen and a nine-month, rifampicin-throughout regimen (supplemented by pyrazinamide during the first two months) among HIV-infected patients.[618] As expected, adverse drug events were much more common in the former than the latter regimen, but survival over a two-year follow-up period was identical.

In Malawi, HIV-infected patients with sputum smear-negative tuberculosis who were treated with a 12-month regimen (12 months of isoniazid plus thioacetazone or ethambutol, supplemented with streptomycin during the first month), had a very high relapse rate approaching 20% (compared to seven per cent among HIV-negative patients).[590] These findings critically challenge the continued use of such a regimen in countries where the prevalence of HIV infection among tuberculosis patients is high.

Choice of re-treatment regimen

Treatment regimens for a national tuberculosis control program should be designed to allow curative treatment of patients requiring a re-treatment regimen, because it is the patient's last chance to get cured. The need for a re-treatment regimen is based on the increased probability of resistance to the medications used in patients who have received prior treatment. That this is the case has been amply demonstrated.[619] An efficacious re-treatment regimen must encompass at all times, throughout treatment, at least two drugs to which the organism is still likely to be susceptible. Countries which do not have access to medications other than the six essential drugs for patients who might require them must choose a re-treatment regimen based on these six drugs.

Because isoniazid is always given in the first-line regimen, a patient failing to respond to the treatment regimen will have a high probability of already having isoniazid resistance at the outset of treatment. To adhere to the principle of a re-treatment regimen incorporating at least two efficacious drugs, neither rifampicin nor ethambutol should have been used as the sole companion drug with isoniazid at the point of failure (defined as sputum smear-positive at five months or later), if either of these drugs is to be effective in a re-treatment regimen. Their use as a sole companion drug with isoniazid constitutes functional monotherapy in such a patient and presents a risk that resistance will have developed to the companion drug (in this case, either rifampicin or ethambutol). This has been the rationale behind the recommendation of the IUATLD to utilize isoniazid plus thioacetazone in the continuation phase. Should bacilli resistant to thioacetazone emerge, re-treatment is still likely to be successful.

This re-treatment regimen proposed by WHO and the IUATLD consists of eight months of isoniazid, rifampicin, and ethambutol, supplemented by pyrazinamide during the first three, and streptomycin during the first two months. This regimen uses the full range of available drugs except thioacetazone. Such a regimen has a high probability of curing any patient who does not commence treatment with organisms already resistant to both isoniazid and rifampicin. Patients with multidrug-resistant strains have, after taking the re-treatment regimen, an outcome that is not appreciably better than reported outcomes in the pre-chemotherapy era.[620]

Treatment of patients with organisms resistant to isoniazid and rifampicin

Patients who fail on directly observed treatment containing isoniazid and rifampicin throughout, i.e., patients failing on a six-month first-line regimen or the above-mentioned eight-month re-treatment regimen, are more likely to harbor organisms resistant to both isoniazid and rifampicin (multidrug-resistant organisms). In most low-income countries such patients are designated “chronic excretors” whose fate has to be left to the natural course of the disease, as alternative drugs (other than the six essential drugs) are not usually available in sufficient quantity.

The emergence of multidrug-resistant tuberculosis has been documented in an increasing number of countries and has, in some countries, reached levels that seriously threaten tuberculosis control.[621,622]

The WHO has addressed this issue in both a formal publication[606] and workshop proceedings.[608,609]

Curative treatment of multidrug-resistant tuberculosis poses a multitude of problems. Amongst these are:

- the high cost of the necessary drugs (currently up to 100 times as expensive per course as a first-line regimen);[609]
- the relative weak activity of most of these drugs against *M. tuberculosis*;
- the high frequency of adverse reactions requiring specialist expertise;
- the prolonged duration (21 months has been proposed as a minimum);[606]
- the logistic difficulties anticipated in implementing such regimens in a national tuberculosis program;
- difficulties in implementing standardized laboratory facilities to correctly identify susceptibility patterns;[623]
- gaps in knowledge as to what approach to treatment (individualized or standardized) is most appropriate.[624]

As there is an increasing demand to utilize such alternative medications, and technical knowledge is generally poor about their proper usage in most countries where the problem has emerged or is emerging, the danger of uncontrolled usage is great. Resistance to these drugs is likely to emerge quickly in unprepared settings.[625] It is hoped that the agenda set forth by WHO[608] will generate sufficient information in an ordered and timely fashion and appropriate technical expertise will accompany implementation of any such project to ensure continued curability of tuberculosis in such settings. Unfortunately, multidrug-resistant tuberculosis has emerged precisely in areas of the world that have demonstrated poor tuberculosis control in the first place, and whether a deterioration of the situation in such settings can be prevented with the introduction of drugs potentially able to cure multidrug-resistant tuberculosis remains to be seen.

Case holding

Prescription of an adequate course of treatment is not sufficient; it must be ensured that the prescribed medications are also actually taken until the successful, curative completion of therapy.

Directly observed therapy

Ensuring regularity of treatment is the key to timely completion of therapy and the prevention of acquisition of drug resistance. The problems with self-administered chemotherapy in ensuring regular adherence have long been recognized,[279] and to ascertain the efficacy of regimens in clinical trials, direct observation of drug intake during part or the entire course of treatment has thus been standard in many investigations.[122]

Directly observed therapy refers to treatment where a qualified person (usually, but not always,[626] a health care worker) ensures that the prescribed medications are taken by observing the patient ingesting them.[627] Directly observed ambulatory therapy has its evidence base in studies in Chennai (formerly Madras) and Hong Kong,[628] and the recognition of the need for alternatives to costly hospitalization.

Directly observed therapy might be conceived of as a coercive procedure, but it may also help to strengthen the relationship between patient and health care worker.[629] If this does not occur, then directly observed therapy may not achieve an increase in the proportion of patients completing therapy.[630]

The major effects of directly observed therapy that might be expected are a reduction in the risk of acquiring drug resistance and in the frequency of relapse following completion of chemotherapy, as convincingly demonstrated in a study in the United States (figure 52).[631]

Can emergence of drug resistance be outpaced in a national tuberculosis program?

Strains resistant to isoniazid should have a comparative advantage, as patients harboring such a strain will, on average, be transmitters for a longer period of time than patients with a fully susceptible strain. Thus, one would expect an increase in the prevalence of primary resistance to isoniazid. This is, however, not the case in well-managed programs.[632,633] Some studies sug-

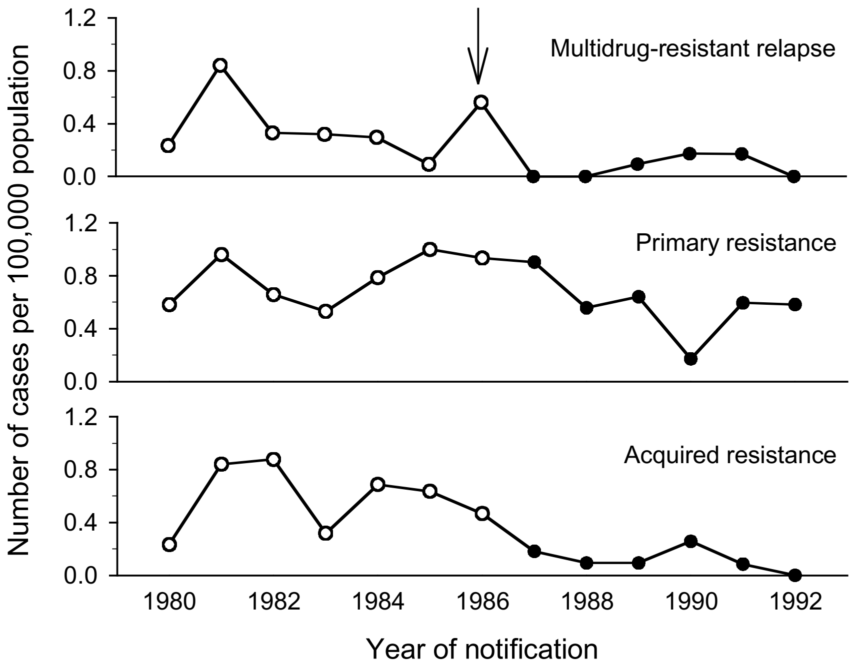

Figure 52. Effect of directly observed therapy on relapse, primary resistance, and acquired resistance, in Tarrant County, Texas, United States. Arrow indicates point in time of introduction of universal directly observed therapy. Reproduced from[631] by the permission of the publisher Massachusetts Medical Society.

gest that the transmissibility is the same for isoniazid-susceptible and isoniazid-resistant strains,[634,635] while others indicate that transmissibility of isoniazid-resistant strains is reduced;[122] thus the question of transmissibility has not been fully resolved. However, strains which are resistant because of *katG* gene deletion have lower virulence in experimental animal models,[636,637] while mutation of the *inhA* gene has no effect on virulence.[636] Thus, a fraction of isoniazid-resistant strains may have a comparative selection disadvantage. In an effective tuberculosis program with a directly observed intensive phase utilizing the four most potent drugs, followed by a self-administered, non-rifampicin-containing continuation phase, no significant multidrug resistance (resistance to at least isoniazid and rifampicin) has emerged over 12 years of usage.[632] This could indicate that a qualitatively good program may outpace the rate of emergence of drug resistance. However, a study from The Netherlands indicates that some specific mutations of the *katG* gene lead to high-level resistance and as great a probability of producing secondary cases as isoniazid-susceptible strains.[638]

Strains resistant to isoniazid alone can virtually always be killed when regimens containing both rifampicin and pyrazinamide are used and rifampicin is given throughout.[603] The introduction of the short-course regimens in countries such as Algeria and Korea was accompanied by a clear decline in resistance to isoniazid and chronic excretors for this reason.[639,640] However, in the case of Algeria, the introduction of short-course regimens was associated with the appearance of and slow increase in cases with multidrug resistance among previously treated patients, possibly related to the fact that directly-observed treatment was not the policy. The rate of decline in cases of tuberculosis (and particularly of re-treatment cases) in that community was greater than the rate of appearance of multidrug resistance, thus outpacing the drug resistance. However, if this community had experienced a rise in the numbers of cases, rather than a decline (as would have occurred if the community was affected heavily by HIV infection), this might not have been the case.

This is one of the main reasons why the IUATLD has preserved a very conservative policy with respect to treatment regimens, in order to preserve the usefulness of rifampicin as an efficacious agent in the overall scheme of treatment policy.

The approach to management of adverse drug events

The major clinical presentations of adverse drug events that may occur in a patient treated with the essential drugs and the approach to managing them will be discussed here. Adverse drug events from second-line drugs should always be dealt with by a specialist in the field. The discussion is limited to the major clinical syndromes occurring in the routine management of tuberculosis in clinical practice.

In any patient who takes prolonged treatment, episodes of ill health may occur which may be ascribed by the patient or the health care provider to adverse effects of the treatment given. This is not necessarily the case. In the large clinical trials of preventive chemotherapy carried out by the US Public Health Service among household contacts of tuberculosis patients, one group of patients was assigned to the treatment arm and another to a placebo in which identical tablets were given which contained no active medication.[641] Neither the patient nor the care provider knew the type of pills that individual patients were taking. The events that occurred during treatment were thus observed without knowledge of the treatment. In a number of cases, the health care provider, based on the assumption that the treatment was causing adverse drug events, discontinued the treatment.

When the code indicating what the patient was taking was broken and the results analyzed, it became apparent that 20% of all episodes considered to have been adverse drug events to the "medication" were, in fact, "placebo" effects.[641] This indicates that the "adverse events" were, indeed, intercurrent illnesses or events unrelated to the treatment itself, although they had every appearance of having been due to the medications.

This has important implications for the evaluation of "adverse events" in patients on treatment for tuberculosis. If one or other of the essential medications used in the treatment of tuberculosis (such as isoniazid or rifampicin) is stopped due to what is (incorrectly) perceived as an adverse drug event, the outcome of the treatment can be seriously affected. Discontinuation of an essential medication in the treatment of a tuberculosis patient for what is perceived as an adverse drug event must be carefully considered and correctly undertaken if the patient's chances of successful treatment are not to be seriously affected.

The patient with hepatitis

Clinical hepatitis is to be suspected in a patient presenting with a syndrome of malaise, nausea, vomiting, anorexia, fever, abdominal pain, hepatomegaly, jaundice or dark urine.[642]

Hepatic disease during anti-tuberculosis chemotherapy is not necessarily caused by the drugs, but may be attributable to other causes, such as alcohol abuse, cirrhosis, infectious hepatitis or indeed the tuberculosis itself. Nevertheless, appropriate management of the patient requires an approach as if one or more of the drugs were responsible.

The key suspect drugs are isoniazid, pyrazinamide, and rifampicin, if the patient is on any of these. In that case, such as in the intensive phase of chemotherapy, all three drugs should be stopped immediately if the symptoms are severe and/or if there is jaundice. The patient should temporarily be placed on ethambutol plus streptomycin in such a case. This combination is unlikely to be hepatotoxic and, while a relatively weak combination, still ensures temporary adequate treatment without a high risk of emerging drug resistance. In the presence of malaise and nausea only (without jaundice), rifampicin might in addition be kept in the regimen as it is rarely a cause of hepatitis.

The patient is maintained on these two drugs until the acute symptoms subside, which usually occurs within one or two weeks.

Isoniazid might then be added in a dosage of 50 mg per day. If there is no clinical deterioration, the dose of isoniazid may then be increased to 100 mg on day 4, to 200 mg on day 7 and to the full dose on day 14.[642] Following the patient for another seven days, rifampicin might then be reintroduced, and if well tolerated, pyrazinamide might finally be added if rifampicin plus isoniazid has been well tolerated for seven days, and if it has been given for less than two months prior to the onset of hepatitis. This schedule can be expected to be successful in over 90% of cases.[642]

Some clinicians prefer to re-introduce isoniazid at the full dose when liver enzymes (where available) have normalized, or if liver enzyme tests are not available after two weeks (Schraufnagel DE, personal written communication, April 3, 2001; O'Brien RJ, personal written communication, April 19, 2001).

The patient with gastrointestinal symptoms

Gastrointestinal symptoms such as nausea, pain and vomiting might be prodromal symptoms of hepatitis, and close clinical observation is mandatory. In addition to isoniazid, rifampicin, and pyrazinamide, thioacetazone frequently causes gastrointestinal symptoms. In a patient on isoniazid and thioacetazone, the latter is probably the cause. Such reactions can often be dealt with easily by taking the medications with a meal or before going to bed. Monitoring of the response is important. If the symptoms do not subside, the isoniazid plus thioacetazone combination should be replaced by isoniazid plus ethambutol. Should the symptoms persist despite the change, isoniazid and the possibility of liver toxicity must be suspected and the patient be placed on streptomycin plus ethambutol until symptoms subside. Isoniazid might be re-introduced subsequently, as described above.

The patient with impaired vision

The most frequent drug-related cause of impaired vision among the medications used for treating tuberculosis is ethambutol. Optic toxicity is not detectable fundoscopically. If ethambutol is suspected, it must be withdrawn immediately and never be given again. If the event occurs in the intensive phase where ethambutol is given as a fourth companion drug, no replacement is necessary (although streptomycin might be used if deemed necessary). If the event occurs in the continuation phase when the patient is on isoniazid plus ethambutol, the latter should be replaced by thioacetazone or rifampicin.

The patient with vestibulo-cochlear toxicity

Vestibulo-cochlear toxicity is virtually always due to streptomycin. It is often, but not always, dose-dependent. Thus, it should first be checked whether the dosage given is appropriate to weight and age (toxicity increases with both). If the dose cannot be reduced or if dose reduction fails to improve the symptomatology, streptomycin should be stopped and not be given again (unless the drug resistance pattern makes its use imperative). As streptomycin is usually given only in the intensive phase as a fourth companion drug, it can be stopped without replacement. Streptomycin should never be given to pregnant women because of the potential risk of causing deafness in the unborn child.

The patient with neurologic symptoms

A distinction should be made between peripheral and central nervous system toxicity from anti-tuberculosis medications.

Peripheral neuropathy, presenting as paresthesia, such as tingling and numbness, starting at the feet with proximal spread is the usual manifestation.[408] Myalgias, weakness, and ataxia may accompany these symptoms. Peripheral neuropathy is usually due to isoniazid, is rare and occurs usually only in malnourished or alcohol-dependent patients. Pyridoxine is effective in treating this condition, but the dosage for treatment should not exceed 50 mg per day, as there might be antagonism with isoniazid,[108] although the clinical relevance of this antagonism is not clear.

Infrequently, toxic psychosis and epileptic convulsions may occur with isoniazid, and very rarely, in patients with signs of malnutrition or malabsorption, a pellagroid syndrome (with dermatitis, diarrhea, and dementia) has been reported. Pyridoxine is usually effective for treating such cases.

The patient with hypersensitivity reactions or muco-cutaneous signs and symptoms of toxicity

Cutaneous adverse drug events, ranging from pruritus, to rashes, and most severely to toxic epidermal necrolysis, sometimes accompanied by fever, may be caused by thioacetazone, isoniazid, rifampicin, streptomycin, or pyrazinamide. Cutaneous adverse drug events are much more frequent among patients with HIV infection than among non-HIV-infected patients. If the patient is on thioacetazone, it is by far the most likely cause. It should be stopped immediately, and never be given again.

In all instances of rash with or without fever, all drugs should be stopped. When the symptoms subside, usually within a day or two, the drug least likely to be the cause should be re-introduced in a test dose. This drug is usually isoniazid and is given at a dose of 150 mg. If the patient was hypersensitive to isoniazid, a rise in temperature, pruritus, or rash will develop within two to three hours.[499] If there is no reaction to the test dose, the next test dose might be tried. Over the following days, the full dose is gradually introduced. Subsequently, rifampicin might be similarly re-introduced, starting with a test dose of 75 mg (or less), and so on. Under strict observation, it might be possible to desensitize with rifampicin much more rapidly, i.e., within two days.[643] If there is pruritus or rash only, desensitization to isoniazid might not be necessary, as symptoms often subside spontaneously.

Very often desensitization is successful, and the full range of medications can be reintroduced within one to two weeks. It should be reiterated that such desensitization should never be attempted with thioacetazone.

The patient with hematologic abnormalities

Blood dyscrasias comprise only 10% of the total number of drug-induced adverse events but account for approximately 40% of fatal reactions related to drug administration.[93] They occur with all six essential anti-tuberculosis medications. In symptomatic patients, the offending drug should be withdrawn and never be given again.

Relative leukopenia and hemolytic anemia due to isoniazid require permanent withdrawal of the drug and often treatment with corticosteroids to reverse hemolysis. Sideroblastic anemia due to isoniazid is usually responsive to treatment with pyridoxine. Rarely, other neutropenia, eosinophilia, and thrombocytopenia may occur, which will respond to withdrawal of isoniazid. Similarly, the rare pure red cell aplasia responds to withdrawal of isoniazid. Complete recovery from agranulocytosis usually occurs following withdrawal of isoniazid.

With the exception of thioacetazone, blood dyscrasias due to anti-tuberculosis drugs are rare events. It is probably exceedingly difficult to identify the offending drug in the field.

The patient with acute renal toxicity

Acute renal toxicity may be the result of a hemolytic anemia, glomerulonephritis and interstitial nephritis. The most likely cause of this rare adverse drug event is rifampicin. The drug should be withdrawn and never be given again. If renal insufficiency has developed, the dosages of ethambutol and streptomycin must be reduced according to the remaining function as these drugs are almost entirely excreted through the kidneys.

The patient with osteo-articular pain

Arthralgia is a frequent adverse drug event resulting from accumulation of uric acid due to pyrazinamide. In many instances, the dosage of pyrazinamide is higher than that recommended in patients who have such reactions and, if so, should be reduced to within the recommended limits. It often occurs towards the end of the intensive phase, when pyrazinamide can be withdrawn without replacement. Alternatively, acetyl salicylic acid commonly alleviates the symptoms. Intermittent administration of pyrazinamide will also reduce the effect of uric acid retention. Allopurinol is ineffective.

The approach to the patient with pre-existing medical conditions

Patients may present not only with tuberculosis but also other medical conditions that require modifications of the standard treatment. In this chapter, some of the major medical conditions that require such adjustments are discussed.

The patient with liver injury

Patients with mild and clinically unrecognizable liver injury, including those who abuse alcohol, may be treated with the standard treatment, which needs to be adjusted only if clinical signs of hepatitis occur as discussed in the previous chapter.

Patients presenting with clinical signs of hepatitis should not be given the drugs with the greatest potential for hepatotoxic reactions. These include isoniazid, rifampicin, and pyrazinamide. Such a patient might be treated with ethambutol plus streptomycin until the acute signs of hepatitis subside. Subsequently, isoniazid and / or rifampicin might be re-introduced under close observation. Depending on the feasibility of introducing the latter, treatment duration will need to be adjusted. If neither rifampicin nor isoniazid can be given, treatment should probably be given for 18 months. The continuation phase with streptomycin and ethambutol should not be given more frequently than three times per week to reduce the cumulative toxicity of streptomycin.

The patient with renal failure

Streptomycin and ethambutol are excreted mainly through the kidneys and are thus safe only if appropriate dose adjustments can be made in patients with renal insufficiency. This is not usually possible without access to monitoring of blood levels or measurement of creatinine clearance, a service not usually available in low-income countries. Such a patient is thus best treated with isoniazid, rifampicin, and pyrazinamide in the intensive phase. In the continuation phase, isoniazid plus thioacetazone or isoniazid plus rifampicin can be given. Treatment duration is not affected.

The patient with impaired hearing or impaired balance

Patients with pre-existing vestibulo-cochlear impairment should not be given streptomycin. Streptomycin may be replaced by ethambutol.

The patient with impaired vision

Patients with impaired vision other than due to myopia, hyperopia or presbyopia, should not be given ethambutol. Ethambutol may be replaced by streptomycin in such cases.

The patient with gastrointestinal malabsorption

Patients recognized or suspected to have gastrointestinal malabsorption may pose serious problems for adequate chemotherapy, as shown in a study on risk factors for acquisition of rifampicin monoresistance.[644] On the other hand, a study among HIV-infected patients in Nairobi has not demonstrated important differences in pharmacokinetic profiles of isoniazid, rifampicin, and ethambutol between patients with and patients without HIV infection, and no association with diarrhea.[584] Similarly, studies in South Africa have shown that malabsorption in asymptomatic HIV-infected patients is not a major issue and no important pharmacokinetic differences have been seen in a series of AIDS patients.[585] Thus, malabsorption of anti-tuberculosis medications in HIV-infected patients may not be that serious a problem. Nevertheless, it is probably reasonable to always include the parenteral streptomycin in patients suspected of having malabsorption.

The pregnant patient

Pregnant women with tuberculosis do not pose particular problems for treatment. Dose adjustment is probably indicated with increasing body weight as the volume of distribution increases. Because of the potential of vestibulo-cochlear toxicity to the fetus, streptomycin should not be given in pregnancy. Isoniazid, rifampicin, ethambutol, pyrazinamide, and thioacetazone are safe in pregnancy, and are not reported to have teratogenic or other adverse effects on the fetus.

Second-line drugs that should be avoided in pregnancy include other aminoglycosides, polypeptides, thioamides, and quinolones.

2. Prophylactic treatment

In this monograph, prophylactic treatment is defined as treatment to prevent acquisition of infection with *M. tuberculosis* in a person exposed to tubercle bacilli. Its aim is to minimize the risk of acquiring latent infection.

Little evidence is available to document the efficacy of such prophylactic treatment. The little that is known is summarized here.

Rationale and experiences with prophylactic treatment

In the early 1950s, Zorini reported experiments with prophylactic treatment in guinea pigs, using various dosages of isoniazid.[645,646] Briefly, guinea pigs were given isoniazid or placebo in their drinking water for one month and then challenged with an endoperitoneal injection of *M. tuberculosis*. The results were unequivocal in that a considerably larger proportion of placebo-treated animals developed tuberculosis in comparison to those receiving isoniazid.

