TOMAN'S TUBERCULOSIS

CASE DETECTION, TREATMENT, AND MONITORING

QUESTIONS AND ANSWERS

SECOND EDITION

WORLD HEALTH ORGANIZATION
GENEVA

TOMAN'S TUBERCULOSIS CASE DETECTION, TREATMENT AND MONITORING :
QUESTIONS AND ANSWERS

Toman's Tuberculosis

Case detection, treatment, and monitoring – questions and answers

SECOND EDITION

Edited by

T. Frieden

WORLD HEALTH ORGANIZATION
GENEVA
2004

WHO Library Cataloguing-in-Publication Data

Toman's tuberculosis case detection, treatment, and monitoring : questions and answers / edited by T. Frieden. – 2nd ed.

1.Tuberculosis, Pulmonary – diagnosis 2.Tuberculosis, Pulmonary – drug therapy 3.Tuberculosis, Multidrug-resistant 4.Antitubercular agents – pharmacology I.Toman, Kurt. II.Frieden, Thomas R. III.Title: Tuberculosis case detection, treatment, and monitoring.

ISBN 92 4 154603 4 (NLM classification: WF 360) WHO/HTM/TB/2004.334

Further information is available at: CDS Information Resource Centre, World Health Organization, 1211 Geneva 27, Switzerland; fax: (+41) 22 791 4285, e-mail: cdsdocs@who.int

Designed by minimum graphics
Typeset in Hong Kong
Printed in China

Contents

[1] Based on the chapter in the previous edition by K. Toman.

Treatment

[1] Based on the chapter in the previous edition by K. Toman.

[1] Based on the chapter in the previous edition by K. Toman.

Monitoring

[1] Based on the chapter in the previous edition by K. Toman.
[2] Based on the chapter in the previous edition by K. Toman.

Preface to the First Edition

One of the basic functions of the World Health Organization (WHO) is the international transfer of scientific knowledge of direct practical value to countries in solving their health problems. A vast store of knowledge and experience has been accumulated in tuberculosis control. Through WHO-assisted projects, simplified and largely standardized control methods have been developed for general use, even in the remotest rural areas of developing countries. The concept of the "national tuberculosis control programme" was formulated by WHO to enable the new technology to be applied effectively. The Organization's policy on tuberculosis control, contained mainly in concisely worded reports of the WHO Expert Committee on Tuberculosis, has given rise to a great many questions and requests for further information. It has long been thought, therefore, that a detailed commentary on the scientific knowledge and practical experience underlying WHO's tuberculosis control policy would be a valuable element of WHO's technical cooperation with Member States. This book, presented in the form of questions and answers, is a first step in that direction. I hope that it will reach all tuberculosis workers in key positions, the organizers and administrators responsible for tuberculosis control in national programmes, and the field staff concerned with the day-to-day problems of tuberculosis control in the community. The book is also directed towards those who teach about tuberculosis control in medical schools, schools of public health, nursing schools, and similar institutions.

H. Mahler
Director-General
Geneva, 1979

Preface to the Second Edition

For more than two decades, Kurt Toman's book *Tuberculosis case-finding and chemotherapy: questions and answers* has been the most authoritative reference on the rational basis of diagnosis and treatment of tuberculosis. Few scientific books last so long, particularly in these times of rapid expansion of knowledge. The book has been reprinted many times by the World Health Organization (WHO) in English, Spanish and Arabic, and translated and printed by the International Union Against Tuberculosis and Lung Disease in French and Portuguese.

Unfortunately, despite the availability of low-cost and accurate diagnosis as well as nearly 100% curative treatment for more than three decades, tuberculosis remains one of the leading infectious causes of death globally, killing nearly two million people a year. Tuberculosis accounts for more than one in four avoidable deaths among adults in developing countries. The HIV epidemic is making this bad situation even worse. Many countries in Africa have experienced a two- to fourfold rise in the incidence of tuberculosis since the advent of HIV.

Over the past decade, in consultation with partners and Member countries, WHO has refined and promoted the tuberculosis control strategy known as DOTS. DOTS ensures accurate diagnosis, reliable cure, and systematic monitoring, as well as the political and administrative support required for effective tuberculosis control. However, the basis of the DOTS strategy is sometimes questioned. DOTS is not dogma, but a framework that is based on extensive basic, clinical, and epidemiological research, and that will continue to evolve as new information becomes available. In this regard, the second edition of *Toman's Tuberculosis* comes at a particularly opportune time. Countries throughout the world are rapidly scaling up DOTS implementation, and programme managers, doctors, medical school professors, and other interested persons often have questions about the basis and background for DOTS strategies and practices.

It must be admitted that the remarkable relevance of a scientific book written 24 years ago is not only a testament to the prescience of Dr Toman, but also a sad testimony to the lack of rapid progress in the field of tuberculosis control over the past two decades. In recent years, there has been renewed interest in tuberculosis. Our understanding of the disease, our ability to diagnose and cure it, and the im-

plementation of effective control strategies should improve sufficiently that much less time will elapse before the next edition is required!

It is my hope that this invaluable book will provide support to those on the front lines of the battle against tuberculosis, including programme managers, policy-makers, doctors, nurses, medical school professors, and members of civil society who work together to stop tuberculosis.

LEE Jong-Wook
Director-General
Geneva, 2004

Introduction

One section of the first edition of K. Toman's *Tuberculosis case-finding and chemotherapy: questions and answers* is entitled, "What were the main landmarks in the development of tuberculosis treatment?" It could accurately be claimed that Toman's text has itself been one of these landmarks. Shortly after publication of the first edition in 1979, K. Styblo and the International Union Against Tuberculosis and Lung Disease (IUATLD) developed a model with all essential elements of tuberculosis control and applied it in several countries of Africa and the Americas. This model, further refined by the World Health Organization, is today known as DOTS, the internationally recommended strategy for effective tuberculosis control. DOTS is based on evidence available from studies and experience gained in more than 100 countries.

Once again, the evidence base for approaches to diagnosis, treatment, and monitoring is presented in a comprehensive and comprehensible form, and is extended in this edition to prevention and control. The information is intended for all persons involved in the diagnosis, treatment, prevention, and control of tuberculosis – clinical specialists and public health practitioners alike.

Toman's concept was to marshall in one place the scientific basis for WHO/IUATLD recommendations on the detection and treatment of tuberculosis. Much of what Toman wrote 24 years ago remains relevant today; that is why some of the chapters required no updating. Toman's use of clear, convincing data, lucid explanations, and sensible approach made the book a touchstone for a generation of tuberculosis experts and many general physicians, particularly in developing countries. His description of the effectiveness of respectful, sensitive treatment of tuberculosis patients is as pertinent today as when it was written. The tightly reasoned and impassioned advocacy for the role of controlled clinical trials, and for adherence to the highest scientific and ethical principles in their conduct, could have been written yesterday. Toman's systematic discussion of drug resistance and of the role and difficulty of treatment with reserve drugs is highly relevant to the current lively discussion of the appropriate role of treatment of multidrug-resistant tuberculosis. And, of course, the entire section on case detection is a classic and brilliant elucidation of the role of acid-fast smears, the role and limitations of chest radiography and culture, and the importance of detection of tuberculosis patients through the general health system.

This second edition of *Toman's Tuberculosis* has attempted to retain the simplicity and clarity of approach of the first, as well as the systematic scientific background for the answers given. The section on case detection has been updated and sections on human immunodeficiency virus, the tuberculin test, and newer diagnostic modalities have been added. Sections on appropriate case detection strategies are also included. The treatment section has, of necessity, been updated with information on short-course treatment, which had not been established when the original text was published. Updated information on host defences, drug resistance, drug dosages, extrapulmonary tuberculosis, treatment adherence, and direct observation of treatment has been added. Sections on the basis, role, and limitations of treatment for tuberculosis infection have been included, as has a section on monitoring programme effectiveness, based largely on the experience of DOTS implementation in various countries. The recording and reporting system established by Styblo is simple, robust, and effective; it serves as the basis for accountability and programme monitoring.

A final point – from the introduction to the first edition – should be noted: "The information given on any particular subject is far from exhaustive. The aim was not completeness but deliberate selection. From among the numerous questions that are asked, those that recur the most frequently and that appear to be most pertinent have been chosen."

Acknowledgements for the First Edition

I am indebted to all those who, directly or indirectly, have made it possible for me to write this book.

I owe much to Dr H. Mahler, who ten years ago conceived the idea of a technical reference manual on tuberculosis control, mainly for non-specialized health personnel in the developing countries.

Grateful thanks are due to the International Union Against Tuberculosis (IUAT). Its former director, Dr J. Holm, and his successor, Dr D.R. Thomson, took the first steps towards the realization of this book and helped in its technical editing; the present director of IUAT, Professor V. Farga, made helpful suggestions. Dr Annik Rouillon, in her various areas of responsibility, gave whole-hearted cooperation. I had stimulating, candid, and fruitful discussions with the late Professor G. Canetti, Chairman of the IUAT Scientific Committees, his successor Dr J.R. Bignall, and the present Chairman of the committees and Director of the Tuberculosis Surveillance Research Unit, Dr K. Styblo. Thanks to the lively interest taken by Dr J. Meijer and the initiative of Dr H.A. van Geuns, the Sonnevanck Foundation, Netherlands, generously met part of the expenses. Dr K.L. Hitze, Chief, Tuberculosis and Respiratory Infections, World Health Organization, lent his active support, counsel and encouragement.

Dr Wallace Fox, Director, Tuberculosis and Chest Diseases Research Unit, Medical Research Council, and Professor D.A. Mitchison, Postgraduate Medical School, Hammersmith, London, who have contributed decisively to the fundamental changes in the treatment of tuberculosis, are to be thanked for their interest and criticism, and for allowing me to draw heavily on their pioneering studies.

Acknowledgements are due to my co-workers and students in developing countries – physicians, health officers, auxiliary workers, educators, and community leaders determined to free their fellow men from unnecessary suffering – who made me realize that tuberculosis and many other health problems can be eliminated only when their cultural, social, and economic interdependence has been understood.

I am grateful to my wife. Without her help and forbearance, this book could not have been written.

K. Toman
1979

Acknowledgements for the Second Edition

This remarkable book remains very much *Toman's Tuberculosis*. Kurt Toman conceived and created a book that can only be regarded as a masterpiece. Written in the late 1970s, it addressed essentially all significant questions relating to the diagnosis, treatment, and control of tuberculosis. It summarized the then state-of-the-art scientific knowledge of tuberculosis – and it did so with admirable clarity and brevity. Therefore, by far the greatest debt for the current edition is to K. Toman, whose book this very much remains.

The era of single-author reference books is over, and this edition of *Toman's Tuberculosis* required the input and assistance of many individuals. It is a remarkable tribute to the esteem and affection in which this text is held by tuberculosis experts around the world that every person asked to write or revise a section readily agreed.

Dr Fabio Luelmo provided the initial impetus for a revised edition, helped conceptualize the outline, contributed many of the new and revised sections, and carefully reviewed the entire manuscript. Other colleagues from WHO in Geneva, including Drs Mario Raviglione, Ian Smith, and Marcos Espinal, provided input to the book as a whole and also contributed many sections. Drs Anthony Harries and Hans Rieder gave generously of their time and considerable expertise to write or revise a substantial number of sections and they, as well as Dr Martien Borgdorff, reviewed the entire manuscript. Many staff of the United States Centers for Disease Control and Prevention (CDC) contributed new and revised sections. We were fortunate to have expert assistance and participation from staff of the Tuberculosis Research Centre, Chennai, India. Other authors/revisers are indicated in the table of contents and the list of contributors; their efforts are greatly appreciated. All worked with good grace to a tight publication schedule. Pre-1965 reference materials were obtained with assistance from CDC, Atlanta, GA, USA; the Medical Library, Chulalongkorn University, Bangkok, Thailand; and the Tuberculosis Research Centre, Chennai, the National Tuberculosis Institute, Bangalore, and the Tuberculosis Association of India, New Delhi, India. Byword Editorial Consultants provided overall project coordination and editorial support.

In 1979, the year in which the first edition of this book was published, Dr Karel Styblo and his colleagues from the International Union Against Tuberculosis and Lung

Disease and the Royal Netherlands Tuberculosis Association began implementing the strategy that has come to be known as DOTS. Notable aspects of this strategy are the remarkably robust monitoring system and the DOTS management package, which has enabled widespread application of the effective diagnostic, treatment, and monitoring strategies described in this book.

The editor has benefited greatly from many hours of discussions with tuberculosis workers in India and throughout south-east Asia, whose keen interest and critical approach helped to identify key questions to be addressed or re-addressed.

Many individuals contributed in many ways; responsibility for errors must rest with the editor.

Thomas R Frieden
New Delhi
India
2003

Contributors

Rani Balasubramanian MD DGO, Deputy Director, Tuberculosis Research Centre, Chennai, India

Naomi Bock MD MS, Medical Officer Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (nbock@cdc.gov)

Kathy DeRiemer PhD, Fellow, Division of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford, CA, USA (kathy@molepi.stanford.edu)

Marcos Espinal MD DrPH, World Health Organization, Geneva, Switzerland (espinalm@who.int)

Thomas R. Frieden MD MPH, Medical Officer, Stop Tuberculosis Unit, WHO Regional Office for South-East Asia, World Health Organization, New Delhi, India (trieden@health.nyc.gov)

Anthony D Harries OBE MD FRCP, Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi (adharriesmalawi.net)

Michael F Iademarco MD MPH, Associate Director for Science, Division of Tuberculosis Elimination, National Center for HIV, TB, and STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (miademarco@cdc.gov)

Ram Koppaka MD PhD, Medical Officer, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (vcr4@cdc.gov)

Kayla F Laserson ScD, Epidemiologist, International Activity Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (klaserson@cdc.gov)

Fabio Luelmo MD MPH, Consultant, TB control programmes, Geneva, Switzerland (luelmof@xs4all.nl)

Dermot Maher MB BCh FRCP, Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland (maherd@who.int)

Dick Menzies MD MSc, Director TB clinic, Montreal Chest Institute, McGill University, Montreal, PQ, Canada (dick.menzies@mcgill.ca)

Ariel Pablos-Mendez MD MPH, Associate Director, Health Equity, The Rockefeller Foundation, New York, NY, USA (APablos-Mendez@rockfound.org)

Rajeswari Ramachandran MD DM PhD, Deputy Director, Tuberculosis Research Centre, Chennai, India

Mario Raviglione MD, Coordinator, TB Strategy and Operations, Stop TB Department, Communicable Diseases, World Health Organization, Geneva, Switzerland (raviglionem@who.int)

Fathima Rehman BSc, Senior Research Officer, Tuberculosis Research Centre, Chennai, India

M. Reichler MD, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control & Prevention, Atlanta, GA, USA (mrr3@cdc.gov)

Hans L. Rieder MD MPH, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France (TBRieder@tbrieder.org)

T. Santha MBBS DTCD, Deputy Director (Senior Grade), Tuberculosis Research Centre, Chennai, India

John A. Sbarbaro MD MPH FCCP, Professor of Medicine and Preventive Medicine; School of Medicine, University of Colorado Health Sciences Center, Denver, CO, USA (John.Sbarbaro@UPIColo.org)

Patricia M. Simone MD, Chief, Prevention Support Office, Office of the Director, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (psimone@cdc.gov)

Peter M. Small MD, Associate Professor, Division of Infectious Diseases and Geographic Medicine, Stanford University School of Medicine Stanford, CA 94305, USA (peter@molepi.stanford.edu)

Ian Smith MD, Stop TB Department, World Health Organization, Geneva, Switzerland (smithi@who.int)

Elizabeth A. Talbot MD, Director TB/HIV Research, The BOTUSA Project, International Activity, Division of TB Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Department of State Washington DC, USA (edt7@cdc.gov)

Zachary Taylor MD MS, Centers for Disease Control and Prevention, Atlanta, GA, USA (Zxt0@cdc.gov)

Armand Van Deun MD, Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium (armand.vandeun@ping.be)

Andrew A. Vernon MD MHS, Supervisory Medical Epidemiologist, Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (avernon@cdc.gov)

Margarita Elsa Villarino MD MPH, Chief, Diagnostic and Therapeutics Studies Section, Research and Evaluation Branch, Division of Tuberculosis Elimination National Center for HIV, STD, and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA (mev1@cdc.gov)

Charles D. Wells MD, Associate Director for International Activities, Division of Tuberculosis Elimination, National Center for HIV, STD, and TB Prevention, Centers for Disease Control & Prevention, Atlanta, GA, USA (mev1@cdc.gov)

The WHO Stop TB Department acknowledges the crucial work of the editor Dr T. Frieden, the valuable comments on the final draft from Drs M. Borgdorff, D.A. Enarson, P. Hopewell, A. Seita, and A. van Deun, and the overall assistance of Dr F. Luelmo.

Case detection

1. What is the role of case detection in tuberculosis control?[1]

F. Luelmo[2]

Detection of the most infectious cases of tuberculosis – sputum smear-positive pulmonary cases – by case-finding in patients attending health facilities is an essential component of the control of tuberculosis. Its objective is to identify the sources of infection in the community, that is, individuals who are discharging large numbers of tubercle bacilli. Treatment of those infectious patients rapidly renders them non-infectious, thereby cutting the chain of transmission. A secondary benefit of case detection is to minimize the delay in initiating treatment, thereby increasing the probability of cure (*1*). If the cases detected cannot be treated effectively – because of lack of drugs, poor organization, or patients' limited access to treatment services – the activity is of little value. Identification of cases without being able to treat them undermines confidence in the health system and increases the number of persistently infectious cases spreading drug-resistant bacilli. Where new cases are not yet treated satisfactorily and reliably cured, resources and efforts should therefore be concentrated on improving treatment outcomes rather than increasing case detection (*2*). In addition to patients consulting for symptoms, the main target group for case detection is persons who attend health facilities for any reason and present persistent cough, i.e. cough of more than 2 or 3 weeks' duration.

In the past, case detection has been based on screening of the community by mass miniature radiography (MMR) – so-called "active case-finding". However, radiological shadows are not specific to the diagnosis of tuberculosis, and, even in patients with active pulmonary tuberculosis, radiographs do not reliably discriminate infectious patients from other cases who do not represent a major risk to the community. Mass screening is not cost-effective since the specificity of the method for identifying sources of infection is low, many cases arise between rounds of screening, and the individuals detected are often not motivated to complete treatment and are frequently lost (*3*, *4*) (see "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?", page 72).

[1] Based on the chapter in the previous edition by K. Toman.

[2] Consultant, TB control programmes, Geneva, Switzerland.

Identification of adults with persistent cough attending health facilities and screening them by examination of sputum smears is more cost-effective than MMR and specifically identifies those who are transmitting tuberculosis. In areas where patients are being reliably cured, community education should be provided so that people are made aware that persistent cough is abnormal, informed where health services are available, and persuaded to consult a health provider promptly for sputum smear examination.

Contacts of smear-positive tuberculosis patients are at high risk of infection and of developing tuberculosis, justifying active case detection in these individuals. Examination of contacts, particularly of contacts of sputum smear-positive patients, is therefore recommended to identify and treat tuberculosis cases and to provide preventive treatment to those at highest risk, such as children and people infected with HIV. Among residents of institutions with a high risk of tuberculosis transmission (such as prisons, shelters for the homeless, and hospitals), evaluation for cough on admission and periodic assessments are useful to detect and treat sources of infection.

References

1. Borgdorff MW, Floyd K, Broekmans JP. Interventions to reduce tuberculosis mortality and transmission in low- and middle-income countries. *Bulletin of the World Health Organization*, 2002, 80:217–227.
2. *WHO Expert Committee on Tuberculosis. Ninth Report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
3. Shimao T. *Tuberculosis case-finding*. Geneva, World Health Organization, 1982 (document WHO/TB/82.131).
4. Fairly IM, Heap BJ. Pulmonary tuberculosis in Gurkhas in Hong Kong in the period 1984–1987 and the role played by routine radiology in case detection. *Journal of the Army Medical Corps*, 1989, 135:31–32.

2. What is a case of tuberculosis?[1]

F. Luelmo[2]

Tuberculosis control aims to reduce the spread of infection. The most efficient method for preventing transmission is identification (through case detection, diagnosis) and cure of the most potent sources of infection – pulmonary tuberculosis patients excreting tubercle bacilli (*1*). In addition, tuberculosis control aims to cure all forms of the disease in order to reduce mortality and human suffering. For the purpose of tuberculosis control programmes, a "case" is therefore defined as a patient in whom tuberculosis has been confirmed bacteriologically or diagnosed by a clinician (*2*).

For programme purposes, cases are classified according to the site of the lesions as either pulmonary (with lesions in the lung parenchyma) or extrapulmonary (with lesions elsewhere but not in the lung parenchyma). Pulmonary cases are further classified as either sputum smear-positive or sputum smear-negative (which includes smear result unknown). The positivity of smears depends on the number of tubercle bacilli (see "How many bacilli are present in a sputum specimen found positive by smear microscopy?", page 11) and correlates with the risk of infecting other individuals and the risk of dying from tuberculosis. Contacts of smear-positive individuals are at much greater risk of being infected with *Mycobacterium tuberculosis* and of developing tuberculosis than contacts of tuberculosis patients positive by culture only (*3*). In countries where culture of sputum samples is readily available, smear-negative cases can be classified as either definite tuberculosis cases (culture-positive for *M. tuberculosis* complex) or others (culture-negative or unavailable).

On diagnosis, patients are classified for registration according to previous TB treatment as:

- new: without or with less than 1 month of previous treatment;
- relapse: smear- or culture-positive patient previously treated and declared cured or treatment completed;
- failure: sputum smear-positive after 5 months or more of treatment (or after 2 months or more of treatment if initially sputum smear-negative);

[1] Based on the chapter in the previous edition by K. Toman.
[2] Consultant, TB control programmes, Geneva, Switzerland.

— return after default: return to treatment after interruption of 2 months or more;
— transfer in: patient transferred from another tuberculosis register to continue treatment; and
— other: all cases that do not fit the above definitions (includes chronic, i.e. patients sputum-positive at the end of a re-treatment).

Although smear-negative pulmonary tuberculosis and extrapulmonary cases may also be relapses, failures, or chronic cases, this is rare and should be supported by pathological or bacteriological evidence (*2*).

For registration, there are six mutually exclusive categories of treatment outcome:

— *cured*: a patient who is sputum smear-negative in the last month of treatment and on at least one previous occasion during treatment;
— *treatment completed*: a patient who completed treatment but does not meet the criteria for cure or failure (or after 2 months or more of treatment if initially sputum smear-negative);
— *treatment failure*: a patient who is sputum smear-positive at 5 months or later during treatment;
— *died*: a patient who dies for any reason during the course of treatment;
— *defaulter*: a patient whose treatment was interrupted for 2 months or more;
— *transfer out*: a patient who has been transferred to another unit and for whom the treatment outcome is not known.

Treatment success is defined as the sum of the patients who are cured and who have completed treatment. In countries where culture is current practice, patients can be classified as cure or failure on the basis of culture results (*2*).

References

1. Rouillon A, Perdrizet S, Parrot R. Transmission of tubercle bacilli: the effects of chemotherapy. *Tubercle*, 1976, 57:275–299.
2. Revised international definitions in tuberculosis control. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:213–215.
3. Rieder HL. *Epidemiologic basis of tuberculosis control*. Paris, International Union Against Tuberculosis and Lung Disease, 1999.

3. What is the role of sputum microscopy in patients attending health facilities?

F. Luelmo[1]

Sputum microscopy is the most efficient way of identifying sources of tuberculosis infection. The method is used to diagnose tuberculosis in persons with suspected pulmonary disease and to identify sources of infection among persons with cough attending health facilities for any reason. Sputum microscopy is also used to monitor the progress of infectious patients during treatment, including confirmation of cure.

Diagnosis

The diagnostic efficiency of sputum smear examination is discussed in "How reliable is smear microscopy?" (page 14). Smear examination has several operational advantages over culture: the results are available sooner, correlate with infectiousness, and identify both patients at high risk of death from tuberculosis if untreated and patients who require more drugs in the initial treatment regimen because of greater bacterial load.

A proportion of the patients attending health facilities consult a physician because of symptoms suggestive of tuberculosis. It is the responsibility of the physician to suspect tuberculosis in these patients and to perform the appropriate diagnostic tests. In diagnosing infectious pulmonary tuberculosis, smear examination in persons with persistent cough is the most important test. Chest radiography is useful for differential diagnosis of pulmonary disease among patients with negative sputum smears. The timing of the diagnostic procedures will depend on the prevalence of tuberculosis in the community. In areas with a high prevalence of tuberculosis, smear examination should be the initial test. For diagnosis of pulmonary disease in areas with a lower prevalence of tuberculosis, smears and chest radiography may be performed simultaneously, a short course of antibiotics nonspecific for tuberculosis may be given, or a chest radiograph may be used as an auxiliary diagnostic procedure before smears and culture. In any case, individuals with abnormal chest radiographs should be asked to submit several sputum samples for smear examination before pulmonary tuberculosis is diagnosed.

[1] Consultant, TB control programmes, Geneva, Switzerland.

Case detection

Infectious pulmonary tuberculosis is often not detected until a late stage, even though the patient may have attended health facilities during the initial stages of the disease. Physicians frequently do not suspect tuberculosis or do not request smear examination in patients with cough, particularly if those patients present with non-respiratory ailments. It is estimated that as many as 5–10% of adults attending outpatient health facilities in developing countries may have a persistent cough of more than 2–3 weeks' duration (*1*, *2*). The proportion of smear-positive pulmonary tuberculosis among these individuals depends on the prevalence of tuberculosis in the community. Systematic identification of adults with persistent cough among outpatients in general health facilities can detect a large proportion of sources of tuberculosis infection (*3*). This reduces treatment delay and identifies infectious patients who are a risk to the community and to other patients and staff at the health facility. Successful treatment of these patients has a rapid effect on tuberculosis prevalence, mortality (*4*), and transmission (*1*).

In heavily used facilities, paramedical or administrative staff should be largely responsible for identification of persons with persistent cough and referral for smear examination. This screening is a public health activity intended only to detect and cure sources of infection, and is additional to diagnostic activities in persons consulting spontaneously. Because the objective is primarily to benefit the community, the procedure must be simple, convenient for the individual, and free of charge, and should not detract from the patient's original purpose in attending the clinic. It is important to record the patient's name and address: if the laboratory detects positive smears the patient must be found immediately and treatment initiated.

Culture is not a priority test for systematic detection of cases. Persons who are positive only on culture are less infectious than those who are also positive to microscopy. Furthermore, culture is more expensive and complex than microscopy, and there is a relatively long delay until the result is available.