Among humans, the effect of isoniazid compared to placebo in preventing tuberculin skin test conversion has been ascertained within the context of clinical trials on preventive chemotherapy.[641] A tuberculin skin test was given before random allocation to either isoniazid or placebo for one year. At the end of treatment, the rate of conversion among persons who were initially tuberculin skin test negative was compared in the two groups. These four US Public Health Service studies were conducted among various groups of patients (patients in a mental institution, contacts of known cases, school children, and contacts of newly diagnosed tuberculosis patients). The protection afforded against conversion from a negative to a positive tuberculin skin test after one year of treatment with isoniazid in these studies is summarized in figure 53.[641] It shows that the confidence intervals are wide (small numbers eligible for assessment), and thus that the extent of protection is uncertain.

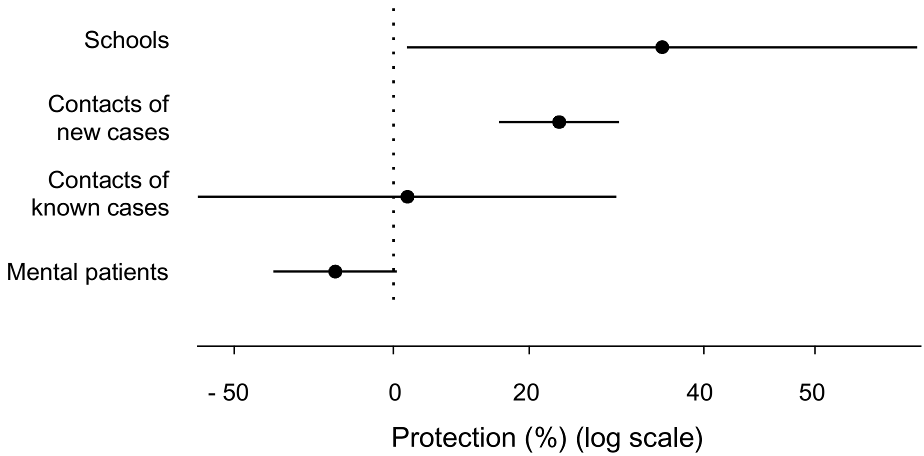

Figure 53. Protection from prophylactic treatment in the prevention of acquisition of tuberculous infection in four clinical trials conducted by the US Public Health Service.[641]

Indications and recommendations for the use of prophylactic treatment

Prophylactic treatment is, for all practical purposes, rarely indicated. Even if the evidence is scant, however, it makes sense to provide it to a newborn child with a potentially infectious parent, especially the mother. This is recommended in industrialized countries,[356] but should most likely be a universal indication.

It is not clear what the appropriate duration of prophylactic treatment should be. It is probably indicated, however, to continue it for perhaps up to three months after relevant exposure has ended.

Children under the age of five years are also at high risk of acquiring tuberculous infection from a person with sputum smear-positive tuberculosis living in the same household and, if they become infected, are at high risk of progression to clinically manifest tuberculosis. The IUATLD has thus recommended systematic treatment with isoniazid of asymptomatic children in such a situation.[8] Some of these children will not yet have been infected (the infected being the primary target group) and will thus receive true prophylactic treatment.

3. Vaccination

Early vaccine development

Vaccination with *Mycobacterium tuberculosis*

Early in the twentieth century, von Behring attempted vaccination (or as he called it, “Jennerization”) of cattle by utilizing increasing doses of living *M. tuberculosis*.[647,648] Similar to these attempts, Webb in the United States tried to make experimental animals resistant to re-challenge with increasing doses of virulent *M. tuberculosis*, and a few children were also “vaccinated” with this approach, apparently with no adverse outcome.[649] While this approach seemed indeed to provide some protection against a subsequent challenge in cattle and other experimental animals compared to controls, protection was incomplete in the case of von Behring’s “bovo-vaccination” and in the guinea pig. Furthermore, with “Jennerization” in cattle there was the potential that the microorganism would appear in milk.[650] Theobald Smith also pointed out that the unknown duration of the incubation period carried great dangers, even if the immediate effect seemed to be innocuous.[650] This approach was therefore only short-lived.

However, more recently, the idea of attenuating *M. tuberculosis* and using such an attenuated strain as a vaccine has been picked up again, and it is expected that the vaccine properties of such mutants will be tested at least experimentally in the near future.[651]

Vaccination with *Mycobacterium chelonae*

Early in the twentieth century, Friedmann proposed vaccination with *M. chelonae*, a mycobacterium recovered from the turtle.[652] Because the argument of vaccination was largely based on the hypothesis that persons ill with tuberculosis could develop increased resistance in suppressing progression from morbidity to death, this method was mainly used in the treatment of clinically manifest tuberculosis.[653] There was probably no effect at all if judged by current standards. Only a very small study was published reporting the results of *M. chelonae* vaccination in children exposed to tuberculosis but without clinical signs of the disease.[654] The study was too small to allow a meaningful interpretation of the efficacy of this vaccination. The method never gained much attention beyond Germany, and fell into oblivion as vaccination with BCG drew increasing attention in the immediately succeeding years.

Vaccination with BCG

Vaccine development

A virulent strain of *M. bovis*, isolated by Nocard in 1902, from milk obtained from a cow with tuberculous mastitis[655] was inoculated for the first time on January 8, 1908, by Albert Calmette (1863-1933) and Camille Guérin (1872-1961)[656] at the Pasteur Institute in Lille, France[657] onto a medium consisting of cooked potato and glycerinated bile.

The strain, to become known as Bacille Calmette-Guérin (BCG), was sub-cultured in 230 passages on bile potato medium until 1921 when it no longer changed its characteristics.

After thirty passages the strain ceased to kill guinea pigs; after sixty it was still slightly virulent for rabbits and horses, but avirulent for guinea-pigs, monkeys, and calves.[655] From 1912 onwards, experiments were conducted among calves, demonstrating their resistance to subsequent infection with virulent bacilli.[655] It may be noted that the main objective in the development of this vaccine was to obtain an effective vaccine against tuberculosis in goats[658] and cattle.[658,659] It is now clear that it was not the glycerinated bile medium that was the reason for the loss of virulence.[660,661] By sub-culturing four bovine strains on Calmette's bile-potato medium over six years, Griffith failed to reproduce Calmette's finding and to induce stable attenuation.[662] The reasons for the loss of virulence of *M. bovis* BCG remain unclear until today.

On July 1, 1921, Weill-Hallé, a pediatrician, requested the vaccine for use in an infant born to a mother who had died of tuberculosis shortly after delivery. The child was to be brought up by a grandmother who was herself suffering from tuberculosis.[663] The child was given 6 mg of BCG orally and developed normally over the next six months without any sign of illness, either from the vaccine or from tuberculosis.[655,663] Over the next three years, 317 infants (67 of whom were born into, and brought up by families with tuberculosis patients) were vaccinated with 30 mg oral BCG vaccine, given in three portions at 48-hour intervals.

Following these early experiments in humans, BCG was distributed to a large number of laboratories, largely in Europe, and given to hundreds of thousands of children within a decade after its introduction.[664-667] Trials to evaluate its impact began in Europe[668-670] and North America.[671,672]

Controlled assessment of the vaccine's efficacy was conspicuously absent, and one of its most violent opponents was Petroff in the USA, who doubted both the vaccine's innocuousness and efficacy.[673,674] Despite the justified concerns about the quality of the data on efficacy given all the methodological problems (such as selection bias), it seemed apparent that BCG reduced case fatality from tuberculosis among exposed children in a variety of settings (figure 54).[666] It also seemed to protect adult student nurses heavily exposed to tuberculosis both from death and disease (figure 55).[668-670,675]

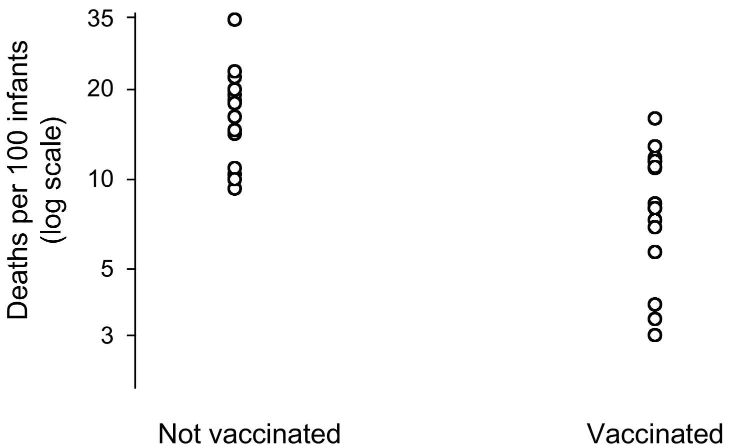

Figure 54. Early, non-controlled comparisons in crude infant mortality before and after introduction of BCG vaccination in 16 countries, reported up to 1932.[666]

The assumption of the safety of BCG vaccination was severely challenged when 72 of 251 children who were presumably vaccinated with BCG between December 10, 1929, and April 30, 1930, died from tuberculosis in Lübeck, Germany.[676-678] While not all circumstances surrounding this disaster have ever become public,[679] it soon became apparent that BCG was not the cause. The preliminary epidemiologic analysis in July 1930 already showed large differences in case fatality by week of vaccination (figure 56), indicating that strains with different virulence had been mixed.[680] This was bacteriologically confirmed by demonstrating that virulent tubercle bacilli, but not BCG, were consistently isolated on autopsy.[676] The epidemiologic

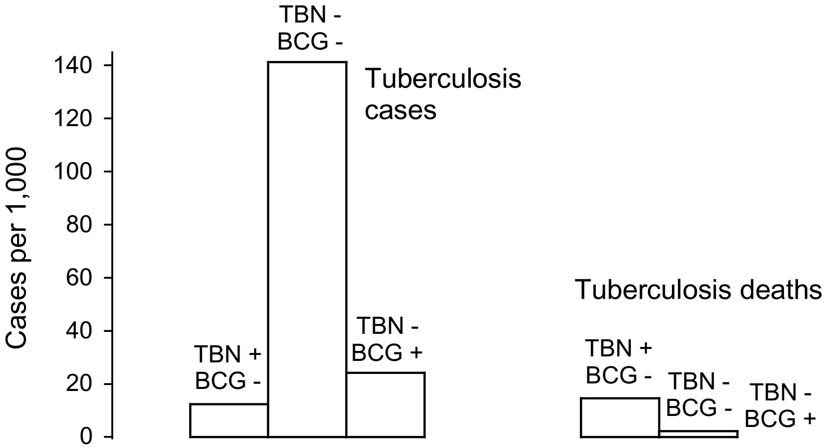

Figure 55. Results from a non-randomized, self-selection evaluation of the effect of BCG vaccination on tuberculosis cases and deaths among student nurses in Norway.[670]

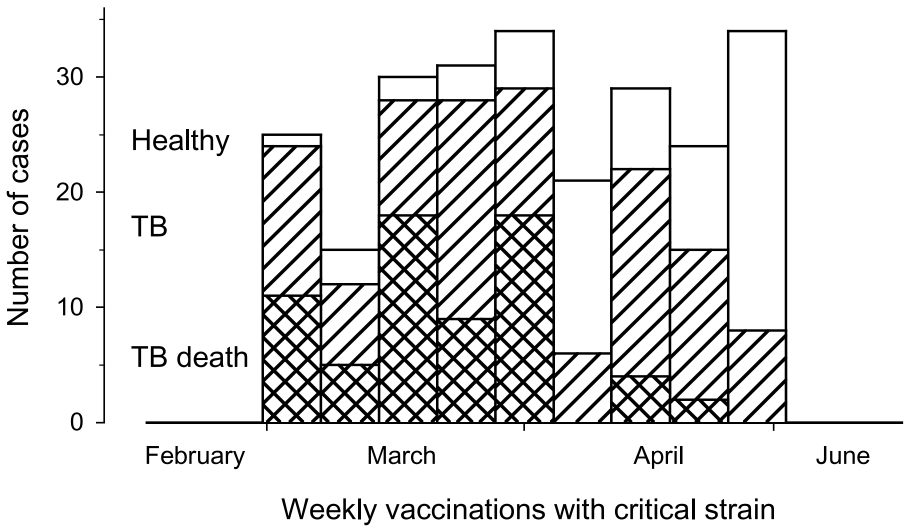

Figure 56. Curve of the tuberculosis epidemic following an accidental mix of BCG vaccine strain with a virulent strain of *Mycobacterium tuberculosis* in Lübeck, Germany, 1930.[676]

and bacteriologic investigations demonstrated conclusively that batches containing both BCG and *M. tuberculosis* in varying proportions had been fed to the infants during the epidemic.[676,678,681,682] Among the 53 fatal cases ascertained by mid-July 1930, the interval between vaccination and death ranged from 34 to 129 days with a median of 79 days.

Petroff's concerns about a reversion to virulence of BCG have never been confirmed, and his observation of different colony morphology with virulent and avirulent colonies[673] have not been confirmed elsewhere.[676]

The BCG strain family

Until the introduction of freeze-drying in Japan in 1943,[683] the only means of maintaining a viable strain was through sub-culturing. With the distribution of the vaccine strain to multiple laboratories in the world, each using slightly different techniques for strain maintenance, it is not surprising that the BCG family shows large diversity.[660] The first freeze-dried French strain (1949) from the Pasteur Institute in Paris was strain 1173-P_2, from which the Glaxo and Danish strains descended.[684]

Recent work based on molecular characterization of the various sub-strains points to various mutations that have occurred at different points in time (figure 57),[685-687] and indicates that the various BCG sub-strains are morphologically and genetically different from each other.

Safety record of BCG vaccination

A large review has shown BCG to be one of the safest vaccines.[688,689] The demarcation between a normal reaction and an adverse reaction is not always clear.[690] The normal reaction is a red indurated area measuring five to 15 mm. A crust is formed around this induration, which is soft at the center for three to four weeks. At six to ten weeks, the crust falls off, leaving a flat scar measuring three to seven millimeters.[690] Regional lymphadenopathy in the absence of erythema or vesicle formation should also be considered a normal reaction to the vaccine.[691] Complications include cutaneous lesions and regional suppurative lymphadenitis; more severe localized or multiple lesions (such as musculo-skeletal lesions);[692-694] and non-fatal and fatal complications resulting from hypersensitivity reactions or mycobacterial dissemination.[688,689,695-702] The risk of complications varies with the type of vaccine and with the age at vaccination. The risk of osteomyelitis ranged from 0.01 to 50 per 1 million vaccinations, that of multiple or generalized lesions from 0.01 to 2 and that of fatal cases from 0.01 to 1 per million vaccinated individuals.[688,689] The lowest complication rates were reported with the Tokyo strain, and the highest with the Gothenburg strain produced in Denmark.[692,703]

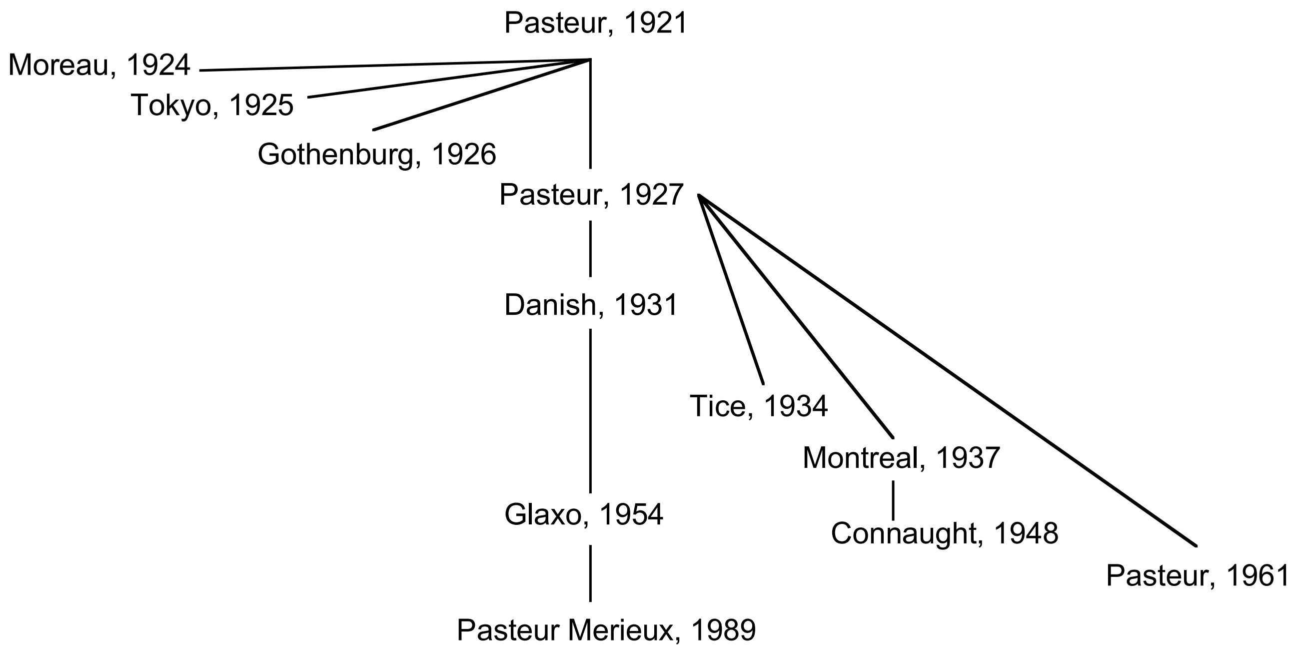

Figure 57. Proposed genealogical tree of BCG vaccine substrains since isolation at the Institut Pasteur in 1921. Reproduced from[686] by the permission of the publisher Churchill Livingstone.

In a prospective study in South Africa among 10,000 neonates receiving the Copenhagen strain intradermally at birth, at six weeks post vaccination the vaccination scar had healed in more than 95% of children, 1.5% had no vaccination scar, and in 3% adverse events were noted.[704] All adverse events were local (oozing, abscesses, rarely combined with lymphadenopathy).

Because BCG is a live vaccine, concerns were raised early on about the safety of its use in persons infected with HIV,[705-707] and several case reports about disseminated mycobacteriosis[708-714] and mycobacterial meningitis due to BCG[708,710,715] have been published. A study among mother-child pairs with and without HIV infection has shown that children of mothers with HIV infection who also had HIV infection themselves had a slightly increased risk of suppurative lymphadenitis, but the manifestations were mild and easily manageable (figure 58).[716] Apparently, living BCG can persist for decades and cause localized[717] or disseminated[718] complications after acquisition of immunosuppression. Nevertheless, most of these case reports appear to be isolated events, although it has been argued that disseminated disease attributable to BCG vaccination in HIV-infected children might be exceedingly difficult to diagnose.[719] However, a study in Zambia among HIV-symptomatic children with a median age of 15 months, showed that mycobacteremia due to BCG must be exceedingly rare.[720] A recom-

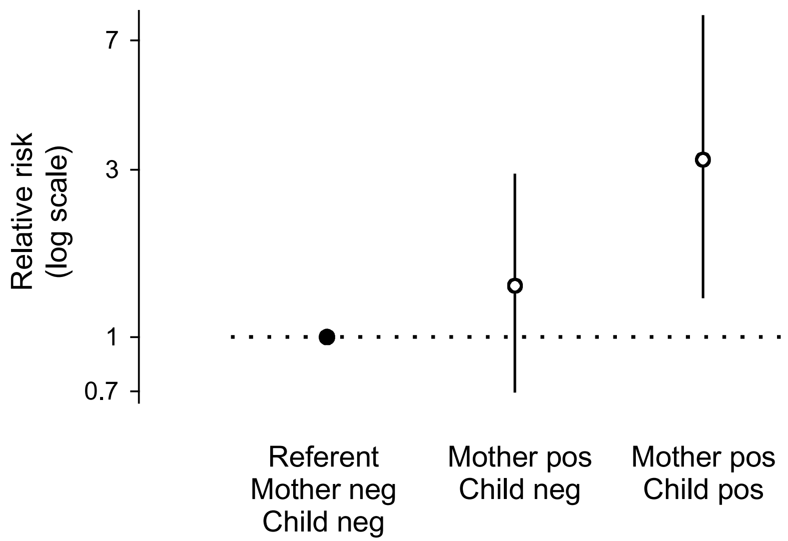

Figure 58. Relative risk of a complication following BCG vaccination among children born to an HIV-infected mother.[716]

mendation by WHO states that no principal changes in BCG vaccine policy are warranted unless children present with symptomatic HIV infection,[721] a statement that has not been challenged.[722,723]

Management of adverse reactions due to BCG vaccination

Children with lymphadenitis due to BCG were randomly allocated to receive either isoniazid or no treatment.[724] There was no difference in the duration of lymphadenitis between the two groups, nor did isoniazid prevent the occurrence of suppuration. Similarly, children with abscess formation were randomly assigned to receive either isoniazid or erythromycin (serving as placebo).[725] The response in each treatment group was the same. In another study, comparing excision, excision plus isoniazid, and isoniazid alone compared to a control group without intervention, no significant differences were observed between the various interventions, and in particular, isoniazid offered no advantage.[726] Non-suppurative lymphadenitis is a normal reaction, and is best left without antibiotic treatment.[690,727]

Patients with suppurative lymphadenitis following BCG vaccination were randomly assigned to treatment with simple needle aspiration, introducing the needle subcutaneously two to three centimeters distant from the node, versus no treatment.[728] Regression was significantly faster in the treated than in the non-treated group, and spontaneous drainage was less frequent.

For osteoarticular mycobacteriosis due to BCG, combination therapy is indicated, but results were not always favorable (both in terms of sequelae and relapses) in a case series from Sweden.[729]

A standard course of treatment (as for clinically manifest tuberculosis) is also indicated in disseminated mycobacteriosis due to BCG. As this is a rare complication, however, treatment regimens have not been amenable to formal study. In treatment, it should be kept in mind that BCG is, like its parent organism, *M. bovis*, naturally resistant to pyrazinamide.

Efficacy and effectiveness of BCG vaccination

Efficacy is the extent to which an intervention produces a beneficial result under ideal conditions. The best setting to address efficacy is thus prospectively, in a controlled clinical trial. In contrast, effectiveness takes the various constraints that are found in the field into account in the actual routine delivery of the intervention.[730] Effectiveness is often ascertained retrospectively, such as in case-control studies. Efficacy (in clinical trials) and effectiveness (in case-control studies) have been ascertained in various settings. The principle underlying the design of prospective and retrospective studies is summarized in table 10. These trials were supplemented by community trials and contact studies. The variation in estimates of protection ranged widely, from harm (more cases among the vaccinated than among controls) to a high level of protection.

The efficacy of BCG vaccination is best ascertained in a prospective clinical trial, while an estimate of its effectiveness in routine application might be obtained through retrospective studies, such as case-control, contact, or case-population studies, although possible confounding effects cannot be controlled so easily.

Briefly, clinical trials are a prospective ascertainment of cases occurring among the exposed. Clinical trials thus start with looking at the exposure (BCG vaccination given or not) and then ascertain the outcome (tuberculosis) in a group of individuals, preferably randomly assigned to exposure (table 10).[731] These are population-based studies and the denominator is

Table 10. Study design of clinical trials and case-control studies.

Design of a clinical trial

Exposure	Outcome		Person-time of observation
	Characteristic present	Characteristic absent	
Exposure present	A	–	E
Exposure absent	C	–	F
Total	A+C	–	E+F

Incidence rate among the exposed: A / E
Incidence rate among the unexposed: C / F
Relative risk: (A / E) / (C / F).

Design of a case-control study

Exposure	Outcome		Total
	Case	Control	
Exposure present	a	b	a+b
Exposure absent	c	d	c+d
Total	a+c	b+d	N=a+b+c+d

Odds among the exposed: a / b
Odds among the unexposed: c / d
Relative odds: (a / b) / (c / d).

the number of person-years of observation. The measures are incidence rates among the exposed and unexposed and the summary measure is the relative risk (the risk among the exposed divided by the risk among the unexposed). Vaccine efficacy (in per cent) is calculated as (1 – relative risk) × 100.[732] The 95% confidence intervals were calculated (or recalculated, where appropriate) using the formula proposed by Orenstein in his review on assessment of vaccine efficacy,[732] unless adjusted or stratified summary estimates were provided by the authors.

To defray the costs incurred in clinical trials and to obtain results more quickly, it was proposed to ascertain the effectiveness of BCG vaccination by means of (retrospective) case-control studies.[733] Briefly, case-control studies start with looking at the outcome (tuberculosis) and then ascertain exposure (BCG vaccination given or not) in a group of patients with the outcome, compared to an appropriately selected control group of persons without the outcome (table 10).[734] A relative risk cannot be calculated as this measurement is confined to population-based studies. The measurement of risk in a case-control study is the odds ratio (or relative odds). For rare diseases the odds ratio approximates the relative risk in a clinical trial.

The advantages and disadvantages in the use of the case-control approach are linked to its being observational, having subjects selected on the basis of disease status, and using controls from the population from which the cases emanated.[735] The advantages of case-control studies include avoidance of ethical problems arising in situations where there is already evidence that the vaccine is better than placebo; allowing much faster conduct than randomized trials; and requiring a much smaller number of subjects. They are thus substantially cheaper to conduct than randomized clinical trials.[735]

The most challenging difficulty in the design of case-control studies is the selection of appropriate controls in that they have to be selected in such a way that they are comparable to cases in every respect except for the outcome. Selection bias resulting from a failure to ensure this comparability may thus invalidate any findings.

The results of some of these case-control studies are summarized below. Vaccine effectiveness (in per cent) from a case-control study is estimated as (1 – odds ratio) × 100.[732] For unmatched case-control studies, the 95% confidence intervals were calculated (or recalculated where appropriate) using Woolf's method.[734] For matched and adjusted analyses, the confidence interval published by the authors of the study was chosen. If not stated for matched studies, the confidence interval around the crude odds ratio was calculated as above.

Prospective and retrospective studies on BCG vaccination

In one of the first clinical trials with a methodologically fairly acceptable design (systematic alternate allocation), BCG was given to children exposed to a parent with tuberculosis and compared to a similar group who did not receive the vaccine.[736] The impact on fatality was dramatic, with an 82% reduction in the risk (figure 59). Nevertheless, suspicion about the efficacy of BCG vaccination persisted, particularly in the United States,[737] but also in the United Kingdom,[679] largely because the design of many studies was dubious at best.

One of the most conspicuous differences observed in the protection afforded by BCG reveals that age at vaccination is important. Of further crucial importance is the type of tuberculosis that is targeted for protection by vaccination.

In the following summary of the best-known studies in the English literature, the studies are identified as being prospective or retrospective. For each of these two study types five classes were examined:

- protection against disseminated and meningeal tuberculosis, and against death from tuberculosis;
- protection afforded to children by vaccination of newborns or infants;
- protection afforded by vaccinating children beyond the age of one year;

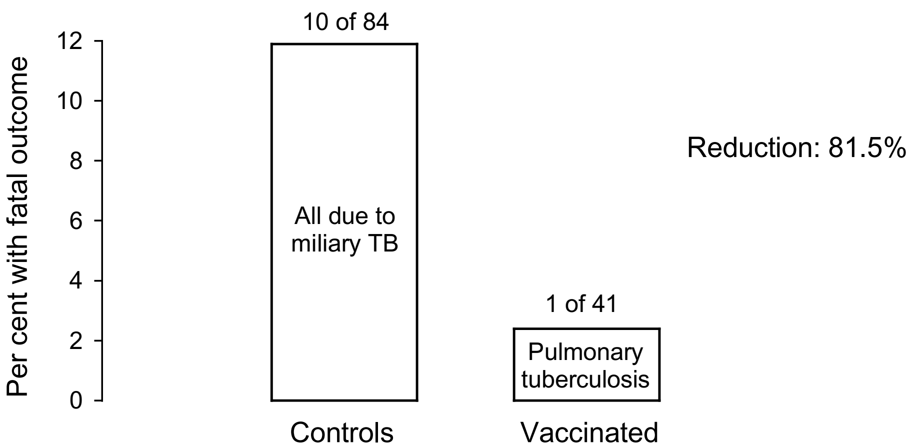

Figure 59. Comparative case fatality from tuberculosis among newborns vaccinated and not vaccinated with BCG in a clinical trial with systematic assignment to the experimental or control arm.[736]

- protection afforded by vaccinating adolescents or adults;
- protection afforded by vaccinating people of various ages.

Protection conferred by BCG vaccination against disseminated and meningeal tuberculosis, and against death from tuberculosis

Five major prospective studies have looked into the protection afforded by BCG vaccination against death from tuberculosis (figure 60).[736,738-744] All of these studies were conducted before the advent of curative chemotherapy. Four of the studies showed a point estimate of the protective efficacy of 80% and above, and one afforded no protection. The confidence interval was wide in all studies, because the number of events was small.

Several retrospective studies (including two using two different control groups) examined the protection against disseminated and meningeal tuberculosis (figure 61).[745-747,747-753] The protective effectiveness was usually in excess of 80% and in no case did the 95% confidence interval include zero.

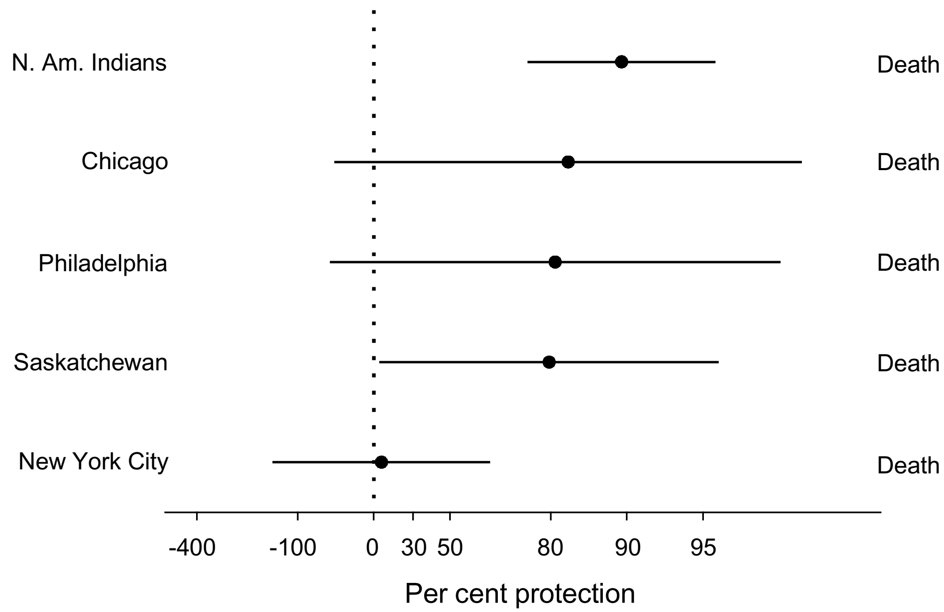

Figure 60. Results from five controlled clinical trials to evaluate the efficacy of BCG vaccination against death from tuberculosis.[736,741-744]

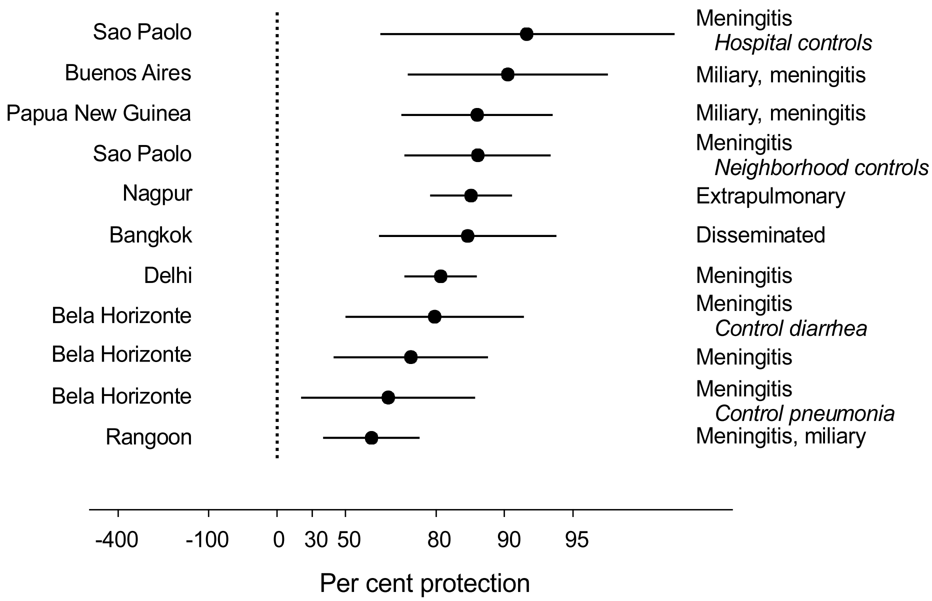

Figure 61. Results from retrospective studies on the effectiveness of BCG vaccination against death from meningeal, other extrapulmonary, or disseminated tuberculosis.[745-747,747-753]

It may be concluded from these studies that BCG affords very good protection against death from tuberculosis, and against disseminated and meningeal tuberculosis.

Protection conferred by BCG vaccination of newborns and infants

Three prospective studies looked into the protective efficacy of BCG given to newborns or infants against all forms of tuberculosis or morbidity (figure 62).[742,743,754] The point estimate of the efficacy was between 50% and 80%.

Several retrospective studies examined the effectiveness of newborn or infant vaccination (figure 63).[747,748,753,755-762] The level of protection in these studies varies widely, but frequently above 50%. Noteworthy is the study from Zambia, which stratified effectiveness estimates by HIV status,[760] showing that HIV-infected children had no protection as compared to 60% protection among HIV-negative children.

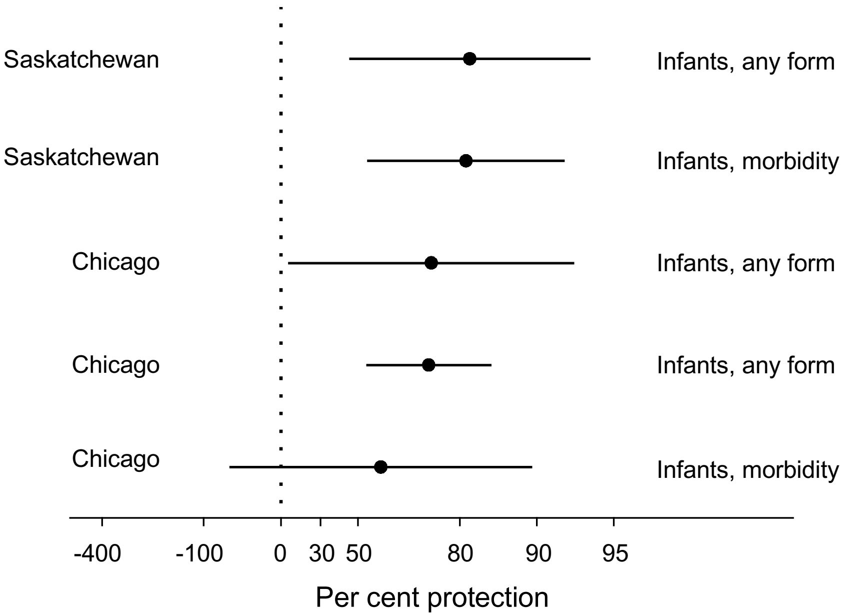

Figure 62. Results from prospective studies on the efficacy of BCG vaccination against tuberculosis in newborns and infants.[742,743,754]

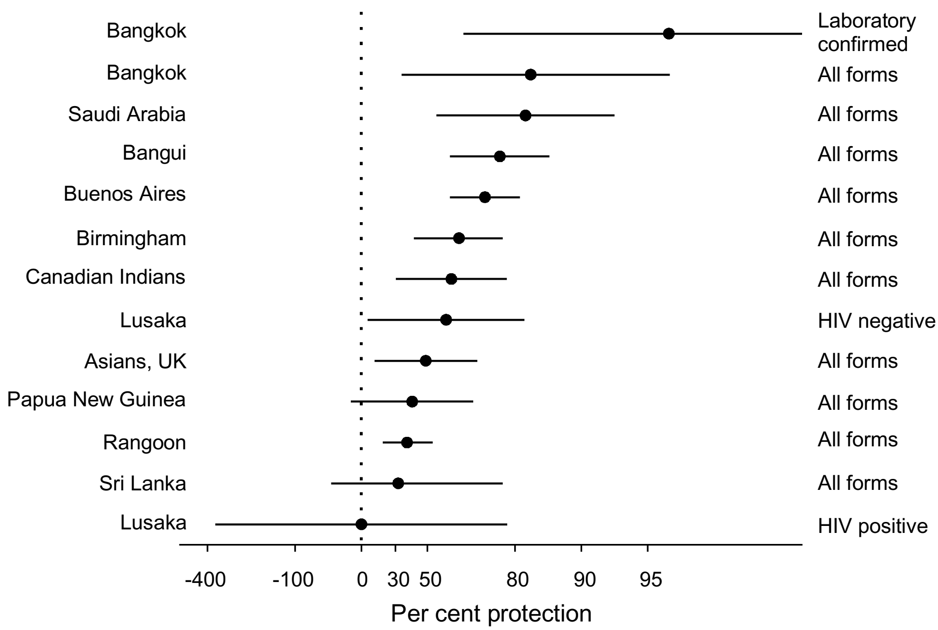

Figure 63. Results from retrospective studies on the effectiveness of BCG vaccination against tuberculosis in newborns and infants.[747,748,753,755-762]

Protection conferred by BCG vaccination of children over one year of age

Only three protective studies of BCG vaccination of older children are available (figure 64).[763-768] All three showed a very low level of protection, of less than 30%. In Chingleput, south India, where BCG gave little or no protection, there was a tendency to provide some protection in children below the age of 15 years, but a similar tendency towards harm (more cases in the vaccinated than the non-vaccinated) in older persons (figure 65).[765]

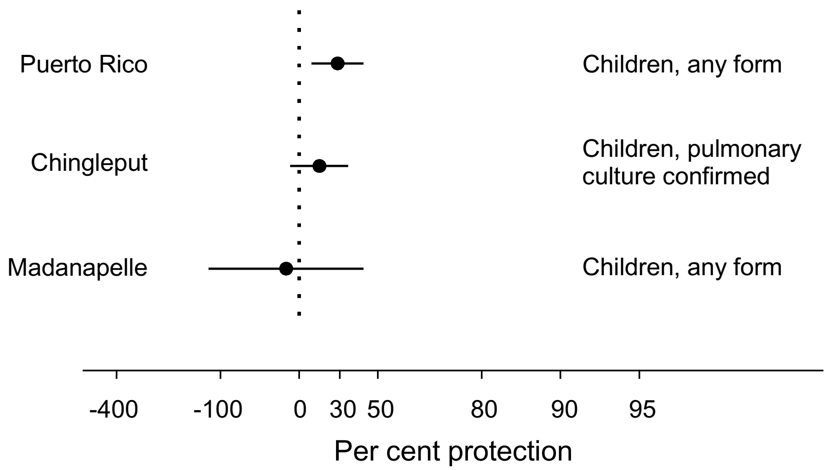

Figure 64. Results from prospective studies on the efficacy of BCG vaccination against tuberculosis in children other than infants.[763-768]

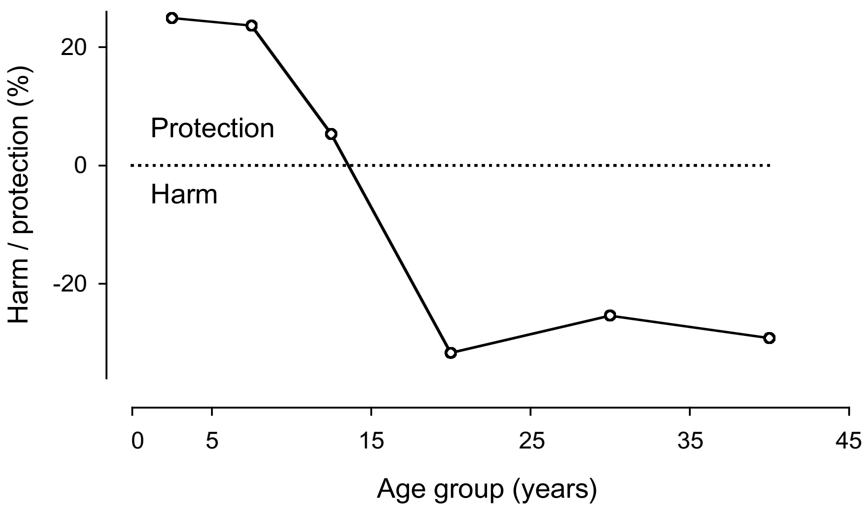

Figure 65. Protection from BCG vaccination by age, Chingleput, India.[765]

Three retrospective studies among children also showed very variable levels of protection, from 16% to 74% (figure 66).[750,769,770]

These studies seem to show that vaccination of older children does not offer protection against tuberculosis that is as reliable as vaccination at an earlier age.

Protection conferred by BCG vaccination among adolescents and adults

Six prospective studies have examined the protection of BCG vaccination against tuberculosis among adolescents or adults (figure 67).[668,670,763-765,767,768,771-778] The study in Ulleval, Norway, was the first ever conducted prospective study.[668,670] It does, however, not live up to current requirements for a controlled trial, as student nurses with a negative tuberculin skin test at entry could choose whether to be vaccinated or not. In this context, the study conducted in England (where *M. microti*, not BCG was used) remains the only study of high standard that has shown a very high level of protection, of close to 80%, in this age group.[771-776] The other studies show little or no protection, with a tendency to reveal a potentially harmful effect in India.[763-765,777] In England, protection appeared to last for about 10 years before dropping rapidly (figure 68).[776] In contrast, in Chingleput, where there was no overall protection, vaccination appeared to confer harm (more cases than in the control group) in the first five years and minimal protection subsequently (figure 69).[765]

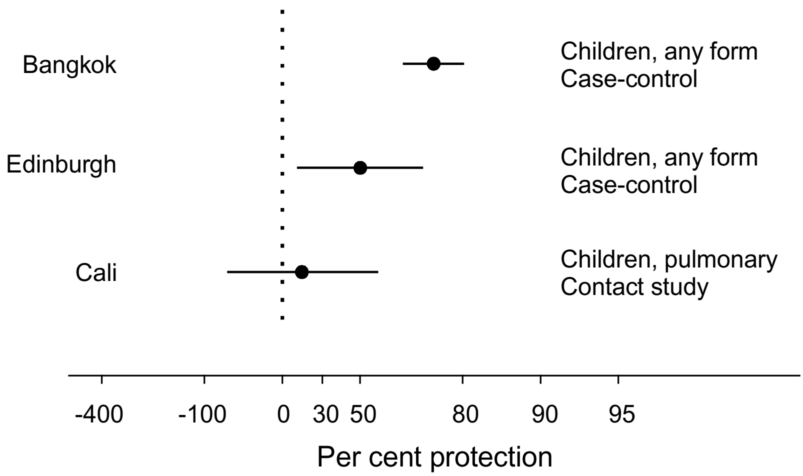

Figure 66. Results from retrospective studies on the effectiveness of BCG vaccination against tuberculosis in children other than infants.[750,769,770]

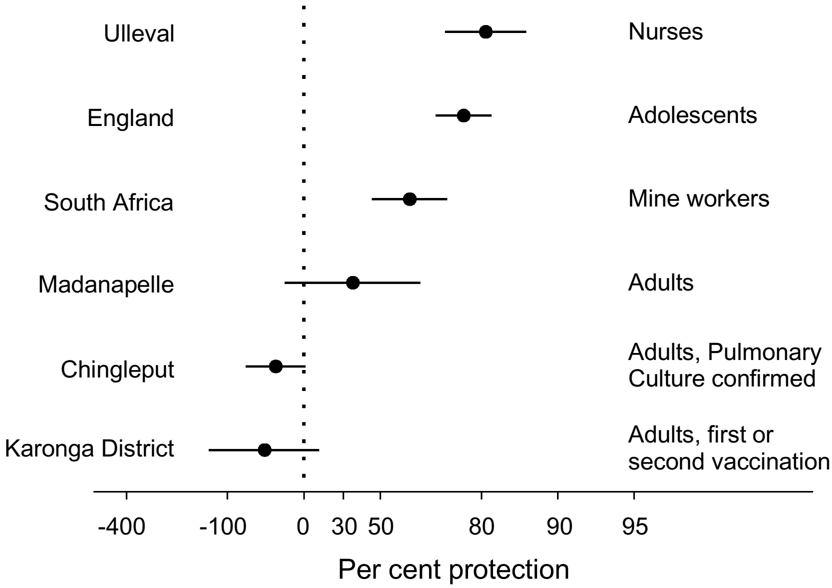

Figure 67. Results from prospective studies on the efficacy of BCG vaccination against tuberculosis in adults.[668,670,763-765,767,768,771-778]

The two retrospective studies show a protective effectiveness of 10%[779] and close to 60%,[780] respectively (figure 70).

These studies seem to indicate that vaccination of adolescents or adults is rarely a useful intervention.