The duration of cough chosen by a country as the threshold for recommending smear examination depends on the prevalence of smear-positive tuberculosis, the frequency of attendance at health facilities by the population, and the laboratory resources available. If the prevalence of tuberculosis is very low, there is no role for systematic case detection with smears in adults with cough (low cost-effectiveness and high risk of false-positive results). Attendance at health facilities varies among countries. People in more developed countries consult earlier and more often, and the duration of cough selected as a basis for screening must be shorter; however, this increases the proportion of patients with nonspecific cough and the workload of the laboratory services, and reduces cost-effectiveness. Studies of prevalence of cough among adults attending outpatient health facilities help determine the optimal duration of cough at which to recommend sputum examination under routine conditions (*2*, *5*, *6*).

Case detection in outpatients by microscopic examination of sputum can significantly increase the number of sources of infection diagnosed. The number of outpatients investigated, the number of smears for diagnosis, and the number of sources detected are indicators of the case-detection activity. In Peru, for instance, 210 905 smear examinations were carried out in 1990, leading to the identification of 24 023 cases of smear-positive pulmonary tuberculosis. In 1993, 602 000 smears from 332 000 persons were examined and 35 646 cases were identified. By 1999 the number of smear-positive cases had decreased to 24 511 despite an increase in the number of smear examinations to 1 938 201 in 1 085 749 persons (*1*, *4*). The proportion of positive smears is an indirect indicator of the impact of the programme in reducing the prevalence of tuberculosis in the community. The rate of smear positivity in persons with respiratory symptoms in Peru was 18.7% in 1990, 14.3% in 1991, 8.5% in 1993, and 2.7% in 1999. Similarly, in Chile the smear positivity rate fell from more than 10% to less than 2% in two decades. By 1999, Peru was examining approximately 5% of the adult population for tuberculosis by smear microscopy every year (*1*).

Microscopic examination of sputum smears during and at the end of treatment

Sputum smear microscopy has a fundamental role in monitoring the response to treatment of infectious cases of pulmonary tuberculosis. Smear examination should be performed at the end of the initial phase of treatment; if smears are still positive, the intensive phase should be extended for an additional month. Smears should be examined during and at the end of the continuation phase to confirm cure. The *conversion rate* at 2–3 months (defined as the proportion of initially smear-positive patients with negative smears out of the total who started treatment) is a good operational indicator. It shows the capacity of the programme to maintain patients on treatment, obtain smear samples, and eliminate sources of infection, and it is an early surrogate of the treatment outcome indicator (*7*). With short-course treatment regimens of high efficacy, smears can be positive at 2–3 months because of dead bacilli in patients with negative cultures. Thus, treatment failure based on positive smear examination is not considered until the fifth month or later (see "How can the progress of treatment be monitored?", page 250). Negative smears during and at the end of treatment are required to declare a patient cured of tuberculosis.

References

1. *Tuberculosis en el Peru 1999.* [*Peru National TB control programme 1999.*] Lima, Ministry of Health, 2000.
2. Baily GV et al. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a district of South India. *Bulletin of the World Health Organization*, 1967, 37:875–892.
3. Banerji D, Anderson S. A sociological study of awareness of symptoms among persons with pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1963, 29:665–683.

4. Suarez PG et al. The dynamics of tuberculosis in response to 10 years of intensive control efforts in Peru. *Journal of Infectious Diseases*, 2001, 184:473–478.
5. Larbaoui D et al. The efficiency of methods of diagnosing pulmonary tuberculosis: an investigation in a chest clinic in Algiers. *Tubercle*, 1970, 51:403–411.
6. Grinspun M, Rojas L. Comparison between radiological and bacteriological finding in tuberculosis. *Revista Medica de Chile*, 1973, 101:797–805.
7. *An expanded DOTS framework for effective tuberculosis control.* Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2002.297).

4. How many bacilli are present in a sputum specimen found positive by smear microscopy?

K. Toman[1]

If a smear is properly prepared, the number of bacilli it contains will correlate with the concentration of bacilli in the sputum. This numerical relationship, which has been investigated by many authors (*1–4*), may be illustrated by the following example.

The amount of sputum on a slide for smear preparation is about 0.01 ml. This is spread over an area of 200 mm^2 (10 × 20 mm). Since the area of an oil-immersion field seen in the microscope is about 0.02 mm^2, 10 000 such fields would need to be screened in order to examine the entire smear at a magnification of 1000×, i.e. 100× for the oil-immersion objective lens and 10× for the eyepiece. (The size of a field in fluorescence microscopy is about 15 times as large with an objective of 25× and an eyepiece of 10×.) By examining one length (20 mm) of a smear, some 100–120 microscopic fields are screened, representing about 1% of the smear. The above calculations are for a smear that is 10 × 20 mm; in actual practice smears of 20 × 30 mm are generally used.

Thus, if a sputum specimen contains about 5000 bacilli per ml, the entire smear (if prepared as described) will contain about 50 bacilli. If these 50 bacilli were evenly distributed over the 10 000 fields of the smear, there would be one bacillus in 200 fields. If 100 fields were examined the chance of finding this bacillus would be 50%. To find at least three acid-fast bacilli (AFB), about 600 fields would have to be screened. If 300 fields were examined, the chance of finding three bacilli would also be 50% (*5–7*).

Furthermore, to find one acid-fast bacillus in every 10 fields (or 10 in 100 fields) would require 1000 such bacilli to be present in the smear (10 000 fields) or 100 000 (10^5) per ml of sputum (Table 1). To find one acid-fast bacillus per field on the average would require 10^6 bacilli per ml of sputum (Table 1). Thus, a specimen that is consistently found to be positive would have to contain at least 100 000 AFB per ml.

These estimates are based on the assumption that the bacilli are evenly dispersed throughout the specimen, i.e. that each portion of material taken from the specimen will contain the same number of AFB spread evenly over the entire smear. However,

[1] Deceased.

Table 1
Estimated numbers of acid-fast bacilli in sputum specimens and probable numbers of bacilli in smears (estimated minimum values)

No. of oil-immersion fields per bacillus	No. of bacilli per smear	No. of bacilli per ml of specimen
100	100	10 000
10	1 000	100 000
1	10 000	1 000 000

it is known that bacilli are not evenly dispersed in a specimen, but are frequently found in clumps. Thus, when several samples are taken from a sputum specimen, the number of bacilli will vary from one sample to another. Nevertheless, when special culture techniques were used to compare the number of bacilli in large numbers of samples taken from different sputum specimens, certain important observations were made. In particular, the number of colonies cultured from samples taken from the same specimen varied only within certain limits, not at random (see "How reliable is smear microscopy?", page 14). Likewise, variations in colony counts among samples from different specimens did not occur randomly, but were due to differing concentrations of AFB in the specimens. Thus, in spite of considerable sampling variation, the number of bacilli in the smear corresponds fairly closely to the concentration of bacilli in the sputum (*4*). Below a certain concentration of bacilli in a sputum specimen, the probability that AFB will be transferred from the specimen to the smear and found by microscopy approaches zero. Although it has been estimated that, with optimal laboratory conditions, a positive smear can be obtained with only 100–1000 organisms per ml (*8*), a more practical estimate is about 10 000 organisms. While a single smear of sputum has a reported sensitivity of only 22–43%, the detection rate goes up considerably when multiple specimens are examined; for example, when 2–3 smears are examined over 2 days, about 50–70% of patients with active pulmonary tuberculosis will have positive smears (*9*).

References

1. de Carvalho E. Was leistet die mikroskopische Untersuchung, das Kulturverfahren und der Tierversuch bei der Ermittlung kleinster Tuberkelbazillenmengen im Untersuchungsmaterial? [How useful are microscopy, culture methods, and animal experiments in determining the smallest amounts of tubercle bacilli in samples?] *Zeitschrift für Tuberkulose*, 1932, 63:305–317.
2. Cruikshank DB. Bacteriology. In: Sellors TH, Livingstone JL, eds. *Modern practice of tuberculosis. Vol. 1*. London, Butterworths, 1952:53–77.
3. Hobby GL et al. Enumeration of tubercle bacilli in sputum of patients with pulmonary tuberculosis. *Antimicrobial Agents and Chemotherapy*, 1973, 4:94–104.

4. David HL. *Bacteriology of the mycobacterioses*. Atlanta, GA, US Department of Health, Education and Welfare, Communicable Disease Center, 1976:147.
5. Smithwick RW. *Laboratory manual for acid-fast microscopy*. Atlanta, US Department of Health, Education and Welfare, Public Health Service, 1976.
6. *Technical guide: sputum examination for tuberculosis by direct microscopy in low-income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
7. American Thoracic Society, Scientific Assembly on Tuberculosis. *Diagnostic standards and classification of tuberculosis and mycobacterial diseases*. New York, American Lung Association, 1974.
8. Wolinsky E. Conventional diagnostic methods for tuberculosis. *Clinical Infectious Diseases*, 1994, 19:396–401.
9. American Thoracic Society and Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *American Journal of Respiratory and Critical Care Medicine*, 2000, 161:1376–1395.

5. How reliable is smear microscopy?

K. Toman[1]

To assess the reliability of smear microscopy quantitatively, answers are needed to the following questions:

1. What is the probability of finding acid-fast bacilli (AFB) in smears prepared from specimens containing few, some, or many bacilli?
2. What is the probability of reporting a (false-)positive result for smears from specimens without tubercle bacilli?
3. What is the frequency of agreement between microscopists or laboratories reporting the results for smears prepared from the same specimens?

Table 1 under "How many bacilli are present in a sputum specimen found positive by smear microscopy?" (page 11) supplies part of the answer to the first question. The figures in that table are derived from experimental findings and have been extrapolated on the assumption that bacilli are evenly distributed throughout specimens. Since the bacillary content varies from one sample to another, however, such measurements must be performed on a large number of specimens, taking the results of culture as a yardstick (*1*). In several studies (*2*, *3*), the bacillary counts of smears were compared with the number of colonies grown on cultures prepared from the same specimen.

In a cooperative study by eight laboratories, it was confirmed that colony counts for samples taken from the same specimen varied from one sample to the next, although these variations were minimal.[2] The disparity of colony counts between samples from different specimens was due mainly to the variation in the concentration of bacilli in these specimens. It was concluded, therefore, that there is a positive correlation between the concentration of culturable bacilli in the specimens, the number of AFB in the corresponding smears, and the probability of their being identified by microscopy. The results (Table 2) show that the chance of finding AFB in a

[1] Deceased.

[2] David HL et al. *Sensitivity and specificity of acid-fast microscopy*. Atlanta, GA, United States Department of Health, Education and Welfare, Centers for Disease Control (unpublished document prepared for the WHO Expert Committee on Tuberculosis, Geneva, 1973).

Table 2
Number of acid-fast bacilli observed in smears, concentrations of culturable bacilli in sputum specimens, and probability of positive results[a]

No. of bacilli observed	Estimated concentration of bacilli per ml of specimen	Probability of a positive result
0 in 100 or more fields[b]	<1000	<10%
1–2 in 300 fields	5000–10 000	50%
1–9 in 100 fields	about 30 000	80%
1–9 in 10 fields	about 50 000	90%
1–9 per field	about 100 000	96.2%
10 or more per field	about 500 000	99.95%

[a] Source: reference *1*.
[b] Approximately 0.01 ml of homogenized sputum was placed on the slide and spread over an area of about 200 mm^2. The area of a microscope field under oil immersion and at a magnification of 1000× is 0.02 mm^2. Thus, a smear would contain about 10 000 such fields (see "How many bacilli are present in a sputum specimen found positive by smear microscopy?", page 11).

smear increases with the concentration of bacilli in the specimen. By plotting the data, a smooth curve is obtained, showing that the 50% probability of finding AFB in the smear occurs at a concentration of about 6000 bacilli per ml. Similar values were reported in earlier studies (*2*, *3*).

In order to crosscheck these findings, David et al. tried to determine the probability of not finding any AFB in the smear for various concentrations of bacilli estimated from viability counts.[2] They examined 431 specimens in three independent experiments. The concentrations of bacilli ranged from 1500 to 300 000 per ml.

Each microscopist was to examine smears from all specimens obtained from a group of selected patients. Uniformity in the technical procedures of smear preparation and examination in the participating laboratories was ensured by a standard protocol. The investigation was designed in such a way that no microscopist could know the results obtained by any other microscopist or the origin of the specimens, or have access to any other information that might result in bias. The proportions of smears reported as negative are shown in Table 3.

Table 3 shows that the probability of not finding AFB in smears decreases steadily as the concentration of bacilli in the specimen increases. When the concentration exceeds 100 000 organisms per ml, the probability of a negative smear result approaches zero. This confirms earlier findings that smears that were consistently positive, at any examination, had been prepared as a rule from specimens containing 10^5–10^6 AFB or more per ml.

However, the use of culture colony counts for the calculation of the bacillary content of sputum has limitations, and it is technically difficult to obtain accurate results with this method. Large numbers of samples need to be examined and a special technique

Table 3
Frequency (probability) of negative results for smears from specimens containing varying concentrations of bacilli estimated by culture (colony counts)[a]

Estimated concentration of bacilli per ml of specimen	Experiment no. 1	2	3	Mean (%)
	negative results (%)			
1 500	–	85	92	88.5
3 000	84	83	77	81.3
15 000	25	28	6	19.6
30 000	16	30	6	17.3
150 000	0	0	5	1.6
300 000	0	0	0	0.0
No. of smears studied	42	100	289	–

[a] Reproduced with minor editorial changes from David HL et al. *Sensitivity and specificity of acid-fast microscopy*. Atlanta, GA, United States Department of Health, Education and Welfare, Centers for Disease Control (unpublished document prepared for the WHO Expert Committee on Tuberculosis, Geneva, 1973).

must be used in order to minimize the technical error occurring when specimens contain a large proportion of bacilli in aggregates. (It is impossible to tell whether a colony on a culture medium has grown from a single bacillus or from a clump of bacilli.) On the other hand, AFB that can be seen under the microscope may not always be able to grow on culture, e.g. because they are dead or nonviable (see "What are the main causes of false-positive and false-negative sputum smears?", page 23). The investigators therefore chose a method that does not depend on culture results.

Since the aim was to measure the reliability (reproducibility of results) of the smear microscopy method, the reports of several proficient microscopists who examined smears from the same specimen were compared. Irrespective of whether a report was right or wrong, the frequency of agreement or disagreement between the microscopists was measured. The smears were read strictly independently, according to a protocol. The experiment was arranged as follows.

Four microscopists read 54 specimens. Four smears (one per microscopist) were prepared from each specimen and examined independently. The four results obtained for each specimen were recorded using the scores: negative, scanty (1–9 bacilli in 100 microscopic fields), or positive (1+, 2+, or 3+). The results for each specimen were compared separately, the result of one microscopist being compared with the results of the other three microscopists in all possible permutations. Thus, 12 results were obtained for each specimen. By this means, it was possible to construct a correlation table (Table 4) showing the frequency of agreement and disagreement between the four microscopists. The total number of comparisons was 648, of which four were not reported.

Table 4
Frequency of agreement or disagreement between four microscopists[a]

Report of one microscopist	Reports of all other microscopists[b]					Total no. of observations	
	Negative	Scanty	1+	2+	3+		
Negative	233	25	8	2	0	268	309
Scanty[c]	24	5	1	7	4	41	
1+	8	2	11	18	4	43	
2+	2	8	16	39	50	115	335
3+	0	4	4	49	120	177	
Total	267	44	40	115	178	644	
	311		333				

[a] Source: David HL et al. *Sensitivity and specificity of acid-fast microscopy.* Atlanta, GA, United States Department of Health, Education and Welfare, Centers for Disease Control (unpublished document prepared for the WHO Expert Committee on Tuberculosis, Geneva, 1973).
[b] The figures in the box are the readings reported by any microscopist as positive, i.e. 1+, 2+ or 3+.
[c] Defined as 1–9 bacilli in 100 microscopic fields.

Table 4 shows that the highest frequency of agreement was on the extreme scores, i.e. negative and 3+ (all identical results are found on the diagonal line). Furthermore, it may be seen from Table 4 that, when one microscopist reported the result as negative or scanty, in only 22 of 309 instances (7%) did other microscopists report a positive result (1+, 2+, or 3+). In other words, there was agreement between the microscopists in 287 of 309 cases (93%). Likewise, when one microscopist reported a positive result, the probability of agreement with the other microscopists was 311 out of 335 (93%).

The lowest frequency of agreement was on results reported as scanty (see Table 4): when one microscopist reported such a result there was an 88% probability (36 out of 41 instances) that other microscopists would disagree. In 24 out of 41 instances (59%) the result reported by other microscopists was negative. This is in accordance with the findings of another investigation, in which sputum specimens from patients with chest symptoms were negative on culture in 3 out of 4 cases when only 1–2 AFB had been seen on the smear (HG ten Dam, 1976, unpublished observations). The definition of scanty used in this classic study was the finding of 1–2 AFB in a smear; such smears should be repeated.

Regarding the grading of positive results, the data show that agreement declined steeply below the score 3+ (Table 5). According to Table 5, agreement on the scores 1+ and 2+ was quite low: 25% and 34% (see data on the diagonal). Thus the differentiation between score 1+ and score 2+ appears to be rather illusory.

The above-mentioned experiment showed the high reliability (reproducibility) of results. By independent examination of smears prepared from the same specimens,

Table 5
Frequency of agreement or disagreement between four microscopists on the score of positive results (data from Table 4 presented in percentages)

		All other microscopists					Total (%)
		Negative	Scanty	1+	2+	3+	
Report of one microscopist	1+	19	5	25	42	9	100
	2+	2	7	14	34	43	100
	3+	0	2	2	28	68	100

the frequency of agreement between equally proficient microscopists may reach 93%. However, these results were achieved under experimental conditions and with experienced laboratory technicians. The question that arises is, "How does smear microscopy work under field conditions, particularly in peripheral health centres of developing countries?" This question is answered below.

Smear microscopy under field conditions in developing countries

In peripheral health centres, sputum collection, the preparation and staining of smears, and their examination by microscopy are usually performed under suboptimal conditions – often by microscopists with limited experience. This applies to most of the peripheral health centres in rural areas, which are attended by the majority of patients complaining of chest symptoms. As a rule, such patients are offered a sputum examination for diagnosis. The standard of case detection in developing countries therefore depends, in addition to operational factors, largely on the technical performance of smear microscopy.

In order to assess the qualitative performance of sputum examination in rural health institutions, several studies were carried out by the National Tuberculosis Institute, Bangalore, India (*4*, *5*). In a South Indian district where a district tuberculosis programme had been implemented about 6 months before the investigation, the performance of nine randomly selected health centres was analysed. The microscopists at these centres were non-specialized health workers who had been trained for 2–4 weeks in the collection and examination of sputum according to a manual that they had been given. They had received on-the-job training from an experienced laboratory technician, who was also a member of the tuberculosis control team (*6*, *7*). The team was responsible for the implementation and supervision of the programme in the entire district (population 1.5 million).

Method of assessment

In each of the nine centres, one sputum sample was collected from every patient complaining of persistent cough and a smear was prepared and examined immediately

(spot sample). The slide was then sent, together with the specimen, to the laboratory at the National Tuberculosis Institute, where it was re-examined. The specimen was used to prepare a fresh (duplicate) smear, as well as for culture. The results obtained at the peripheral health centre were then compared with those of the reference laboratory, i.e. the results of:

— re-examination of the smear made at the peripheral centre;
— examination of the duplicate smear; and
— culture examination.

The results – in terms of under- or over-reading – were analysed and tabulated for each health centre separately. The result of culture was taken as the yardstick. Of 1681 specimens, 228 (13.6%) were found to be culture-positive and 1453 (86.4%) culture-negative.

Over-reading of culture-negative specimens

In order to estimate the extent of over-reading by the peripheral health centres, the culture-negative specimens were taken as the standard and were compared with the results of the corresponding smears reported by the peripheral centres and by the reference laboratory (Table 6).

There were 1453 specimens negative by culture, of which 2.6% were reported by the health centre as positive. The same smears were re-examined at the reference lab-

Table 6
Over-reading of smears (prepared from culture-negative specimens) read at the peripheral health centre and at the reference laboratory[a]

Centre	Total no. of culture-negative specimens	Read as smear-positive at:	
		peripheral health centre	reference laboratory
A	306	5	4
B	233	8	1
C	159	7	7
D	156	2	2
E	108	12	2
F	111	3	1
G	100	1	1
H	84	0	1
I	196	0	0
Total	1453 (100%)	38 (2.6%)	19 (1.3%)

[a] Source: reference *5*.

oratory, which reported 1.3% as positive. Thus over-reading was, on average, higher at the peripheral health centres than at the reference laboratory. However, a more detailed analysis shows that this difference was attributable mainly to one centre (E). When this centre was excluded from the analysis, the proportion of over-reading fell to 1.9%. The proportion of over-reading by duplicate smear examination was 1.2%, compared with 1.3% by re-examination (*5*).

Under-reading of culture-positive specimens

In order to estimate the extent of under-reading at the peripheral health centres, the culture-positive specimens were taken as the standard and were compared with the results of the corresponding smears reported by the peripheral centres and by the reference laboratory (Table 7).

There were 228 specimens positive by culture, of which 87 (38.2%) and 67 (29.4%), respectively, were reported by the peripheral health centres and by the reference laboratory as smear-positive. Thus, under-reading at the peripheral health centre was worse than at the reference laboratory (38.% and 29.4%, respectively). This difference was caused mainly by the poor performance of two centres (D and H). When these two centres were excluded from the analysis, the degree of under-reading at the peripheral centres and at the reference laboratory was practically the same: 23% and 26%, respectively.

The authors of the study concluded (*5*) that over-reading by the microscopists of

Table 7
Under-reading of smears (prepared from culture-positive specimens) read at the peripheral health centres and at the reference laboratory[a]

Centre	Total no. of culture-positive specimens	Read as smear-positive at:	
		peripheral health centre	reference laboratory
A	101	27	26
B	21	7	8
C	23	7	5
D	22	19	9
E	15	6	6
F	16	5	4
G	15	7	5
H	10	8	3
I	5	1	1
Total	228 (100%)	87 (38.2%)	67 (29.4%)

[a] Source: reference *5*.

the peripheral health centres was a problem in only one of the nine centres. Additional training, supervision, or other corrective action would rectify the deficiency observed. This also applies to under-reading in two of the centres, where corrective training and proper supervision were needed. Comparison of the results with those obtained in other tuberculosis laboratories in India (*8*, *9*) revealed a similar range of over- and under-reading when culture results were taken as the basis.

The authors also concluded that non-specialized staff of general health institutions are capable of carrying out satisfactory smear microscopy. Taking into consideration the short period of training usually received, it may be expected that, with continuous supervision and corrective retraining, the performance of such microscopists could be maintained at a satisfactory level (see "What are the main causes of false-positive and false-negative sputum smears?", page 23).

In a similar study reported from Algeria (*10*), the results of re-examination of smears prepared and read by non-specialized staff at a peripheral health centre and re-read at a central laboratory were comparable. Thus, double reading of 104 smears yielded 95% identical results. Of 86 smears classified as negative by the central laboratory, 2 were read as positive by the peripheral health centre, and of 18 smears read as positive at the central laboratory, 3 were judged to be negative at the peripheral health centre. The authors recommended the use of direct smear microscopy at peripheral health centres under the supervision of a central laboratory. Furthermore, they pointed out that it makes little sense to strive for more refined diagnostic techniques or greater precision as long as the health services remain unable to provide adequate treatment for every case diagnosed – the principal purpose of case detection.

Both field studies have indicated that smear microscopy performed by non-specialized health workers may be reliable. Training can be given, even on the job, by qualified technicians. To achieve a satisfactory level of proficiency, however, retraining of those whose performance is below standard must be ensured. Re-examination of smears and examination of duplicate smears prepared from the same specimens are valuable techniques for the supervision and technical assessment of smear microscopy in peripheral health centres. At a later stage, when culture facilities are introduced, culture should be used primarily to assess diagnosis by direct smear examination and then, if possible, for clinical diagnosis and evaluation of treatment.

References

1. David HL. *Bacteriology of the mycobacterioses*. Atlanta, GA, United States Department of Health, Education and Welfare, Communicable Disease Center, 1976:147.
2. de Carvalho E. Was leistet die mikroskopische Untersuchung, das Kulturverfahren und der Tierversuch bei der Ermittlung kleinster Tuberkelbazillenmengen im Untersuchungsmaterial? [How useful are microscopy, culture methods, and animal experiments in determining the smallest amounts of tubercle bacilli in samples?] *Zeitschrift für Tuberkulose*, 1932, 63:305–317.

3. Cruickshank DB. Bacteriology of tuberculosis. In: Sellors TH, Livingston JL, eds. *Modern practice of tuberculosis. Vol 1.* London, Butterworths, 1952:53–77.
4. Rao KP et al. Assessment of diagnosis of pulmonary tuberculosis by sputum microscopy in a district tuberculosis programme. *Indian Journal of Tuberculosis*, 1971, 18:10–21.
5. Nagpaul DR et al. Case-finding by microscopy. *Bulletin of the International Union Against Tuberculosis*, 1968, 61:148–158.
6. Toman K. Tuberculosis. The training of key-organizers. *Bulletin of the International Union Against Tuberculosis*, 1970, 43:165–169.
7. Nagpaul DR. Tuberculosis control teams. *Indian Journal of Tuberculosis*, 1972, 19:3–11.
8. Holst E, Mitchison DA, Radhakrishna S. Examination of smears for tubercle bacilli by fluorescence microscopy. *Indian Journal of Medical Research*, 1959, 47:495–499.
9. Sikand BK, Ranga Rao R. A simple pre-treatment technique for sputum comprising the use of a combination of pancreatin and cetavlon for the routine cultivation of tubercle bacilli. *Indian Journal of Tuberculosis*, 1958, 5:76–86.
10. Boulahbal F, Mazouni L, Chaulet P. Prospective study of the organization and supervision of the bacteriological diagnosis of pulmonary tuberculosis in a case-finding network in Algeria. *Bulletin of the International Union Against Tuberculosis*, 1976, 51:313–321.

6. What are the main causes of false-positive and false-negative sputum smears?

K. Toman[1]

False-positive results

Acid-fast particles other than tubercle bacilli

Occasionally, a sputum specimen or smear may contain particles other than *Mycobacterium tuberculosis* that are acid-fast, i.e. retain their red stain (carbol fuchsin) when treated by the Ziehl–Neelsen method and resist decolorization with acid–alcohol. These red particles sometimes resemble tubercle bacilli. They include certain food particles (e.g. waxes, oils), precipitates, other microorganisms, inorganic materials, and artefacts (*1–6*).