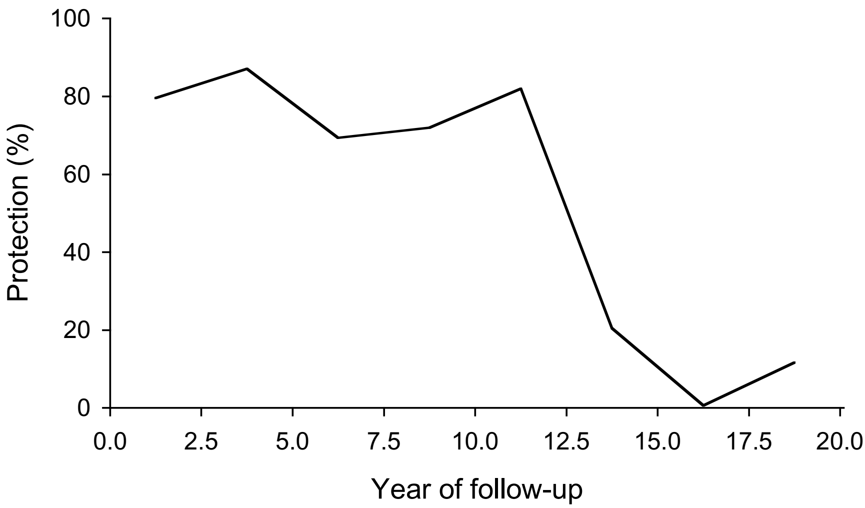

Figure 68. Protection from BCG vaccination among British school children during follow-up.[776]

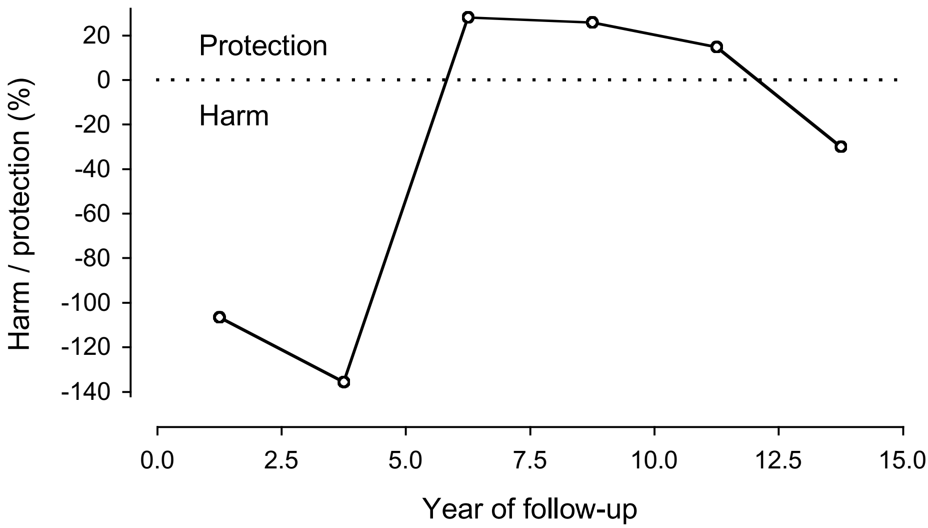

Figure 69. Protection from BCG vaccination in Chingleput, India during follow-up.[765]

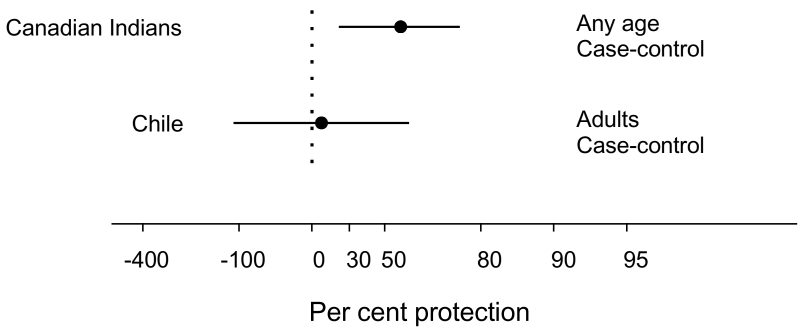

Figure 70. Results from retrospective studies on the efficacy of BCG vaccination against tuberculosis in adults.[779,780]

Protection conferred by BCG vaccination across various age groups

Of the seven clinical trials studying protective efficacy across a wide range of age groups, with a preponderance of persons other than infants, two showed a high level of protection, of around 80%, while all of the others showed little or no protection (figure 71).[738,763-765,767,768,781-787]

These observations reconfirm that utilization of BCG vaccination in age groups other than infants is rarely an effective intervention.

One retrospective study from the Gambia reported that 35 patients among 200 without a BCG scar died during chemotherapy, while none of

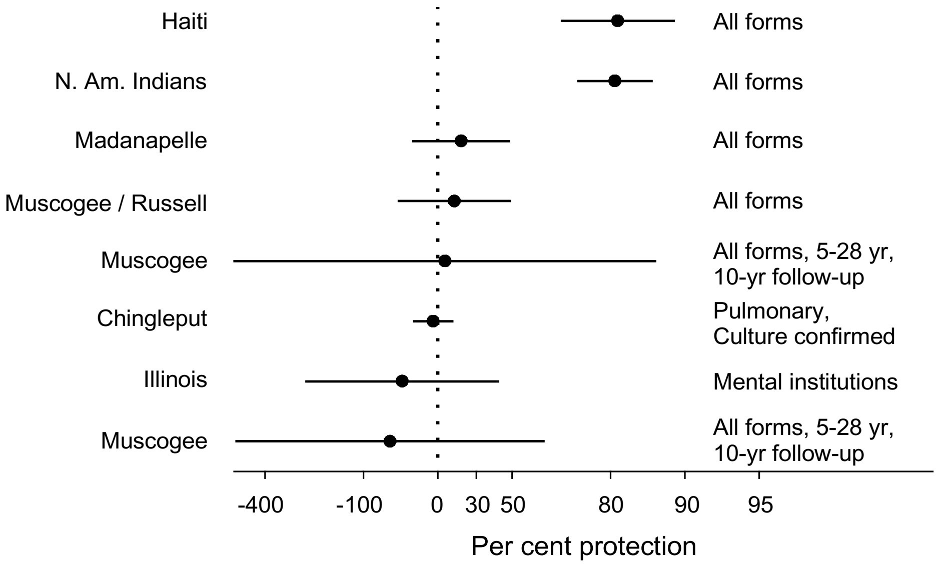

Figure 71. Results from prospective studies on the efficacy of BCG vaccination against tuberculosis in all ages.[738,763-765,767,768,781-787]

85 with a BCG scar did so.[788] While considerable attention was paid to adjustment for potential confounding factors (yet the effect remained), the authors were still cautious in concluding that BCG vaccination reduces case fatality from pulmonary tuberculosis.

Hypotheses about the variation in the efficacy of BCG vaccination

While the overall evidence is quite clearly in favor of a protective effect of BCG vaccination, the observed variations are large in both prospective and retrospective studies. A number of hypotheses have been formulated to address these discrepancies. Smith[789] and Smith and Fine[790] have comprehensively reviewed the evidence, and the following outline is guided by, and draws heavily on, their assessment.

The principal hypotheses to explain the variations observed in the protection offered by BCG include:

- Differences in methodological stringency;
- Differences in vaccine strains;
- Differences in vaccine dose;

- Differences in virulence of *M. tuberculosis* strains;
- Differences in risk attributable to exogenous reinfection tuberculosis;
- Differences in genetic make-up of vaccinees;
- Differences in nutritional status of vaccinees;
- Differences in prevalence of infection with environmental mycobacteria;
- Other factors.

Differences in methodological stringency

Quite obviously, not every study can be methodologically as rigorously conducted as ideal standards of study design and conduct call for.[731,734] Among the clinical trials, several have been excluded from major reviews and meta-analyses such as those conducted by Colditz and collaborators.[791,792] These authors found that study validity score explained 66% of the variation in prospective clinical trials and 36% in retrospective case-control studies,[791] and only 15% in case-control studies on BCG protection against infant tuberculosis.[792] Nevertheless, perhaps the most relevant trial showing no protection against bacteriologically confirmed tuberculosis, conducted in Chingleput, India, was judged to be of high scientific quality by a WHO expert committee specifically charged to ascertain the trial's validity.[793]

It must be kept in mind that the range of protection cannot be taken at face value, but must also be seen in the context of what the study in question sought to address. BCG trials (be they prospective or retrospective) ascertained protection against various outcomes such as morbid state (tuberculosis or death from tuberculosis) and site of disease, e.g., pulmonary, extrapulmonary single site, and disseminated tuberculosis, taking into account such things as bacteriologic certainty of the case, age of the patients, and time elapsed since vaccination. What seems apparent from the studies is the tendency of BCG to provide its greatest protection within the few years following vaccination, against death from tuberculosis, disseminated disease manifestations, and bacteriologically unconfirmed tuberculosis. In summarizing these effects, BCG is generally most effective against serious forms of tuberculosis occurring shortly after infection acquired at an early age. Thus, any evaluation of the protective efficacy of BCG vaccination should be stratified according to these variables.

Differences in vaccine strains

The available BCG vaccine strains differ widely in phenotype and genotype.[660,661,685,686] It has been proposed[794] that differences in vaccine strains may account for observed variations in vaccine efficacy. In the rabbit model, not all BCG (and *M. microti*) strains provided the same level of protection.[795] However, the most powerful argument against this hypothesis arises from the Chingleput study, where two vaccine strains were used[763-765] that had documented high efficacy in other settings but were not shown to be efficacious in Chingleput. Furthermore, one of the studies (a case-control study from Indonesia) cited for evidence of differential effectiveness of strains, examined successive vaccination policies, and was thus by necessity a non-concurrent study which additionally failed to adjust for time elapsed since vaccination.[796]

Differences in vaccine dose

BCG has been administered through various routes, initially orally, then parenterally. The latter administration may have been given intradermally or transdermally via multipuncture devices. The dosage reaching the target thus may well have varied. Nevertheless, the following observations seem to contradict the argument of an influence of differential dosage effect. Three controlled clinical trials with low efficacy used multipuncture administration,[768,785,786] and one with high efficacy did so too.[742] Furthermore, the trial in Chingleput specifically considered in its design the possibility of deterioration of vaccine potency in the field, and allocated vaccinees also to two arms receiving a ten-fold difference in dose, with no difference in effect.[763-765]

Differences in virulence of *M. tuberculosis* strains

That not all tubercle bacilli are equally virulent has been demonstrated repeatedly both for *M. bovis* BCG[797] and *M. tuberculosis* in general,[798,799] and for isoniazid-resistant strains in particular.[38,800-802]

The hypothesis that the relative frequency of more or less virulent tubercle bacilli affects the observed protective efficacy of BCG vaccination is based on the argument that tubercle bacilli of lower virulence might also cause tuberculin skin test reactions of smaller size. Such persons then might be classified as “non-reactors”, i.e., persons not infected with tubercle bacilli, thus becoming eligible for vaccination. Vaccination of actually infected persons may thus mask any protective effect of BCG vaccination, as vaccination is not expected to provide protection against those who are already infected.[803]

The argument fails to account for the fact that BCG provided no protection at all in some trials. Depending on the proportion of individuals who had escaped infection with environmental mycobacteria at the point of BCG vaccination, masking of protection by BCG vaccination would be expected to be incomplete.

Differences in risk attributable to exogenous re-infection tuberculosis

BCG vaccination is expected to provide protection against tuberculosis resulting from infection acquired subsequent to vaccination. It is not expected to provide greater protection than a naturally acquired primary infection. Protection conferred by a primary infection against disease from re-infection is incomplete.[804-811] Thus, the protective efficacy of BCG might be increasingly masked as the contributory fraction of cases attributable to re-infection increases.[812,813] Thus, following this argument, the protection afforded by BCG is expected to be lower where the risk of infection with *M. tuberculosis* (and thus re-infection) is high.

This is not borne out by observations. The annual risk of infection in the United Kingdom decreased considerably over time,[814] yet the level of protection afforded by BCG remained high and virtually unchanged.[761]

Differences in genetic make-up of vaccinees

Because differences in protection from BCG among males and females were observed in at least one study,[766] other genetic factors may also play a role in the differential protection conferred by BCG. Nevertheless, the finding that BCG gave virtually no protection to children in Chingleput,[765] but high protection in children from the Indian sub-continent living in the United Kingdom[758,761] would tend to disfavor this hypothesis.

Differences in nutritional status of vaccinees

As nutritional status affects the functioning of the cellular immune system, it might be expected that poor nutritional status would adversely affect the protective efficacy of BCG vaccination. However, BCG provided very high protection against tuberculosis death among poorly nourished North American Indian children, even somewhat higher than among well-nourished British adolescents,[776] a finding that would tend to contradict this hypothesis.

Differences in prevalence of infection with environmental mycobacteria

BCG vaccination has been used not only for protection against tuberculosis, but also against leprosy,[815-821] often with more success than in the prevention of tuberculosis.[777,822,823] It is thus apparent that different mycobacterial species (in this case *M. tuberculosis*, *M. bovis* BCG, *M. microti*, and *M. leprae*) exert a modification of the immunologic response to infection with another mycobacterial species.[824] It is thus postulated that infection with one species of mycobacterium triggers a cellular immune response prepared to act more swiftly in the killing of mycobacteria of another species acquired during a subsequent infection. This is most apparent from the (limited) protection provided by infection with *M. tuberculosis* against superinfection with tubercle bacilli,[810] and the apparently similar effect of *M. bovis* BCG under certain circumstances. That BCG can also afford protection against leprosy would indicate that cross-protection is not limited to closely related mycobacterial species.

It has been postulated that different mycobacterial species induce different immunologic responses, some beneficially increasing protection against super-infection with another mycobacterial infection, while others may increase susceptibility to progression to clinically overt disease.[825] In experimental models, protection afforded by vaccination with *M. bovis* BCG, *M. fortuitum*, *M. avium*, *M. kansasii*, and *M. scrofulaceum* (then called Gause strain) against *M. tuberculosis* was examined in the guinea pig.[826] All environmental mycobacteria used in this study provided some protection, but with a wide variation, yet none provided as high a level of protection as BCG vaccination. It has therefore been postulated that the low protection afforded by BCG in Georgia as compared to the high protection observed in Britain may be attributable to a differential prevalence of infection with environmental mycobacteria.[826] Edwards and colleagues demonstrated similar protection by vaccinating with *M. avium* complex against *M. tuberculosis* isolated in Chingleput as with the Danish BCG strain.[827] Orme and Collins demonstrated that airborne infection with *M. avium* in mice was as effective as intravenous BCG in protection against a challenge with virulent tubercle bacilli.[828] Brown and colleagues administered *M. vaccae* in drinking water to mice, subsequently challenged them with BCG and measured the proliferative response of spleen cells.[829] The results showed that, depending on the timing of the exposure of the mice to *M. vaccae* before BCG vaccination, *M. vaccae* could enhance, mask or interfere with the expression of sensitization by BCG.

If environmental mycobacteria do indeed provide protection against *M. tuberculosis*, and infection with them occurs before the administration of BCG, then the effect of the latter will be at least partially masked.[813] This may explain the larger protection conferred by BCG given earlier in life than if given later as demonstrated in Chingleput.[765]

Furthermore, the risk of tuberculosis would be expected to be greater in initially tuberculin negative persons than in individuals with small tuberculin skin test reaction sizes (more likely attributable to infection with environmental than tubercle bacilli).

In Puerto Rico, protection from BCG was lower in rural areas, where non-specific sensitivity was higher than in urban areas, where protection from BCG was higher.[830] However, in Chingleput, the rate of tuberculosis among persons with a reaction size of more than nine millimeters to a sensitin produced from *M. avium* complex (PPD-B) was identical to that among those with zero to nine millimeters reaction sizes.[765]

In the United Kingdom, the risk of tuberculosis was higher among initially tuberculin skin test negative adolescents than among those reacting to 100 tuberculin units only, but the risk decreased over time (figure 72).[776] The protection afforded against tuberculosis by a tuberculin skin test reaction that can be elicited only by this large dose of tuberculin is remarkably similar (but smaller) to that imparted by BCG vaccination (figure 73).

In the Karonga, Malawi, trial the risk of tuberculosis during follow-up was lowest among those with an initial tuberculin skin test reaction size of six to 10 mm (figure 74).[831] After adjustment for age and sex, the risk was also lower among those with reactions of one to five millimeters than among non-reactors.[832]

That different species of mycobacteria seem to act on the immune system has also been demonstrated by observations from Sweden. After the cessation of mass BCG vaccination, there was a large increase in peripheral lymphadenitis due to environmental mycobacteria (figure 75) ([703,833,834] and Romanus V, personal written communication, Feb 18, 2000). Similarly, in the Czech Republic, the incidence of lymphadenitis among children due to *M. avium* following cessation of BCG vaccination was 3.6, compared to 0.2 per 100,000 person-years among children vaccinated on the insistence of their parents,[835] suggesting a protection of 95% (95% confidence interval 88% to 98%) from BCG against lymphadenits due to *M. avium*.

While not all findings are consistent with the hypothesis that environmental mycobacteria may mask the protection that BCG can confer in their absence,[832] it may explain to a considerable extent certain variations in observed efficacy.

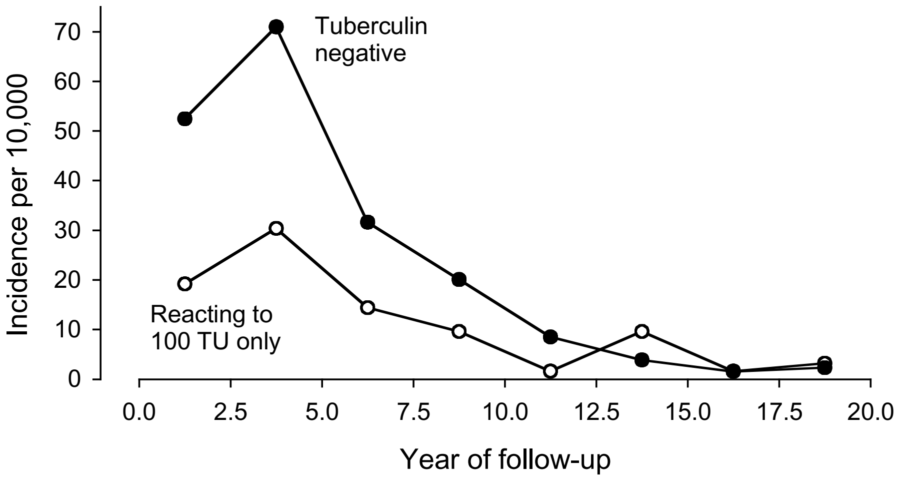

Figure 72. Risk of tuberculosis during follow-up of British school children, by initial tuberculin skin test reaction size, among placebo recipients, BCG trial, Great Britain.[776]

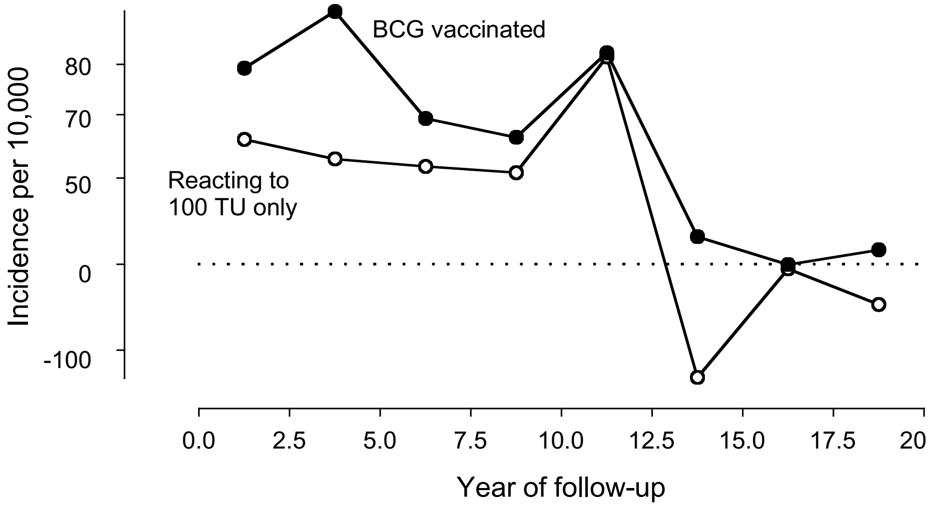

Figure 73. Comparative protection from BCG vaccination and presumed infection with environmental mycobacteria among British school children during follow-up.[776]

Other factors

It has been suggested that infestation with parasites, in particular with helminths, may affect the human T cell immune responses to mycobacterial antigens.[836] Treatment of helminths resulted in significant improvement

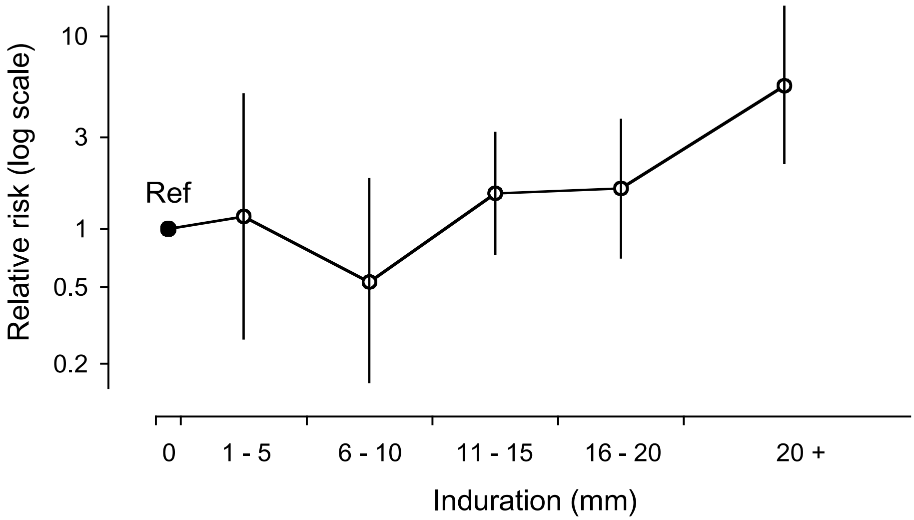

Figure 74. Risk of tuberculosis during follow-up by size of initial tuberculin skin test reaction, Karonga District, Malawi. Reproduced from[831] by the permission of the publisher Elsevier Science.

of T cell proliferation and interferon-gamma production. This could explain to some extent the reduced efficacy of BCG in countries in the world where helminthic infestation is common.[836]

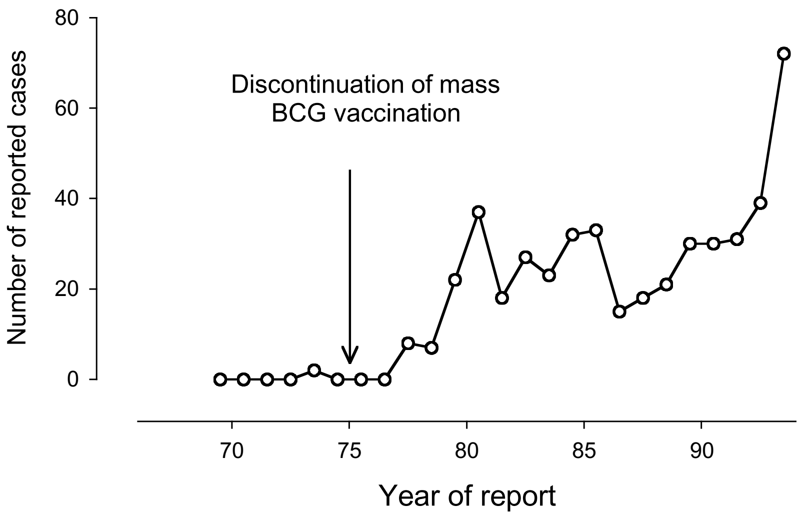

Figure 75. Reported cases of mycobacteriosis due to *M. avium* complex, Sweden, 1969-1993. Data courtesy Victoria Romanus, Swedish Institute for Infectious Diseases.

BCG re-vaccination

It is or has been the policy in many countries to re-vaccinate with BCG at school entry or later in life. There is no evidence that this increases protection against tuberculosis,[723,837,838] but in northern Malawi it has been shown to considerably increase protection against leprosy.[777] Re-vaccination schemes often fall into the lowest tuberculosis risk period in life (age five to 14 years) and target a population where protection from BCG vaccination is dubious or variable at best.

Effects of BCG other than those directed against tuberculosis

BCG has been shown to be protective against leprosy in some situations [815-818,839] while not in others.[819] It has also shown to be effective against *M. ulcerans*, albeit with an apparently very short-lived protection.[840]

The best known indications for BCG against other than mycobacterial diseases are its use as an immunotherapeutic agent in the treatment of superficial bladder cancer[841-850] and, to a lesser extent, malignant melanoma.[851] It has also been suggested that BCG reduces the risk of atopy and asthma,[852-854] and reductions in the risk of intestinal nematodes in children[855] and HIV-infected patients have been reported.[856,857]

Indications and recommendations for the use of BCG vaccination

Approximately 100 million children now receive BCG every year.[723] The number of doses produced in the year 2000, in descending order, were the Copenhagen 1331 strain, D2PB302, Tokyo 172, Sofia SL 222, Pasteur 1173, Glaxo 1077, and the Russian strain.[723]

While there have been wide variations in the protection afforded by BCG vaccination in different trials, the evidence is overwhelming that BCG provides protection against tuberculosis, especially against tuberculous meningitis and death from disseminated tuberculosis in children. Where it worked, its protective effect waned over time, to disappear after 15 to 20 years. The evidence for protection against bacteriologically confirmed tuberculosis in adults has been less consistent.

Because BCG vaccination is given early in life, the protection afforded is limited in time, and its effect on bacteriologically confirmed tuberculosis in adults is inconsistent, it cannot be expected to have a great impact on the epidemiology of tuberculosis.[858,859]

It seems inappropriate to conclude from meta-analyses that BCG provides some average protection.[791,792] The observed range in protection is real and remains largely unexplained.

In light of the evidence, WHO recommends its use in newborn children or as early in life as possible.[793,860] This is still sound policy for those countries in the world where tuberculosis is highly prevalent, and tuberculous meningitis is a frequent, disabling or fatal occurrence. It fails to address the role of BCG where tuberculosis in children has become a rare occurrence.

The IUATLD has developed recommendations on criteria for the discontinuation of mass BCG vaccination.[861] Three key issues enter into the decision making process on the discontinuation of BCG vaccination.

The first is the extent of protection BCG actually imparts in a given location. In the USA, the low efficacy of BCG vaccination in Georgia, Georgia-Alabama, and Puerto Rico had an important impact on the decision not to routinely utilize BCG vaccination. As such prospective studies are usually beyond the realm of resource availability, effectiveness might alternatively be studied utilizing the case-control or contact study approach.

The second is the frequency of serious forms of tuberculosis in children (meningitis, disseminated forms) weighted against the frequency of adverse reactions from the vaccine itself. This has been best studied in Sweden where the frequency of serious adverse reactions from BCG vaccination (osteoarticular and disseminated mycobacteriosis due to BCG) outweighed the incidence of cases that the vaccine was intended to prevent (figure 76).[703] Similarly, BCG vaccination may become non-cost-effective as the frequency of childhood tuberculosis decreases, so that an increasing number of children need to be vaccinated to prevent one case.

The third consideration is the value attached to the preservation of the utility of the interpretation of tuberculin skin test results. BCG vaccination induces tuberculin sensitivity and complicates the interpretation of tuberculin skin testing results. In industrialized countries with an elimination strategy in mind, the tuberculin skin test is an important means of identifying persons with tuberculous infection at a high risk of progression to tuberculosis who would benefit from preventive chemotherapy.

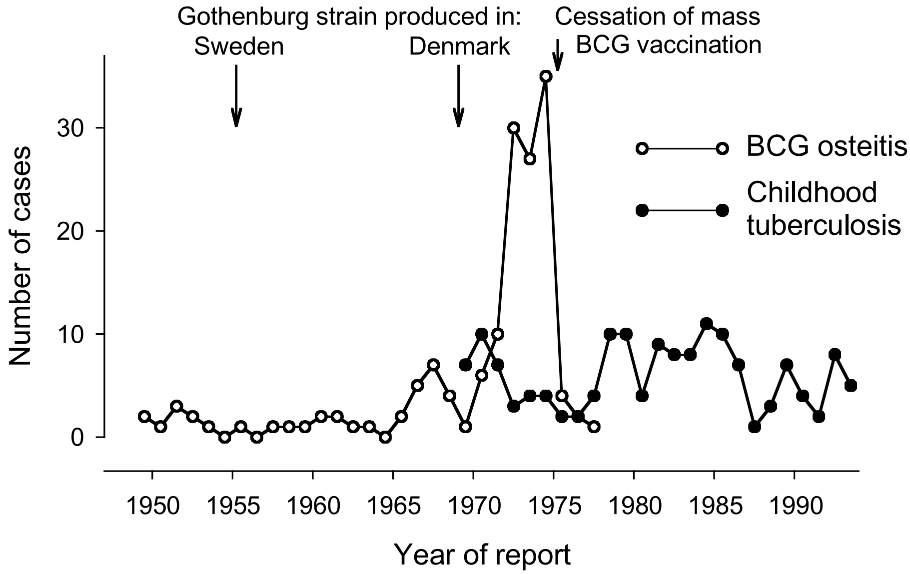

Figure 76. Osteitis due to BCG vaccination and incidence of pulmonary tuberculosis among Swedish-born children, Sweden 1949-1993.[703]

WHO discourages re-vaccination because there is no evidence of its usefulness.[862] Lack of evidence is, however, not synonymous with lack of efficacy. Re-vaccination at school entry is likely to be inefficient (even if it were efficacious), because it falls into the period in life when the risk of tuberculosis is lowest.

Finally, concerning HIV infection, the WHO has concluded after careful review of available data, that BCG vaccination schemes do not need to be altered unless HIV infection is symptomatic (AIDS).[721] This, too, seems to be a reasonable recommendation given the lack of evidence of an increased frequency of serious adverse events in BCG-vaccinated children who also have acquired HIV infection from their mother. However, it appears that HIV infection lowers the protective effect against extrapulmonary tuberculosis.[863] In industrialized countries, where the need for BCG vaccination is generally lower, it is usually recommended not to give BCG vaccination to individuals known to have HIV infection.[864]

The freeze-dried vaccine should be kept refrigerated and protected from light, and diluted only immediately before vaccination. In most countries, BCG vaccine is given by the intradermal route, generally by injection with a 25 or 26 gauge needle, in the deltoid insertion region of the upper arm.[865] Most manufacturers (including all those who provide vaccine for UNICEF, the largest purchaser in the world) recommend a 0.05 mL dose for infants, and the double dose for children.

Difficulties have arisen for decision makers about the value of vaccinating health care workers at increased risk of infection with *M. tuberculosis*, particularly in settings where multidrug-resistant tuberculosis is common. The uncertainty stems from the scarcity of data on protection against tuberculosis among adults, and the generally low level of protection (or none at all) among adults in clinical trials. While decision analyses appear to favor the use of BCG vaccination in such settings,[866] such a conclusion has been disputed, largely based on the argument that it deprives those vaccinated from ever learning whether they have acquired tuberculous infection or not (loss of specificity of the tuberculin test).[867] Nevertheless, in areas where BCG has been demonstrated to provide appreciable protection against tuberculosis among adults, where there is a high risk for health care workers of becoming infected, and where multidrug-resistant tuberculosis is common, a BCG vaccination policy for health care workers might deserve consideration. Where these conditions are not met, non-vaccination of health care workers might be more appropriate.

In summary, barring a better alternative, BCG vaccination remains a useful adjunct for the individual protection against disabling and lethal forms of childhood tuberculosis in most parts of the world where tuberculosis remains highly prevalent. It cannot be expected, however, to have great impact on the epidemiologic situation of tuberculosis.[858,859]

4. Preventive chemotherapy

In the early 1950s Lincoln described her observations with chemotherapy and its effect on case fatality from primary tuberculosis.[868] In particular, fatality from tuberculous meningitis fell from 100% to 17% with streptomycin and para-aminosalicylic acid, and to 12% with the introduction of isoniazid. None of the patients with miliary tuberculosis treated with isoniazid alone or in combination with other drugs developed tuberculous meningitis. She concluded that:

"...the use of isoniazid will have to be considered for every child with active primary tuberculosis and probably also for children with known recent conversion of tuberculin tests even if chest roentgenograms are normal. The duration of therapy would most likely be for a year in order to cover the period during which meningitis would be most likely to develop..."[868]

While credit for the idea of preventive chemotherapy might be shared by various investigators,[641] this is almost certainly one of the earliest accounts to spell out so clearly the research agenda on which the US Public Health Service, and subsequently other bodies, would engage.

It is noteworthy that two issues are raised here. The first is the prevention of complications from clinically manifest tuberculosis; the second is the notion of prevention of disease from recently acquired asymptomatic infection. In this monograph the term preventive chemotherapy is defined as treatment of latent, asymptomatic tuberculous infection with the intent to reduce the risk of progression to clinically manifest disease, and not what is essentially chemotherapy of active tuberculosis. Nevertheless, the first US Public Health Service controlled trial dealt precisely with that, and provided evidence of a 70% protection with isoniazid monotherapy against development of complications from primary tuberculosis.[641,869,870] Similarly, a controlled trial conducted in India among patients with minimal radiographic lesions, not certain to be active or inactive, offered evidence for a 68% protection against bacteriologically confirmed pulmonary tuberculosis.[871] This type of investigation will not be dealt with further at this point.

Numerous clinical trials of preventive chemotherapy (in the stricter sense of the definition used here) have been conducted. They encompassed a range of variables, including persons at varying risk of tuberculosis, choice of anti-tuberculosis agent, and duration of therapy. While no attempt is made here to provide a comprehensive list of all of the trials, the best known have been selected to review the efficacy that preventive chemotherapy has offered in randomized controlled clinical trials in various settings.

In order to provide comparable results, Wald 95% confidence intervals[731] were calculated for all trial efficacy estimates, unless (in some recent publications) the authors provided adjusted risk ratios or provided insufficient data to recalculate confidence intervals. In this case, the confidence intervals provided by the authors were used.

Prevention of disease in tuberculin skin test reactors

Persons who react to tuberculin, but whose acquisition of tuberculous infection lies in the remote past, have a relatively small annual risk of progression to clinically active tuberculosis compared with persons who have recently acquired infection.[1] While the exact point of acquisition of infection is rarely known for an individual, several studies have been conducted among patients whose tuberculous infection has been unlikely, to have been of recent origin on average (wide spread of acquisition points in time). The first point of interest is the efficacy of preventive chemotherapy in providing protection against progression to tuberculosis during, and only during, the length of treatment. Three of the four trials for which such information is available used isoniazid for twelve months[641,872-874], and in one it was given for nine months.[875] The results obtained by the end of the treatment period are summarized in figure 77.

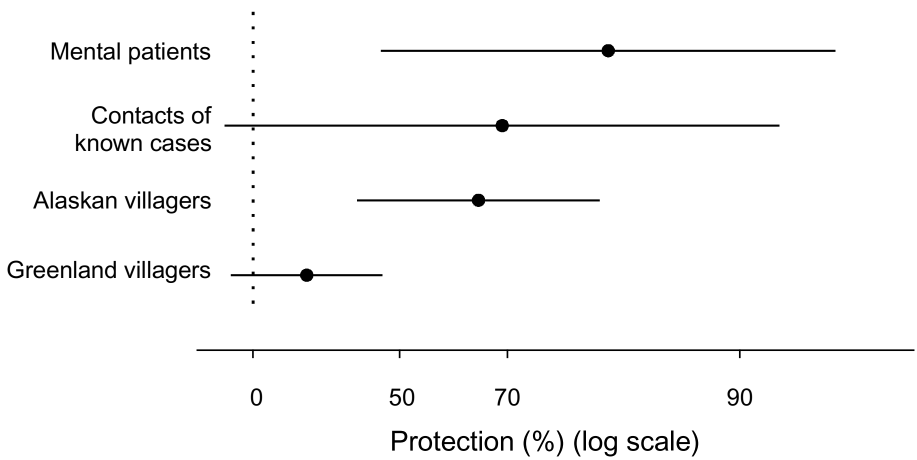

Figure 77. Protection from isoniazid preventive therapy against tuberculosis among tuberculin skin test reactors during the year of treatment.[641,872-875]

Tuberculosis was much more frequent among mentally ill patients in institutions than in the general population in the United States, and it was natural to consider this group for preventive chemotherapy to reduce the risk of endogenous reactivation disease.[872] People of all ages were included, but older patients made up the bulk of participants, with an average age of around 50 years. After exclusion of those participants known to have had a negative tuberculin skin test at intake, the protection afforded by isoniazid during the treatment year was 81%.

Persons in contact with notified tuberculosis patients for various lengths of time were included in another US Public Health Service clinical trial.[874] Some of the index cases had long since been cured of active disease, while others were still on treatment. Contacts who had already developed tuberculosis at the time of enrolment were excluded from the trial. Over half of the enrolled were initially tuberculin negative and stratification by initial tuberculin skin test result was not provided. The risk of tuberculosis during the treatment year was very low and the confidence interval around the observed point estimate of protection of 69% was thus very wide. However, eight of the nine observed cases in the placebo group had occurred among those with an initially positive tuberculin skin test.

In Alaska, a community preventive chemotherapy trial was started when the annual infection rate was almost 100 times greater than in the continental United States.[641,873] In the Bethel Hospital service area where the trial was conducted, the annual risk of infection was 25%, a rate far exceeding any reported risk elsewhere in the world.[876] By the time of starting the trial the risk of infection had already substantially decreased. Because of the adverse climatic and transport conditions it was not feasible to test all persons with tuberculin. Approximately one third of those tested had a tuberculin skin test diameter of less than five millimeters. During the treatment year the protection from isoniazid was 66%. Protection was demonstrated at all levels of adherence (amount of isoniazid taken), with an indication that six months of isoniazid might have sufficed.[876]

In Greenland it had been realized, by the mid-1950s, that the majority of tuberculosis cases developed in the years immediately after primary infection. A trial was thus undertaken to study the efficacy of isoniazid preventive chemotherapy at the community level.[875,877] Children below the age of 15 years were excluded from the trial. Placebo or isoniazid were given weekly for a total duration of nine months. Half of the participants received all dosages and over 80% received at least three quarters of the intended dosages. The crude protection afforded by isoniazid during the year following commencement of treatment was 22%. For reasons that are not understood, there was no protection observed in those aged less than 25 years, in contrast to 56% protection in those aged 25 to 34 years, and intermediate protection in the other age groups.

Prevention of disease in persons with risk factors

The risk of tuberculosis among persons with long-standing tuberculous infection (those studied in the above presented trials) is fairly small, thus the effectiveness of a preventive chemotherapy scheme is relatively modest. Conversely, it is of special interest to study the efficacy of isoniazid preventive chemotherapy in persons with a recognized increased risk of tuberculosis, because the attributable fraction of cases that can be prevented is relatively large if the prevalence of the risk factor is also high.

Recently acquired infection

Recently acquired tuberculous infection is not only associated with an increased risk of progression to tuberculosis, but it is also a frequent event. Four studies of preventive chemotherapy among contacts of newly diagnosed index cases of tuberculosis are selected here to illustrate the point (figure 78).[878-881]

In April 1960, a patient with pulmonary tuberculosis in a marine camp of the Royal Netherlands Navy infected a large number of his mates in a

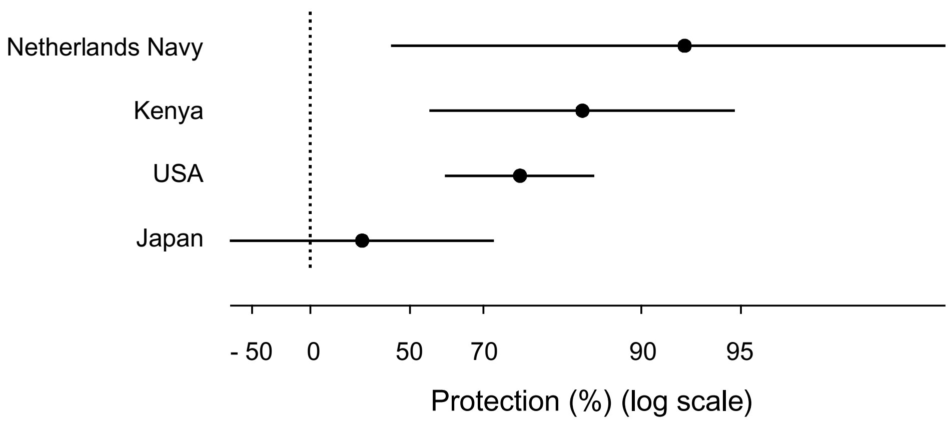

Figure 78. Protection from isoniazid preventive therapy against tuberculosis among contacts of tuberculosis patients.[878-881]

barracks.[878] On entering service in January, 59 of the men sharing the barracks had a negative tuberculin skin test, while by the beginning of April, 56 of them had become converters. In the entire camp 305 conversions were registered among 1,105 initially negative men. A double-blind controlled trial was carried out among the 261 converters who were not excluded due to departure or because they had already contracted tuberculosis at the time of starting the trial. After one year, nine cases had developed tuberculosis in the placebo group compared to only one in the isoniazid group. During follow-up for a total observation period of four years, three additional cases developed, all in the placebo group, indicating an overall protection of 93%.

In Nairobi, Kenya, contacts of newly diagnosed tuberculosis cases were randomly assigned to receive isoniazid or placebo for one year.[880] During the treatment year and the two-year follow-up period, preventive chemotherapy provided 85% protection against culture-confirmed pulmonary tuberculosis.

A large trial was conducted by the US Public Health Service among contacts of newly identified cases of tuberculosis.[879] Contacts found to have tuberculosis during the initial examination were excluded from the trial. Over 25,000 contacts were eligible for enrolment. Of these, 48% had tuberculin skin test reaction sizes of five or more millimeters of induration. Approximately two thirds of contacts were less than 20 years old. About two thirds of study participants were estimated to have taken all of their medications, and about 80% three quarters or more. Among those who could be reexamined at the end of the 12-month period of medication, isoniazid gave 77% protection against tuberculosis.

In Japan, contacts of new cases of tuberculosis were randomly assigned to receive placebo or isoniazid.[881] The protection afforded was only 30%, with confidence intervals including zero.

Infection with the human immunodeficiency virus

Infection with HIV is the strongest yet identified risk factor for progression from tuberculous infection to tuberculosis. Because HIV alters the biological response to *M. tuberculosis* so fundamentally, it could not be taken for granted that isoniazid preventive chemotherapy would work as well as in immunocompetent patients.

Tuberculosis is accompanied by an increase in tumor necrosis factor alpha (TNF-α). TNF-α also increases *in vitro* replication of HIV.[882] It might be expected, therefore, that prevention of development of tuberculosis would also delay onset of AIDS among HIV infected patients (figure 79). There is, however, as yet little epidemiological evidence that this is the case.[883]

A series of controlled clinical trials has been undertaken in various settings to evaluate the efficacy of isoniazid (and other compounds) compared to placebo in protecting HIV-infected individuals against tuberculosis (figure 80).

The first study of this kind was conducted in Port-au-Prince, Haiti.[884] The efficacy of 12 months of isoniazid compared to placebo was ascertained. The protection among persons with five or more millimeters of induration to a tuberculin skin test was 83%. The population was small, however, and the confidence intervals were consequently wide. An additional finding was a significant delay in onset of HIV disease in the isoniazid group compared to those receiving placebo. Survival analysis also demonstrated significant protection against AIDS-defining illnesses and AIDS-attributable death among tuberculin-positive, but not among tuberculin-negative, patients.

In Lusaka, Zambia, HIV-positive individuals were randomly assigned to receive twice-weekly isoniazid for six months or placebo and a third arm

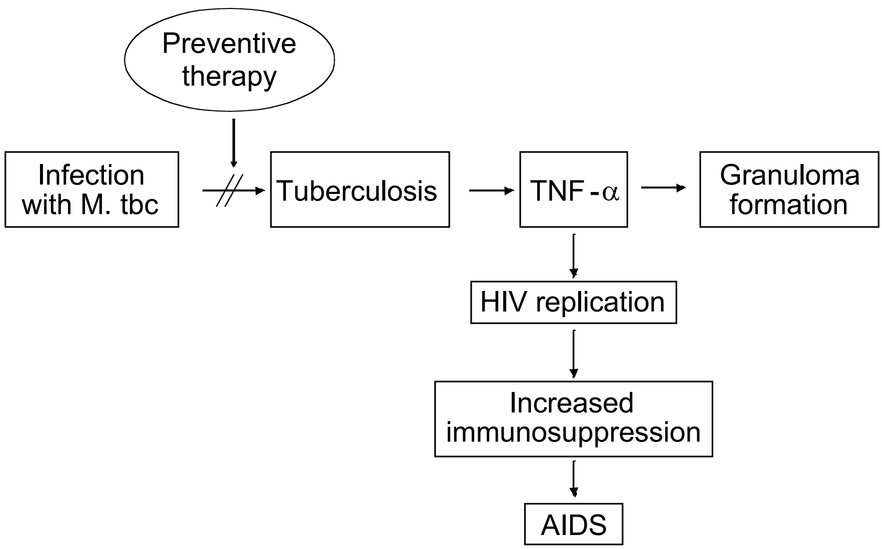

Figure 79. Schematic presentation of the impact of tuberculosis on TNF-α production and HIV replication, and prevention of the chain of events with preventive therapy.

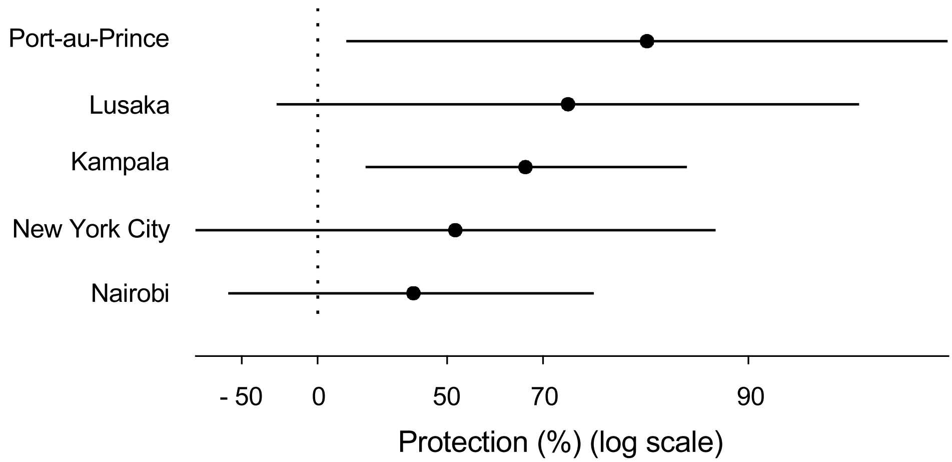

Figure 80. Protection from isoniazid preventive therapy against tuberculosis among HIV-infected persons.[884-888]

with a rifampicin plus pyrazinamide containing regimen.[885] They were followed up for a median of 1.8 years. The main outcome measures were incidence of tuberculosis and death. Among those with a tuberculin skin test reaction of five or more millimeters of induration, the point estimate of protection from isoniazid was 74%, yet because of the small number, the confidence intervals were wide and included zero. There was no difference in mortality between preventive chemotherapy and placebo groups. An important observation was that the effect of preventive chemotherapy declined following cessation of treatment so that by 18 months after the completion of therapy incidence rates in treated and non-treated groups were the same.

In Kampala, Uganda, HIV-infected patients were enrolled in a randomized trial to receive one of four arms: placebo, isoniazid for six months, or two rifampicin-containing regimens (one with, the other without pyrazinamide). Among patients with a tuberculin skin test reaction of five or more millimeters of induration, isoniazid reduced the risk of tuberculosis over a mean follow-up time of 15 months by 67%.[886] Survival did not differ between the groups.

Collaborating centers in New York City and elsewhere conducted a randomized trial to assess the efficacy of isoniazid in patients with HIV infection who were anergic.[887] Anergy was defined as reacting with more than five millimeters of induration to tuberculin and less than two millimeters to both mumps antigen and tetanus toxoid. Patients were additionally considered to belong to groups at risk of tuberculous infection. Only nine cases of tuberculosis occurred in the entire cohort of more than 500 patients during a follow-up period of 30 months following cessation of treatment with six months of either placebo or isoniazid: three in the isoniazid group and six in the placebo group. This corresponds to an overall protection of 52%, yet with 95% cent confidence intervals including zero.

In Nairobi, Kenya, HIV-positive patients were randomly assigned to receive either daily isoniazid for six months or placebo (irrespective of the tuberculin skin test result).[888] Outcome measures were incidence of tuberculosis and death. The follow-up period from enrolment onwards was a median of 1.8 years. The protection among persons with positive tuberculin skin test reactions (not further defined) was 40%, yet with confidence intervals overlapping zero. There was a slight, statistically significant reduction in risk of death among tuberculin-positive isoniazid recipients compared to the controls.

Spontaneously healed tuberculosis with fibrotic residuals

Patients with tuberculosis that has healed spontaneously with fibrotic lesions are frequently found, and remain an important source of reactivation tuberculosis, particularly in countries where the tuberculosis risk has been rapidly declining and most cases are the result of endogenous reactivation. Three such studies are shown here (figure 81).