Food particles. To eliminate food particles, the patient should rinse the mouth with clean water (without using toothpaste or disinfectant) before producing the sputum specimen. It is better if the specimen is produced before breakfast.

Precipitated stains. Although precipitated stains are quite easy to differentiate from acid-fast bacilli, they may hamper reading or occasionally mislead an inexperienced microscopist. They can be removed by filtration of staining solutions. However, it is safer to use freshly prepared solutions, filled into carefully cleaned bottles, rather than stale staining solutions.

Environmental acid-fast bacilli. Acid-fast bacilli occur naturally in soil and water, and may occasionally contaminate a specimen or smear during processing. This can be avoided by using distilled water from scrupulously clean containers.

Non-tuberculous mycobacteria and Nocardia species. These occasionally occur in sputum specimens. When they cause pulmonary disease, they may be present in large numbers.

Spores of Bacillus subtilis. They are very rare, mostly of ovoid shape, and larger than tubercle bacilli.

Yeasts. Yeasts may stain slightly red. After heat fixation, they may break into groups of large granules.

Fibres and pollens. Fibres, including those of wool, cotton, filter paper, and bamboo, usually occur singly, most often in only one microscopic field. The

[1] Deceased.

pollen of certain pine trees is seen as short, coccoid rods occurring rarely in specimens.

Scratches on the slide. Scratches may sometimes retain the red stain and confuse inexperienced microscopists. They are usually seen in parallel rows, are generally longer than AFB, and are undulated. They can be identified easily because they are found in a deeper layer on the slide, below the smear, and disappear when the microscopist focuses on the cells (e.g. leukocytes) in the smear.

Contamination through the transfer of bacilli from one smear to another

Acid-fast bacilli may be transferred accidentally from a positive slide to a negative one when several slides are treated simultaneously in staining or decolorization tanks. This can be avoided by processing each slide separately, e.g. on a rack. Contamination may also occur when the wire loop used for making the smear is not correctly flamed. Contamination from this source can be avoided by using disposable wooden sticks for making smears.

Acid-fast bacilli may also be transferred accidentally when the glass rod or dropper used for placing immersion oil on the slide touches the surface of a positive slide and rubs off some of the material onto the next slide. This can also happen if the oil-immersion lens touches the slide or when blotting paper is used for drying several stained smears consecutively. For these reasons, the oil dropper should not touch the smear – the oil should be allowed to drip freely onto the slide – and the oil-immersion objective should never touch the surface of the slide. Before a new smear is examined, the oil should be wiped off the lens with special lens-cleaning paper or a piece of clean cotton tissue. Blotting paper should not be used at all, or for no more than one slide. Slides should never be used more than once for the detection of AFB.

False-negative results

False-negative results (*1–6*) may be due to deficiencies in the preparation, staining, or examination of the smear. Proper collection of the specimen and subsequent selection of sputum particles are essential to the preparation of a smear and should receive special attention. Poor quality of the sputum sample is the most common reason for a negative sputum smear in a patient with smear-positive tuberculosis. The most common reasons for false-negative results are described below.

Improper sputum collection

Patients are sometimes not told clearly enough what constitutes a proper sputum specimen and how to produce one. It must be made clear that saliva and nasopharyngeal discharge are unsuitable for examination. Patients should be encouraged to stand and be given time to produce bronchial sputum from "deep in the chest". They should be asked to take several deep breaths, coughing as hard and as deeply as they can. If repeated attempts fail, tickling of the inner surface of the epiglottis or trachea

with a swab may provoke a vigorous cough with sputum. Other techniques to stimulate the production of sputum, such as aerosol induction, administration of beta-agonists, gastric aspiration, and bronchoscopy, may be required in some patients. Inhalation of a warmed solution of hypertonic (3%) saline administered by nebulizer has been shown to induce production of sufficient material for analysis (*7*). Specimens produced in the early morning are more likely to be AFB-positive than those produced later in the day. If an early-morning sputum specimen is required, patients should be given a container and instructed to place in it the very first sputum produced in the morning, before breakfast.

Improper storage of sputum specimens and stained smears

Stained smears may lose their staining as a result of exposure of the specimen to direct sunlight, radiation (e.g. ultraviolet light), excessive heat, or long periods (more than a week) of storage in hot and humid conditions (*8*). However, even after a month of storage in tropical climates, specimens have nearly the same rate of smear positivity; all submitted samples should therefore be examined.

Fluorochrome-stained smears lose their fluorescence with storage.

Failure to select suitable sputum particles for smear preparation

Tubercle bacilli are most likely to be found in small roundish masses ("lentils") of greenish-grey or yellowish matter of a thick, creamy consistency. (Such masses usually consist of dead caseous tissue discharged from a cavity in the lung.) If the sputum is not treated by a special concentration procedure involving centrifugation, these masses have to be carefully separated from the rest of the sputum and transferred to a slide. They can be seen more easily in the sputum against a dark background.

Improper preparation of smears or staining of slides

False-negative results may also be obtained when:

— too little material has been spread on the slide, so that the smear is too thin;
— the smear is too thick, so that sufficient light cannot pass through it;
— the slide was overheated during fixing of the smear;
— the smear has not been sufficiently fixed and parts of the material have been washed off;
— the staining with carbol fuchsin was too short or was overdone by boiling; or
— the counterstaining was too intense, so that the AFB have been obscured.

Improper examination of the smear

If the microscopic examination of the smear is performed erratically or too briefly, too few fields may be examined. False-negative results may also be obtained if the

examiner is unable to distinguish the red-stained AFB because of colour blindness or other visual problems.

Other reasons for false results

Administrative errors

False results may occasionally be obtained because of administrative errors. Such errors may include:

— misidentification of patients, misspelling of names, or confusion of names or of code numbers on specimens and slides;
— mistakes in labelling containers (e.g. writing the identification on the lid instead of the side of the container); and
— falsification of recording or reporting.

Reading errors

Reader or observer error occurs in practically all diagnostic clinical and laboratory work. The nature of this phenomenon, often referred to as the "human factor", is to a large extent unknown. Nevertheless, under certain conditions, it is measurable. The degree and frequency of errors – over-reading as well as under-reading – vary from one person to another and also in the same individual at different times.

Inter-individual reader variation in smear microscopy has been repeatedly studied and its frequency has been found to be relatively low compared with, for instance, that associated with the reading of chest radiographs (see "How reliable is smear microscopy?", page 14, and "How reliable is chest radiography?", page 51). Several studies have been carried out to compare the results of different readers who independently examined smears prepared from the same specimens. When the readers were asked whether the smear was positive for acid-fast bacilli, the frequency of agreement was 93%. Such a high level of agreement has never been observed among readers of chest radiographs, even in response to such basic questions as: "Is the lung radiograph normal?" and "Is there a cavity present?" (see "How reliable is chest radiography?", page 51).

Many reader errors would be avoided if microscopists were properly trained and strongly advised to report what they actually see (rather than what they think they are expected to see). Diagnostic bias in favour of sickness – or, in treated patients, in favour of cure – is a known reason for reading error. However, discrepancies in the results of smear microscopy are due far more often to deficiencies in sputum collection and smear preparation than to reader errors.

References

1. Kubica GP, Dye WE. *Laboratory methods for clinical and public health mycobacteriology*. Atlanta, GA, United States Communicable Disease Center, Public Health Service, 1967 (Public Health Service Publication, No. 1547).

2. Smithwick RW. *Laboratory manual for acid-fast microscopy*. Atlanta, GA, United States Department of Health, Education and Welfare, Public Health Service, 1976.
3. David HL. *Bacteriology of the mycobacterioses*. Atlanta, GA, United States Department of Health, Education and Welfare, Public Health Service, 1976.
4. Takahashi S. *Handbook of direct smear examination of sputum for tubercle bacillus*. Tokyo, South-East Asian Medical Information Centre, 1975.
5. *Technical guide: sputum examination for tuberculosis by direct microscopy in low-income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
6. Weyer K et al. *Laboratory services in tuberculosis control. Part II: microscopy*. Geneva, World Health Organization, 1998 (document WHO/TB/98.258).
7. American Thoracic Society and Centers for Disease Control and Prevention. Diagnostic standards and classification of tuberculosis in adults and children. *American Journal of Respiratory and Critical Care Medicine*, 2000, 161:1376–1395.
8. Van Deun A et al. Reproducibility of sputum smear examination for acid-fast bacilli. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:823–829.

7. What are the main consequences of false-positive and false-negative sputum smears?

T. Frieden[1]

False-positive smears

The main consequences of false-positive sputum smears are (*1–3*):

False-(over-)diagnosis of tuberculosis

As a result:

- *Patients and their contacts are started on tuberculosis treatment unnecessarily, with possible complications.* Drug interactions can also cause problems if patients and their contacts are receiving other medications.
- *Delay in a correct diagnosis.* Once a positive result is obtained, the patient is started on tuberculosis drugs; further investigations for other diagnoses are generally not conducted. As the response to treatment in tuberculosis is slow, many clinicians wait 1–2 months or more before considering an alternative diagnosis. This delay in establishing the correct diagnosis may lead to increased morbidity and mortality from the actual non-tuberculous condition.
- *Emotional stress.* Many patients suffer emotional stress as a consequence of the diagnosis. In many societies, the diagnosis of tuberculosis still carries significant stigma.
- *Medications will be wasted.* A false-positive sputum test will result in unnecessary administration of antituberculosis drugs.
- *Financial loss.* Free treatment is not available everywhere for all patients. A false-positive diagnosis may therefore be associated with an unnecessary financial burden on the patient.
- *Patients and the community may lose confidence in the tuberculosis control programme.* Health workers should tell patients and the community that patients must continue to take medicines for 6 months, failing which they may become severely ill or even die. However, if a smear was falsely positive and a patient does not in fact have tuberculosis, that patient may discontinue treatment after only a few weeks and feel completely healthy. This may reduce the likelihood that patients who

[1] Medical Officer, Stop TB, WHO Regional Office for South-East Asia, New Delhi, India.

actually have tuberculosis will present for care promptly and take medicines as prescribed. The confidence of the community is important for effective programme implementation.
- *Unnecessary evaluation and treatment of children* if contact examination is undertaken.

False information about the progress or outcome of treatment

As a result:

- *Treatment may be continued for longer than necessary,* in the case of false-positive follow-up examinations.
- *Patients may be incorrectly considered to have failed to respond to treatment* and be given re-treatment regimens unnecessarily.

False-negative smears

The main consequences of false-negative sputum smear results are (*1–3*):

- *Patients with tuberculosis may not be treated, resulting in suffering, spread of tuberculosis and death.* If tuberculosis is not diagnosed and treated, it may become more severe and lead to destruction of the lung parenchyma, with extensive fibrosis. The resulting loss of lung function will be greater than if treatment had been initiated at an earlier stage. The disease may also spread to other people in the community.
- *Patients, physicians and the community may lose confidence in the programme.*
- *Treatment of infectious patients may be inadequate* (Category III instead of Category I, see "What are the diagnostic categories and what is the rationale for these categories?", page 128) *and of insufficient duration* (in the case of smears taken at the end of the intensive phase). This may result in an increased risk of drug resistance, inadequate treatment, relapse, and spread of tuberculosis. When clinical suspicion of tuberculosis is high, empirical treatment may be started but with fewer drugs than required because the patient is considered to be smear-negative. This may lead to treatment failure and possibly to emergence of drug resistance.
- *Unnecessary investigations.* False-negative sputum smears may lead to lengthy and unwarranted investigations for other conditions.
- *Financial loss.* Delay in the diagnosis of tuberculosis may result in expensive tests being done in the search for other possible conditions.

Laboratory staff must be adequately trained, supported, and supervised so that the preparation, staining, and reading of sputum smears for acid-fast bacilli are carried out correctly and consistently. Quality control of smears is essential (*4*). Accuracy of results is of particular importance where diagnosis of pulmonary tuberculosis is based mainly on sputum smear examination.

References

1. *RNTCP: module for laboratory technicians*. New Delhi, Ministry of Health and Family Welfare, Central Tuberculosis Division, 1997.
2. *Technical guide: sputum examination for tuberculosis by direct microscopy in low-income countries,* 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
3. Weyer K et al. *Laboratory services in tuberculosis control. Part II: microscopy*. Geneva, World Health Organization, 1998 (document WHO/TB/98.258).
4. Nguyen TN et al. The importance of quality control of sputum smear microscopy: the effect of reading errors on treatment decisions and outcomes. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:483–487.

8. What are the advantages and disadvantages of fluorescence microscopy?

K. Toman[1]

Fluorescence microscopy for the detection of acid-fast bacilli was introduced in the 1930s. At first, the microscopes had many technical shortcomings: they were difficult to handle and had to be used in dark rooms. Because of these difficulties, fluorescence microscopy was not widely accepted. The microscopes have since been substantially improved, and examination of sputum smears by fluorescence microscopy has become a well-established method in some high-volume laboratories.

The main advantage of fluorescence microscopy is that it uses a low-power (25×) objective. The field seen is thus many times larger than that seen in conventional bright-field microscopy through an oil-immersion objective: in fluorescence microscopy the field is about 0.34 mm^2, whereas that seen with an oil-immersion objective is only about 0.02 mm^2. Fluorescence microscopy allows the same area of a smear to be scanned in a much shorter time than can be achieved by conventional microscopy after staining with the Ziehl–Neelsen technique. A microscopist can properly examine at least 100 smears per day by fluorescence microscopy compared with only 30–40 Ziehl-Neelsen-stained smears (*1*–*3*).

Since about 15 times as many fields can be scanned by fluorescence microscopy as by conventional microscopy in the same period, there is a higher probability of finding AFB, particularly if a smear contains only a few bacilli. This was confirmed by a large comparative study, which showed that fluorescence microscopy carried out for 1 minute gave more true-positive – and no more false-positive – findings than conventional microscopy for 4 minutes, as judged by culture results (*1*).

The two techniques have been compared in a number of studies. In one investigation, 175 sputum specimens were examined in parallel (David et al., 1975, unpublished data). Duplicate smears were prepared from each specimen and examined independently by conventional microscopy and by fluorescence microscopy. The results obtained with each technique were recorded for every pair of smears separately and used to construct a correlation table (Table 8). Results that were identical are plotted on the diagonal. If the differences in grading of positive smears were disregarded, 157 of the 175 pairs of smears gave identical results, i.e. there was 90% agreement.

[1] Deceased.

Table 8
Correlation between bright-field microscopy (Ziehl–Neelsen technique) and fluorescence microscopy

Ziehl–Neelsen microscopy	Fluorescence microscopy: 0 or scanty	Fluorescence microscopy: Positive	Total
0 or scanty	10	12	**116**
Positive	6	53	**59**
Total	**110**	**65**	**175**

In another study comparing both techniques with the culture method (*3*), 1383 sputum specimens were collected, a pair of smears and one culture being made from each. The smears were examined independently, one by conventional Ziehl–Neelsen microscopy and the other by fluorescence microscopy (Table 9). The main purpose of the study was to assess the efficacy of each technique compared with culture. Another aim was to see whether fluorescence microscopy yielded false-positive results and, if so, how many. This information was essential because it had been suggested that sputum might often contain naturally fluorescent particles that could be confused with AFB (*4*).

For convenience of comparison, the data from Table 9 are been presented in two separate forms in Table 10. Comparison of the positive yield of fluorescence and Ziehl–Neelsen microscopy with that of culture showed a very slight advantage in favour of fluorescence microscopy. Of the 655 specimens that were positive by culture, 441 (67.7%) were positive by fluorescence microscopy and 433 (66.1%) by conventional microscopy.

There was practically no difference between the two methods as regards false-positive results. Of the 456 specimens positive by fluorescence microscopy, 15 (3.3%) were not confirmed by culture, compared with 14 (3.1%) of 447 specimens positive by conventional microscopy. In other words, 97% of the positive yield of either technique was unequivocally confirmed by culture. Thus, the fears about low specificity of the fluorescence technique seem to have been unwarranted (*5*). The examinations were carried out by regular laboratory personnel with experience in fluorescence microscopy. The results may thus be regarded as a standard performance for reasonably competent technicians. More recent studies confirm the similar results of using both methods in field conditions. Nevertheless, care must be taken to avoid a small number of inorganic acid-fast objects being mistaken for a scanty positive smear. With

Table 9

Results of examining 1383 sputum specimens by fluorescence microscopy (FL) and Ziehl–Neelsen microscopy (ZN) and by culture[a]

Category	Smear results		Specimens	
	FL	ZN	No.	%
1 Smear + / Culture +	+	+	405	33.9
	+	–	36	
	–	+	28	
2 Smear + / Culture –	+	+	11	1.2
	+	–	4	
	–	+	3	
3 Smear – / Culture +	–	–	186	13.4
4 Smear – / Culture –	–	–	681	51.5
Contaminated cultures	–	–	29	
Total			1383	100.0

[a] Source: reference *3*.

Table 10

Comparison of fluorescence microscopy with culture and Ziehl–Neelsen microscopy with culture

	Fluorescence microscopy		Total
	+	–	
Culture +	441	214	655
Culture –	15	713	728
Total	**456**	**927**	**1383**

	Ziehl–Neelsen microscopy		Total
	+	–	
Culture +	433	222	655
Culture –	14	714	728
Total	**447**	**936**	**1383**

regard to possible scanty false-positive results by fluorescence microscopy, the adage, "All that glistens is not AFB" should be remembered.

The disadvantages of fluorescence microscopy are the relatively high costs of a microscopy unit and of its maintenance. Nevertheless, in central or other large laboratories where the workload exceeds that of three technicians working with three conventional microscopes (e.g. more than 100–150 slides/day), it may be cheaper to use one fluorescence microscope instead. That calculation applies to places where the salaries of technicians are low, e.g. in developing countries (*6*). In countries where salaries are higher, fluorescence microscopy is generally less expensive than conventional microscopy even at lower volumes, because it requires fewer costly personnel (*7*, *8*).

A further disadvantage of fluorescence microscopy is that the handling and maintenance of the optical equipment require advanced technical skill. The fluorescence microscope is also less robust than conventional instruments. Component parts, particularly bulbs, have to be replaced from time to time, and may be expensive and difficult to procure; repairs are occasionally necessary. In addition, a continuous supply of standard electrical power with minimal voltage fluctuations is needed. These requirements are often difficult to meet in developing countries. It should be noted that reference laboratories that adopt fluorescence microscopy must continue to use light microscopy for quality control and for training of field staff.

References

1. Bennedsen J, Larsen SO. Examination for tubercle bacilli by fluorescence microscopy. *Scandinavian Journal of Respiratory Diseases*, 1966, 47:114–120.
2. Smithwick RW. *Laboratory manual for acid-fast microscopy*, 2nd ed. Atlanta, GA, United States Department of Health, Education and Welfare, 1976.
3. Holst E, Mitchison DA, Radhakrishna S. Examination of smears for tubercle bacilli by fluorescence microscopy. *Indian Journal of Medical Research*, 1959, 47:495–499.
4. Ritterhoff RJ, Bowman MG. Demonstration of tubercle bacilli by fluorescence microscopy. *American Journal of Clinical Pathology (Technical Section)*, 1945, 9:39–41.
5. Mitchison DA. *Proceedings of the 6th International Congress of Tropical Medicine and Malaria, Lisbon, 5–13 September 1958. Vol 4.* Porto, Imprensa Portuguesa, 1959.
6. Mitchison DA. Examination of sputum by smears and culture in case finding. *Bulletin of the International Union Against Tuberculosis*, 1968, 41:139–147.
7. Mitchison DA. Bacteriological aspects of mycobacterial infections. *British Medical Journal*, 1972, 1:424–425.
8. Mitchison DA. Bacteriology of tuberculosis. *Tropical Doctor*, 1974, 4:147–153.

9. What is the role of mycobacterial culture in diagnosis and case definition?[1]

A. van Deun[2]

Role of mycobacterial culture in the diagnosis of tuberculosis

The probability of finding acid-fast bacilli (AFB) in sputum specimens by smear microscopy is directly related to the concentration of bacilli in the sputum (see "How many bacilli are present in a sputum specimen found positive by smear microscopy?", page 11, and "How reliable is smear microscopy?", page 14). At concentrations below 1000 organisms per ml, the chance of observing bacilli in a smear becomes less than 10%. In comparison, mycobacterial culture can detect far lower numbers of AFB, the detection limit being around 100 organisms per ml. Moreover, culture makes it possible to identify the mycobacterial species on the basis of biochemical and other properties. Smear microscopy cannot reliably differentiate between the various pathogenic and non-pathogenic mycobacteria, which are all acid-fast and morphologically alike. It therefore seems that, for the diagnosis of tuberculosis, both the sensitivity and the specificity of culture methods are far better than those of smear microscopy.

In practice, however, the diagnostic effectiveness of any method will also be influenced by its sensitivity to technical deficiencies and by the circumstances in which it is used. In the case of AFB smear microscopy, technical errors almost never affect the extremely high specificity (see also "How reliable is smear microscopy?", page 14). Because of its higher sensitivity, *Mycobacterium tuberculosis* culture is more susceptible to reduced specificity as a result of contamination: various manipulations may result in transfer of bacteria from positive to negative samples. To investigate the magnitude of this problem in the East African collaborating laboratories of the British Medical Research Council, positive sputum specimens marked with a rifampicin-monoresistant strain were mixed with negative samples. This exceptional strain could later be traced back to nearly 1% of the negative specimens (*1*). Even at a true positivity rate of about 25% within these series, this meant that 1.6–4.7% of culture isolates in fact constituted false-positives. More recently, using DNA fingerprinting

[1] Based on the chapter by K. Toman in the first edition.

[2] Mycobacteriology Unit, Institute of Tropical Medicine, Antwerp, Belgium.

techniques, similar percentages of cross-contamination have been found repeatedly in routine laboratories in countries where the prevalence of tuberculosis is low (*2*, *3*).

In countries with a high prevalence of tuberculosis, the specificity of smear microscopy may thus be superior to that of culture. This may be true even for the diagnosis of tuberculosis (*4*), since AFB demonstrated in direct sputum smears would then almost invariably represent *M. tuberculosis*, even in areas with a high burden of HIV (*5*). By contrast, in countries with a low prevalence of tuberculosis, culture (or alternative techniques of species identification) will often be indispensable to the differentiation of tuberculosis from other mycobacterial diseases.

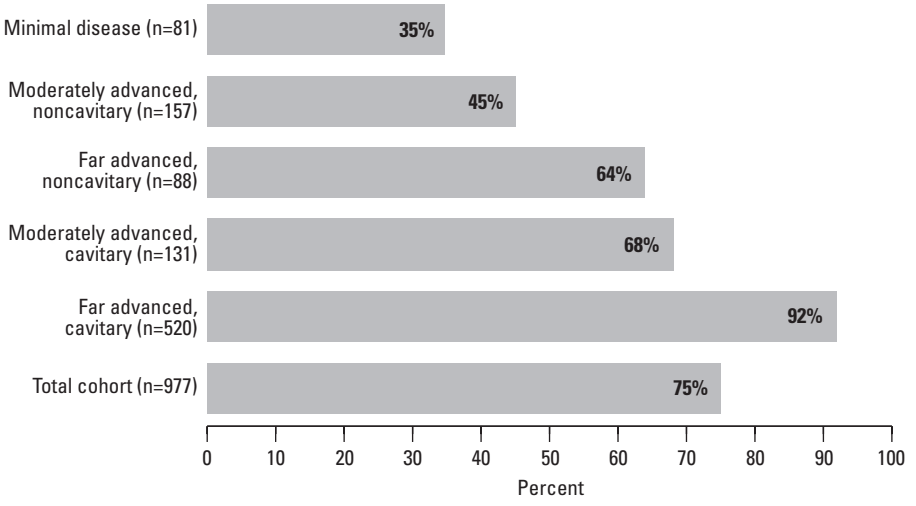
Furthermore, health services in high-prevalence countries are often inaccessible because of geographical, financial, or cultural factors, and patients frequently present at an advanced, cavitary stage of the disease. The concentration of bacilli in the sputum is determined largely by the type of tuberculous lesion from which the bacilli originate. Thus, a cavity about 2 cm in diameter (opening into a bronchus) may contain some 100 million tubercle bacilli, whereas a non-cavitated nodular lesion of the same size may contain only 100–1000 bacilli (*6*). Sputum from patients with tuberculous lung cavities that contain softened necrotic particles with enormous numbers of bacilli will almost invariably be found positive by direct smear microscopy. In contrast, sputum from patients with nodular, encapsulated lesions discharging only small amounts of bacilli will usually be negative by smear microscopy. This pathology-related aspect of susceptibility was clearly shown in a study by Kim et al. (*7*) that compared radiographic severity and extent of culture-positive disease with microscopy results in concentrated sputa (Figure 1).

With this background, it is also easy to understand that the difference in sensitivity between culture and microscopic detection will be greater in active case-detection or in surveys. Substantially more cases will then be encountered with less severe or even subclinical disease, and a smaller proportion of cases will have reached a cavitary stage with high numbers of bacilli. This was illustrated by a comparison of the yield from microscopy versus culture in different surveys and studies conducted by the National Tuberculosis Institute in Bangalore, India. While microscopy could detect only 40–50% of culture-positive cases found in the surveys, its yield rose to about 85% in persons self-reporting with chest symptoms (*8*).

Provided that careful techniques are used, the diagnostic yield from smear microscopy can still be high in the context of HIV (*9*, *10*) (see also "How does the diagnosis of tuberculosis in persons infected with HIV differ from diagnosis in persons not infected with HIV?", page 80). The relative sensitivity of culture and microscopy is illustrated by Table 11 below from a publication by Urbanczik (*11*). Since then, even higher rates (more than 80%) have been reported from high-prevalence areas, including those with a serious HIV burden (*5*, *10*).

It thus appears that the yield of microscopy compared with culture is highly variable in practice. Some of the observed variation can be explained by differences

Figure 1
Percentage of smear-positive cases out of all culture-positive pulmonary tuberculosis patients by severity of disease on chest radiography[a]



[a] Source: reference *7*.

Table 11
Percentage smear-positive out of all culture-positive pulmonary tuberculosis[a]

Country/area	Year	Percentage smear- and culture-positive
USA	1976	62
USA	1975	22
USA	1976	43
Africa/Europe	1980	53 (Ziehl-Neelsen)
Asia/USA	1980	63 (fluorescence)
USA	1975	24
United Kingdom	1992	53
Germany	(no date)	54
USA	1977	50
USA	1980	25
Germany	(no date)	37

[a] Modified from reference *11*.

between populations (high- versus low-prevalence countries, early or late case presentation) and details of the techniques used (e.g. fluorescence microscopy, concentration techniques). Some, however, must be due to deficiencies in the execution of the tests.