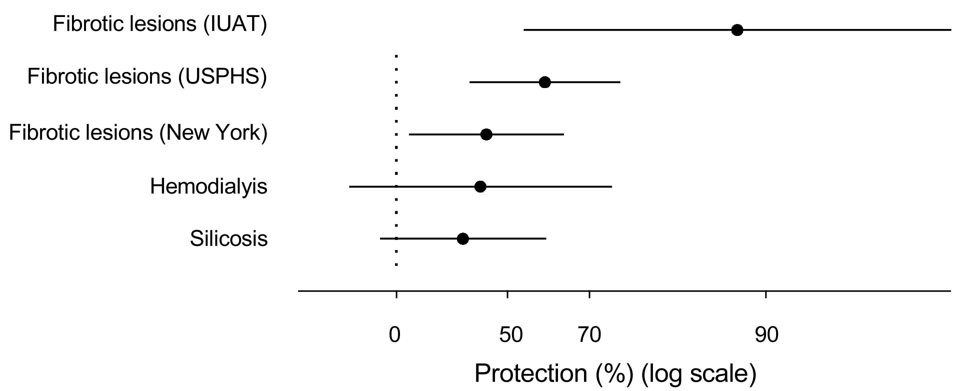

Figure 81. Protection from isoniazid preventive therapy against tuberculosis among patients with fibrotic lesions, hemodialysis, or silicosis.[123,641,891-893]

A large trial was conducted in Europe by the International Union Against Tuberculosis Committee on Prophylaxis among patients with fibrotic lesions.[123,889] Patients were randomly assigned to four groups, each consisting of close to 7,000 patients. A control group received placebo, and three groups received three, six or twelve months, respectively, of isoniazid. They were followed up to five years following intake. Among persons completing twelve months of, and adhering to, the prescribed course of chemotherapy the protection afforded by isoniazid was 93%. The effect was greater among those with larger than among those with smaller radiographic lesions.

Similarly, the US Public Health Service conducted a trial among patients with inactive lesions and followed them up for five years following enrolment into a randomized trial of twelve months isoniazid versus placebo.[641] The protection afforded by isoniazid was 60%.

In New York City, another study with two years of isoniazid was conducted among patients with inactive lesions.[890,891] The number of patients enrolled was small, and the protection afforded was 43% over a period of six years from enrolment.

Silicosis

Silicosis is a well-recognized risk factor for tuberculosis and is highly prevalent in countries where mining industries and other environments (granite quarry workers) offer poor protection against silica dust inhalation. In a study jointly organized by the Hong Kong Chest Service, the Tuberculosis Research Centre, Madras, and the British Medical Research Council, patients in Hong Kong were enrolled into a double-blind randomized trial with six months of isoniazid (and two rifampicin-containing arms) compared to a placebo group.[892] During the five-year follow-up period, isoniazid offered a protection of 34%, but the 95% interval included zero (figure 81).

Renal failure

A relatively small study with 184 patients on renal dialysis or after renal transplant were randomly assigned to receive either one year isoniazid or placebo. They were followed up for one year following cessation of therapy. Among those who completed therapy, the protection afforded by isoniazid was 41%, but the confidence interval overlapped zero (figure 81).[893]

Prevention of disease following cessation of preventive chemotherapy

One consideration has been the duration of efficacy of isoniazid preventive chemotherapy. In the three studies shown here, the protection remained unaltered over four to five years following cessation of preventive chemotherapy (figure 82).[123,875,876] Similar maintenance of efficacy over even longer periods was shown in other studies.[641] In the longest follow-up reported, from the Bethel, Alaska area, protection persisted for more than 19 years.[894]

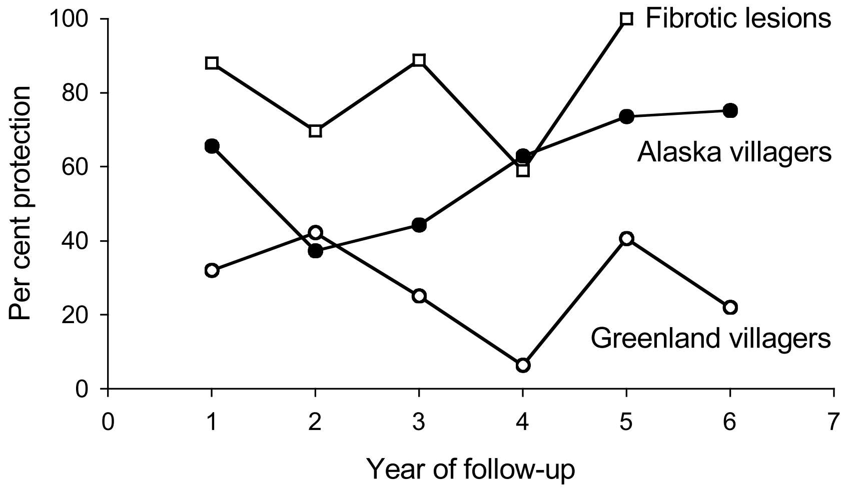

Figure 82. Long-term efficacy of preventive chemotherapy with isoniazid.[123,641,876]

Nevertheless, in areas where the risk of infection is high and a large proportion of cases is emanating from recently infected persons, protection might be expected to decline over time. However, once the tubercle bacilli have been eliminated from the body, one might expect some protection to be afforded against super-infection leading to disease, similar to that expected from BCG vaccination.

Prevention of disease with different durations of treatment

The duration necessary to provide optimum protection from isoniazid has not been satisfactorily determined. In fact, the only study seeking direct evidence was the trial of the International Union Against Tuberculosis Committee on Prophylaxis (figure 83).[123] Among "completer-compliers" the answer is quite clear-cut. Most benefit was obtained with twelve months chemotherapy with 93% protection, while six months offered 69% protection, and three months 32%.

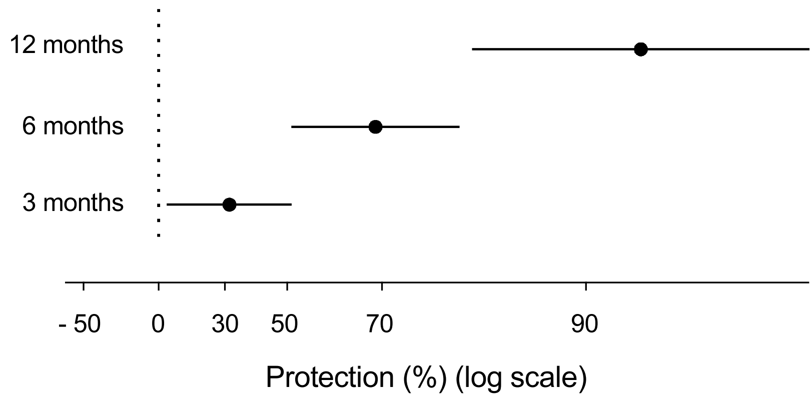

Figure 83. Impact of duration of intake of isoniazid preventive therapy on protective efficacy.[123]

However, if all patients were analyzed (and not only "completer-compliers"), the differences between six months and twelve months became much smaller, as adherence dropped with increasing length of treatment. For this reason and considering the cumulative risk of adverse drug events and personnel costs, it has been suggested that six months of preventive chemotherapy with isoniazid was more cost-effective than twelve months.[895]

However, the primary decision that has to be taken in the selection of a regimen (curative or preventive) is efficacy; the second is effectiveness.

In consideration of these findings, recommendations have been made for preventive chemotherapy to be given for six to twelve months, with every effort made to ensure adherence for six months.[356] The isoniazid preventive chemotherapy trials in the United States showed that the optimum duration might lie somewhere around nine months (figure 84).[896] The American Thoracic Society and the US Centers for Disease Control now recommend nine months of isoniazid treatment.[897] The British Thoracic Society recommends six to twelve months for preventive chemotherapy, the longer duration recommended for HIV-positive patients.[898,899]

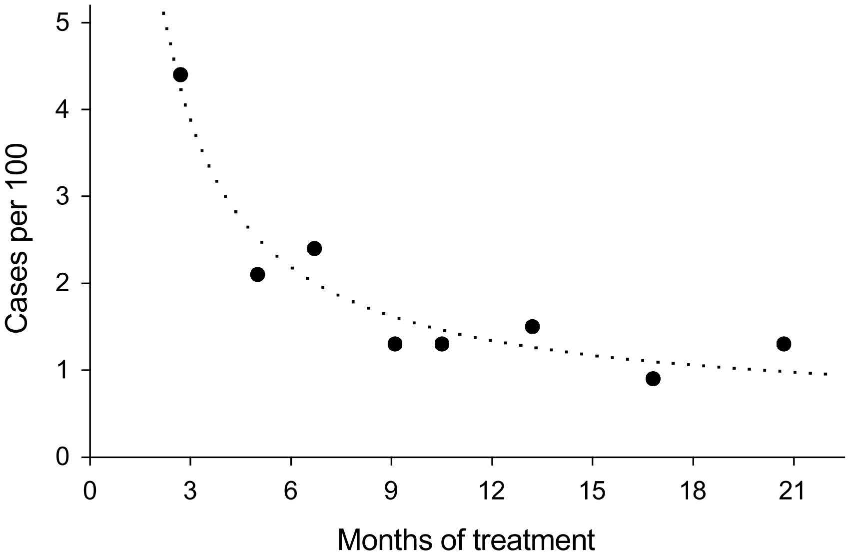

Figure 84. Tuberculosis risk and duration of intake of isoniazid preventive therapy in the Bethel, Alaska, preventive chemotherapy studies. Reproduced from[896] by the permission of the publisher International Union Against Tuberculosis and Lung Disease.

Prevention of disease with alternatives to isoniazid

Rifampicin has been remarkably effective in shortening the required duration of chemotherapy of tuberculosis.[122,504] It is postulated to act particularly well on mycobacterial sub-populations with only short bursts of metabolic activity.[456] Such a situation probably exists in the case of latent tuberculous infection and it is thus appealing to hypothesize that rifampicin might be effective in preventive chemotherapy and may also reduce the duration of the required treatment period compared to isoniazid.

In a mouse model, Lecoeur and collaborators tested the efficacy of rifampicin with or without other drugs in combination as a preventive chemotherapy tool in comparison with isoniazid.[900]

Latent, sub-clinical infection was produced by vaccination with BCG and subsequent challenge with *M. tuberculosis*. After an initial increase in viable tubercle bacilli, this produced a stable count of bacilli in the spleen, indicating that the relatively limited population was no longer actively multiplying in the spleen when drug treatment was given. In a first experiment, mice were assigned to five groups: 1) no treatment, 2) isoniazid for six months, 3) rifampicin for two months, 4) rifampicin plus isoniazid for two months, and 5) rifampicin plus isoniazid plus pyrazinamide for two months (figure 85). From this experiment, it was shown that two months of rifampicin-containing preventive chemotherapy was as effective as six months of isoniazid.[900]

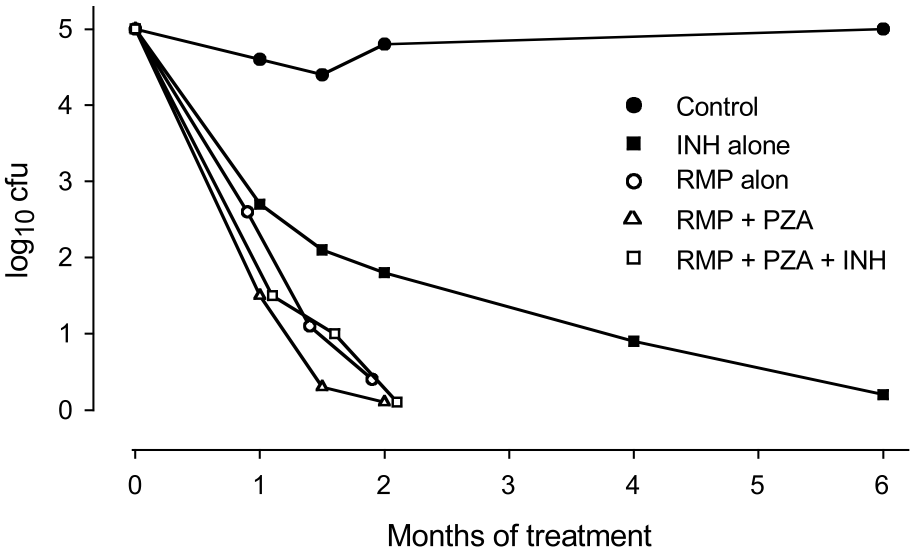

Figure 85. Mouse model of latent tuberculous infection and efficacy of various durations and combinations of preventive therapy on spleen bacillary count. Reproduced from[900] by the permission of the publisher American Thoracic Society at the American Lung Association.

In a second experiment, in comparison to isoniazid the relative efficacy of various combinations with rifampicin of different durations was evaluated. Mice received 1) six months of isoniazid, 2) three months of rifampicin plus isoniazid plus pyrazinamide, 3) three months of rifampicin, or 4) two months of rifampicin plus pyrazinamide. The experiment was calibrated in such a way as to ensure that viable bacilli remained at cessation of therapy to allow their culture from spleen at cessation and after a follow-up of a six-month period without treatment. All rifampicin combinations proved superior to isoniazid treatment for six months (figure 86).[900] The best combination was rifampicin plus pyrazinamide (without isoniazid). Rifampicin alone for three months was also very effective.

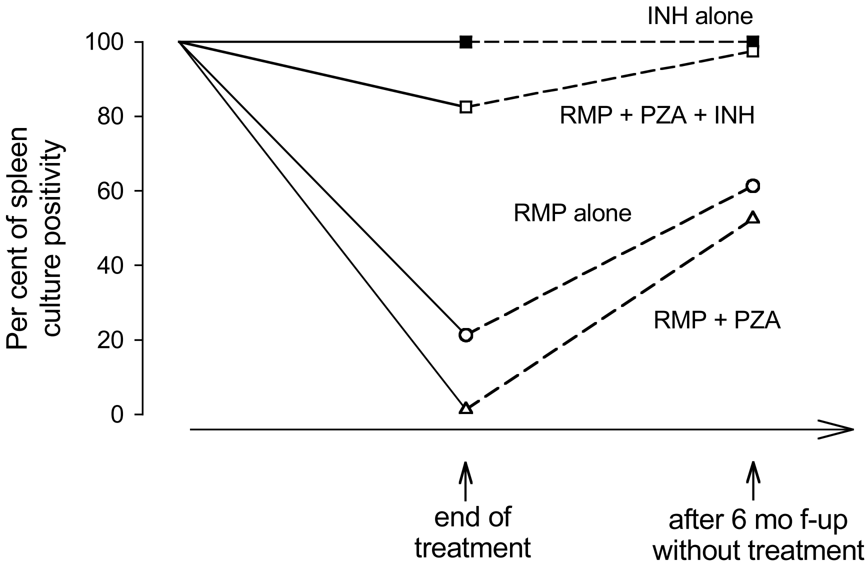

Figure 86. Mouse model of latent tuberculous infection and efficacy of various rifampicin combinations of preventive therapy on spleen bacillary count. Reproduced from[900] by the permission of the publisher American Thoracic Society at the American Lung Association.

Two types of studies are available to test the hypothesis in human subjects that rifampicin with or without isoniazid is first, efficacious, and second, equivalent or better than isoniazid alone, even if given for shorter durations. The first type consists of comparisons of rifampicin and rifampicin combinations with placebo, the second comparisons of rifampicin and rifampicin combinations with isoniazid (equivalence studies). The hypothesis and sample size requirements differ in the two approaches.

Rifampicin and rifampicin combinations in comparison to placebo

Studies comparing rifampicin (and combinations) with placebo have been carried out among patients with silicosis and patients with HIV infection (figure 87).[885,886,892]

In Kampala, Uganda, two arms had rifampicin-containing regimens. Compared to placebo, daily rifampicin plus isoniazid for three months gave 60% protection among tuberculin-positive patients with HIV infection. Rifampicin plus isoniazid plus pyrazinamide given daily for three months offered 49% protection.[886]

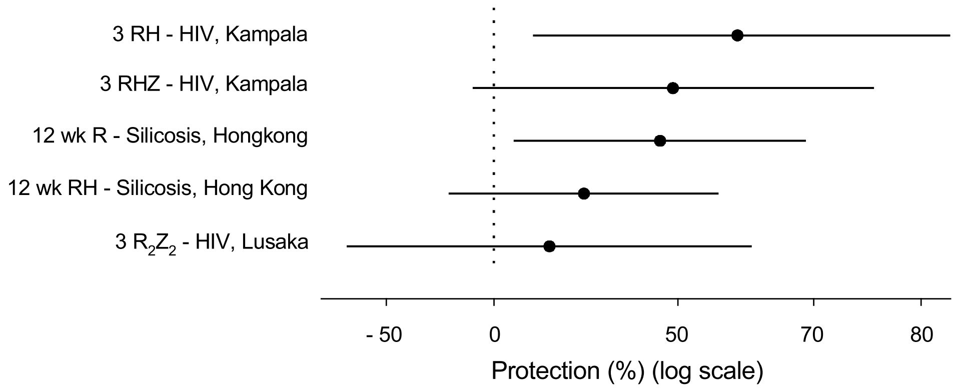

Figure 87. Protection against tuberculosis with rifampicin containing preventive therapy among persons with HIV infection or silicosis.[885,886,892]

In the study on patients with silicosis in Hong Kong presented above, in addition to the isoniazid (for six months) and placebo arms, two additional arms contained rifampicin. One of these consisted of twelve weeks of rifampicin alone and the second of twelve weeks of rifampicin plus isoniazid.[892] All drugs were given daily. Rifampicin alone for twelve weeks gave 46% protection. Rifampicin plus isoniazid for the same duration offered 29% protection, with the confidence interval including zero.

In Lusaka, Zambia, a twice-weekly regimen of rifampicin plus pyrazinamide given for three months gave 19% protection (the confidence intervals overlapping zero) against confirmed tuberculosis in HIV-infected patients.[885]

Rifampicin and rifampicin combinations in comparison to isoniazid

A few studies have provided information on the equivalence of rifampicin-containing preventive chemotherapy with isoniazid preventive chemotherapy (figure 88).[885,892,901,902] Again, these studies were carried out among patients with risk factors (silicosis and HIV infection).

In Hong Kong, twelve weeks of rifampicin provided 44% protection compared to six months of isoniazid, a statistically significant superiority, while the 25% comparative effect of twelve weeks with rifampicin plus isoniazid was not statistically different from the protection offered by isoniazid.[892] Thus, the overall protection against tuberculosis with preventive chemotherapy among silicosis patients was relatively poor, and rifampicin alone appeared to be superior to rifampicin plus isoniazid.

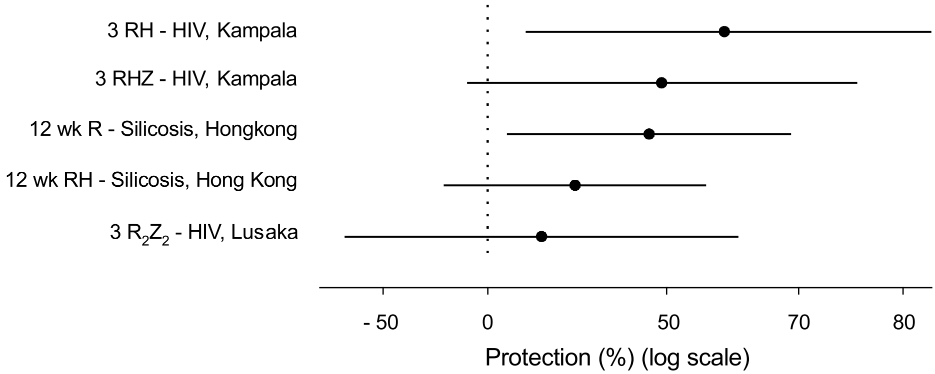

Figure 88. Protection against tuberculosis with rifampicin containing preventive therapy compared to isoniazid preventive therapy (equivalence studies) among persons with HIV infection or silicosis.[885,892,901,902]

In Cité Soleil and Petit Place Cazeau, Haiti, patients with HIV infection and a tuberculin skin test induration of five or more millimeters were randomly assigned to receive either isoniazid for 24 weeks or rifampicin plus pyrazinamide for eight weeks.[901] All drugs were given twice weekly, the first weekly dose directly observed, the second self-administered. The overall protection afforded by the rifampicin-containing regimen was minus 30%, with confidence intervals overlapping zero. During the first ten months after entry, the risk among isoniazid recipients was significantly lower than among rifampicin recipients.

Similarly, in Lusaka, Zambia, isoniazid for six months gave better protection than rifampicin plus pyrazinamide for three months, but the confidence intervals were wide, the difference was not statistically significant, and the protective effect from both arms was lost after two to three years.[885] The long-term evaluation showed that protection lasted for about two and a half years and none of the regimens appeared to have an effect on HIV progression or mortality.[903]

In a multi-center study involving 53 treatment units in Brazil, Haiti, Mexico, and the United States, a total of 1,583 HIV-infected patients were randomized to receive either isoniazid for twelve months (control arm) or rifampicin plus pyrazinamide for two months (experimental arm).[902] Among the inclusion criteria were the presence of a tuberculin skin test reaction of five or more millimeters of induration. For bacteriologically confirmed cases, the relative protection of the two-month regimen was 33% for bacteriologically confirmed, and five per cent for confirmed and probable cases. The 95% confidence interval was reasonably narrow, overlapped zero, and thus suggested equivalence (the hypothesis of the study) between the two regimens. Completion of therapy was superior in the experimental compared to the control arm.

In the United States, preventive chemotherapy regimens using rifampicin (plus pyrazinamide) of two to four months' duration have been recommended.[897] However, recent reports on fatal and severe hepatitis associated with preventive therapy using rifampicin plus pyrazinamide[904] have led to a change of the recommendation and advising great caution in the use of this combination.[904]

Effectiveness of preventive chemotherapy

There can be little doubt about the efficacy of preventive chemotherapy, at least with isoniazid if given for twelve months to persons with tuberculous infection without additional risk factors. There are indications that a regimen of nine months' duration might still be similarly efficacious in reducing the risk of tuberculosis. The efficacy of isoniazid in patients with risk factors is much less well established, and many studies dealing with HIV-infected patients suffer from inadequate sample sizes. It also seems that rifampicin-containing regimens of shorter duration can afford similar protection, but the optimal duration and the role of companion drugs have not been sufficiently well established. A short-coming of most preventive chemotherapy trials has been the self-administration of medications, thus portraying more the effectiveness than the potential efficacy of the regimen in question.

All studies that have evaluated that component have clearly demonstrated the adverse effect of non-adherence on the regimen's efficacy, as would be expected. This has been the case even in the setting of clinical trials where adherence might be better than under daily operations within the context of a national program.

Several studies have also demonstrated that the type of patients who are selected for preventive chemotherapy is important, and that large numbers may have to be treated to prevent a single case if the persons selected have a low risk of tuberculosis.

In a simplified form, operational effectiveness can thus be summarized as the product of tuberculosis risk given the presence of tuberculous infection, the efficacy of the regimen, and adherence to the prescribed medications. In a few examples, table 11 summarizes different situations and the

Table 11. Preventive therapy – effectiveness. Effectiveness of preventive therapy in dependence of risk of tuberculosis, efficacy of treatment regimen, and adherence to the regimen. All parameters are shown as fractions. Risk of tuberculosis is allowed to vary from 0.05 (estimated cumulative risk subsequent to the first five years following infection) to 0.30 (estimated cumulative risk of a person dually infected with *M. tuberculosis* and HIV).