Despite the higher sensitivity of culture, use of the technique may not be particularly rewarding for the examination of persons presenting spontaneously with chest symptoms. In high-prevalence countries, with or without HIV being present, and given correct use of both methods, the gain by culture over microscopy is estimated to be about 25% (*12*). In low-prevalence countries, this gain will be greater, possibly doubling the proportion of patients with positive bacteriological findings. Moreover, culture has the added advantage of allowing identification of the mycobacterial species, which is not possible with microscopy.

Thus, from the bacteriological point of view, two main categories of patient may be distinguished: one much more infectious, discharging large numbers of tubercle bacilli in almost every sputum specimen and easily detectable by microscopy, and the other much less infectious, discharging smaller numbers of bacilli, usually not found except by culture. As mentioned earlier, patients in the latter category may discharge bacilli only intermittently (see "What is the additional yield from repeated sputum examinations by smear microscopy and culture?", page 46). Obviously, these two categories also differ significantly in clinical and epidemiological respects.

Sputum status and clinical prognosis

The prognosis for patients with pulmonary lesions discharging small numbers of bacilli, demonstrable only by culture, is generally more favourable prognosis than that for smear-positive patients. In southern India, where an epidemiological survey had been repeated at intervals, the fate of newly discovered cases was analysed (*13*, *14*). Of patients who had been smear-negative (two specimens) but positive by culture at the time of detection of their disease, more than half were classified as cured (i.e. negative by both smear and culture) within 18 months and about two-thirds within 3 years. Moreover, the excess death rate was about one-third of that for smear-positive cases. Thus, even under the living conditions of a very poor rural population, and without treatment, the prognosis for smear-negative, culture-positive patients was relatively favourable.

Though smear-negative cases were known to have a lower mortality, they were thought to be at an early stage of the disease and it was assumed that they would deteriorate further and become smear-positive later on. To prevent this, it was often considered important to detect patients "early", i.e. at a stage where the extent of the disease is minimal and the lesion(s) are likely to contain a small number of bacilli demonstrable only by culture. It has also been assumed that these patients rarely have symptoms and thus may be detected best by indiscriminate mass radiography. Surprisingly, this hypothesis has not withstood the test of time.

In a carefully conducted longitudinal study (see "How does pulmonary tuberculosis develop and how can it be detected at an early stage?", page 66), the population of a district in the then Czechoslovakia underwent radiological and bacteriological examinations at intervals of 2–3 years (*15*). Coverage of the eligible population was almost complete (95%). With each round, appreciable numbers of new patients were detected who had small radiographic lesions and were positive by culture but negative by smear microscopy (specimens collected on 3 consecutive days). All these patients were immediately put on treatment, which was successful. According to the hypothesis, these patients were prevented from deteriorating and developing advanced, smear-positive tuberculosis. It was therefore expected that the frequency of new smear-positive cases would decline rapidly as a result. However, the intensive case detection and treatment measures had surprisingly little effect: despite extensive efforts, at and between examination rounds, a large proportion of newly detected cases were already at an advanced stage and were smear-positive.

These and other studies have thus shown that the development of new smear-positive tuberculosis does not necessarily go through an early, smear-negative stage (see "How does pulmonary tuberculosis develop and how can it be detected at an early stage?", page 66). The prognosis for patients with smear-negative but culture-positive lesions has proved to be far better than was previously assumed, with most such lesions either healing or remaining unchanged. Only a few patients deteriorate, and thus only a few smear-positive cases would be prevented by the use of additional, more sensitive detection methods such as mycobacterial culture.

Sputum status and infectivity

From the epidemiological point of view, as well, the difference between these two types of case is striking. Patients who are definitely negative by smear are substantially less infectious than are smear-positive patients. This is not surprising, in view of the enormous difference in the numbers of bacilli discharged by the two categories of patient. The risk of exposure to smear-positive sources of infection is aggravated because such persons usually cough more frequently and violently (*16*). For household contacts of smear-negative, culture-positive patients, for instance, the excess risk of becoming infected is only a small fraction of that for household contacts of smear-positive patients. Excess risk is the risk in addition to the basic risk of exposure to the immediate, extra-domiciliary, neighbourhood. The basic risk is naturally higher in crowded or slum conditions than the average risk for the total population – often wrongly used for comparison. Moreover, the risk for household contacts of contracting the disease from culture-positive, smear-negative patients is only about 10–20% of that for contacts of smear-positive patients (*17*, *18*) (see "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?", page 72). These findings have been confirmed by DNA fingerprinting studies on the relatedness of strains of *M. tuberculosis* isolated in San Francisco, USA, from 1991 to 1996: only 17%

of the disease transmission could be attributed to smear-negative, culture-positive index patients (*19*).

The detection of patients with lesions that harbour and discharge small numbers of bacilli thus seems to have a relatively low priority in tuberculosis control. If identification of such patients is attempted in a tuberculosis programme, it should never be at the expense of the top priority of case detection, i.e. the identification of sources of infection. Taking into account all the rates mentioned so far, it is certain that more than 90% of the sources of infection in high-prevalence countries can be detected by well-executed smear microscopy.

There are other reasons why mycobacterial culture is less used in tuberculosis diagnosis. In high-prevalence countries, culture facilities are scarce and difficult to set up because of financial and technical constraints. Mycobacterial culture using conventional media (egg-based, i.e. Löwenstein–Jensen medium, or agar-based, i.e. Middlebrook medium) is 5–10 times more costly per sample than smear microscopy. The necessary equipment is more difficult to obtain and trained personnel more difficult to find. Even in centres where such culture facilities are available, the method is used mainly for confirmation of diagnosis in cases already being treated for tuberculosis. This is because most cultures become positive about 3 weeks after inoculation, so that the results of conventional mycobacterial culture are available only after a delay of at least a month. Clinicians will not wait for the results, particularly since a small proportion of cases yield negative cultures and are diagnosed only on radiography. Radiographic diagnosis as part of a systematic diagnostic algorithm will thus be automatically preferred to culture (see "What are the relative merits of chest radiography and sputum examination (smear microscopy and culture) in case detection among new outpatients with prolonged chest symptoms?", page 61). Using modern liquid media and more sensitive growth detection systems, positive culture results can be available earlier – within 1–2 weeks. However, the commercial systems needed for this are costly to install and operate, and demand a high level of technical expertise. Moreover, diagnostic evaluation based on a standard algorithm will generally result in treatment being initiated at least as quickly, and much more cheaply, than culture based on these systems.

For all these reasons, the role of mycobacterial culture in the diagnosis of tuberculosis becomes more important only with declining prevalence of the disease. As prevalence falls, clinicians will be less likely to suspect, and less expert in recognizing, the disease, so that even a late culture result will be useful. Cases will present with less severe disease, with consequently lower proportions of smear-positive tuberculosis. Other less pathogenic mycobacteria will become relatively more frequent etiological agents, making species identification of the various AFB essential. Finally, a decline of tuberculosis will generally be accompanied by economic improvement, making installation of equipment and optimal use of culture more feasible.

As long as tuberculosis remains highly prevalent, the role of mycobacterial culture will be secondary to that of careful smear microscopy and radiographic/clinical

diagnosis. If available, culture should be used for extrapulmonary tuberculosis easily accessible to sampling, e.g. glandular tuberculosis. In HIV-positive patients particularly, this would greatly reduce diagnostic and treatment error. Culture also remains essential for susceptibility testing for the surveillance of drug resistance.

Role of mycobacterial culture in tuberculosis case classification

Mycobacterial culture is useful for definitive confirmation of tuberculosis. However, under programme conditions, the role of culture can be largely taken over by microscopy. The longitudinal surveys in southern India (*15*), which provided insight into differential survival, were also analysed in this respect. Culture and smear microscopy had been done for all persons considered probably to be suffering from active tuberculosis on radiographic screening, with follow-up of the evolution in the absence of treatment. Provided that a threshold for positivity of more than three AFB per smear was respected, only 10% of smear-positive cases failed to yield growth of *M. tuberculosis* in culture. By contrast, almost two out of every three radiological cases could not be confirmed by culture, nor was there other evidence of progressive tuberculosis. Later studies (*20*) have confirmed the reliability of smear microscopy as a proxy for culture in the classification of tuberculosis cases, with only 3–6% of smear-positives having negative cultures. Many of these apparent false-positives of microscopy may be due to treatment, since rechecking of slides can often confirm the presence of (non-viable) AFB.

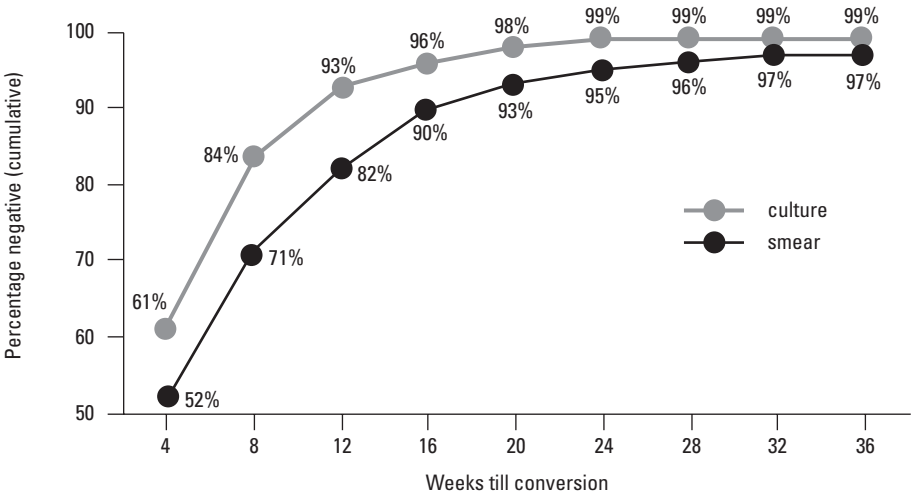
The definitions of "sputum smear-positive" and "sputum smear-negative pulmonary tuberculosis case" take into account the limited sensitivity of smear microscopy. At the same time they emphasize the primary importance of smear-positive pulmonary tuberculosis cases for control of the disease.

Culture might be more relevant for the definition of cure, failure, and relapse. Several studies, for example that by Al-Moamary and colleagues (*21*), have documented the delayed conversion of smear from positive to negative compared with culture (Figure 2).

In the sputum of some patients, non-viable bacteria remain microscopically visible even after 5 months or more of treatment. In a study by Rieder (*22*), only 2 out of 8 cases that were smear-positive at 5 months or later needed re-treatment. Culture allows a more accurate classification of such cases, but it is not a practical solution in most areas: for programme purposes, failure is defined as the presence of bacilli after 5 months or more of treatment. Another cause of sputum smear-positive, culture-negative results is laboratory error.

On the other hand, without culture, some patients in whom treatment fails will go unrecognized, especially if microscopy is not performed well. These patients may present as early "relapse". Microscopy-based classification of both failure and relapse is thus less reliable. However, with the scarcity and complexity of facilities and the delay in culture results, the definitions of cure, failure, and relapse are

Figure 2
Conversion in smear and culture of initially smear-positive pulmonary tuberculosis patients[a]



[a] Source: reference *21*.

based primarily on smear examination, with culture as an option where this is available.

References

1. Aber VR et al. Quality control in tuberculosis bacteriology. 1. Laboratory studies on isolated positive cultures and the efficiency of direct smear examination. *Tubercle*, 1980, 61:123–133.
2. Burman WJ et al. The incidence of false-positive cultures for *Mycobacterium tuberculosis*. *American Journal of Respiratory and Critical Care Medicine*, 1997, 155:321–326.
3. Frieden TR et al. The molecular epidemiology of tuberculosis in New York City: the importance of nosocomial transmission and laboratory error. *Tubercle and Lung Disease*, 1996, 77:407–413.
4. Levy H et al. A re-evaluation of sputum microscopy and culture in the diagnosis of pulmonary tuberculosis. *Chest*, 1989, 95:1193–1197.
5. Githui W et al. Cohort study of HIV-positive and HIV-negative tuberculosis, Nairobi, Kenya: comparison of bacteriological results. *Tubercle and Lung Disease*, 1992, 73:203–209.
6. Canetti G. *The tubercle bacillus in the pulmonary lesion; histobacteriology and its bearing on the therapy of pulmonary tuberculosis*. New York, Springer, 1955.
7. Kim TC et al. Acid-fast bacilli in sputum smears of patients with pulmonary tuberculosis. Prevalence and significance of negative smears pre-treatment and positive smears post-treatment. *American Review of Respiratory Disease*, 1984, 129:264–268.

8. Rao KP et al. Some operational factors influencing the utility of culture examination in the diagnosis of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1966, 34:589–604.
9. Smith RL et al. Factors affecting the yield of acid-fast sputum smears in patients with HIV and tuberculosis. *Chest*, 1994, 106:684–686.
10. Karstaedt AS et al. The bacteriology of pulmonary tuberculosis in a population with high human immunodeficiency virus seroprevalence. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:312–316.
11. Urbanczik R. Present position of microscopy and of culture in diagnostic mycobacteriology. *Zentralblatt fur Bakteriologie Mikrobiologie und Hygiene. Series A*, 1985, 260:81–87.
12. Mitchison DA. Organisation of laboratory services for tuberculosis in developing countries. *Bulletin of the International Union Against Tuberculosis*, 1982, 57:142–149.
13. Narain R et al. Problems in defining a "case" of pulmonary tuberculosis in prevalence surveys. *Bulletin of the World Health Organization*, 1968, 39:701–729.
14. National Tuberculosis Institute, Bangalore. Tuberculosis in a rural population of South India: a five-year epidemiological study. *Bulletin of the World Health Organization*, 1974, 51:473–488.
15. Styblo K et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. Report for the first 4 years of the study (1961–64). *Bulletin of the World Health Organization*, 1967, 37:819–874.
16. Loudon RG, Spohn SK. Cough frequency and infectivity in patients with pulmonary tuberculosis. *American Review of Respiratory Disease*, 1969, 99:109–111.
17. Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. *American Review of Respiratory Disease*, 1969, 54:724–732.
18. Grzybowski S, Allen EA. The challenge of tuberculosis in decline. *American Review of Respiratory Disease*, 1964, 90:707–720.
19. Behr MA et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*, 1999, 353:444–449.
20. Chan W et al. Bacteriological measures for the detection of cases of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1971, 45:551–558.
21. Al-Moamary MS et al. The significance of the persistent presence of acid-fast bacilli in sputum smears in pulmonary tuberculosis. *Chest*, 1999, 116:726–731.
22. Rieder HL. Sputum smears conversion during directly observed treatment for tuberculosis. *Tubercle and Lung Disease*, 1996, 77:124–129.

10. What is the probability of obtaining a negative culture from a sputum specimen found positive by smear microscopy?

K. Toman[1]

In a study of the efficacy of bacteriological measures under the conditions of the Singapore tuberculosis control programme (*1*), 1162 new patients with clinical and radiological signs suggesting tuberculosis were examined as follows.

Two sputum specimens were collected from each patient – one on each of two consecutive days – in the presence of a trained supervisor. All specimens were examined independently by direct smear microscopy in one laboratory and by culture in another laboratory (one smear and one culture per specimen). Of the 1162 patients, 500 had a positive smear from one or both specimens, as shown below.

	Number of new patients smear-postitive for acid-fast bacilli
Yield from first specimen	428
Additional yield from second specimen	72
Total	500

The results of two culture examinations of the sputum of these smear-positive patients are given in Table 12. In 17 of 500 patients, i.e. less than 4%, the positive smear results were not confirmed by two culture examinations. Assuming that the contaminated cultures were all negative, the proportion of unconfirmed results would amount to 6% at the most. A further analysis (not tabulated) showed that, of the 115 patients found positive in only one of two smears, 101 (almost 90%) were confirmed by culture to be excreting tubercle bacilli.

The authors concluded from these results that, when tubercle bacilli were identified by smear examination, culture examination of two specimens confirmed the smear result in all but a very small proportion of cases; hence, culture confirmation of a positive result based on two smear examinations did not appear to be necessary. This is particularly true in populations with a high prevalence of tuberculosis, where

[1] Deceased.

Table 12
Results of culture examinations on two consecutive sputum specimens from 500 new patients smear-positive for acid-fast bacilli

	No. of patients	%
Total examined	500	100
Confirmed by first culture	399	80
Confirmed by second culture (additional)	73	14
Contaminated (both cultures)	11	2
Not confirmed by either culture	17	4

patients seek medical attention only because of haemoptysis or prolonged chest symptoms such as a productive cough.

A negative culture result with a specimen containing tubercle bacilli may be due to various causes. In patients receiving treatment, the organisms may have lost their ability to grow on culture media and be practically dead. Patients being treated with a rifampicin-containing regimen often become culture-negative by about the third week of treatment, although they may still be sputum smear-positive: bacilli are dead or non-viable. In patients who have not had treatment, sputum specimens may have been exposed to sunlight or heat, stored too long, dried out, or contaminated. Excessive decontamination procedures before inoculation, over-heating during centrifugation, inadequate culture media, and deficient incubation may also result in a negative culture. In a few instances, positive smears may be caused by non-tuberculous mycobacteria.

The probability of obtaining a positive culture in patients with both sputum specimens smear-negative is a quite different problem, dealt with under the heading "What is the role of mycobacterial culture in diagnosis and case definition?" (page 35).

Reference

1. Chan W et al. Bacteriological measures for the detection of cases of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1971, 45:551–558.

11. What is the additional yield from repeated sputum examinations by smear microscopy and culture?

A. Harries[1]

Studies were carried out at the National Tuberculosis Institute of India (*1*, *2*) to determine the additional case yield when eight sputum specimens from each individual with suspected pulmonary tuberculosis were examined by both smear microscopy and culture (see also "What are the relative merits of chest radiography and sputum examination (smear microscopy and culture) in case detection among new outpatients with prolonged chest symptoms?", page 61).

For each of 194 individuals who had abnormal radiographic lung shadows and complained of prolonged chest symptoms suggestive of tuberculosis, eight successive sputum specimens (four collected on the spot and four produced overnight and collected by a home visitor) were examined concurrently by smear microscopy (Ziehl–Neelsen method) and culture. The number of specimens thus examined was 1552; each was examined independently, the laboratory technician having no knowledge of the persons examined or of previous results. Tubercle bacilli were found in the sputum of 75 patients (Table 13).

Table 14 shows the yield of new cases resulting from examination of the first and subsequent specimens, in chronological order. In successive examinations – whether by smear microscopy or by culture – most new positive results are clearly obtained from the first and second specimens. The upper half of the table shows that 45 (85%) of all smear-positive patients were already positive by examination of the first two specimens; for the smear-positive cases confirmed by culture, 41 (89%) were positive on the basis of the first two examinations. Thus, a second culture increased culture sensitivity from 63% to 84%. Accordingly, the optimal number of cultures is two, or at the most three.

Another important finding of this investigation (Table 14) was that the first two smears detected about the same number of new cases (45) as the first culture examination (43). It may therefore be concluded that, in new, untreated patients with prolonged chest symptoms and abnormal lung radiograph shadows, two consecutive smear examinations (e.g. of on-the-spot and overnight sputum) are practically

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

Table 13

Results of concurrent examinations of eight sputum specimens by smear microscopy and culture

(For each of 194 patients, four specimens were collected on the spot and four in the early morning.)

Specimens examined		1552
Patients examined		194
Patients negative (all smears and cultures)		119
Patients positive:		
at least one smear and one culture	46	
at least one culture (all smears negative)	22	75
at least one smear (all cultures negative)	7[a]	

[a] Two of these patients had smears with three or fewer acid-fast bacilli.

Table 14

Yield in cases from concurrent smear (S) and culture (C) examinations of eight consecutive sputum specimens from each of 194 persons with lung radiographic shadows and prolonged chest symptoms suggesting tuberculosis

Bacteriological category		No. of cases	Number of cases according to serial number of specimen yielding first positive result							
			I	II	III	IV	V	VI	VII	VIII
	S+ C+	46	34	7	1	1	–	–	1	2
			41 (89%)							
Smear-positive	S+ C–	7	2	2	–	–	–	1	1	1
	Total	53	36	9	1	1	–	1	2	3
			45 (85%)							
	C+ S+	46	34	7	1	1	–	–	1	2
Culture-positive	C+ S–	22	9	7	1	1	1	1	2	–
	Total	68	43	14	2	2	1	1	3	2

equivalent to one culture examination. This inference concords with the results of other studies, such as that undertaken in new patients attending the Tuberculosis Research Centre, Chennai, India (formerly the Tuberculosis Chemotherapy Centre, Madras) (*3*), and another study on bacteriological case-detection procedures in patients attending health services in Singapore (*4*). In the latter study, covering 1162 new patients with radiographic signs and chest symptoms suggestive of tuberculosis, culture of the first sputum specimen revealed 535 cases, whereas two consecutive smears detected 500 cases (see "What is the probability of obtaining a negative culture from a sputum specimen found positive by smear microscopy?", page 44).

All the above-mentioned findings confirm Mitchison's observations (*5*) that: ". . . smear examination, especially of several specimens from each patient, is almost as efficient as culture examinations in clinics in developing countries." This may apply also to other high-prevalence situations or to preselected groups of patients who have been prompted by symptoms (such as prolonged cough, purulent sputum, and haemoptysis) to attend a health centre (*6*).

Another significant observation in the study was that the 46 patients who were found positive by smear and culture were discharging tubercle bacilli practically every day (of a total of 368 specimens from these 46 patients, 347 (94%) were culture-positive). In contrast, out of 176 specimens from patients negative by smear microscopy and positive only by culture, only 62 (35.2%) were positive on culture. This latter category of patients therefore discharges bacilli only about every third day or in only every third specimen (see Table 11 in "What is the role of mycobacterial culture in diagnosis and case definition?", page 35). This confirms that patients positive only by culture and negative by smear microscopy have significantly less epidemiological impact than those who are positive by smear (and culture).

A similar study was carried out at the same institute in connection with an epidemiological survey of a district of southern India (*2*). Eight consecutive sputum specimens were collected from each of 1652 persons with an abnormal chest radiograph and examined as in the study previously reported. The results were comparable. In 86.7% of those positive by smear microscopy and culture, the first smear was positive, with the second smear adding another 10% of positive results. In those who were positive only by culture, the first specimen yielded only 32% of positive results, and the second yielded 18%. It was also observed in this study that patients discharging large numbers of bacilli provided positive specimens almost every time, whereas those who were culture-positive but smear-negative frequently produced specimens containing no bacilli (see "What is the role of mycobacterial culture in diagnosis and case definition?", page 35).

In areas of sub-Saharan Africa with a high prevalence of HIV, evidence suggests that two sputum smears could also serve as the basis for evaluation of chronic cough. In the United Republic of Tanzania (*7*), the routine results of direct examination of sputum smears for acid-fast bacilli from 61 580 patients with suspected tuberculosis were analysed. The average proportion of smear-positive cases found was 18.9%.

Among patients in whom a complete set of three sputum smears was examined, the incremental yield of smear-positive cases was 83.4% with the first specimen, 12.2% with the second specimen, and 4.4% with the third specimen. In a study in Malawi (*8*) of 280 persons with chronic cough, weight loss, and no improvement after a course of antibiotics, 71 patients were sputum smear-positive. Among patients with smear-positive tuberculosis, the diagnosis was made from the first specimen in 83% of cases, from the second specimen in 13%, and from the third specimen in 4%.

In one district in Malawi, two- and three-smear strategies were compared for 6 months (*9*). In both, 16% of patients with suspected tuberculosis were smear-positive. The clinical pattern of tuberculosis, especially with regard to smear-positive pulmonary tuberculosis cases, was similar with the different strategies. The strategies with two and three sputa were compared in an area of rural Africa with high HIV prevalence (*10*), with fluorescence microscopy and confirmation of the positive smears with Ziehl-Neelsen staining. Of the cases detected with three smears, 97% would have been detected with the first two.

Three smears are preferable. The vast majority of patients with positive smears will have two or three positive smears, whereas in patients with a single positive smear the result may be a false-positive because of mislabelling or technical error (see "What are the main causes of false-positive and false-negative sputum smears?", page 23). Even in otherwise well-functioning microbiology laboratories, 1–4% of positive cultures may be false-positives (*11*, *12*). This supports use of the algorithm recommended by WHO, in which further evaluation is required if patients have only a single positive smear. In addition, three smears cause no greater inconvenience to the patient than two if they are done in 2 days (spot – early morning – spot). However, in areas where human and financial resources are significantly limited, a two-sputum smear strategy has been successfully employed.

References

1. Nagpaul DR, Naganathan N, Prakash M. Diagnostic photofluorography and sputum microscopy in tuberculosis case-findings. *Proceedings of the 9th Eastern Region Tuberculosis Conference and 29th National Conference on Tuberculosis and Chest Diseases, Delhi, November 1974*. Delhi, Tuberculosis Association of India, 1975.
2. Nair SA et al. Precision of estimates of prevalence of bacteriologically confirmed pulmonary tuberculosis in general population. *Indian Journal of Tuberculosis*, 1976, 23:152–159.
3. Andrews RH, Radakrishna S. A comparison of two methods of sputum collection in the diagnosis of pulmonary tuberculosis. *Tubercle*, 1959, 40:155–162.
4. Chan W et al. Bacteriological measures for the detection of cases of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1971, 45:551–558.
5. Mitchison DA. Examination of sputum by smears and culture in case finding. *Bulletin of the International Union Against Tuberculosis*, 1969, 41:139–147.
6. Nagpaul DR, Vishwanath MK, Dwarakanath G. A socio-epidemiological study of outpatients attending a city tuberculosis clinic in India to judge the place of specialized centres

in a tuberculosis control programme. *Bulletin of the World Health Organization*, 1970, 43:17–34.

7. Ipuge YA, Rieder HL, Enarson DA. The yield of acid-fast bacilli from serial smears in routine microscopy laboratories in rural Tanzania. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1996, 90:258–261.
8. Harries AD et al. Sputum smears for diagnosis of smear-positive pulmonary tuberculosis. *Lancet*, 1996, 347:834–835.
9. Harries AD et al. Screening tuberculosis suspects using two sputum smears. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:36–40.
10. Crampin AC et al. Comparison of two versus three smears in identifying culture-positive tuberculosis patients in a rural African setting with high HIV prevalence. *International Journal of Tuberculosis and Lung Disease*, 2001; 5:994–999.
11. Frieden TR et al. The molecular epidemiology of tuberculosis in New York City: the importance of nosocomial transmission and laboratory error. *Tubercle and Lung Disease*, 1996, 77:407–413.
12. Gascoyne-Binzi DM et al. Rapid identification of laboratory contamination with *Mycobacterium tuberculosis* using variable number tandem repeat analysis. *Journal of Clinical Microbiology*, 2001, 39:69–74.

12. How reliable is chest radiography?[1]

R. Koppaka[2] *& N. Bock*[3]

The introduction of radiography as a diagnostic tool was a landmark in our knowledge of the natural history of tuberculosis and its diagnosis. It is therefore no wonder that the enthusiasm with which radiography was received and applied sometimes caused the method to be overrated. It is still widely believed that pulmonary tuberculosis can be diagnosed by chest radiography alone. However, practical experience and many studies have shown that no radiographic pattern is diagnostic of tuberculosis. Many diseases of the lung show a similar radiographic appearance and can easily mimic tuberculosis. Similarly, the lesions of pulmonary tuberculosis can take almost any form on a radiographic picture (*1*).

Chest radiography can help to localize abnormalities in the lung, but further examination is required in order to establish the tuberculous etiology of an abnormality, and only bacteriology can provide proof.

Observer error

Many widely used clinical tests and laboratory procedures that are regarded as precise and objective are in fact subject to varying degrees of observer error. Examples of such tests include blood-pressure measurement, electrocardiography, manual blood cell counts, endoscopies, visual colorimetric tests, and chest radiography. The usefulness of chest radiography is determined largely by the reader's ability to detect abnormal opacities and interpret them correctly. This implies not missing or under-reading radiographic opacities and, conversely, not over-reading normal opacities as abnormalities. This ability may vary not only from one reader to another (inter-observer variation), but also between viewings of the same film by a single reader (intra-observer variation).

Observer error in interpretation of chest radiographs was studied several decades ago when antituberculosis campaigns were started in many developed countries. Most of

[1] Based on the chapter in the previous edition by K Toman.

[2] Medical Officer, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

[3] Medical Officer, Research and Evaluation Branch, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

the early studies were designed or conducted by Yerushalmy, a biostatistician, to explore the efficacy of various radiographic and photofluorographic techniques and equipment.

Over- and under-reading

One trial, designed to examine the effects of the size of film on the results of chest radiography, suggested that this variable was far less important than the degree of observer variation (*2*). Each of five experts missed (under-read) approximately 25% of the "positive" films in each series (Table 15). When the same films were read again after about 3 months, the experts changed their mind in about one-fifth of the cases they had previously classified as "positive" (an intra-individual inconsistency of 20%).

Additional studies confirmed that 26–43% of films might be under-read (*3*, *7*, *8*). A Danish group (*5*, *9*) consisting of three experienced readers examined 5000 unselected small films independently (Table 15). On average, under-reading occurred in 32% of cases and over-reading in 2%. These observations were later confirmed in the United Kingdom (*10*).

In a large study in the USA (*4*, *6*) on the usefulness of periodic chest radiograph screening, photofluorograms were taken of each of 15 000 first-year university students (Table 15). The films were read by a panel of 50 readers composed of equal numbers of radiologists and chest specialists. According to a randomization scheme, each reader provided 3000 readings, thus ensuring 10 independent readings of each film. Students whose films were interpreted as positive by one or more readers were examined by bacteriology, tuberculin test, and tomography, and followed for the duration of their stay at the university. Ultimately, 249 films were classified as

Table 15
Observer error: under-reading and over-reading of radiographs (mostly unselected survey radiographs)

Study (reference)	Under-reading (%)	Over-reading (%)
1. Five expert readers (*2*)	25	–
2. Readers with varying experience (*3*)	27	1.7
3. Mass radiography (*4*)	32	1.7
4. Danish Tuberculosis Index, mass radiography (*5*)	32	1.6
5. Reader panel (mass radiography of 15 000 students, 10 readings per film) (*6*)		
(a) all 50 readers	39	1.2
(b) the five "best" readers selected from a panel of radiologists and chest specialists		
Group A	21	0.5
Group B	26	0.3

Table 16
Observer error: under-reading and over-reading of chest radiographs[a,b]

Experience		Number of readers	Under-reading (%)	Over-reading (%)
(a)	1–4 years[c]	37	28.0	18.0
	5–9 years	37	19.2	19.0
	>10 years	88	17.6	17.0
	or			
(b)	1–500 films annually	43	22.4	17.5
	5000–20000 films annually	48	24.0	18.0
	>20000 films annually	41	15.2	15.5
Average of all readers			21.8	19.5

[a] Using a 70 mm mirror reflex camera
[b] Source: reference *11*.
[c] Results from physicians who had practised reading for less than 1 year or had read fewer than 1000 films annually were excluded from analyses.

"definitely positive" by a small group of umpire readers who had access to all the necessary information. The level of under-reading by the whole panel of 50 readers was, on average, 39% of the 249 "definitely positive" films. Conversely, 1.2% (156) of the films were over-read. When only the results of the 10 "best" readers (five radiologists and five chest specialists) were considered, the rates of under-reading and over-reading were appreciably lower, but still unsatisfactorily high (Table 15).

Influence of experience on chest radiograph reading results

The Research Institute of Tuberculosis, Tokyo, examined the extent of over-reading and under-reading by 192 physicians participating in the Japanese National Tuberculosis Case-finding Programme (*11*). Special attention was paid to the effect of experience in radiograph reading on the degree of reader variation (Table 16).

Radiographs from 50 persons whose health status was well known to the Institute were selected for independent reading; 25 of them had confirmed tuberculosis or other chest diseases, 5 had healed tuberculosis lesions, and 20 no abnormalities. The chosen readers' experience of reading films varied from less than 1 year to more than 10 years, and they read from 1000 to 20000 or more films annually (Table 16). They were asked only to decide whether or not further examination was indicated. Failure to request further examination of a person with an abnormality was recorded as under-reading and request for further examination of a person with a normal radiograph was considered as over-reading.

Table 17
Disagreement between readings of chest films of 900 patients[a]

Readers		Inter-individual disagreement (%)	Intra-individual disagreement (%)
(a)	Two groups of experts (Three radiologists and three chest specialists)		
	Group A	29	19
	Group B	27	24
(b)	Two expert readers (reading the same material)	30	21

[a] Source: reference *6*.

The average rate of under-reading was 21.8%, and that of over-reading 19.5%. The rates of under-reading among readers who had more than 10 years' experience or who had been reading more than 20 000 films a year were lower about 6–8% than those among the other readers. However, there was not a single reader who did not make at least two misreadings. The investigators estimated that, in the mass radiographic examinations carried out in Japan, probably about one-fifth of cases with active tuberculosis were being missed.

Disagreement between readings of chest radiographs for follow-up

Disagreement among observers occurs not only when radiographs are read for the purposes of case detection and diagnosis, but also when serial films of cases already diagnosed are compared for follow-up. In one study (*6*), two films (measuring 35.6 × 43.0 cm) taken from each patient at five different times (9000 pairs of films in all) were read. Readers were asked to report whether the second film showed evidence of improvement or deterioration, or no change. The results (Table 17) differed little whether the films were read by two groups composed of three radiologists and three chest specialists respectively, or by two expert readers only. The level of disagreement between readers was 27–30%, and in 19–24% of cases individual readers were likely to disagree with their own earlier reading.

IUAT international study on chest radiography classification

The International Union Against Tuberculosis (IUAT) organized one of the most important comparative studies of the reading and interpretation of chest films. The main goal of the study was to develop a uniform nomenclature and interpretation of radiographic findings that could serve as a basis for an international classification of chest radiographs (*12*, *13*).

A sample of 1100 films was chosen from among several hundred thousand taken during one of the mass radiography surveys of the adult population of Norway. The sample included 200 films from patients with infectious tuberculosis, 400 from

patients with previously active tuberculosis, 100 from persons with minimal findings not requiring referral or follow-up, 300 from persons without abnormal findings, and 100 from patients with verified non-tuberculous lung disease. The films were mounted together in seven film rolls, and 10 copies of each roll were made.

Films were read by 90 experienced physicians (radiologists and chest physicians), 80 of whom were from nine countries where mass radiographic examinations had been carried out for many years: Czechoslovakia, Denmark, Finland, France, Norway, Sweden, the United Kingdom, the United States of America, and Yugoslavia.[1] The remaining 10 readers were selected from WHO project staff.

The study was designed primarily to measure the extent of agreement or disagreement between readers, not the observer error resulting in under-reading or over-reading (*14*). A set of questions, prepared in advance, was answered by each reader independently. Most of the questions required a "yes" or "no" answer, e.g. "Is there an abnormality in the lung?"; "Is there a cavity present?"; "Does the patient need clinical attention?".

The material was evaluated according to a special statistical procedure (*15*) by which a series of values was obtained for each question. These values were used to construct a curve that characterized the level of disagreement between readers for a given question (Figure 3). The extent of disagreement was expressed as an index with a value from 0 to 100-0 meaning no disagreement and 100 meaning complete disagreement. The nearer the curve is to the zero point of the two axes, the lower the disagreement; the flatter the curve, or the farther it is removed from the axes, the higher the disagreement. The method showed that there was less disagreement on question 1 than on question 3.

Comparison of reader disagreement in chest radiography and smear microscopy

A similar study was undertaken by IUAT to measure the extent of disagreement between microscopists reading sputum smears for acid-fast bacilli (J. Nyboe, unpublished data, 1971). A series of 250 sputum smears from patients were examined independently in 10 laboratories by experienced laboratory technicians. Figure 4 illustrates the curves of disagreement for three criteria of positivity. The extent of disagreement was lowest (index 10) when the criterion for a positive result was the demonstration of at least eight AFB; it was only slightly higher (index 12) when three AFB were required as the minimum. The extent of disagreement was highest (index 18) between readers when one AFB was accepted as sufficient evidence of positivity. However, even the highest level of disagreement between microscopists was substantially lower than the lowest level of disagreement between readers of chest radiographs.

Curve 1 in Figure 4 illustrates the lowest level of disagreement recorded (index 28)

[1] Country names given are those that were valid at the time of the study.

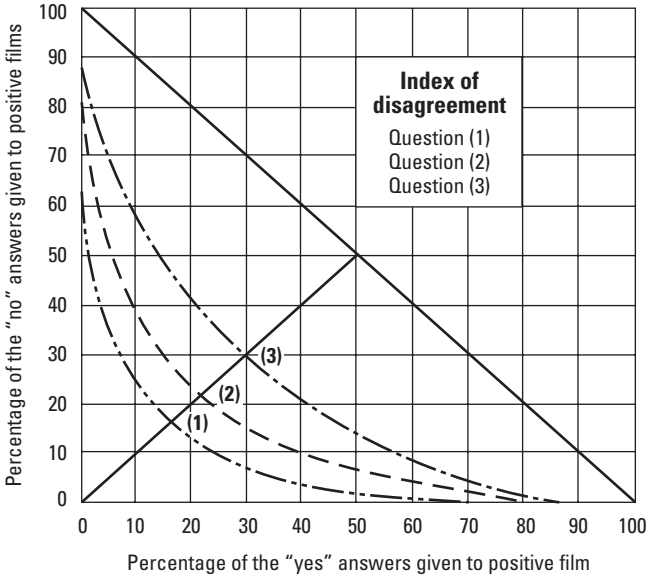
Figure 3

Disagreement between readers in the IUAT study on radiography classification[a]

The index of disagreement was based on the following questions:

1. Is there any abnormality in respiratory organs?
2. Is there any abnormality in lymph nodes?
3. Is there any calcification in lymph nodes?

The index is calculated as the sum of percentages of discordant answers at the point on the curve where they are equal. i.e. where the curve is intersected by the oblique line starting from the zero corner.



[a] Source: reference *14*.

between radiograph readers, i.e. in reply to the question: "Is a cavity present?". Disagreement on the question: "Is the smear positive for acid-fast bacilli?" was substantially lower, whatever the limit chosen – even a single AFB. The investigators concluded that there was consistently better agreement among sputum smear readers, no matter what criterion was used for a positive smear, than among radiograph readers (see also "How reliable is smear microscopy?", page 14).

Levels of disagreement on the interpretation of chest radiographs and conclusions

Indices of disagreement on several other questions are listed in Table 18. The questions were selected with a view to using them for a classification of radiographic findings. They include questions with the lowest and highest levels of disagreement.

Figure 4
Examples of curves of disagreement in radiographic and sputum-smear examinations

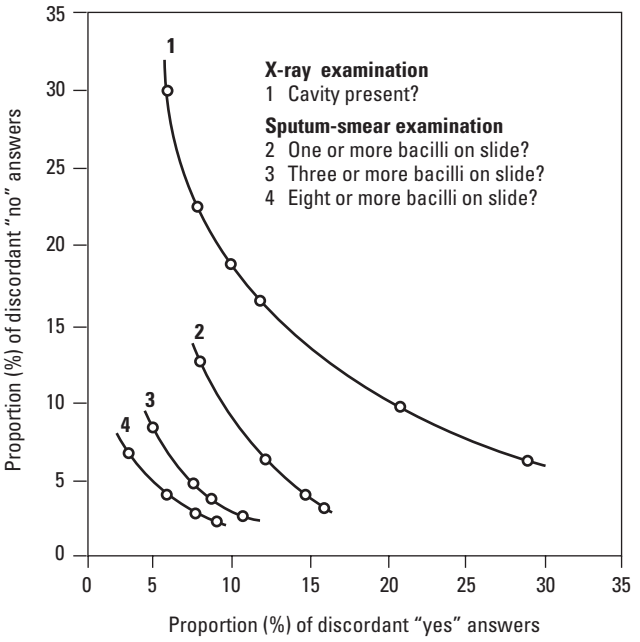


Table 18
IUAT international study on radiographic classification: indices of disagreement on various questions[a]

Question	Index of disagreement
Abnormality in lymph nodes?	60
Abnormality in lung, probably tuberculous?	45
Calcification in lung?	42
Non-calcified abnormality, probably tuberculous?	37
Is the film abnormal?	34
Need for medical action?	31
Cavity present?	28

[a] Source: reference *14*.

The level of disagreement on the question about the presence of any pulmonary abnormality was quite unexpected, as was the poor agreement on the question about calcification. The discrepancies regarding abnormalities of the lymph nodes, including calcifications (one of the most frequently described radiographic findings), were particularly striking. The highest level of agreement – or rather the least disagreement – was seen in response to the question about cavities. This information has to be seen in the context of medical action. Thus 5% of patients with smear-positive tuberculosis were reported as having a normal radiograph, 17% as having some (probably non-tuberculous) abnormality, and 24% as not requiring clinical action for a tuberculous lesion. If treatment had been restricted to patients in whom 50% or more of the readers judged cavitation to be present, only one-third of those with positive sputum smears would have received treatment. On the other hand, among those who were regarded by 50% or more readers as probably tuberculous and in need of treatment, about four or five times as many bacteriologically negative persons as sputum-positive patients would have received treatment (a disproportion similar to that frequently observed in clinics where diagnosis is made merely on radiographic grounds) (*16*).

Co-morbidity with HIV infection and tuberculosis further diminishes the reliability of chest radiography for the diagnosis of pulmonary tuberculosis. As noted above, extensive inter- and intra-observer variation in chest film interpretation was documented among highly trained and experienced radiologists and chest physicians in the decades before HIV-associated tuberculosis. Since the emergence of HIV/AIDS, clinical studies have consistently documented the atypical radiographic pattern seen in patients with both pulmonary tuberculosis and HIV. Hilar or mediastinal adenopathy, middle or lower lung field infiltrates, and absence of pulmonary infiltrates and cavities are common in such patients (*17*), as are normal and minimally abnormal chest radiographs (*18*).

In Malawi, where HIV infection is present in up to 75% of patients with tuberculosis, two hypothetical diagnostic strategies were compared in 402 adults seeking care for symptoms of pulmonary tuberculosis (*19*). In one strategy, the first diagnostic step would have been chest radiograph, followed by sputum smear examination in patients whose chest films were consistent with tuberculosis. Of 172 patients whose chest films were read as not consistent with tuberculosis, 13 (8%) had AFB smear-positive tuberculosis and 53 (31%) either AFB smear- or culture-positive disease. All these cases would have been missed with this screening strategy. Conversely, of 230 patients with chest films consistent with tuberculosis, who would have been treated for "smear-negative" tuberculosis, 27% had smear- and culture-negative sputum.

In the second strategy, the patients would have first been evaluated with sputum smears, followed by chest radiograph in those who had negative sputum smears. Of 291 patients with negative sputum smears, 159 (55%) had chest radiographs not consistent with tuberculosis and would not have been diagnosed, although 40 (25%) were actually culture-positive. This strategy would therefore have resulted in fewer patients, and none of those with smear-positive tuberculosis would have been missed. However,

chest radiograph as the diagnostic second step for patients with negative smears was not sensitive. Conversely, of the 132 patients with negative smears who had chest radiographs consistent with tuberculosis and who would have been treated with this strategy, 47% had smear- and culture-negative sputum tests.

In summary, the experience of many decades of detailed data collection and analysis indicate that chest radiography for diagnosis or follow-up of pulmonary tuberculosis cases, with or without HIV co-infection, is unreliable (*19*, *20*).

References

1. American Thoracic Society. Diagnostic standards and classification of tuberculosis in adults and children. *American Journal of Respiratory and Critical Care Medicine*, 2000, 161:1376–1395.
2. Birkelo CC, Chamberlain WE, Phelps PS. Tuberculosis case finding: a companion of the effectiveness of various roentgenographic and photofluorographic methods. *Journal of the American Medical Association*, 1947, 133:359–366.
3. Garland LH. On the reliability of roentgen survey procedures. *American Journal of Roentegenology and Radium Therapeutic Nuclear Medicine*, 1950, 64:32–41.
4. Yerushalmy J et al. The role of dual reading in mass radiography. *American Review of Tuberculosis*, 1950, 61:443–464.
5. Groth-Petersen E, Løvgreen A, Thillemann J. On the reliability of the reading of photofluorograms and the value of dual reading. *Acta Tuberculosis Scandinavica*, 1952, 26:13–37.
6. Garland LH. Studies on the accuracy of diagnostic procedures. *American Journal of Roentegenology and Radium Therapeutic Nuclear Medicine*, 1959, 82:25–38.
7. Garland LH. Conditions to be differentiated in the roentgen diagnosis of pulmonary tuberculosis. *Annals of Internal Medicine*, 1948, 29:878–888.
8. Newell RR, Chamberlain WE, Rigler L. Descriptive classification of pulmonary shadows: a revelation of unreliability in the roentenographic diagnosis of tuberculosis. *American Review of Tuberculosis*, 1954, 69:566–584.
9. Groth-Petersen A, Møller V. Observer error in the interpretation of photofluorograms and the value of dual reading in the Danish mass campaign. *Acta Tuberculosis Scandinavica*, 1955, 30:209–230.
10. Cochrane AL, Garland LH. Observer error in the interpretation of chest films: an international investigation. *Lancet*, 1952, 2:505–509.
11. Nakamura K et al. Studies on the diagnostic value of 70 mm radiophotograms by mirror camera and the reading ability of physicians. *Kekkaku*, 1970, 45:121–128.
12. Springett VH. Results of the study on x-ray readings of the Ad Hoc Committee for the study of classification and terminology in tuberculosis. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1968, 41:107–109.
13. Springett VH. Results of the international study on x-ray classification. Conclusions. *Bulletin of the International Union Against Tuberculosis*, 1968, 41:125–129.
14. Waaler HT. Descriptions of the study material and organization of the study. *Bulletin of the International Union Against Tuberculosis*, 1968, 41:110–114.
15. Nyboe J. Results of the international study on x-ray classification. *Bulletin of the International Union Against Tuberculosis*, 1968, 41:115–124.

16. *WHO Expert Committee on Tuberculosis*. *Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
17. Pitchenik AE, Rubinson HA. The radiographic appearance of tuberculosis in patients with the acquired immune deficiency syndrome (AIDS) and pre-AIDS. *American Review of Respiratory Disease*, 1985, 131:393–396.
18. Greenberg SD et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology*, 1994, 193:115–119.
19. Harries AD et al. Screening pulmonary tuberculosis suspects in Malawi: testing different strategies. *Transactions of the Royal Society of Tropical Medicine Hygiene*, 1997, 91:416–419.
20. Enarson DA et al. *Management of tuberculosis: a guide for low-income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

13. What are the relative merits of chest radiography and sputum examination (smear microscopy and culture) in case detection among new outpatients with prolonged chest symptoms?[1]

A. Harries[2]

This question was one of several investigated in a comprehensive socio-epidemiological study of 2229 randomly selected new outpatients, undertaken by the National Tuberculosis Institute, Bangalore, India (*1*, *2*). The outpatients, who presented with chest symptoms (cough for 2 weeks or more, chest pain and fever for 4 weeks or more, or haemoptysis), were examined radiographically and bacteriologically. A sputum specimen was collected on the spot from each patient and examined by direct smear microscopy and culture. Smear examination was carried out with the Ziehl–Neelsen method while the patient waited. Culture was performed on two slopes of Löwenstein–Jensen medium. All positive cultures were then tested in vitro for identification of the organism and drug susceptibility. Experienced technicians at the research laboratories of the National Tuberculosis Institute did the bacteriological work.

Table 19 shows that 227 of the 2229 patients were classified by radiography as tuberculous (and thus in need of treatment), but that 81 of these were not confirmed as tuberculous by bacteriological examination. Among the remaining 2002 patients classified as normal or as having a disease other than tuberculosis, there were 31 in whom tubercle bacilli were found by sputum culture and/or smear microscopy.

Because sputum culture is regarded as the most reliable diagnostic method, a correlation was made between the results of radiography and culture. The data given in Table 20 are identical to those in Table 19, except that the two groups of radiographically normal and non-tuberculous persons were pooled. Taking the results of culture as the criterion of correct diagnosis, 20 (12%) of 162 culture-positive patients would have been missed because they had been misclassified by radiography as normal or non-tuberculous. On the other hand, among the 227 patients classified radiographically as tuberculous, 85 (37%) were not confirmed as such by culture.

The results of direct smear microscopy and culture were also correlated. As Table 21 shows, 32 (20%) of the 162 culture-positive patients would have been missed by direct smear microscopy of a single spot specimen, while 15 (10%) of the 145 smear-positive patients proved to be negative by culture.

---

[1] Based on the chapter by K Toman in the previous edition.

[2] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

Table 19

Results of radiographic examination compared with those of sputum smear microscopy (S) and sputum culture (C) in outpatients with clinical signs suggestive of tuberculosis[a]

Classification by radiography	No. of patients	Result of sputum examination			
		S+ C+	S– C+	S+ C–	S– C–
Tuberculosis	227	122	20	4	81
Other abnormal shadows (non-tuberculous)	304	8	4	1	291
Normal	1698	–	8	10	1680
Total	2229	130	32	15	2052

[a] Source: reference *2*.

Table 20

Correlation of the yield of radiographic examination and sputum culture in patients with clinical signs suggestive of tuberculosis

Radiography	Culture		
	Positive	Negative	Total
Positive	142	85	227
Negative	20	1982	2002
Total	162	2067	2229

Taking the results of sputum culture as the criterion for correct diagnosis, the findings of the study may be summarized as follows: among 162 tuberculosis patients in whom the diagnosis was verified by culture, 32 (20%) would have been missed by smear microscopy and 20 (12%) by radiography.

Among 145 patients positive by smear, 130 (90%) were confirmed by culture. The remainder (10%) gave an apparently false-positive result, because of either a reading error or the presence of artefacts, or because the bacilli seen under the microscope had lost their ability to grow on culture. There are many possible reasons for the latter occurrence. In patients under treatment, the bacilli may have been killed or seriously harmed by effective treatment. In untreated patients, the capacity of tubercle bacilli to grow on cultures may have been impaired, e.g. by exposure of the specimen to heat

Table 21
Correlation of the yields of two cultures and of direct smear microscopy of a single spot specimen in patients with clinical signs suggestive of tuberculosis

Smear	Culture		
	Positive	Negative	Total
Positive	130	15	145
Negative	32	2052	2084
Total	162	2067	2229

or sunlight, long storage, excessive decontamination procedures, or an overheated centrifuge or incubator. However, patients whose first spot specimen is indisputably positive by smear microscopy but negative by culture have a fairly high chance of being positive by both examinations in subsequent specimens (see "What is the additional yield from repeated sputum examinations by smear microscopy and culture?", page 46). Therefore, if persons with signs and symptoms suggestive of tuberculosis are treated on the basis of properly performed and clearly positive smear microscopy, not confirmed by culture, there is little likelihood of serious over-treatment.

On the other hand, of the 227 patients classified by radiography as "tuberculous and in need of treatment", a sizeable proportion (37%) did not have tuberculosis confirmed by culture. The patients in this study had been examined because they had symptoms. This proportion is likely to be much higher in populations examined by indiscriminate mass radiography, i.e. irrespective of the presence of symptoms. Several studies have indeed shown that persons with chest radiographic shadows of unknown origin, who have no history of previous tuberculosis and in whom tubercle bacilli cannot be demonstrated by smear microscopy and/or culture, particularly when repeated, are in fact rarely true cases of tuberculosis. Follow-up studies (*3*–*6*) have demonstrated that, although there is a greater likelihood of such persons becoming culture-positive than those with a normal radiograph, only a small proportion (0.4–4.8%) actually did so within the first year of observation. The risk declined in subsequent years.

Treating persons with chest film shadows of unknown origin as a matter of routine would therefore be to treat many, or even most, of them unnecessarily or wrongly.

In areas with a high prevalence of HIV, it is also inappropriate to screen persons suspected of having tuberculosis with chest radiography. In a study of 402 suspected tuberculosis cases in Malawi (*7*), 230 patients had chest films thought to be typical of tuberculosis. Sputum smears were positive in 43% of these patients and sputum cultures were positive in 71%. On the other hand, in 172 patients with a normal chest

film or with an abnormal chest film not typical of tuberculosis, 13 (8%) were sputum smear-positive and 49 (28%) were culture-positive. Screening by chest radiography, followed by sputum smears in those with chest films typical of tuberculosis, was more costly and less sensitive than screening by sputum smears and performing chest radiography only in those with negative results on sputum smear examination.

Some technical and operational aspects of chest radiography, sputum culture and smear microscopy

Screening by radiography alone, even in areas of sub-Saharan Africa with high HIV prevalence, will result in a high rate of over-diagnosis. Moreover, the operational shortcomings of radiography in developing countries are considerable. X-ray units are expensive and their operation requires specially trained technicians. There are frequent prolonged interruptions due to the breakdown of equipment, lack of spare parts and repair facilities, scarcity of films, or unreliability of the electricity supply. Another operational disadvantage is that the results of radiographic examination are commonly available only after 2–3 days, and sometimes later. A sizeable proportion of patients do not return to the centre for their results, and efforts to retrieve them are often unsuccessful.