Risk of tuberculosis	Efficacy of regimen	Adherence to treatment	Overall effectiveness	Number to treat to prevent 1 case
0.05	0.60	0.30	0.009	111
0.10	0.60	0.30	0.018	56
0.30	0.60	0.30	0.054	19
0.30	0.90	0.30	0.081	12
0.30	0.90	0.50	0.135	7
0.30	0.90	0.80	0.216	5

impact on overall operational effectiveness. The risks of tuberculosis shown here are for persons with long-standing tuberculous infection, recently acquired tuberculous infection and concomitant HIV infection (0.05, 0.10, and 0.30 for the respective risks of tuberculosis). Efficacy examples have been taken from isoniazid-preventive chemotherapy ranges, and adherence has been made up to vary as might be expected among different patients with a condition that is not symptomatic. The overall effectiveness is the product of these three variables and the number of patients that must be treated to prevent one case is the reciprocal value of effectiveness. The example shows that effectiveness will greatly vary depending on the selection of patients, the type of regimen and the extent to which patients adhere to treatment. Although reality is not quite as straightforward as in this example (it assumes that each component proportionally reduces effectiveness), it may help in deciding under which circumstances preventive chemotherapy is to be recommended. The specific indication will depend on the availability of resources, as the overall effectiveness is, under any circumstance, relatively modest. Not accounted for in this model is the probability of tuberculous infection actually being present when a "positive" tuberculin skin test is recorded.

A study in Kampala, Uganda, ascertained the operational feasibility and effectiveness of preventive chemotherapy in a high-risk population, apparently motivated to attend voluntary testing sites for HIV.[905] Among patients who were found to be HIV-positive, only about 60% returned to obtain their result and to receive counseling (figure 89) and of these only

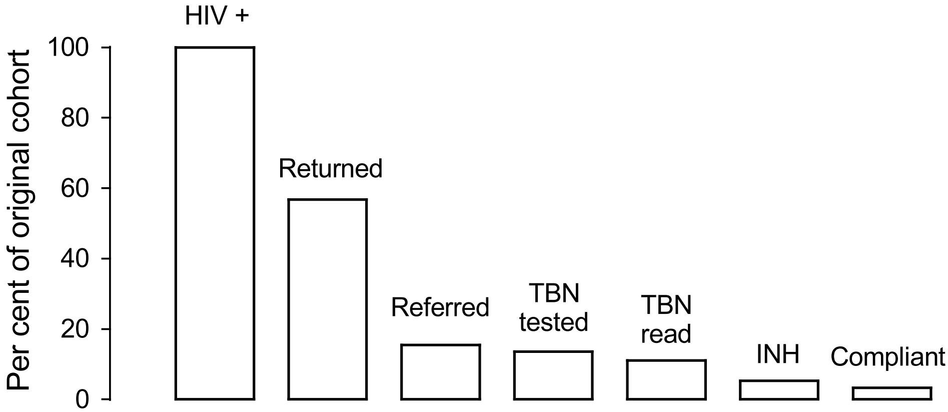

Figure 89. Operational feasibility of preventive therapy usage in a voluntary counseling and testing site for HIV infection.[905]

a small fraction was actually referred for evaluation of eligibility for preventive chemotherapy. Quite obviously, the collaboration was poor despite the study setting. Additional patients were lost for tuberculin testing and reading, only a fraction of these were actually eligible for preventive chemotherapy, and not all of those who were eligible were actually adherent. Only three per cent of the initial cohort completed preventive chemotherapy, and the efficacy was never assessed.

Indications and recommendations for the use of preventive chemotherapy

It is apparent that the place preventive chemotherapy will have within the context of a national tuberculosis control program will depend foremost on the epidemiologic situation and on the availability of resources. Rapid improvement in the epidemiologic situation and sufficient resources often go together, while the reverse is also the case.[906]

In industrialized countries embarking on strategies to eliminate tuberculosis, preventive chemotherapy will play an important role, yet the situation is rather different in countries with a high or even increasing tuberculosis burden where resources are very tight even to secure the treatment of all known cases of bacteriologically confirmed tuberculosis.

Within the context of resource availability, it should be considered that the costs for isoniazid are probably of least concern in most settings.

Logistical problems may, however, impose substantial impediments in some settings in low-income countries. Of critical importance is the capability to exclude the presence of active tuberculosis. This is particularly the case in adults, where the bacterial load of unrecognized tuberculosis might be sufficiently high to favor selection of isoniazid-resistant mutants if monotherapy is being given. In the Uganda study,[905] a sizeable portion of HIV-infected patients who were examined had active pulmonary tuberculosis, and not all had positive sputum smears on direct microscopic examination. For good reasons, WHO has thus recommended that both sputum smear microscopy and chest radiography are mandatory in HIV-infected patients before commencing preventive chemotherapy.[907]

The IUATLD limits the recommendations for preventive chemotherapy in low-income countries to asymptomatic children under the age of five years who live in the same household as a newly discovered sputum smear-positive case.[8] This is a group of persons with a high risk of becoming infected because of the closeness of contact. Preventive chemotherapy (or prophylactic treatment in the portion of children who have escaped infection) can be administered without prior investigation except for a clinical assessment of health. Even in the presence of an asymptomatic primary complex, the bacillary load will be too small in such children to pose the problem of selecting isoniazid-resistant bacilli. The drug of choice is isoniazid (5 mg/kg body weight), as it is the least expensive and the drug with which there is most experience. The duration of treatment might be pragmatically adjusted to the length of the tuberculosis treatment regimen prescribed for the index person, i.e., between six and twelve months.

For national programs wishing to expand their preventive chemotherapy program to other risk groups, the above measures to exclude active tuberculosis before initiating preventive chemotherapy should be strictly enforced.

Appendix 1
Adjunctive treatment

Adjunctive therapy with corticosteroids

The role of corticosteroids in the treatment of tuberculosis is not precisely known and the opinion concerning their use in different clinical situations is often somewhat controversial. The available evidence for and against their use is reviewed here, following the extensive review by Dooley *et al.*,[908] supplemented by additional reports.

Pulmonary tuberculosis

The value of corticosteroids in the treatment of pulmonary tuberculosis has been evaluated in several controlled trials.[909-920]

Sputum conversion was not affected by corticosteroid therapy in any of these studies; early sputum conversion was faster in the control group in one study and faster in the corticosteroid group in another.

On the other hand, clinical and radiologic improvement was generally more rapid in the corticosteroid treated group, particularly among the more seriously ill patients. In the United States Public Health Service trial, prednisolone produced more frequent and more rapid radiologic clearing of the infiltrate in black patients, but was of no benefit in white patients.[918]

In the five-year follow up of the United States Veterans Administration study, patients treated with corticosteroids were less likely to have died due to relapse of their tuberculosis, or due to respiratory illnesses such as bronchitis, respiratory insufficiency, or pneumonia.[917]

A controlled clinical trial from India[920] is significant in two ways. First, it is the only study using corticosteroids as adjunct therapy together with rifampicin-containing regimens. Second, it revealed that patients treated with corticosteroids who had strains initially resistant to isoniazid and streptomycin had a poorer bacteriologic response than those not treated with steroids. The deleterious effect of steroids in patients with sub-optimal chemotherapy had been observed earlier.[921] This had previously been shown in animal models as well,[922,923] and is not unexpected.

In an uncontrolled study in Zambia, HIV-infected patients treated for tuberculosis who had adjunct therapy with corticosteroids developed herpes zoster and Kaposi's sarcoma significantly more often, while generalized lymphadenopathy improved.[924]

The routine use of corticosteroids as adjunct therapy for pulmonary tuberculosis cannot, therefore, be recommended. In addition to the multitude of known adverse effects directly related to steroid use, in tropical countries parasitic infestation is common and corticosteroids in such patients may precipitate dissemination[925] and abscesses.[926]

The indication for the use of corticosteroids in pulmonary tuberculosis should be restricted to patients so seriously ill that their prognosis is judged to be very poor and thus the steroids are potentially life-saving.[7,927]

Extrapulmonary tuberculosis

Tuberculosis of serous membranes

Pleural tuberculosis

A number of studies have been reported evaluating the use of corticosteroids in pleural tuberculosis.[928-937] Not all of the studies were conducted with the same rigor and only eight provide sufficient information for an adequate evaluation.[928-933,936,937]

Most studies showed a more rapid resolution of effusions in those given corticosteroids. In the studies that evaluated residual pleural thickening as the crucial endpoint, three found less thickening in the steroid treated group[930-932] and two found no difference between placebo and steroid treated groups.[936,937]

From these studies it would appear that the value of corticosteroids in the treatment of pleural effusion is doubtful. Weighted against the possible adverse effects, steroids should probably not be routinely used in tuberculous pleural effusion.

Pericardial tuberculosis

The efficacy of corticosteroid therapy for tuberculous pericarditis may differ for the different physiological stages of the disease (effusive, effusive-constrictive, and constrictive).[908] Several retrospective studies fail to address these points and lack well-defined endpoints.[938,939] In a retrospective study addressing the critical issue of stage of disease, patients on corticosteroids had a more rapid decrease in pericardial effusion as compared to those not given corticosteroids.[940]

Prospective studies evaluating the use of corticosteroids in the treatment of tuberculous pericarditis were conducted in the Transkei area of South Africa.[941-944] These studies showed that fewer patients with acute effusive pericarditis on corticosteroids required repeated drainage,[941] and patients with effusive-constrictive pericarditis had faster improvement.[942] In neither study were there differences in constriction, but among patients with acute effusive pericarditis, corticosteroid recipients had a lower risk of death. Among HIV-infected patients in Harare, Zimbabwe, corticosteroids significantly reduced case fatality.[945]

From these studies it would seem that adjuvant treatment with corticosteroids is indicated in patients with pericardial tuberculosis.

Peritoneal tuberculosis

Because of the similarity in the pathogenesis of peritoneal and pericardial tuberculosis, both involving serous membranes, a beneficial effect of corticosteroid use in peritoneal tuberculosis similar to that in pericardial tuberculosis might be expected.[946] Alternatively one may argue that tuberculous peritonitis is more similar to tuberculous pleurisy. In a retrospective study from Saudi Arabia, the frequency of recurrent abdominal pain and emergency department visits were used as endpoints to compare the usefulness of corticosteroid adjunctive therapy.[947] Corticosteroids appeared to have an effect in reducing the frequency of these events. However, as the study was a retrospective evaluation of a case series comparing patients who were given corticosteroid therapy with patients who had not received corticosteroids, it is not possible to draw firm conclusions. A prospective trial, allocating patients to a three-month course with either prednisone or placebo, was carried out with death and intestinal obstruction evaluated as endpoints.[948] Corticosteroid-treated patients fared better, but the small sample size did not detect a significant difference in the frequency of these events.

The evidence for the usefulness of corticosteroid treatment as adjunctive treatment in peritoneal tuberculosis is sufficiently convincing to recommend its routine use.

Meningeal tuberculosis

Adjunctive treatment with corticosteroids in meningeal tuberculosis has been widely reported.[949-964] However, not all of the published reports were prospective, controlled trials.

In none of the nine prospective trials was treatment outcome worse in the group treated with corticosteroids, as compared to the control group. Survival in the corticosteroid treated group was improved in four,[957,960,961,964] tended to be better in one,[963] and was not better in four.[955,956,959,964] Fewer sequelae in the corticosteroid-treated group were found in four studies.[959,960,963,964]

Studies that looked at the stage of disease and the effects of corticosteroids found a lack of effect in mild and terminal disease stages (assessed by the degree of neurologic impairment), but a significant benefit for patients with intermediate disease stage.[954,957,960] One of these studies[957] determined that there was no difference in treatment outcome between doses of 1 mg and 10 mg of dexamethasone. The duration of corticosteroid treatment in this study was one month.

There is sufficient evidence to recommend the use of corticosteroids in moderate to severe meningeal and cerebral tuberculosis to improve survival, although not all patients will benefit from adjunctive corticosteroid treatment.

Corticosteroid treatment in other forms of tuberculosis

Corticosteroids have been given for other forms of tuberculosis.

In the treatment of endobronchial tuberculosis, adjunctive therapy with corticosteroids has been shown to be beneficial.[965,966] In children with bronchial obstruction due to hilar lymphadenopathy, resolution of symptoms was faster and complications less frequent in corticosteroid-treated children compared to controls.[967]

Patients with peripheral lymphatic tuberculosis are known to frequently develop new nodes and draining abscesses during chemotherapy which are bacteriologically sterile and thought to represent an immunologic reaction.[535] It would be desirable to evaluate the potential usefulness of adjunctive corticosteroid treatment, yet no controlled trial has investigated this issue.

The use of corticosteroids in the treatment of genitourinary tuberculosis has been reported,[968,969] but the design of the studies was insufficient to draw conclusion on their efficacy in reducing ureteral strictures.

The role of surgery in the chemotherapy era

Surgery has played a major role in the history of treatment of tuberculosis, and thoracic surgery was actually largely developed around the treatment of pulmonary tuberculosis.[679,970,971] Efficacious chemotherapy has removed the need for surgical intervention in the routine treatment of patients.

The usual indications for surgery in the treatment of tuberculosis are for the treatment of complications. This is true for pyopneumothorax, respiratory distress due to massive pleural effusion, extensive restrictive pleural thickening, restrictive pericarditis, obstructive hydrocephalus, long-tract neurological signs in tuberculous spondylitis, and ureteral obstruction. There are, with the exception of extensive drug resistance, virtually no indications for surgery for primary treatment of tuberculosis. The guidelines for such surgery follow those for any other cause of such complications.

In industrialized countries, surgery has also been used with some success as an adjunct in patients with strains resistant to all or virtually all medications.[972-976] Such services are not usually available in national tuberculosis control programs of low-income countries, and are fortunately still rarely needed in most countries.

What will be summarized here are indications that are frequent and do not require sophisticated surgical procedures.

Surgical treatment in respiratory tract tuberculosis

Tuberculous pyopneumothorax

The development of an empyema or, more precisely, a tuberculous pyopneumothorax is a well-recognized complication in patients with cavitary tuberculosis whose cavities are located near the pleura.[977,978] In such patients, penetration of anti-tuberculosis medications into the pleural space and the empyema might be sub-optimal and may even lead to acquisition of drug resistance.[979] Furthermore, in contrast to pleural effusions, resorption of an empyema is less likely to occur, thus draining of the pus is usually indicated.

In the field, the most simple and effective approach is insertion of a drain, laid in such a way that it leads over two or three ribs before penetrating into the pleural space. The drain should be sutured to the skin. The patient is offered a bed that is about one meter above the floor, and the drainage is led into a bottle filled with water serving as a water lock. In patients whose entire lung is collapsed, full expansion of the lung can be expected, often leaving pleural thickening, however. As decortication is not usually an option, this is the best possible result that might be expected in such cases.

Pleural tuberculosis

Massive pleural effusions often require draining to relieve the patient from respiratory distress. Care should be taken not to drain more than about one liter in a single session to prevent cardiovascular and electrolyte disturbances. Accompanied by adequate chemotherapy, resolution of the accumulated fluid is usually prompt. Some authorities recommend complete draining of the effusion,[937] but it is uncertain whether this is really required.

Surgical treatment in tuberculosis of the spine

As previously shown (Chapter 1), chemotherapy alone of tuberculosis of the spine yields excellent results. Only the “radical Hong Kong operation” improves the results of chemotherapy somewhat, but not importantly so.[562] Because of the sophistication required, this procedure is beyond the capacity in the periphery of national programs where adequate chemotherapy alone is the key to success.

Superficial abscess might be drained by needle aspiration, but might also recur after the procedure.[980]

Appendix 2
Active agents other than essential drugs and drug classes (second-line drugs)

Numerous drugs other than the first-line anti-tuberculosis drugs discussed in Chapter 1, and often called "second-line drugs", have shown activity against *M. tuberculosis*. Generally, these medications are less efficacious, associated with a higher frequency of adverse drug events, and are more expensive. In most low-income countries, these drugs are not routinely available in national programs. Where they are, their use is best limited to specialists with experience in dealing with adverse drug events.

Nevertheless, the global emergence of multidrug resistance (resistance to at least isoniazid and rifampicin) has brought up the discussion about their use on a wider scale.[605,607-609,611,981-983] For this reason, brief summaries of these drugs are presented here.

Aminoglycosides (other than streptomycin)

Amikacin

Amikacin is a semi-synthetic aminoglycoside, synthesized by Kawaguchi and collaborators through acetylation of the 1-aminogroup of the 2-desoxistreptamine moiety of kanamycin A at the Bristol-Banyu research laboratories in Japan,[984] and reported in 1972.[985]

Amikacin has broad activity, particularly against gram-negative bacteria[986] and is active against *M. tuberculosis*.[987] Some researchers have found it to be usually more active against *M. tuberculosis* than other aminoglycosides.[224,283] Cross-resistance with other aminoglycosides may occur,[283] and is particularly frequent with kanamycin, and incomplete with the polypeptide capreomycin.[988] Amikacin is frequently active against streptomycin-resistant strains of *M. tuberculosis*.[989] However, it appears to have little early bactericidal activity.[990] Like other aminoglycosides, amikacin is not absorbed orally and the usual route of administration is intramuscular or intravenous, at a dose of 7.5 mg/kg to 15 mg/kg (depending on the dosage interval).

Like other aminoglycosides, amikacin affects the neuromuscular junction and may lead to neuromuscular blockade,[409,410,991] an effect that may be reduced by lithium,[992] but not reversed by neostigmine.

Indomethacin may interact with amikacin in newborns by increasing serum levels to toxic concentrations.[993] Neurotoxicity might be increased by muscle relaxants such as tubocourarine, succinylcholine or decamethonium.

Kanamycin

Kanamycin was isolated from *Streptomyces kanamyceticus* by Umezawa and collaborators in 1957.[994] It is a mixture of kanamycin A, B, and C.[995-997]

Kanamycin is active against a range of gram-negative bacteria and mycobacteria including *M. tuberculosis*.[998]

Kanamycin is not absorbed orally, but intramuscular administration leads to peak serum levels within an hour and the serum half-life is about four to six hours.[998] It is mainly excreted through the kidneys and thus, as with all aminoglycosides, dose adjustments are warranted in patients with renal failure.[998]

The usual dosage of kanamycin is 0.5 g to 1 g per day.[998]

Similar to other aminoglycosides, eighth cranial nerve toxicity is the most important. Auditory toxicity is more pronounced than vestibular toxicity[998] and is very frequent, affecting up to 20% of patients after three months, and up to 60% if treatment lasts for six months.[999] Like other aminoglycosides, kanamycin may cause neuromuscular blockade.[409] Other adverse drug events include renal toxicity and, rarely, allergies.[998]

As with other aminoglycosides, resistance is thought to be acquired through a single extrachromosomal plasmid factor with multi-step selection.[1000] Capreomycin resistant strains are not usually resistant to kanamycin.[476] The inverse seems to be the case for low, but not for high kanamycin resistance.[476]

Capreomycin

Capreomycin, a polypeptide antibiotic, was isolated from *Streptomyces capreolus* by Herr and collaborators at the Lilly Research Laboratories in 1959.[1001]

Capreomycin is active against various species of mycobacteria, including *M. tuberculosis*.[1002,1003]

Similar to aminoglycosides, capreomycin causes auditory, vestibular, and renal toxicity.[1004] Also like aminoglycosides, it is not orally absorbed and the usual administration is intramuscular. Rare adverse drug events include hypokalemia.[1004]

Cross-resistance between kanamycin and capreomycin is incomplete.[1005]

Cycloserine

Cycloserine (originally called orientomycin) was first isolated in 1952 from a *Streptomyces* strain, designated strain K-300 by Kurosawa.[1006] The identity with the compound discovered two years later in the United States was elucidated by Shoji,[1007] and Mitui and Imaizumi in 1957,[1008] but not before Lederle Laboratories also isolated the compound and recognized its identity with oxamycin, isolated by the Merck Laboratories,[1009-1011] and the Pfizer Laboratories which also isolated the compound.[1012] Cycloserine can be isolated from *Streptomyces orchidaceus, S. garyphalus*, or *S. lavendulae*.

Cycloserine is active against *M. tuberculosis* and several species of gram-positive bacteria.[1006]

Cycloserine inhibits cell wall synthesis[1013,1014] by inhibiting the synthesis of peptidoglycan by blocking action of D-alanine racemase and D-alanine:alanine synthase.[46]

Cycloserine is rapidly absorbed after oral administration, with a peak serum level of 10 to 50 mg/L following administration of 0.75 g to 1 g after 0.5 to 4 hours.

The usual dosage is two to three times daily (250 mg/day),[1015] but it is often given as a single dose.

The main adverse drug events due to cycloserine are neurologic and psychiatric,[159,1016-1022] although it has also been used in the treatment of mentally ill tuberculosis patients without observation of major mental toxicity.[1023] In a summary of several reports, cycloserine toxic adverse drug events were reported in over 20%.[1006] Most frequently reported or observed were vertigo and disorientation. Neuropsychiatric changes including drowsiness, slurred speech, psychoses, epileptiform reactions,[1016] as well as electroencephalographic changes and coma, were frequently noted. These effects of cycloserine are probably due to an interaction with the action of some monoamine oxidase inhibitors, as shown in experimental animals.[1024]

Cardiac depression, pareses, paresthesias and headache, pruritic rashes, drug fever, liver enzyme elevations, and gastrointestinal disturbances were less frequently reported adverse drug events. Smaller doses, and administration twice rather than once per day, reduce the frequency of adverse drug events. Stevens-Johnson syndrome has been reported in an HIV-infected patient.[1025]

Cycloserine appears to interact with alcohol, increasing the toxic effects of alcohol.[1026]

Determination of resistance to cycloserine is difficult, and the correspondence of laboratory results with clinical data is poor (figure 90).[466]

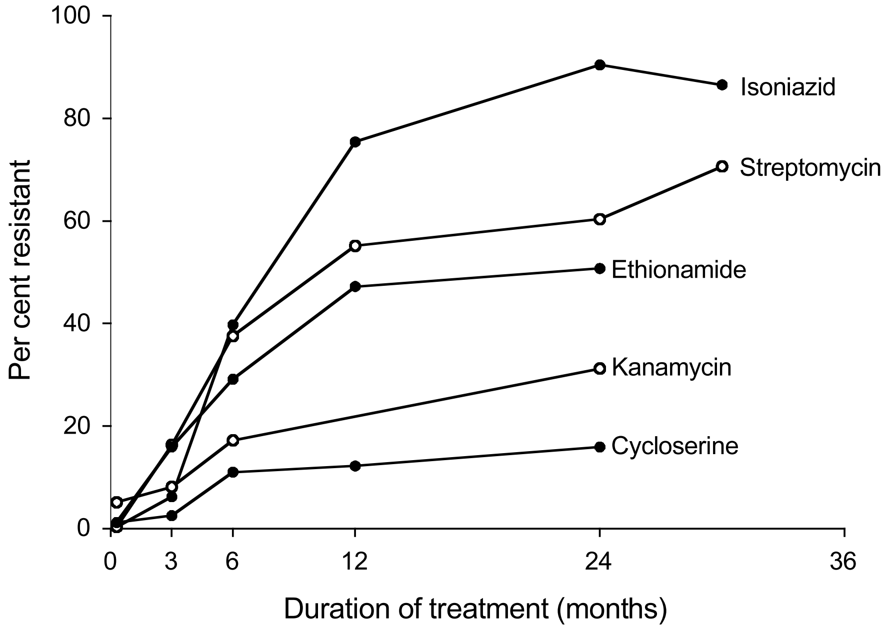

Figure 90. Proportion of strains of *M. tuberculosis* from resected lungs, *in vitro* resistant to anti-tuberculosis drugs, as a function of duration of treatment, the strain containing no susceptible organisms. Reproduced from[466] by the permission of the publisher American Thoracic Society at the American Lung Association.