As a diagnostic method, sputum culture is known to be more sensitive than smear microscopy. It differentiates tubercle bacilli from other microorganisms and therefore provides definite identification of the bacilli. The technical superiority of culture over smear microscopy is largely due to quantitative factors. Whereas the amount of sputum on a smear is 0.01 ml (see "How many bacilli are present in a sputum specimen found positive by smear microscopy?", page 11), the size of an inoculum for culture is usually 0.1 ml, i.e. about 10 times as much. Moreover, usually only about 1% of the smear (100 oil-immersion fields) is examined by bright-field microscopy, whereas in the culture test-tube the whole yield of colonies may be seen practically at a glance. Although a large proportion of organisms are destroyed by decontamination procedures, the quantitative differences are still so large that the probability of finding bacilli by culture is higher than by direct smear microscopy. This is an obvious advantage in cases where a specimen contains only small amounts of acid-fast bacilli (see "How reliable is smear microscopy?", page 14).

Unfortunately, culture has a number of disadvantages, mainly of an operational nature. The method requires specially trained and skilled personnel, of whom there is a shortage in most developing countries. There is also a need for special facilities and equipment, a permanent supply of water and electricity, and reliable thermoregulation of the hot room. In hot and humid climates particularly, air-conditioning facilities and special air filters are needed to prevent airborne contamination of cultures. Properly ventilated inoculation cabinets and other safety measures must be provided. For all these reasons, culture methods are practicable in only a few laboratories in developing countries.

One of the greatest shortcomings of sputum culture is the long interval before results become available: 4–6 weeks or more with solid media. In developing coun-

tries, this delay leads to many patients being "lost". They may never return to the health centre and often cannot be traced. Thus the benefits of culture are often outweighed by the losses occasioned by the long wait for results, and the higher sensitivity is largely counterbalanced by operational disadvantages of culture.

Direct smear examination certainly has a number of technical shortcomings, but its operational advantages are obvious. It is relatively easy to perform, much less expensive than radiography or culture, and does not require highly specialized personnel. The fact that the diagnosis of tuberculosis in persons discharging large amounts of bacilli may be established and treatment started on the same day is without doubt the greatest operational advantage of smear microscopy. It reduces to a minimum "losses" of patients due to long waiting periods, and it is also the only diagnostic method practicable almost everywhere. For these reasons, case detection and diagnosis in high-prevalence countries will have to rely on this method for some time to come.

References

1. Nagpaul DR, Vishwanath MK, Dwarakanath G. A socio-epidemiological study of outpatients attending a city tuberculosis clinic in India to judge the place of specialized centres in a tuberculosis control programme. *Bulletin of the World Health Organization*, 1970, 43:17–34.
2. Nagpaul DR, Naganathan N, Prakash M. Diagnostic photofluorography and sputum microscopy in tuberculosis case-findings. *Proceedings of the 9th Eastern Region Tuberculosis Conference and 29th National Conference on Tuberculosis and Chest Diseases, Delhi, November 1974*. Delhi, The Tuberculosis Association of India/International Union Against Tuberculosis, 1975.
3. Nagpaul DR et al. Case-finding by microscopy. *Bulletin of the International Union Against Tuberculosis*, 1968, 41:148–158.
4. Horwitz O, Wilbek E, Erickson PA. Epidemiological basis of tuberculosis eradication. 10. Longitudinal studies on the risk of tuberculosis in the general population of a low-prevalence area. *Bulletin of the World Health Organization*, 1969, 41:95–113.
5. Steinbruck P et al. The risk of tuberculosis in patients with fibrous lesions radiologically diagnosed. *Bulletin of the International Union Against Tuberculosis*, 1972, 47:144–171.
6. Gothi GD, Chakraborty AK, Banerjee GC. Interpretation of photofluorograms of active pulmonary tuberculosis patients found in epidemiological survey and their five-year fate. *Indian Journal of Tuberculosis*, 1974, 21:90–97.
7. Harries AD et al. Screening pulmonary tuberculosis suspects in Malawi: testing different strategies. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1997, 91:416–419.

14. How does pulmonary tuberculosis develop and how can it be detected at an early stage?

K. Toman[1]

On clinical and epidemiological grounds, emphasis has rightly always been laid on early diagnosis of tuberculosis. However, this has led to a certain confusion. Early or incipient tuberculosis has frequently been considered to be synonymous with minimal tuberculous disease. Likewise, advanced tuberculosis has usually been regarded as synonymous with old or chronic tuberculosis. Yet the terms "early", "incipient", "chronic", and "old" are strictly and exclusively concerned with time, while "minimal", "moderate", and "advanced" indicate merely the extent of the disease, i.e. the volume of lung tissue involved. Terms such as "early" and "minimal" have by no means a constant relationship, nor are they necessarily linked. In fact, a lesion of a few months' duration may be minimal or far advanced, and the extent of a lesion gives surprisingly little indication of its duration.

The age of a fresh lesion can be estimated only when radiographic evidence of a previously normal lung is available. A few longitudinal radiographic surveys demonstrate the history of early tuberculosis.

In one such survey in a population of about 100 000 in Kolín, Czechoslovakia,[2] persons aged 14 years and older were screened repeatedly.[1] The study (*1*, *2*) lasted 12 years, during which each member of the eligible population was X-rayed five times, at 2- or 3-year intervals. Between radiographic rounds, the search for cases was continued by the local health services, which patients attended because of symptoms or for regular check-up. Each film was carefully filed and could therefore always be compared with the most recent film. Thus, it was possible to determine the period within which a new lesion had developed. The films were read independently by two readers and an umpire reader (Table 22).

In 165 persons in whom tuberculosis had been newly detected and whose previous radiographs had been normal, the time between the last normal chest radiograph and the first abnormal one was measured. Patients were grouped into three categories: those who were sputum smear-positive as well as culture-positive, those who were

[1] Deceased.
[2] Country name valid at the time of the study cited.

Table 22
Interval between last normal chest radiograph and diagnosis of pulmonary tuberculosis[a]

Interval (months)	Number of smear+, culture+	Cumulative %	No. of smear–, culture+	Cumulative %	Number diagnosed at autopsy
≤12	8	16	14	14	6
<24	18	52	39	53	7
<36	16	84	31	86	1
≥37	8	100	14	100	3
Total	50		98		17

[a] Source: references *1, 2*.

smear-negative but culture-positive, and those in whom the diagnosis had first been made at autopsy and verified by bacteriological examination (*1*, *2*).

Table 22 shows that, within 12 months, 28 bacteriologically positive cases had developed. Surprisingly, a significant proportion of these already had advanced tuberculosis with positive sputum by direct smear microscopy. Even more striking was the finding that six cases had developed so fast that they were found only at autopsy – less than 12 months after the last normal chest radiograph. (In some of these cases, tuberculosis had been identified by the pathologist as the leading cause of death.) During the second part of the Kolín study (1965–1972), 10 previously unknown cases of new tuberculosis were first diagnosed at autopsy – some of them shortly after a normal radiograph. These 10 cases constituted one-quarter of all deaths from tuberculosis during that period – and that in spite of systematic and intensive screening of the entire population. The actual number might well have been even higher, because only one-quarter of all persons who died in the study area (mainly those who died in hospital) were subjected to necropsy (*2*).

The data presented in Table 22 might perhaps be biased, since the interval between radiographic rounds was never less than 2 years and was usually 3 years. In this regard, very instructive data are available from Japan, where mass radiography of the population has been carried out at yearly intervals (*3*). Similar data are also available from an epidemiological study (*4*) in Niigata Prefecture, Japan (population 2 350 000).

As discussed elsewhere (see "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?", page 72), more than half of the cases positive by direct smear microscopy had developed tuberculosis within 12 months of the last normal radiograph. Since only one-fifth of the new cases had been detected by mass radiographic surveys, the majority (72%) were found by the health services, where patients attended mainly because of symptoms. The same applied to new patients who were positive by culture only (*4*).

The conclusions to be drawn from the findings of the above-mentioned studies are the following:

- A large proportion of new cases, starting in a normal lung, developed within months.
- Even cases already so advanced that they were discharging large numbers of bacilli demonstrable by microscopy, and were probably cavitary, developed rapidly.
- A case of advanced smear-positive tuberculosis, when seen for the first time, is not necessarily old or chronic: it may well be as recent as a case with minimal lesions that is positive by culture only.
- Both types of disease – advanced, smear-positive tuberculosis and minimal, only culture-positive tuberculosis – developed within the same time. Thus it is likely the smear-positive cases developed so fast that they did not pass through a perceptible minimal phase. Rapid development of disease should not be confused with so-called "galloping consumption". This form of fulminant tuberculosis, running an exceptionally rapid course, has been described in the older literature and observed occasionally in individuals who are under extraordinary stress and physical vulnerable.

Every experienced clinician knows that, after a few days of sometimes vague or uncharacteristic complaints (and an initially normal chest radiograph), tuberculous pleuritis with an effusion of as much as 1 litre can appear suddenly; or that sometimes an extensive pneumonic lesion may develop in an initially normal lung within a few days and cavitation may take place within a week (*5*).

In a study in the USA of 1000 patients with early tuberculosis (*6*, *7*), the authors concluded that:

- Sudden symptomatic onset of pulmonary tuberculosis is not less frequent than insidious onset.
- The extent of the lesion does not bear a direct relation to the duration of the disease (of all patients reaching an advanced stage of the disease, the majority do so within the first 6 months).
- Cavitation is not a late occurrence: its frequency is nearly the same at all temporal stages of the disease.

Another investigation determined the intervals at which persons at special risk (e.g. contacts) should be re-examined to discover all cases at the earliest possible stage (*5*). Such persons were usually examined at yearly intervals; however, one series conducted examinations every 6 months and another did so at shorter intervals. In none of these series were all cases diagnosed with minimal lesions. Even with examinations at 4-monthly intervals, 21% of patients were found to be in the moderately advanced stage and a smaller proportion even at the far-advanced stage of the disease. The conclusion was that a 6-monthly interval between examinations is too long to prevent the occurrence of advanced, severe cases.

However, even in the most affluent countries, screening the adult population by indiscriminate radiography at intervals shorter than 12 months has not been found practicable. Moreover, as data from Japan have shown, even if more frequent examination were feasible, a large proportion of cases of bacteriologically verified disease would be found at an advanced, smear-positive stage. It is obvious that mass radiography will fail to detect the majority of cases soon after the onset of disease.

Incipient tuberculosis and symptoms

It is sometimes asserted that screening of a population by mass radiography is essential because about half of all new patients have no symptoms (*2*). The literature on this issue is extensive. It is well known that the taking of case histories is arbitrary and unreliable, and the fact that many new patients are found by mass screening of apparently healthy individuals does not necessarily mean that these people have no symptoms. Likewise, when a new patient is asked about the presence of symptoms and gives a negative answer, this should not be taken as objective evidence of the absence of symptoms.

Few of the prospective studies reported so far have been designed in such a way as to eliminate bias, at least to a large extent. Some were designed by sociologists and carried out by specially trained personnel using a standardized interviewing technique according to a protocol. In one series of studies, persons were examined and interviewed in parallel without knowing the results of their examinations (*8–13*). In socio-epidemiological studies of a poor rural population in India in the early 1960s, it was found that 95% of patients who were positive by direct smear microscopy were aware of one or more symptoms suggesting tuberculosis. About 70% complained of cough as the leading symptom, while the rest gave greater importance to other complaints (*8*, *14*). About two-thirds had symptoms of only 1–3 months' duration (*9*, *10*). This was surprising in a population believed to be unaware of symptoms.

In another prospective study on case detection in a population of about 6 million, some 1600 smear-positive patients were interviewed about symptoms (*11*). The study was carried out in parallel to the Kolín study (see Table 22) as one of the projects of the Tuberculosis Surveillance Research Unit, and the two study populations were of similar composition. The results were strikingly similar to those of the above-mentioned studies: 73% of patients complained of cough, ranking it first or second in importance as a symptom. The remaining 20% complained of fever or an influenza-like illness, and only 7% denied having any subjective symptoms. The duration of symptoms was also similar, with 62% having had symptoms for less than 3 months and 83% for up to 6 months.

It thus seems that symptoms are present in more than 90% of patients with sputum positive by direct smear microscopy, and that these symptoms are apparent in the early phase of the disease.

The question may arise as to whether the development of less serious disease – with sputum negative by smear and positive by culture only – is asymptomatic. In the

socio-epidemiological study carried out in India (*8*), 54% of the smear-negative, culture-positive patients had one or more symptoms suggesting tuberculosis. In the longitudinal survey carried out in Kolín during the period 1961–1964 (*1*), 91 (51%) of 180 new patients positive only by culture had symptoms. In the Niigata study (*4*), 63 (57%) of 109 persons positive only by culture had symptoms that, in four-fifths of cases, had lasted less than 3 months.

Since more than 90% of infectious patients develop perceptible symptoms within a few weeks of the onset of tuberculosis, early detection is possible – not by traditional mass radiography, but also by sputum examination of symptomatic persons. Mass radiography would detect most of these cases only 1–3 years after the onset of the disease (*14*), by which time most of the harm had already been done to the community (see "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?", page 72).

The WHO Expert Committee on Tuberculosis emphasized the importance of case detection among patients with symptoms at its eighth and ninth meetings (*13*, *15*). The Committee also stressed the need to increase the awareness of symptoms suggestive of tuberculosis in the community and among all health workers. Patients with cough of several weeks' duration should have their sputum examined by microscopy as the first priority for case detection. If found to be sputum-positive, these patients are the first priority for treatment.

The search for patients positive only by culture is of secondary epidemiological importance. Patients without symptoms are not an urgent public health concern. Their prognosis is likely to be favourable and their infectiousness, if any, is slight. Indeed, it has been proved that there is practically no transmission of infection if patients do not have cough (*16*).

References

1. Styblo K et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. Report for the first 4 years of the study (1961–64). *Bulletin of the World Health Organization*, 1967, 37:819–874.
2. Krivinka R et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. Second report (1965–1972). *Bulletin of the World Health Organizatio*n, 1974, 51:59–69.
3. Iwasaki T. The tuberculosis situation at the beginning of this century. *Bulletin of the International Union Against Tuberculosis*, 1974, 49:30–51.
4. Shimao T et al. A study on the mode of detection of newly registered pulmonary tuberculosis patients with special reference to their symptoms. *Reports on Medical Research Problems of the Japan Anti-Tuberculosis Association*, 1974, 21:17.
5. Pinner M, ed. *Pulmonary tuberculosis in the adult. Its fundamental aspects*. Springfield, IL, Thomas, 1945.
6. Douglas BH, Nalbant JP, Pinner M. Acute sub-apical versus insidious apical tuberculosis. *American Review of Tuberculosis and Pulmonary Disease*, 1935, 31:162–173.

7. Douglas BH, Pinner M. Acute sub-apical versus insidious apical tuberculosis; pathogenesis and clinical significance. *American Review of Tuberculosis and Pulmonary Disease*, 1930, 21:305–326.
8. Andersen S, Banerji D. A sociological study of awareness of symptoms among persons with pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1963, 29:665–683.
9. Nagpaul DR, Vishwanath MK, Dwarakanath G. A socio-epidemiological study of outpatients attending a city tuberculosis clinic in India to judge the place of specialized centres in a tuberculosis control programme. *Bulletin of the World Health Organization*, 1970, 43:17–34.
10. Baily GV et al. Potential yield of pulmonary tuberculosis cases by direct microscopy of sputum in a district of South India. *Bulletin of the World Health Organization*, 1967, 37:875–892.
11. Meijer J et al. Identification of sources of infection. *Bulletin of the International Union Against Tuberculosis*, 1971, 45:5–54.
12. Alexander CA. Collective participation in the tuberculosis control program. *Bulletin of the International Union Against Tuberculosis*, 1972, 47:107–121.
13. *WHO Expert Committee on Tuberculosis. Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
14. Toman K. Identification of the sources of tuberculosis infection in countries with a low incidence of tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1974, 49:208–221.
15. *WHO Expert Committee on Tuberculosis. Eighth report*. Geneva, World Health Organization, 1964 (WHO Technical Report Series, No. 290).
16. Riley RL, O'Grady F. *Airborne infection: transmission and control*. New York, Macmillan, 1961.

15. What is the role of case detection by periodic mass radiographic examination in tuberculosis control?[1]

H. Rieder[2]

Case detection means the early detection of individuals discharging and transmitting tubercle bacilli. But case detection is not an end in itself: it is carried out in order to treat the sources of infection so as to alleviate their suffering and to render them non-infectious.

The capacity of excretors of tubercle bacilli to infect others varies considerably. Bacteriological and epidemiological studies have revealed fundamental differences in the degree of infectiousness of different categories of patients with pulmonary tuberculosis.

A comprehensive study was made of the bacterial content of pulmonary lesions in patients who had never been given treatment (*1*). The investigators found that the number of tubercle bacilli in the various types of lesions varied substantially. In an encapsulated, solid nodule, 2 cm in diameter, having no communication with the bronchi, the number of bacilli ranged from about one hundred (10^2) to not more than a few thousand (10^4). In contrast, a cavitary lesion of the same extent might contain about 10 million to a billion bacilli (10^7–10^9), i.e. 100 000 times as many as in non-cavitary lesions. Such enormous quantities of tubercle bacilli discharged with the sputum can invariably be demonstrated by simple smear microscopy, while the small numbers coming from non-cavitary lesions are often demonstrable only by culture or amplification techniques.

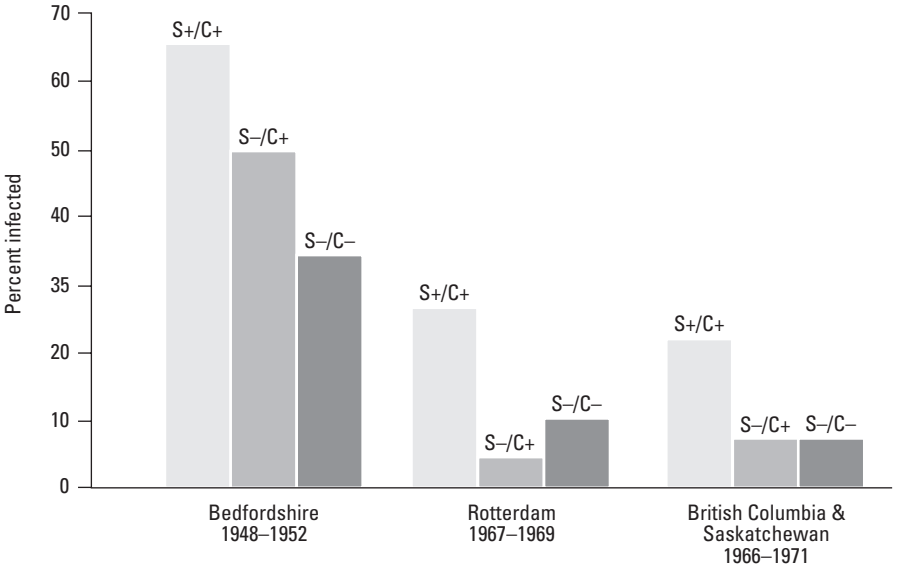
This may explain why patients with non-cavitary tuberculosis, negative sputum smears, and positive sputum cultures have a comparatively favourable clinical prognosis. They are more likely to undergo spontaneous healing than patients with cavitary lesions discharging large numbers of tubercle bacilli demonstrable by direct microscopy. By the same token, patients with different bacteriological sputum status – discharging small or large quantities of tubercle bacilli – do not have the same epidemiological relevance.

Several experimental (*2*) and epidemiological (*3–5*) studies have examined the

[1] Based on the chapter in the previous edition by K Toman.

[2] Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.

Figure 5
Risk of infecting contacts according to the bacteriological status of the pulmonary TB source
(S+/C+ indicates contacts of smear- and culture-positive cases, S–/C+ contacts smear-negative and culture-positive case, and S–/C– contacts of smear and culture-negative source cases.)



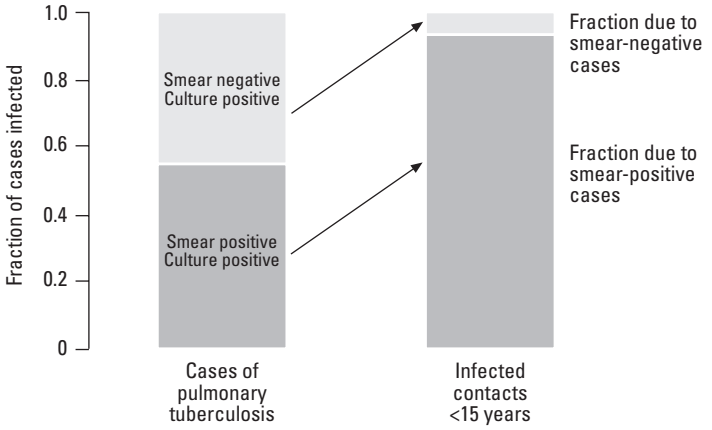
[a] Source: references *4–6*.

relationship between the frequency of infection and the bacteriological status of the source of infection. Figure 5 summarizes the major findings from three epidemiological studies. In each of the studies, children under the age of 15 years who were contacts of tuberculosis cases were tested with tuberculin and grouped according to the source case to which they had been exposed.

The absolute differences between the studies are not important (they were done at different times in different settings and probably used different definitions of contact). What matters is that all the studies clearly demonstrate that smear-positive cases are the major sources of infection: the highest prevalence of tuberculous infection was consistently found among children who had been exposed to sputum smear-positive tuberculosis cases.

From the study in British Columbia and Saskatchewan (*5*), the proportion of infections attributable to sputum smear-positive cases could be estimated as shown in Figure 6. In this setting, more than 90% of all infections were attributable to smear-positive source cases. Similarly, a recent study from San Francisco, USA, using

Figure 6
Proportion of transmission attributable to smear-positive and to culture-only-positive pulmonary tuberculosis in British Columbia and Saskatchewan[a]



[a] Source: reference *6*.

molecular epidemiological techniques, showed that more than 80% of all transmission was attributable to smear-positive cases (*6*).

Once the category of sputum smear-positive patients had been shown to be the most significant epidemiologically, the questions that arose were: "How are infectious patients currently being discovered?" and "What is the contribution of mass radiography to the detection of this high priority group?"

Detection of sputum smear-positive tuberculosis cases: results of mass radiography

Table 23 summarizes the results of WHO-assisted investigations, mainly carried out in cooperation with the Tuberculosis Surveillance Research Unit (*7*). In all the countries participating in this investigation, mass radiography for tuberculosis case detection had been a routine procedure for about 20 years.

As Table 23 shows, mass radiography made a surprisingly small contribution to the detection of smear-positive cases. The majority of cases were discovered by other means, mostly through people seeking medical help on their own initiative because of symptoms.

Another important observation from the study projects, particularly in the Netherlands and in the Kolín study, carried out in areas with populations of about 100 000, was that the proportion of smear-positive cases among those with newly detected tuberculosis had changed little despite intensive mass radiography carried out at 2–3-year intervals. Thus, in the Netherlands, although the annual incidence rates of tuberculosis were steadily decreasing, the proportion of smear-positive cases remained

Table 23
Mode of detection of sputum-positive tuberculosis cases[a]

Project	Study period	No. of smear-positive cases	Mode of detection		
			Mass radiography (%)	Symptoms (%)	Other (%)
Saskatchewan	1960–1969	265	12	66	22
Ontario	1967–1968	632	15	66	19
Kolín	1965–1972	132	23	54	23
Netherlands	1951–1967	9301	25	39	36

[a] Source: references *8, 9*.

Table 24
Smear-positive cases detected in Kolín district, Czechoslovakia,[a] ***1965–1972***[b]

Method of detection	1965	1966	1967	1968	1969	1970	1971	1972	Total
Symptoms	16	6	7	9	8	7	8	10	71
Mass radiography	–	14	–	–	11	1	–	4	30
Other	6	4	2	5	3	3	4	4	31
Total	22	24	9	14	22	11	12	18	132

[a] Country name valid at the time of the study.
[b] Source: reference *9*.

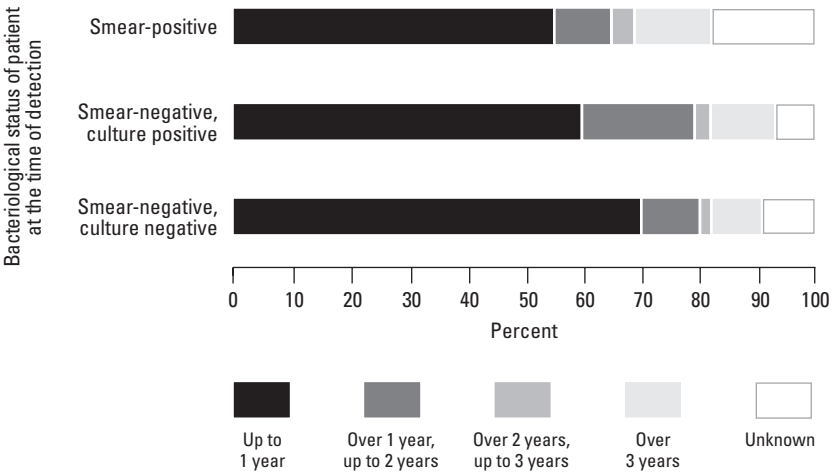
unchanged during the observation period (1951–1967). Of every 100 new patients discharging tubercle bacilli, 46 were smear-positive, despite 17 years of mass radiography at 3-year intervals (*7*).

An equally puzzling observation emerged from the Kolín study (Table 24). The proportion of new smear-positive cases was not substantially influenced by repeated surveys with 95% coverage of the eligible population aged 14 years and above (*8*). Three-quarters of these new cases developed in persons who had had a normal chest radiograph at the previous survey. The possibility that these advanced cases had developed from pre-existing, but overlooked, lesions could safely be ruled out. Two readers and one referee assessed each radiograph independently, and a WHO expert also examined a random sample of the films. For each new case in which there was an abnormal finding, all the previous films were carefully scrutinized to ascertain whether any radiographic lung shadow had existed before but had been missed or misinterpreted.

Figure 7

Interval between the last normal radiograph and the development of tuberculosis in persons of differing bacteriological status (Niigata, Japan)[a]

Each bar represents all cases with the bacteriological status indicated at the time of detection.