Para-aminosalicylic acid

In 1940, Bernheim demonstrated that salicylic acid and benzoic acid increased the oxygen consumption and carbon dioxide production of *M. tuberculosis*.[1027] Based on these observations, Lehmann investigated more than 50 derivatives of benzoic acid with the purpose of finding a substance possessing activities against *M. tuberculosis*. The most active compound he identified in the experiments was para-aminosalicylic acid, first published as preliminary results in the Lancet in 1946.[1028] Soon thereafter the first reports appeared, demonstrating its considerable anti-tuberculosis activity in experimental models.[256] The use of para-aminosalicylic acid became a core component in early combination therapy until its replacement by the better tolerated ethambutol.[122]

It is likely that para-aminosalicylic acid, and not streptomycin, was the first anti-tuberculosis drug tested specifically against *M. tuberculosis,* as suggested in an editorial[1029] and correspondence of Lehman (reproduced with the permission of the South African Medical Journal):[1030,1031]

> *"Dear Dr Dubovsky,*
>
> *Your letter to the Director of the Central Laboratory at Sahlgrens Hospital was forwarded to me. It was the most remarkable letter I have received for many years. You are the first outside Sweden who has paid attention to the fact that PAS was in clinical use before streptomycin, eight months before ... Perhaps you wonder why I published the first paper on PAS so long after it was taken in clinical use. The reason was that as Ferrosan, a small company, had not taken out a patent on PAS, I didn't dare to publish the formula on PAS as other greater companies could take over the production of PAS ..."*

The MIC of *M. tuberculosis* is 1 mg/L.[1032]

In analogy with the observation that benzoic acid inhibits the respiration of tubercle bacilli,[1027] para-aminosalicylic acid might be built into coenzyme F of the bacterium instead of para-aminobenzoic acid, and thereby inhibit growth.[430]

Maximum serum concentrations with twice 4 g granular para-aminosalicylic acid are achieved within five to eight hours and remain above the minimum inhibitory concentration over the entire dosing interval.[1032]

The granular form of para-aminosalicylic acid is better tolerated than the previously used tablet form. A dosage of 4 g twice daily of the granular form produces serum concentrations above the minimum inhibitory concentration over the entire dosing interval.[1032] Good experiences with infusion therapy have also been reported.[1033]

Para-aminosalicylic acid has been an unpleasant drug to take because of the bulk required and the frequency of adverse drug events,[1034] which include gastrointestinal and cutaneous adverse drug events.[1035] Para-aminosalicylic acid may cause hypothyroidism,[1036,1037] and intestinal malabsorption.[1038,1039] Among hematologic changes are thrombocytopenia in adults[1040,1041] and children.[1042]

Para-aminosalicylic acid has been reported to increase isoniazid blood levels.[1043-1045] It may cause hypoglycemia in diabetics.[1046]

Quinolones

Quinolones have a potential in the treatment of susceptible and drug-resistant tuberculosis. Quinolones that have been considered include ciprofloxacin,[1047-1056] clinafloxacin,[1051] difloxacin,[1055] enoxacin,[1055] fleroxacin,[1057] gatifloxacin,[1058] levofloxacin,[1051,1058-1060] lomefloxacin,[1061,1062] moxifloxacin,[1061,1063] norfloxacin,[1055] ofloxacin,[1051,1053-1055,1064-1068] sitafloxacin,[1058] sparfloxacin,[1051] temafloxacin,[1051] and tosufloxacin.[1051] Most clinical experience has been accumulated with ofloxacin and ciprofloxacin. Some of the quinolones have little or no activity against *M. tuberculosis*, while the potential of others is far greater.[1069]

Fluoroquinolones inhibit DNA gyrase of *M. tuberculosis*.[176]

The MICs of ciprofloxacin and ofloxacin are well below levels that can be achieved in serum.[1054] The early bactericidal activity of ciprofloxacin is, however, not as pronounced as that of isoniazid,[1056] and is inferior to that of ofloxacin.[27] Clinically, there is anecdotal evidence that even prolonged ciprofloxacin may not prevent reactivation of tuberculosis.[1047]

Ciprofloxacin levels in bronchial biopsy specimens exceed those in the serum, indicating an accumulation of the compound in the lung parenchyma.[1052]

A dosage of 600 mg to 800 mg ofloxacin per day has been used successfully.[1067]

In animals, quinolones induce changes in immature articular cartilage of weight-bearing joints, but these concerns have not been substantiated in children and adolescents.[1070] However, cases of arthropathy from ofloxacin among adults have been reported.[1071]

Antacids appear to lower serum concentrations of quinolones.[1072]

Resistance to fluoroquinolones arises rapidly, and cross-resistance between quinolones is the rule.[1073] The most common cause of resistance results from mutations in the *gyrA* gene encoding the DNA gyrase,[1073] an enzyme required for replication and gene transcription.[1074] Quinolones should be used in combination with at least two other anti-tuberculosis drugs, as resistance might develop rapidly in a large proportion of patients.[1075]

Rifamycins other than rifampicin

Rifabutin

Rifabutin is a semi-synthetic spiropiperidyl derivative of rifamycin S,[1076] which was synthesized in the research laboratories of Farmitalia Carlo Erba by Marsili *et al.*; its synthesis was announced in 1981.[1077]

Rifabutin is active against a wide range of microorganisms, including gram-negative and gram-positive bacteria, and mycobacteria.[1078,1079] In particular, among mycobacteria, it is more active against environmental species that are naturally resistant to rifampicin,[1080,1081] including *M. avium* complex.[1081-1085] While there is considerable cross-resistance with rifampicin, it is also active against a relative small subset of *M. tuberculosis* strains that have low resistance to rifampicin.[1083] However, this proportion is too small to make it a generally useful drug in rifampicin-resistant disease.[1086] Treatment results among patients with drug-susceptible organisms are similar to those obtained with rifampicin.[1087-1089] However, studies on early bactericidal activity suggest that it is less active on extracellular bacilli than rifampicin.[1090]

Rifabutin is more lipid soluble than rifampicin, thus tissue penetration is superior.[1091] It has a longer terminal half-life, and is extensively metabolized.[1091]

The daily (and twice-weekly) recommended dosage of rifabutin is 5 mg/kg body weight.[897]

Adverse drug events reported with rifabutin treatment are similar to those with rifampicin treatment and include rash, hepatitis, fever, thrombocytopenia, orange-colored body fluids, arthralgia, uveitis, and leukopenia.[897,1076] Some of these reactions may be potentiated through the interaction with anti-retroviral protease inhibitors.

Rifabutin induces hepatic metabolism, but not as markedly as rifampicin.[1091] It does not affect the pharmacokinetics of antiretroviral drugs that are excreted in the urine.[1091] A number of results from interaction studies show that rifabutin is a less potent inducer of the cytochrome P-450 family, and thus causes fewer clinically significant interactions than rifampicin,[1092] or they are less pronounced.[281] In particular, interactions with protease inhibitors are generally less than with rifampicin,[897,1093] and it is the rifamycin of choice for patients receiving highly active anti-retroviral therapy.

Resistance in sub-inhibitory concentrations is less rapidly acquired than with rifampicin.[1094] Similar to rifampicin, acquisition of resistance is frequently accompanied by mutations in the *rpoB* gene.[1095] However, up to 20% of rifampicin-resistant mutants with mutations in the *rpoB* gene are susceptible to rifabutin.[1096] This difference is not due to additional mechanisms of resistance, it is just that some of the mutations selected by rifampicin do not sufficiently modify the *rpoB* structure as to render this protein resistant to rifabutin (Telenti A, personal written communication, March 15, 2001).

Rifapentine

Rifapentine (cyclopentyl rifamycin SV) is a semisynthetic derivative of rifampicin, synthesized at the Lepetit laboratories in Italy. Its properties were first described in a publication in 1981.[1097]

Rifapentine is comparable in its spectrum of activity to that of rifampicin.[1098,1099] It is active in the experimental mouse model both against latent infection with *M. tuberculosis*[1100] and clinical active disease.[1101]

Rifapentine is an RNA synthesis inhibitor like rifampicin.[1099]

The most conspicuous property of rifapentine is shown in a comparison of its pharmacokinetics with rifampicin. The serum elimination half-life is much longer in rifapentine[176] than rifampicin (figure 91).[181] The serum elimination half-life $t\beta_{1/2}$ is 14 to 18 hours,[1102,1103] and is similar in adults and adolescents.[1104] Intrapulmonary concentrations of rifapentine are below those in serum.[1105] In contrast to rifampicin, higher peak levels are achieved following food intake than after fasting.[1102] Pharmacokinetics are not influenced by HIV status.[1102] A key issue that needs to be addressed is its high degree of plasma binding, which might require higher dosages than used so far.

The usual dosage is currently 600 mg twice-weekly.[1099] However, higher doses are now being studied.

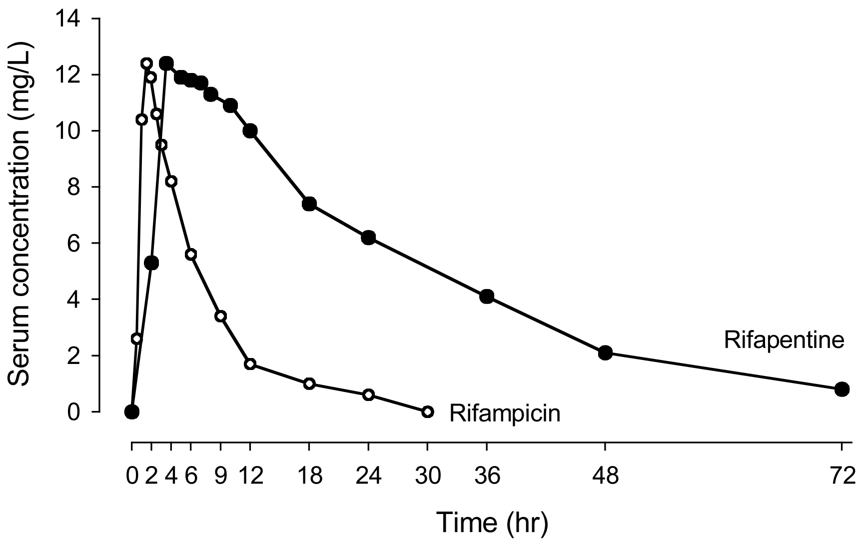

Figure 91. Comparative pharmacokinetics of rifampicin and rifapentine. Reproduced from[181,1102] by the permission of the publisher ASM Press.

Adverse drug events similar to those associated with the use of rifampicin have been reported.[1099]

Interactions that are expected most likely resemble those with rifampicin.

The pattern and mechanism of resistance to rifapentine is identical to that of rifampicin.

Thioamides

Following on from the discovery of the pyridine-containing isoniazid, numerous pyridine derivatives were tested, and the activity of thio-isonicotinamide against *M. tuberculosis* was found by several groups,[1106,1107] ethionamide, one of these thioamides, was introduced by the group of Liberman, Rist, and Grumbach.[1106-1108]

Thioamides are active against *M. tuberculosis* and to a lesser extent against other mycobacteria.[1109]

The mechanism of action of ethionamide is, like isoniazid, at the level of synthesis of mycolic acids.[46]

Prothionamide is rapidly absorbed and rapidly excreted.[1110] Therefore, the daily dosage is usually divided into two doses. Ethionamide has excellent penetration into cerebrospinal fluid.[570]

The usual dosage of both ethionamide and prothionamide is 500 to 1,000 mg per day, divided into two doses.[1111]

The most important adverse drug event from thioamides are gastrointestinal disturbances and hepatotoxicity.[1112-1119] It also appears to potentiate the hypothyroid effect of para-aminosalicylic acid. Comparisons between ethionamide and prothionamide seem to indicate that the latter might be less toxic than the former,[1111,1120] though the difference might not be important.

Although isoniazid and thioamide have the same parent compound, isonicotinic acid, isoniazid-resistant bacilli are often susceptible to ethionamide.[1108]

Drugs and drug classes with potential activity against *M. tuberculosis* under investigation and development

There can be little doubt about the necessity for the development of new anti-tuberculosis medications, given the limited amount of available choices.[1121] The Global Alliance for Tuberculosis Drug Development has published a scientific blueprint for drug development that should assist in overcoming some of the barriers that impede the development, testing, and marketing of new compounds.[1069]

Among the currently most promising candidates are long-acting rifamycins and fluoroquinolones (discussed above), oxazolidinone compounds, and nitroimidazopyrans. These and some other compounds under investigation are briefly summarized here.

Acetamides

Acetamides belong to a new class of compounds designed to inhibit the β-ketoacyl synthase reaction of fatty acid synthesis in mycobacteria.[1122] Because of their specific target, they exhibit virtually no activity against microorganisms other than mycobacteria. The MICs of the most potent compounds compare to those obtained with the most efficacious first-line drugs.[1122]

Amoxicillin plus clavulanic acid

M. tuberculosis possesses a beta-lactamase that might be responsible for its natural resistance to beta-lactam antibiotics.[1123-1125] Thus, beta-lactam antibiotics are essentially inactive against tubercle bacilli. Clavulanic acid is a beta-lactamase blocker and, if given simultaneously with amoxicillin, makes the latter active against beta-lactam producing microorganisms. This combination has also been proposed and used in the treatment of drug-resistant tuberculosis.[1126,1127]

Amoxicillin was synthesized in the Beecham Research Laboratories, patented in 1964, and described for the first time in 1970/71.[1128,1129]

The addition of clavulanic acid to amoxicillin has shown *in vitro* activity against *M. tuberculosis*.[1130-1133] Since then, several reports have appeared demonstrating successes in the treatment of patients with multidrug-resistant tuberculosis who also received amoxicillin plus clavulanic acid.[1134-1137]

The daily dosage might be 2 g of the combination.[402]

The most important adverse drug event seen with beta-lactam antibiotics are hypersensitivity reactions, which might be immediate (urticaria, laryngeal edema, bronchospasm, hypotension, or local swelling), late (morbilliform rashes, serum sickness, or urticaria), or other than late reactions (toxic epidermal necrolysis, interstitial nephritis, pulmonary infiltration, vasculitis, hemolytic anemia, neutropenia, or thrombocytopenia).[1138]

Clarithromycin

Erythromycin, the prototype of the macrolide antibiotics, was first used to treat infections in 1952.[1139]

Clarithromycin is a macrolide that differs from erythromycin by the methylation of the hydroxyl group at position 6 on the lactone ring.[1140]

Clarithromycin has a wide anti-bacterial spectrum that includes mycobacteria.[1132,1139,1141-1147] Most frequently it has been used as prophylactic agent or against disease caused by *M. avium* complex.[1147-1154] While it shows *in vitro* activity against *M. tuberculosis* complex in human macrophages,[1145] the concentrations needed to inhibit growth appear to exceed those achievable in the serum and lung tissue of humans.[1155] It has therefore not been widely used in the treatment of tuberculosis.

Clarithromycin is usually rapidly absorbed and reaches C_{max} after two to three hours.[1140] Its serum elimination half life $t\beta_{1/2}$ is 2.5 to 5 hours. It undergoes extensive hepatic metabolism. Because of its predominant renal excretion, dose adjustment might be necessary in patients with severe renal impairment.[1140]

Twice-daily 500 mg clarithromycin in AIDS patients was well tolerated, prevented *M. avium* complex disease and reduced mortality.[1148] In the treatment of *M. avium* complex disease, a dosage of twice daily 1,000 mg has been given.[1149,1156]

Fullerene derivatives

Fullerenes show an absolute lack of solubility in any polar solvent, and covalent attachment of solubilizing chains was therefore developed, resulting in the formation of water-soluble fulleropyrrolidines.[1157] Certain such ionic fullerene derivatives have shown equally good activity against both susceptible and multidrug-resistant isolates of *M. tuberculosis*.

Nitroimidazopyrans

A series of nitroimidazopyrans, originally investigated as radiosensitizers for use in cancer chemotherapy,[1158] were shown to have *in vitro* and *in vivo* activity against *M. tuberculosis*.[1141,1159] However, the original compounds were shown to be mutagenic.[1160] Newer derivatives showed substantial activity against *M. tuberculosis* and lacked the mutagenicity shown previously with bicyclic nitroimidazoles.[1161] There is considerable *in vivo* activity in the mouse model against *M. tuberculosis*, which is comparable to that of isoniazid.[1162] It appears that the action is on both protein and lipid synthesis,[1161] inhibiting fatty acid and mycolic acid synthesis.[1163]

Similar to the nitroimidazoles (to which metronidazole belongs), nitrofurans show substantial *in vitro* bactericidal activity against bacilli held in a hypoxic stationary phase.[1164]

Because the recently synthesized nitroimidazopyran compound acts against multidrug-resistant tubercle bacilli,[1161] it might prove a valuable agent in the future.

Oxazolidinones

Oxazolidinones are a class of protein synthesis inhibitors and include linezolid and eperezolid.[1165,1166]

Oxazolidinones have promising activity against a range of microorganisms including, and other than, *M. tuberculosis*.[1166]

Oxazolidinones appear to inhibit a step in the protein synthesis.[1167] It has been proposed that they inhibit protein synthesis by binding to the 50S ribosomal subunit.[1168]

In experimental animals, oxazlidinones appear to be rapidly absorbed.[1166]

Paromomycin

Paromomycin is an aminocyclosidic antibiotic complex, isolated from *S. rimosus* forma *paromomycinus* in 1959 in the Parke-Davies laboratories[1169] in the same year as aminosidin was isolated from *S. chrestomyceticus* in the Farmitalia laboratories. It is also identical to catenulin, which was isolated from *S. catenulae* in 1952 in the Pfizer laboratories. Paromomycin is an antibiotic complex consisting of at least six antibiotics, and belongs to the neomycin family.[1170]

Its potential in the treatment of tuberculosis lies with the advantage that there is little cross-resistance with either streptomycin or with amikacin/kanamycin. Its early bactericidal activity indicates that it is at least as effective as amikacin.[1171] Its toxicity (similar to that of neomycin) may, however, preclude its prolonged parenteral use.

Phenothiazines

Phenothiazines are derivatives of methylene blue and are used in the management of psychosis. Originally, Paul Ehrlich had reported that methylene blue immobilized bacteria, and their evaluation as potential antimicrobial agents was thus only natural.[1172-1174] However, the concentrations needed to exert activity by far exceed what is achievable within the non-toxic range. The argument for considering phenothiazines for the treatment of tuberculosis stems from the fact that pulmonary macrophages concentrate chlorpromazine (the first phenothiazine developed) 100-fold above what is found in plasma, concentrations that are active against mycobacteria *in vitro*[1172] and *in vivo*.[1175] Thioridazine, a well tolerated phenothiazine, has been shown to be active against both susceptible and resistant tubercle bacilli.[1176-1178] Chlorpromazine has a titrable ability to slow the growth of intracellular tubercle bacilli *in vitro*.[1179] Phenothiazines have not yet been tested for their activity against tuberculosis in humans.

Tuberactinomycin

Tuberactinomycin, a polypeptide, was isolated in the Toyo Jozo research laboratories in Japan from *Streptomyces griseoverticullatus* var. *tuberacticus* in 1966.[1180] and was shown to be active against both kanamycin-susceptible and -resistant strains.[1181,1182] Tuberactinomycin-N was semisynthetically derived from this compound and found to have stronger antimycobacterial activity and to be associated with less ototoxicity.[1183,1184] Its use has been largely limited to East Asia, where it was found to be a useful alternative to capreomycin in the treatment of multidrug-resistant, aminoglycoside-resistant tuberculosis.

Appendix 3
Current vaccine development strategies

The incomplete protection that BCG provides against tuberculosis and its dismally disappointing effects in some areas have challenged researchers to develop a vaccine with better and more consistent performance. It is uncertain whether a much better vaccine can be developed in the near future, as the development of vaccines against bacteria that do not exert their pathogenicity through toxins has been fraught with difficulties. Vaccine development strategies currently being pursued include:[1185-1188]

- Immunotherapy;
- Vaccination with saprophytic (environmental) mycobacteria;
- Auxotrophs;
- DNA vaccines;
- Recombinants;
- Subunits.

Immunotherapy with *M. vaccae*

M. vaccae is an environmental mycobacterium not known to cause disease in humans. A killed suspension of *M. vaccae* has been proposed, not to vaccinate against future tuberculosis, but to increase therapeutic response in the treatment of clinically manifest tuberculosis.[1189]

Numerous anecdotes have been published to illustrate its putative effects, but a clinical trial utilizing rigorous scientific standards has not shown any beneficial effect in addition to chemotherapy alone.[1190] Another controlled clinical trial indicates that immunotherapy with *M. vaccae* may be effective. In that trial, sputum culture conversion at one month (but not at two months) was significantly higher among persons receiving *M. vaccae* compared to controls. In addition, radiographic improvement was swifter.[1191] In yet another trial, no relevant differences during treatment and a four-year follow-up were found.[1192]

However, an effect is difficult to demonstrate in the case of fully drug-susceptible tuberculosis, which responds superbly to chemotherapy. What is perhaps needed is to study its value in the treatment of multiple drug-resistant tuberculosis, where the unequivocal outcome of death is a frequent enough event to permit a more definitive evaluation of the claims for improved immunologic response.

Vaccination with saprophytic (environmental) mycobacteria

The experiments by Palmer and Long have shown that various species of environmental mycobacteria provide some protection against experimental tuberculosis, but to different degrees and never exceeding that of BCG.[826] As mentioned above, the trial in the United Kingdom and the observations in Malawi have lent further credibility to the hypothesis that certain environmental species might offer some protection against tuberculosis. This line of experimentation has been further pursued and evidence accumulated that animals vaccinated with environmental mycobacteria have an increased resistance to a subsequent challenge with virulent tubercle bacilli compared to non-vaccinated animals.[828] So far, none of these vaccinations have been superior to BCG vaccination.

Auxotrophs

Another approach has been the development of so-called auxotrophic vaccines, where BCG and *M. tuberculosis* have been used to generate selected auxotrophs by insertional mutagenesis.[1185] The advantage of such a vaccine might be that it would gradually die in the host (an advantage in immunocompromised hosts) and that a weakened auxotrophic *M. tuberculosis* might be more immunogenic than BCG.[1185] However, survival time of the vaccine might be critical and has not yet been characterized sufficiently well to demonstrate superiority over BCG vaccination in experimental models,[1193] but certain mutations in genes involved in amino-acid biosynthesis have been promising in experimental models.[1194]

DNA vaccines

Most efforts currently being undertaken are in the development of a DNA vaccine,[1195-1204] but none of the experimental models has yet shown superiority to BCG vaccine. There is, however, some experimental evidence that this type of vaccine may not only protect against subsequent infection with *M. tuberculosis*, but may stimulate the immune response even among experimental animals with active disease.[1205] There are indications that the combination of priming with a DNA vaccine followed by a booster with BCG might induce higher protective efficacy in mice than BCG vaccination alone.[1206]

Recombinants

Recombinant vaccines use existing microorganisms, e.g., vaccinia viruses[1207] or BCG,[1208,1209] which are genetically modified to produce additional antigens thought to enhance the immune response.[1185] This approach is fairly recent and needs further research, which will most likely be aided by the deciphering of the entire sequence of the *M. tuberculosis* genome.[1210] *In vitro*, BCG engineered to secrete recombinant human interferon-alpha was substantially more active than unaltered BCG in inducing interferon gamma in human peripheral blood mononuclear cells[1209] In a guinea pig model, such a recombinant vaccine was superior than two BCG strains in preventing gross lesions and dissemination.[1211]

Subunits

Particular components (subunits) of *M. tuberculosis* may be better suited to inducing protective immunity than an entire organism. Recent research is thus evaluating the protective efficacy of such subunits.[1212] Preliminary experimental studies appear to be promising, providing protection similar to that obtained with BCG vaccination.[1213,1214] Subunits are potentially specific and safe. A disadvantage of subunit vaccines is their limited persistence and thus potentially reduced duration of immune response.[1215] In experimental mice models, re-challenge with a mycloyl transferase protein significantly boosted the protection against challenge with *M. tuberculosis* in animals whose immune protection had waned following BCG vaccination at birth.[1216]

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