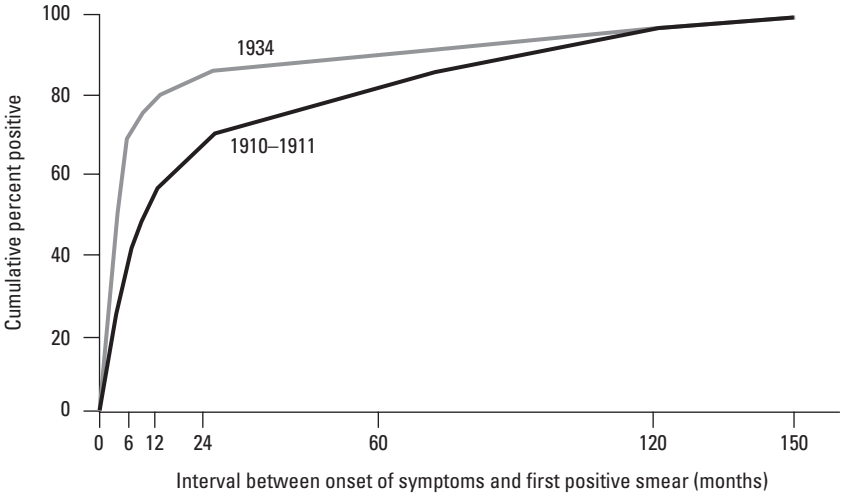


[a] Source: references *8–10*.

All cases of tuberculosis and all individuals with abnormal chest radiographs discovered in any of the surveys were either treated or closely followed up. It was therefore expected that new cases discovered in subsequent surveys would be mainly in persons with previously normal radiographs. Thus they would be found at a very early stage – at worst when the sputum was positive by culture only. Yet, year after year, a considerable proportion of the newly diagnosed cases already had advanced smear-positive tuberculosis. Since in the majority of cases (about 75%) no detectable lung lesion had existed at the previous examination, the only possible conclusion was that most of the new cases with smear-positive tuberculosis must have developed rapidly. This conclusion was tested and confirmed (*8–10*); see Figure 7.

Figure 7 shows that more than 50% of the newly discovered, smear-positive cases developed in less than 1 year. The cases positive by culture (usually with minimal lung lesions) developed within the same time. It looks as if new tuberculous lesions develop either slowly or quickly, right from the beginning. For reasons not yet fully known, tubercle bacilli grow very slowly in certain lesions and thus are present only in small numbers, but multiply rapidly in other lesions, reaching enormous counts within a few weeks. It would therefore be wrong to regard all patients with cavitary, smear-positive tuberculosis as old or chronic cases due to delayed diagnosis, because of the patient's or doctor's negligence. As Figure 7 shows, smear-positive tuberculosis of the

Figure 8
Cumulative percentage of sputum smear-positivity after onset of symptoms among patients who were ultimately smear-positive, Sweden 1910–1911 and 1934[a]



[a] Source: reference *11*.

lung can be as old or as recent as a small lung lesion positive only by culture, since at least half of such cases developed in less than 1 year in apparently healthy persons with normal radiographs.

Data from the Kolín study also showed that about four-fifths of new patients who had normal chest radiographs at the previous mass radiography developed the disease within 3 years. Thus it appears that mass radiography, carried out at intervals of 3 years, may to a large extent fail to detect cases sufficiently soon after the onset of disease. Even intervals of 6 months may be too long, as a Swedish study has shown (*11*). Progress from onset of symptoms to sputum smear-positive tuberculosis was very rapid in a large proportion of patients (Figure 8).

Conclusions

It has been proved that the early detection of all cases with smear-positive pulmonary tuberculosis – the most dangerous sources of infection – by means of periodic mass radiography is impractical, even when such radiography is repeated at short intervals (*12*). The great majority of sputum smear-positive cases develop in a shorter time than the shortest practical interval between two mass radiography survey rounds. Moreover, 90% of patients with rapidly progressive pulmonary tuberculosis have objective symptoms, such as cough, fever, loss of weight, sputum, and haemoptysis (*13*). These symptoms develop rather soon after the onset of the disease, prompting the patient

to seek medical advice. Most smear-positive tuberculosis cases are therefore not detected in periodic case-detection campaigns but rather by regular health services that patients can consult whenever they feel ill.

For these reasons, mass radiography is not a recommended case-detection method. Additional obstacles to the effective operation of periodic mass radiography are the lack of good roads, the high breakdown rate of vehicles and X-ray machinery, and the high cost and scarcity of spare parts and repair facilities.

In its ninth report (*14*), the WHO Expert Committee on Tuberculosis noted that "mass miniature radiography is a very expensive screening procedure for tuberculosis, even when the prevalence is high. Other disadvantages of mass radiography are as follows:

1. It contributes only a small proportion of the total number of cases found.
2. It has no significant effect on the occurrence of subsequent smear-positive cases, as they usually develop so rapidly that they arise between the rounds of mass radiography examinations (thus it follows that case-detection and treatment facilities should be constantly available for an indefinite period to come).
3. It requires the services of highly qualified technicians and medical staff who could be better used in other health service activities.
4. The apparatus or the vehicles used to transport it are often out of service because of mechanical breakdown for months on end, especially where spare parts are in short supply.

The Committee concluded that the policy of indiscriminate tuberculosis case-finding by mobile mass radiography should now be abandoned."

References

1. Canetti G. The John Burns Amberson lecture. Present aspects of bacterial resistance in tuberculosis. *American Review of Respiratory Disease*, 1965, 92:687–703.
2. Riley RL et al. Infectiousness of air from a tuberculosis ward. Ultraviolet irradiation of infected air: comparative infectiousness of different patients. *American Review of Respiratory Disease*, 1962, 85:511–525.
3. Shaw JB, Wynn-Williams N. Infectivity of pulmonary tuberculosis in relation to sputum status. *American Review of Respiratory Disease*, 1954, 69:724–732.
4. van Geuns HA, Meijer J, Styblo K. Results of contact examination in Rotterdam, 1967–1969. *Bulletin of the International Union Against Tuberculosis*, 1975, 50:107–121.
5. Grzybowski S, Barnett GD, Styblo K. Contacts of cases of active pulmonary tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1975, 50:90–106.
6. Behr MA et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*, 1999, 353:444–449.
7. Meijer J et al. Identification of sources of infection. *Bulletin of the International Union Against Tuberculosis*, 1971, 45:5–54.
8. Krivinka R et al. Epidemiological and clinical study of tuberculosis in the district of Kolín,

Czechoslovakia. Second report (1965–1972). *Bulletin of the World Health Organization*, 1974, 51:59–69.

9. Styblo K et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. Report for the first 4 years of the study (1961–64). *Bulletin of the World Health Organization*, 1967, 37:819–874.
10. Shimao T et al. A study on the mode of detection of newly registered pulmonary tuberculosis patients with special reference to their symptoms. *Reports on Medical Research Problems of the Japan Anti-Tuberculosis Association*, 1974, 22:17–41.
11. Berg G. *The prognosis of open pulmonary tuberculosis. A clinical–statistical analysis*. In: Lund, Sweden, Håkan Ohlson, 1939:1–207.
12. Toman K. Mass radiography in tuberculosis control. *WHO Chronicle*, 1976, 30:51–57.
13. Banerji D, Andersen S. A sociological study of awareness of symptoms among persons with pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1963, 29:665–683.
14. *WHO Expert Committee on Tuberculosis. Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).

16. How does the diagnosis of tuberculosis in persons infected with HIV differ from diagnosis in persons not infected with HIV?

A. Harries[1]

Pulmonary tuberculosis is the most common manifestation of tuberculosis in adults infected with HIV. Tuberculosis occurs at various stages of HIV infection, with the clinical pattern correlating with the patient's immune status. In the early stages of HIV infection, when immunity is only partially compromised, the features are more typical of tuberculosis, commonly with upper lobe cavitation, and the disease resembles that seen in the pre-HIV era. As immune deficiency advances, HIV-infected patients present with atypical pulmonary disease resembling primary tuberculosis or extra-pulmonary and disseminated disease, commonly with hilar adenopathy and lower lobe infection (*1*).

Diagnosis of pulmonary tuberculosis

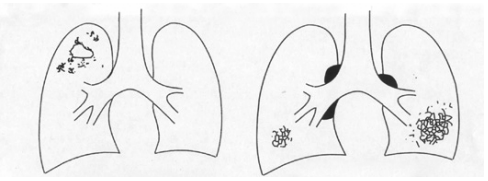
Clinical features in pulmonary tuberculosis are generally similar in HIV-infected and HIV-negative patients. However, cough is reported less frequently by HIV-infected patients, probably because there is less cavitation, inflammation, and endo-bronchial irritation as a result of a reduction in cell-mediated immunity (*2*). Similarly, haemoptysis, which results from caseous necrosis of the bronchial arteries, is less common in HIV- infected patients.

Tuberculin skin tests have limited value for individual adult diagnosis, although they are useful for measuring the prevalence of tuberculous infection in a community. In the presence of active tuberculosis, the tuberculin skin test may be negative. For example, one study of HIV-positive pulmonary tuberculosis patients in Zaire found cutaneous anergy in 8% of those with a CD4-lymphocyte count >500/µl and 54% in those with a CD4-lymphocyte count <200/µl (*3*).

Sputum smear microscopy remains the cornerstone of tuberculosis diagnosis, even in areas of high HIV prevalence. Systematic studies in sub-Saharan Africa have shown that most HIV-infected pulmonary tuberculosis patients are sputum smear-positive, although the proportion of patients with smear-negative, suspected pulmonary tuberculosis is greater in HIV-infected than in HIV-negative tuberculosis patients (*1*, *4*).

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

Figure 9
Radiographic findings in tuberculosis patients with HIV infection



Early HIV

Late HIV
(severe immunocompromise)

HIV-infected, smear-positive patients also tend to excrete significantly fewer organisms in sputum than HIV-negative patients, which can lead to acid-fast bacilli being missed if insufficient high-power fields are examined by microscopy.

Chest radiography is needed for persons who are suspected of having tuberculosis, are sputum smear-negative, and do not respond to a course of broad-spectrum antibiotics. Bronchitis and pneumonia with *Streptococcus pneumoniae*, *Haemophilus influenzae*, and other common pathogens are frequent in HIV-infected persons. No radiographic pattern is diagnostic of tuberculosis, although the classical hallmarks of the disease are cavitation, apical distribution, pulmonary fibrosis, shrinkage, and calcification. HIV-infected patients with relatively well-preserved immune function will often show these typical features; as immunosuppression worsens, however, chest radiographs more often show atypical features such as pulmonary infiltrates affecting the lower lobes and intrathoracic lymphadenopathy. Sometimes the chest radiograph is normal (*1*, *4*): in one study in the United States of America, 21% of smear- and/or culture-positive tuberculosis patients with a CD4-lymphocyte count <200/µl had normal chest radiographs (*5*).

Diseases other than tuberculosis can cause both the classical and atypical chest radiographic features. If sputum smears are negative, other conditions have to be considered in the differential diagnosis.

Important HIV-related pulmonary diseases that may be confused with pulmonary tuberculosis include bacterial pneumonia, *Pneumocystis carinii* pneumonia, Kaposi sarcoma, fungal infections, and nocardiosis.

Extrapulmonary tuberculosis

The main manifestations of extrapulmonary tuberculosis in HIV- infected patients are lymphadenopathy, pleural effusion, pericardial effusion, and miliary tuberculosis (*1*, *4*). The definitive diagnosis of extrapulmonary tuberculosis is often difficult because of the scarcity of diagnostic facilities: in the United Republic of Tanzania, only 18% of patients with extrapulmonary tuberculosis had laboratory confirmation of the diagnosis (*6*).

Presentation of extrapulmonary tuberculosis in HIV-infected patients is generally no different from that in HIV-negative patients. However, HIV-related tuberculosis lymphadenopathy can occasionally be acute and resemble an acute pyogenic bacterial infection. Diagnosis can be made using simple techniques such as needle aspiration, inspection of lymph nodes biopsies for macroscopic caseation, and examination of direct smears from the cut surface. In tuberculous meningitis, the cerebrospinal fluid may be completely normal in HIV-infected patients. Disseminated tuberculosis may be extremely difficult to diagnose. In Côte d'Ivoire, for example, the condition was found in 44% of patients with HIV wasting syndrome who came to autopsy; the diagnosis had not been made ante mortem (*7*). Bacteraemia with *Mycobacterium tuberculosis* may not be uncommon, and may be accompanied by cough and abnormal chest radiographs in less than half of cases (*8–10*). Pericardial tuberculosis is not rare and may be diagnosed presumptively from the characteristic balloon-shaped appearance of the cardiac shadow on chest radiography.

Diagnosis in childhood tuberculosis

As in adults, pulmonary tuberculosis is the most common manifestation of tuberculosis in HIV-positive children. The diagnosis of pulmonary tuberculosis in children under 4 years old has always been difficult, and HIV infection further compounds this diagnostic challenge. There is a high incidence of cutaneous anergy in HIV-positive children with tuberculosis, and most cases are diagnosed according to nonspecific clinical and radiographic criteria. Because it is often difficult to distinguish HIV-related pulmonary disease from pulmonary tuberculosis, childhood pulmonary tuberculosis is probably over-diagnosed in many areas.

Implications of diagnostic difficulties

The advent of HIV has made the diagnosis of tuberculosis more difficult, and false diagnoses of tuberculosis probably occur frequently among patients affected by other HIV-related illnesses. Although little has been done to solve or even delineate this important problem, these false-positive diagnoses generally account for only a small proportion of all forms of tuberculosis notified, and thus do not negate the huge increases observed in tuberculosis notifications in HIV-endemic areas. Sputum smear remains the cornerstone of diagnosis, identifying infectious patients so that transmission can be stopped.

References

1. Raviglione MC et al. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11:S115–S123.
2. Elliott AM et al. Impact of HIV on tuberculosis in Zambia: a cross-sectional study. *British Medical Journal*, 1990, 301:412–415.
3. Mukadi Y et al. Spectrum of immunodeficiency in HIV-1 infected patients with pulmonary tuberculosis in Zaire. *Lancet*, 1993, 342:143–146.

4. Harries AD. Tuberculosis in Africa: clinical presentation and management. *Pharmacology and Therapeutics*, 1997, 73:1–50.
5. Greenberg SD et al. Active pulmonary tuberculosis in patients with AIDS: spectrum of radiographic findings (including a normal appearance). *Radiology*, 1994, 193:115–119.
6. Richter C et al. Extrapulmonary tuberculosis – a simple diagnosis? *Tropical Geographical Medicine*, 1991, 43:375–378.
7. Lucas SB et al. Contribution of tuberculosis to slim disease in Africa. *British Medical Journal*, 1994, 308:1531–1533.
8. Shafer RW et al. Frequency of *Mycobacterium tuberculosis* bacteraemia in patients with tuberculosis in an area endemic for AIDS. *American Review of Respiratory Disease*, 1989, 140:1611–1613.
9. Archibald LK et al. Fatal *Mycobacterium tuberculosis* bloodstream infections in febrile hospitalized adults in Dar es Salaam, Tanzania. *Clinical Infectious Diseases*, 1998, 26:290–296.
10. McDonald LC et al. Unrecognized *Mycobacterium tuberculosis* bacteraemia among hospital inpatients in less developed countries. *Lancet*, 1999, 354:1159–1163.

17. What is the role of tuberculin skin testing in the diagnosis of tuberculosis?

D. Menzies[1]

The tuberculin skin test seems attractive because it involves low technology, is inexpensive, and is relatively easy to administer and read. However, its interpretation remains a subject of controversy and misunderstanding, some of which arises from widely discrepant findings reported in different studies. This wide variation in results does not reflect variation in sensitivity or precision of the test. Rather, the differences reflect considerable variation in the prevalence of true-positive and true-negative as well as in the occurrence of false-positive and false-negative results in different populations.

For the diagnosis of tuberculosis infection, the tuberculin test is practically the only tool currently available. Its usefulness depends on the clinical situation and population, as well as on the availability of resources to manage tuberculin reactors. The tuberculin test is useful for identifying individuals at high risk of disease, such as those with HIV infection or close contacts of infectious tuberculosis patients, who would benefit from treatment of latent tuberculosis infection (see "What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?", page 220).

However, the test is not useful for the diagnosis of tuberculosis disease, and will often be misleading because of false-negative and false-positive results. At the time of diagnosis, the tuberculin test is falsely negative in 10–47% of patients with active disease (*1*–*4*). The likelihood of false-negative reactions increases with the extent of disease and the age of the individual. Interestingly, this tuberculin anergy appears to be temporary; more than 95% of patients tested after 1 month or more of treatment will have a positive test result (*5*). In the presence of co-infection with HIV, a far higher proportion of patients with active disease will have a false-negative test result. This is related to the degree of immunosuppression: a false-negative tuberculin test will be seen in 30% of patients with a CD4 T-lymphocyte cell count of >500/µl, compared with close to 100% of patients with a CD4 T-lymphocyte cell count of <200/µl (*6*, *7*).

Tuberculin testing is a nonspecific measure of prior mycobacterial sensitization. It may be positive in individuals who have had prior BCG vaccination – although, if

[1] Director, TB Clinic, Montreal Chest Institute, McGill University, Montreal, Canada.

BCG is given in infancy, a reaction of more than 10 mm is rare after the age of 5 years (*8*). In persons vaccinated at an older age, such as in primary school, 15–25% will remain positive for as long as 20–25 years (*8–10*). A false-positive test also commonly results from cross-reacting sensitivity to non-tuberculous mycobacterial antigens (*11*), which are very common in tropical and subtropical climates (*5*, *12*, *13*).

The most important limitation of the tuberculin test for diagnosis of disease is its inability to distinguish latent, or dormant, infection from infection associated with active disease. If a test is used to investigate patients with respiratory symptoms, a positive result only marginally increases the probability that the patient has tuberculosis. This is because, even among patients with a positive test resulting from true tuberculosis infection, the vast majority will not have active tuberculosis disease at the time of assessment.

In screening situations, the tuberculin test is even less useful for detecting disease. In situations of high prevalence of tuberculosis, such as in developing countries, a negative test may be misleading.

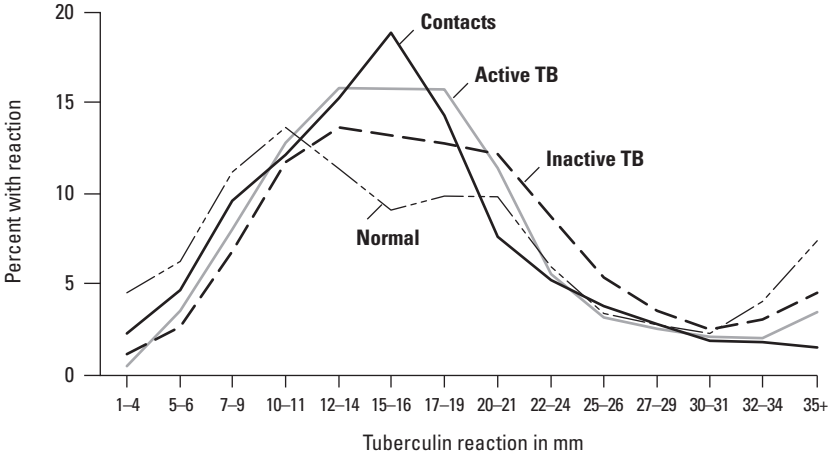
Does the size of reaction help in distinguishing infection from disease?

Large tuberculin reactions are always more impressive to patients and health care providers alike. It is a common misconception that larger tuberculin reactions are more likely to indicate active disease. As Figure 10 shows, this is not the case. It is true

Figure 10

Pattern of tuberculin reactions in patients with active and inactive tuberculosis, in contacts of active cases, and in normal individuals[a]

Curves smoothed by moving three-point average. Tuberculin reactions of 0 mm not shown.



[a] Adapted from reference *1*.

that the likelihood of disease will vary depending on whether the tuberculin test is more or less than 5 mm. However, beyond 5 mm, the size of the reaction does not distinguish in any way between those with active tuberculosis disease, inactive tuberculosis (abnormal chest radiograph), recent infection (close contacts), or remote infection. Therefore, beyond a certain threshold, size does not matter in the interpretation of a tuberculin reaction (*1*).

References

1. Al Zahrani K, Al Jahdali H, Menzies D. Does size matter? Utility of size of tuberculin reactions for the diagnosis of mycobacterial disease. *American Journal of Respiratory and Critical Care Medicine*, 2000, 162:1419–1422.
2. Rooney JJ et al. Further observations on tuberculin reactions in active tuberculosis. *American Journal of Medicine*, 1976, 60:517–521.
3. Holden M, Dubin MR, Diamond PH. Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. *New England Journal of Medicine*, 1971, 285:1506–1509.
4. Harrison BDW, Tugwell P, Fawcett IW. Tuberculin reaction in adult Nigerians with sputum-positive pulmonary tuberculosis. *Lancet*, 1975, 1:421–424.
5. WHO Tuberculosis Research Office. Further studies of geographic variation in naturally acquired tuberculin sensitivity. *Bulletin of the World Health Organization*, 1955, 22:63–83.
6. Graham NM et al. Prevalence of tuberculin positivity and skin test anergy in HIV-1-seropositive and -seronegative intravenous drug users. *Journal of the American Medical Association*, 1992, 267:369–373.
7. Markowitz N et al. Tuberculin and anergy testing in HIV-seropositive and HIV-seronegative persons. *Annals of Internal Medicine*, 1993, 119:185–193.
8. Menzies R, Vissandjee B. Effect of bacille Calmette–Guérin vaccination on tuberculin reactivity. *American Review of Respiratory Disease*, 1992, 145:621–625.
9. Comstock GW, Edwards LB, Nabangxang H. Tuberculin sensitivity eight to fifteen years after BCG vaccination. *American Review of Respiratory Disease*, 1971, 103:572–575.
10. Horwitz O, Bunch-Christensen K. Correlation between tuberculin sensitivity after 2 months and 5 years among BCG vaccinated subjects. *Bulletin of the World Health Organization*, 1972, 47:49–58.
11. Palmer CE et al. Experimental and epidemiologic basis for the interpretation of tuberculin sensitivity. *The Journal of Pediatrics*, 1959, 55:413–428.
12. Edwards LB et al. An atlas of sensitivity to tuberculin, PPD-B, and histoplasmin in the United States. *American Review of Respiratory Disease*, 1969, 99:1–132.
13. Paul RC et al. Multiple skin testing of Kenyan schoolchildren with a series of new tuberculins. *The Journal of Hygiene (London)*, 1975, 75:303–313.

18. What is the current and potential role of diagnostic tests other than sputum microscopy and culture?

D. Menzies[1]

The sputum smear examination for acid-fast bacilli (AFB) is a low-cost, highly specific means of identifying the infectious sources of spread of tuberculosis. However, it has limitations in that it is relatively labour-intensive. If there is a lack of training, motivation, time, or supervision of laboratory technicians, performance of the AFB smear under programme conditions may be far below its potential. In Africa, where tuberculosis caseloads in some countries have increased 2–4-fold, as many as one in four patients diagnosed as having smear-negative tuberculosis actually have positive smears (*1*). Furthermore, the AFB smear requires two visits to the health facility by the patient, and will not, even when optimally performed, identify patients with small numbers of bacilli in their sputum that are positive by culture only (see "What is the role of mycobacterial culture in diagnosis and case definition?", page 35). Although these patients contribute only a small proportion of transmission and of mortality due to tuberculosis, their diagnosis and management may absorb a significant proportion of the effort of the clinical and public health staff responsible for tuberculosis control. A rapid, low-cost test that is simpler to perform than the AFB smears and/or that can identify smear-negative and extrapulmonary tuberculosis is therefore desirable. Chemical tests used to suggest a diagnosis of extrapulmonary tuberculosis (e.g. adenosine deaminase, tuberculostearic acid) are not considered here.

Immunological tests

The tuberculin skin test

The tuberculin skin test has been in clinical use for more than 90 years (see "What is the role of tuberculin skin testing in the diagnosis of tuberculosis?", page 84). However, it does not distinguish between tuberculosis infection and disease, and some patients with tuberculosis disease initially have negative tuberculin tests. The test therefore has little role in the diagnosis of tuberculosis disease in adults.

[1] Director, TB Clinic, Montreal Chest Institute, McGill University, Montreal, Canada.

Serology

The term "serology" refers here to the measurement of humoral (antibody – most commonly IgG) response to *Mycobacterium tuberculosis* through blood tests. Robert Koch introduced the first serological test in 1898, yet after more than a century of development, no currently available serological test offers adequate sensitivity and specificity. This is most probably because the primary immune response to *M. tuberculosis* is cell-mediated, not humoral (*2*). Recent evidence suggests that the humoral response to *M. tuberculosis* is heterogeneous (*3*, *4*). In one study of 59 patients with active tuberculosis, 52 (88%) had detectable antibody response to at least one of 10 mycobacterial antigens, but less than 50% responded to any single antigen (*4*).

Earlier serological tests used crude extracts such as tuberculin skin test material and had poor sensitivity and specificity (*2*). More recent tests, using highly purified antigens, have better sensitivity and specificity (*2*). The major advantage of these tests is that results are available within an hour and, because they involve simple technology, minimal equipment and little training are needed. In recent years, many manufacturers have marketed serological tests (*5*); these are readily available and relatively inexpensive (about US$ 1 per test), which makes them attractive in resource-poor countries, where they may be aggressively marketed. However, the major disadvantages remain their poor sensitivity and specificity (*5*, *6*). Sensitivity is highest in patients with smear-positive disease (*3*, *7*, *8*), but is much lower in children (*9*), patients with extrapulmonary disease (*8*, *10*), HIV-infected individuals (*11*), and smear-negative cases (*8*, *10*), i.e. the patients in whom another rapid test would be helpful because the AFB smear is insensitive. Specificity appears best in healthy volunteers in non-endemic countries (*3*, *7*). It is much lower in appropriate test populations, such as close contacts of active cases, patients in whom active tuberculosis is suspected, and populations from endemic areas (*6*). Serological tests cannot reliably distinguish active tuberculosis from infection with *M. tuberculosis*. At present (2003), therefore, serological tests have no role in the diagnosis of tuberculosis.

Assays of cell-mediated immunity

In the past decade, molecular biological advances have spawned the development of tests to estimate cell-mediated immunity against *M. tuberculosis*. Circulating lymphocytes are extracted from samples of venous blood and exposed to purified antigens of *M. tuberculosis*; 6–24 hours later, the production of cytokines (inflammatory mediators, most commonly interferon gamma (*12*)) is measured.

The major theoretical advantage of this technique is that it measures the primary immune response of humans to tuberculosis. On the other hand, 20–47% of patients with extensive disease may be anergic at the time of diagnosis (*13–16*). Although temporary – resolving after a month or more of treatment (*17*) – this phenomenon could diminish the sensitivity and usefulness of this type of test, particularly in high-prevalence settings. A further disadvantage is that this is a highly complex test,

currently performed in only a few technically advanced research laboratories in industrialized countries. Further research to simplify and automate the technique, followed by validation work to estimate sensitivity, specificity, and predictive values, would be required before this test could be available for clinical use.

Amplification tests

Amplification tests, developed for many different microorganisms including *M. tuberculosis*, represent another application of molecular biological research to clinical practice. Highly specific nucleic acid probes (primers) recognize and attach to specific segments of the target DNA. The microorganism's DNA and the primer are replicated over many cycles so that the DNA is copied over and over – or "amplified". Once amplification is complete, a DNA probe is added that binds only with the amplified DNA from the microorganism, producing a colorimetric reaction that can be measured (*18*).

The major advantages of this technique are that: results can be available in several hours (although some amplification tests take several days (*19*)); specificity can be 98–100% (*20*); sensitivity of these tests is greater than 95% in sputum that is AFB smear-positive, although only 50–60% in smear-negative, culture-positive specimens (*21–23*). Recently developed amplification tests may have better sensitivity in smear-negative specimens, while retaining the same high degree of specificity (*19*, *20*, *24*).

The major disadvantages are cost, complexity, and lower specificity (higher proportion of false-positives) under field conditions (*25*, *26*). "In-house" tests may be cheaper but they take longer, are more difficult to perform (*19*), and require more highly trained technicians. Highly automated systems are available but initial capital costs and recurrent cost per test are both high, exceeding US$ 15 per test. High costs and/or complexity currently make these tests inappropriate for application in high-prevalence, resource-poor settings. However, a test that costs as much as US$ 6 may be cost-effective in such settings because patients with active disease are detected earlier and treatment is avoided in patients who are clinically suspect yet do not actually have active tuberculosis. The promise of amplification tests has often been limited by a high proportion of false-positive results obtained under programme conditions. Lack of sensitivity for sputum-negative patients and inability both to quantify mycobacteria and to distinguish viable from non-viable bacilli also limit the incremental benefits of this test, beyond the information provided by the AFB smear.

Summary

The AFB smear is inexpensive and highly specific, but it is labour-intensive and does not detect patients with smear-negative and extrapulmonary tuberculosis. Newer immunodiagnostic tests are the focus of active research, as they offer the promise of rapid and accurate diagnosis using equipment, materials, and personnel appropriate

for a resource-limited setting. At present, however, no serological test is available that can be recommended for routine clinical use, and tests of cell-mediated immune response to *M. tuberculosis* antigens are applicable only in research settings. Amplification tests are promising because they have good sensitivity and potential for good specificity and can be applied directly to clinical specimens such as sputum. At the moment, the high cost of equipment and materials and low specificity under field conditions make them inappropriate for resource-poor settings. None of the newer tests allows quantification of *M. tuberculosis* in sputum. Thus, even if a new, low-cost, simple method were to become available, the AFB smear might still be required to identify and monitor the most contagious and seriously ill patients.

References

1. Hawken MP et al. Under-diagnosis of smear-positive pulmonary tuberculosis in Nairobi, Kenya. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:360–363.
2. Daniel TM, Debanne SM. The serodiagnosis of tuberculosis and other mycobacterial diseases by enzyme-linked immunosorbent assay. *American Review of Respiratory Disease*, 1987, 135:1137–1151.
3. Verbon A et al. Evaluation of different tests for the serodiagnosis of tuberculosis and the use of likelihood ratios in serology. *American Review of Respiratory Disease*, 1993, 148: 378–384.
4. Lyashchenko K et al. Heterogeneous antibody responses in tuberculosis. *Infection and Immunity*, 1998, 66:3936–3940.
5. Pottumarthy S, Wells VC, Morris AJ. A comparison of seven tests for serological diagnosis of tuberculosis. *Journal of Clinical Microbiology*, 2000, 38:2227–2231.
6. Somi GR et al. Evaluation of the MycoDot test in patients with suspected tuberculosis in a field setting in Tanzania. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:231–238.
7. Amicosante M et al. Sensitivity and specificity of a multi-antigen ELISA test for the serological diagnosis of tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:736–740.
8. Zhou AT et al. Detection of pulmonary and extrapulmonary tuberculosis patients with the 38-kilodalton antigen from *Mycobacterium tuberculosis* in a rapid membrane-based assay. *Clinical and Diagnostic Laboratory Immunology*, 1996, 3:337–341.
9. Swaminathan S et al. Serodiagnosis of tuberculosis in children using two ELISA kits. *Indian Journal of Pediatrics*, 1999, 66:837–842.
10. Al Zahrani K et al. Accuracy and utility of commercially available amplification and serologic tests for the diagnosis of minimal pulmonary tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 2000, 162:1323–1329.
11. Daniel TM et al. Reduced sensitivity of tuberculosis serodiagnosis in patients with AIDS in Uganda. *Tubercle and Lung Disease*, 1994, 75:33–37.
12. Mazurek GH et al. Comparison of whole blood interferon gamma assay with tuberculin testing for detecting *Mycobacterium tuberculosis* infection. *Journal of the American Medical Association*, 2001, 286:1740–1747.

13. Holden M, Dubin MR, Diamond PH. Frequency of negative intermediate-strength tuberculin sensitivity in patients with active tuberculosis. *New England Journal of Medicine*, 1971, 285:1506–1509.
14. Al Zahrani K, Al Jahdali H, Menzies D. Does size matter? Utility of size of tuberculin reactions for the diagnosis of mycobacterial disease. *American Journal of Respiratory and Critical Care Medicine*, 2000, 162:1419–1422.
15. Harrison BDW, Tugwell P, Fawcett IW. Tuberculin reaction in adult Nigerians with sputum-positive pulmonary tuberculosis. *Lancet*, 1975:421–424.
16. Rooney JJ et al. Further observations on tuberculin reactions in active tuberculosis. *American Journal of Medicine*, 1976, 60:517–521.
17. WHO Tuberculosis Research Office. Further studies of geographic variation in naturally acquired tuberculin sensitivity. *Bulletin of the World Health Organization*, 1955, 22:63–83.
18. Eisenach KD et al. Detection of *Mycobacterium tuberculosis* in sputum samples using a polymerase chain reaction. *American Review of Respiratory Disease*, 1991, 144:1160–1163.
19. Kambashi B et al. Utility of nucleic acid amplification techniques for the diagnosis of pulmonary tuberculosis in sub-Saharan Africa. *International Journal of Tuberculosis and Lung Disease*, 2000, 5:364–369.
20. Catanzaro A et al. The role of clinical suspicion in evaluating a new diagnostic test for active tuberculosis. Results of a multicenter prospective trial. *Journal of the American Medical Association*, 2000, 283:639–645.
21. Clarridge JE et al. Large-scale use of polymerase chain reaction for detection of *Mycobacterium tuberculosis* in a routine mycobacteriology laboratory. *Journal of Clinical Microbiology*, 1993, 31:2049–2056.
22. Abe C et al. Detection of *Mycobacterium tuberculosis* in clinical specimens by polymerase chain reaction and the gen-probe amplified *Mycobacterium tuberculosis* direct test. *Journal of Clinical Microbiology*, 1993, 31:3270–3274.
23. Wobester WR et al. Evaluation of Roche Amplicor PCR Assay for *Mycobacterium tuberculosis. Journal of Clinical Microbiology*, 1996, 34:134–139.
24. Bradley SP, Reed SL, Catanzaro A. Clinical efficacy of the amplified *Mycobacterium tuberculosis* direct test for the diagnosis of pulmonary tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 1996, 153:1606–1610.
25. Burkardt HJ. Standardization and quality control of PCR analyses. *Clinical Chemistry and Laboratory Medicine*, 2000, 38:87–91.
26. Doucet-Populaire F et al. A blind study of the polymerase chain reaction for the detection of *Mycobacterium tuberculosis* DNA. Azay Mycobacteria Study Group. *Tubercle and Lung Disease*, 1996, 77:358–362.
27. Roos BR et al. Cost-effectiveness of the polymerase chain reaction versus smear examination for the diagnosis of tuberculosis in Kenya: a theoretical model. *International Journal of Tuberculosis and Lung Disease*, 1997, 2:235–241.

19. How can public and private sectors cooperate to detect, treat, and monitor tuberculosis cases?

T. Frieden[1]

Accountability is a fundamental principle of tuberculosis control. In each geographical area, one individual (the District or Municipal Tuberculosis Control Officer) is responsible for the prompt detection, effective treatment, and systematic monitoring of tuberculosis cases. Poor treatment practices in any part of the health sector will increase the risk of drug resistance, spread of tuberculosis, and death. The tuberculosis officer must therefore be responsible for *every* tuberculosis patient in the jurisdiction, and not only for patients in the public health system.

In many countries, public health care institutions provide a decreasing proportion of health care services (*1*). Other providers include charitable organizations and health care services for government employees, insured workers, prisoners, and armed forces personnel and their families. In many countries, a significant proportion of patients with tuberculosis first consult private health care providers (*2*). These providers include licensed and unlicensed doctors and, in a large number of countries, trained and untrained pharmacists who sell tuberculosis drugs without prescription. Patients' use of these providers may reflect dissatisfaction with services offered by the public health care system. Unfortunately, care by private providers often results in delayed diagnosis, partial and non-standard treatment, drug resistance, spread of infection, and unnecessary expenditure by the patient.

There is no one perfect means to achieve coordination between public and private sectors in all countries. Effective programmes employ several, or all, of the approaches outlined below, but, whatever the approach, effective governmental services are a prerequisite for success.

Competition

To some extent, competition is a factor in nearly all tuberculosis control programmes: "Well-organized outpatient chemotherapy, especially if provided free of charge, will attract symptomatic cases from far and wide" (*3*). This approach can be effective if governmental services are free, convenient, patient-friendly, and reliably curative, and are widely recognized as such.

[1] Medical Officer, Stop Tuberculosis Unit, WHO Regional Office for South-East Asia, New Delhi, India.

Exclusion

Another approach is to exclude the private sector. All developed and some developing countries ban over-the-counter sales of anti-tuberculosis drugs, and in some countries these drugs are available only through the public sector. Only a few countries, however, control the medications that doctors can prescribe. Tuberculosis control programmes should try to prevent over-the-counter sales of anti-tuberculosis drugs, but any more ambitious form of exclusion requires political, cultural and social acceptance, as well as reliable tuberculosis control services within the public sector. These conditions exist in relatively few areas.

Contracting

The public sector can contract tuberculosis control services to private groups. The government does not have to provide all care; clinical services can be delegated to other health service providers. However, it remains the government's responsibility to ensure that effective clinical services are reliably available to patients. Clear expectations and clearly defined roles are essential for successful contracting.

Engagement

Some programmes actively engage the private sector in tuberculosis care. In many countries, public health programmes and professional groups, such as national chest societies, collaborate to establish standards of care that apply to both public and private sectors, and to revise medical school curricula to reflect these consensus standards. The New York City tuberculosis control programme illustrates this approach. In New York City, all doctors, including those in training, receive compact reference guides on diagnosis and treatment of tuberculosis, including information on where and how to refer tuberculosis patients. Standards of care for diagnosis and treatment are also disseminated widely through conferences, lectures, grand rounds, and circulars. High-quality laboratory services are provided to private patients free of charge; private laboratories and hospitals transport specimens to the Department of Health laboratory for testing. The Department of Health strongly encourages referral of patients to its chest clinics and urges doctors not to initiate treatment unless they can ensure its completion. The Department also provides observation of treatment by public health workers as a service to patients of private doctors, as long as the private doctors prescribe standard treatment regimens. Moreover, the Department provides free medications to patients of private doctors, provided that these medications are given in standard regimens and by direct observation. A "hotline" for physicians provides clinical consultation as well as patient-specific information.

There is often a long tradition of mutual disrespect between medical school providers and the public health system. This antagonism can be overcome only by sustained, concerted and technically sound efforts.

Reporting

Reporting, or notification, has been critical for effective tuberculosis control in many areas (*4*). Public health agencies that conduct active surveillance of laboratories, preferably with the authority to revoke laboratory licences for poor performance or failure to report cases, can greatly increase the reporting of smear-positive (and culture-positive) tuberculosis cases. The names of bacteriologically confirmed patients can be entered into a register and their treatment can be monitored. It is then possible to evaluate the outcome in every patient with bacteriologically confirmed tuberculosis from every institution in a reporting area. The approach taken should be supportive and collegial, and the process should create minimal disturbance for the laboratory. Laboratories can be sent regular updates about tuberculosis and about recent developments in the field. Laboratory directors can be involved in discussions about how to improve coordination, possibly through an advisory group representing directors of major laboratories. This approach can greatly increase detection rates, particularly when combined with efforts to educate doctors about the importance of acid-fast bacilli smears in diagnosis and with assured laboratory quality. It also focuses public health attention on bacteriologically positive cases, which account for most tuberculosis transmission and mortality. The system greatly facilitates surveillance, because there are many fewer laboratories than there are individual physicians.

As a minimum, public health programmes should maintain a list of all large providers of care, and should attempt to involve them in standardized diagnosis, treatment, and monitoring of tuberculosis. Tuberculosis control programmes relying on the public sector have been highly successful (*5–9*). As the level of government effectiveness increases, private facilities can be more effectively monitored, care standardized, and reporting ensured. Provided that private providers adhere to policies for care and reporting, public agencies can usefully support these providers. Thus, the role of the public sector should be not only to provide care but also to ensure high-quality care in all sectors – that is, to be accountable for all, or nearly all, patients in the area.

References

1. *Health systems: improving performance. The World Health Report 2000*. Geneva, World Health Organization, 2000.
2. *Involving private practitioners in tuberculosis control: issues, interventions, and emerging policy framework*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.285).
3. Styblo K. *Epidemiology of tuberculosis. Vol. 24*. The Hague, Royal Netherlands Tuberculosis Association, 1984.
4. Frieden TR, Lerner BH, Rutherford BR. Lessons from the 1800s: tuberculosis control in the new millennium. *Lancet*, 2000, 355:1088–1092.
5. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. China Tuberculosis Control Collaboration. *Lancet*, 1996, 347:358–362.

6. Khatri GR, Frieden TR. The status and prospects of tuberculosis control in India. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:193–200.
7. Marrero A et al. Towards elimination of tuberculosis in a low-income country: the experience of Cuba, 1962–97. *Thorax*, 2000, 55:39–45.
8. Suarez P et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases*, 2001, 184:473–478.
9. Tanzania Tuberculin Survey Collaboration. Tuberculosis control in the era of the HIV epidemic: risk of tuberculosis infection in Tanzania, 1983–98. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:103–112.

Treatment

20. What were the main landmarks in the development of tuberculosis treatment?

K. Toman[1]

1. The discovery, in 1940, of the bacteriostatic effect of sulfonamides in guinea-pigs infected with tubercle bacilli. For the first time, it was demonstrated that a chemotherapeutic agent – a derivative of dapsone, known as promin (glucosulfone sodium) – was capable of stopping the progress of otherwise fatal tuberculosis in guinea-pigs (*1*). However, the effect of dapsone and other sulfone derivatives on tuberculosis in humans was disappointing, although these compounds were found to be effective in the treatment of leprosy, and dapsone remains a basic antileprosy drug (*2*).

2. In 1944, streptomycin – an antibiotic newly isolated by Waksman from the soil organism *Streptomyces griseus* – showed a striking therapeutic effect on experimental tuberculosis in guinea-pigs. Soon afterwards, it was used for the first time in human patients (*3*, *4*) (see "What is the therapeutic effect and what is the toxicity of antituberculosis drugs?", page 110).

3. In 1949, it was discovered that *p*-aminosalicylic acid (PAS) prevented the emergence of drug resistance if given in combination with streptomycin. Since then, the administration of two or more drugs in combination has been recognized to be essential for adequate tuberculosis treatment.

4. The discovery, in 1952, of the antituberculosis activity of isoniazid – a chemical compound synthesized 40 years earlier. Since its introduction, isoniazid has been an important component of all primary drug regimens because it is highly effective, of relatively low toxicity, and inexpensive.

5. The startling results, in 1956, of trials in Madras (now Chennai) demonstrating that ambulatory, domiciliary treatment was highly effective without increasing the risk of infection for family contacts (see "What were the main findings of the Madras study comparing home and sanatorium treatment?", page 173). These findings prompted a radical departure from the traditional sanatorium treatment and opened new prospects for nationwide treatment programmes in developing countries.

[1] Deceased.

6. The consistent finding that a substantial proportion of patients do not take medications as prescribed, even with extensive health education (*5*, *6*). This finding, together with the risk of emergence and spread of drug-resistant tuberculosis, eventually led to the recognition of direct observation of tuberculosis treatment as the standard of care (*7–9*).

7. The demonstration, in 1964, that intermittent regimens can be as effective as daily regimens, thereby offering the advantage of convenient, directly observed treatment (see "What is intermittent treatment and what is the scientific basis for intermittency?", page 130, and "What are the advantages of direct observation of treatment?", page 183).

8. The discovery in the late 1960s of rifampicin as perhaps the most effective medication for tuberculosis (*10*). Rifampicin is a broad-spectrum antibiotic used predominantly for the treatment of tuberculosis. Use of rifampicin led to the emergence of modern and effective short-course regimens.

9. Monumental work done by the British Medical Research Council and partners around the world led to the development of standard short-course chemotherapeutic regimens (*11*, *12*). The studies established a number of key points that provided the framework for the development of modern treatment. These points include the following:

    - Regimens of 6 and 8 months' duration are extremely effective in achieving a high cure rate with a low relapse rate.
    - Rifampicin-containing regimens allow effective short-course treatment even of patients with smear-positive cavitary disease.
    - For 6- and 8-month regimens, both rifampicin and pyrazinamide are necessary, but pyrazinamide is required only for the initial phase of treatment (*13*).
    - Relapses with short-course treatment generally occur within the first year and relapses that occur following multidrug therapy are usually caused by organisms that retain their original susceptibility.
    - Multiple drugs can be given with minimal toxicity.

10. Studies in the 1980s that evaluated regimens with a treatment duration of less than 6 months demonstrated high relapse rates (11–40%) in patients with sputum smear-positive pulmonary tuberculosis (*14*).

11. Standardized and simplified regimens using fully intermittent, directly observed 6-month treatment (*15*, *16*) have been shown to be effective on a mass basis.

References

1. Barry VC. Development of the chemotherapeutic agent for tuberculosis. In: Barry VC, ed. *Chemotherapy of tuberculosis*. London, Butterworths, 1964.

2. *WHO Expert Committee on Leprosy. Fifth report.* Geneva, World Health Organization, 1977 (WHO Technical Report Series, No. 607).
3. Schatz A, Bugie E, Waksman SA. Streptomycin, a substance exhibiting antibiotic activity against Gram-positive and Gram-negative bacteria. *Proceedings of the Society of Experimental and Biological Medicine*, 1944, 55:66–69.
4. Hinshaw HC, Feldman WH. Streptomycin in the treatment of clinical tuberculosis; a preliminary report. *Proceedings of the Staff Meeting of Mayo Clinic*, 1945, 20:313–318.
5. Fox W. The problem of self-administration of drugs with particular reference to pulmonary tuberculosis. *Tubercle*, 1958, 39:269–274.
6. Fox W. Self-administration of medicaments. A review of published work and a study of the problems. *Bulletin of the International Union Against Tuberculosis*, 1961, 31:307–331.
7. Sbarbaro JA. The patient-physician relationship: compliance revisited. *Annals of Allergy*, 1990, 64:326–332.
8. Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis – we can't afford not to try it. *New England Journal of Medicine*, 1993, 338:576–578.
9. Centers for Disease Control and Prevention. Initial therapy for tuberculosis in the era of multidrug resistance. Recommendations of the Advisory Council for the Elimination of Tuberculosis. *Morbidity and Mortality Weekly Report*, 1993, 42:1–8.
10. Sense P. History of the development of rifampicin. *Respiratory and Infectious Disease*, 1983, 5:402–406.
11. East African/British Medical Research Council. Controlled clinical treatment of short-course (6 months) regime of chemotherapy for treatment of pulmonary tuberculosis. Third report. *Lancet*, 1974, 2:237–248.
12. Fox W, Ellard GA, Mitchison DA. Studies on the treatment of tuberculosis undertaken by the British Medical Research Council tuberculosis units, 1946–1986, with relevant subsequent publications. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S231–S279.
13. Hong Kong Chest Service/British Medical Research Council. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide: results at 30 months. *American Review of Respiratory Disease*, 1991, 143:700–706.
14. East African and British Medical Research Councils. Controlled trials of 5 short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. First report of 4th study. *Lancet*, 1978, 2:334–338.
15. China Tuberculosis Control Collaboration. Results of directly observed short-course chemotherapy in 112 842 Chinese patients with smear-positive tuberculosis. *Lancet*, 1996, 347:358–362.
16. Khatri GR, Frieden TR. The status and prospects of tuberculosis control in India. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:193–200.

21. How does tuberculosis treatment work?

K. Toman[1]

Before the discovery of antituberculosis drugs, tuberculosis treatment consisted of attempts to strengthen the patient's resistance to the disease. This included altering local and general host factors through traditional measures such as the avoidance of physical and mental strain, prolonged bedrest, a rich diet, artificial pneumothorax, and thoracoplasty.

Nowadays, host factors (see "What is the role of host factors in the pathogenesis, prevention, and treatment of tuberculosis?", page 106) are considered to be less relevant for cure, and the action of drugs on the tubercle bacillus has assumed overwhelming importance. In other words, treatment is strictly antimicrobial.

The goal of tuberculosis treatment is to ensure relapse-free cure while preventing the emergence of drug resistance. The effect of treatment should therefore be judged not by the anatomical healing of lesions but by their sterilization, or at least by the elimination of bacilli from the sputum. *Mycobacterium tuberculosis* is a slow-growing aerobic organism that can remain dormant for a prolonged period. Consequently, prolonged treatment with multiple drugs is required to ensure relapse-free cure and to prevent the emergence of resistance. The effect of treatment is determined mainly by bacteriological, environmental (anatomical and biochemical), and pharmacological factors.

Bacteriological factors

The numerical factor

The number of tubercle bacilli varies widely with the type of lesion. According to data on lung specimens resected from untreated patients (*1*), the number of bacilli in a medium-sized cavity communicating with the bronchi is about 10^8 (100 million), whereas, in an encapsulated nodular lesion of the same size with no bronchial communication, the number can be as low as 10^2 (100). (The numbers are also rather low in extrapulmonary lesions of the skin, lymph glands, meninges, and bones.) The larger the bacterial population, the higher is the probability that resistant mutant strains are

[1] Deceased.

present even before treatment is started (see "How does drug resistance develop?", page 193, and "How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?", page 203). This fact must be borne in mind when choosing the regimen.

The metabolic factor

Drugs kill organisms that metabolize actively and multiply continuously, but in each bacterial population there are bacilli with a very low metabolic rate. Some are inhibited owing to a low pH; others are dormant most of the time and grow – if at all – only during short periods. These organisms remain unaffected by most drugs; only rifampicin or pyrazinamide may attack them effectively under certain conditions. They survive even in the presence of such potent drugs as isoniazid and streptomycin and despite their susceptibility to these drugs. These organisms are also called "persisters". This phenomenon explains to some extent why not all bacilli are killed during treatment, and why drug-susceptible bacilli are coughed up for some time thereafter. Relapse with drug-susceptible organisms after the end of treatment or endogenous reactivation may be due to bacilli that have persisted for a long time in a dormant state in residual lesions.

Environmental factors

The anatomical factor

The type of tissue harbouring tubercle bacilli may affect drug action because not all drugs are able to penetrate into all tissues and cells or permeate biological membranes, including the normal blood–brain barrier. Isoniazid, rifampicin, and pyrazinamide readily cross biological membranes, whereas streptomycin fails to enter many cells and is much less effective against intracellular than extracellular bacilli (*2*, *3*). In humans, bacilli – particularly those in cavitary lesions – are mostly extracellular (*4*).

Biochemical factors

Environmental pH and partial oxygen pressure (pO_2) are important biochemical factors that influence the antimicrobial effect of a drug. At a neutral pH, as in cavity walls, all the bactericidal antituberculosis drugs are highly effective; streptomycin, however, is at its most active in a slightly alkaline (extracellular) environment, whereas pyrazinamide acts largely in an acidic medium such as that found inside cells. Little is known about the factors causing dormancy in bacilli, but it is suggested that dormant organisms survive within cells or in necrotic areas of old encapsulated lesions that do not communicate with a bronchus. There the pH is usually on the acidic side and the pO_2 is decreased. That the pO_2 is an important factor is shown by the small numbers of bacilli found in closed extrapulmonary lesions.

Pharmacological factors

Dosage

Drugs must be given in doses large enough to produce an inhibitory concentration at the sites where bacilli are found, but it is not necessary to keep this concentration at a constant level. In fact, studies on the role of dosage and serum levels of isoniazid (*4*) showed that it was the peak level that was important for the response to the drug. Thus, 400 mg of isoniazid given once daily was therapeutically superior to the same dose divided into two parts and administered at 12-hour intervals (*4*).

Combinations of drugs

Regimens should contain a combination of three or more drugs, particularly in the initial phase of treatment (see "What is the purpose of the initial intensive phase of two-phase treatment?", page 122). In patients whose lesions contain large numbers of bacilli, the regimen should include at least two drugs to which the bacilli are susceptible, otherwise treatment failure due to the emergence of drug resistance is the likely consequence (see "How does drug resistance develop?", page 193, and "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185). In the early days of treatment, patients were given one drug; if that failed, further drugs were successively substituted or added, one at a time, with the result that these people eventually became chronic patients with organisms resistant to all the drugs they had received. Thus, treatment of tuberculosis disease should never be attempted with a single drug, nor should a single drug be added to a failing regimen.

The "lag period" factor

In vitro experiments have shown that, when tubercle bacilli are exposed to a drug for a short time (6–24 hours) and, after careful removal of the drug, are transferred to a drug-free medium, the surviving bacilli start to grow again after an interval of several days. This interval is called the "lag period", and varies with the type and concentration of the drug and with the length of exposure. (Regarding the lag period after pulsed exposure to various drugs, see "What is intermittent treatment and what is the scientific basis for intermittency?", page 130). All tuberculosis drugs have been tested for their ability to produce a lag period, in order to determine whether they are suitable for intermittent regimens. However, certain drugs are incapable of inducing this phenomenon, and the bacilli start to grow again immediately after removal of the drug. Such drugs seem to have only a bacteriostatic effect and are not suitable for intermittent use.

References

1. Canetti G. *The tubercle bacillus in pulmonary lesion of man; histobacteriology and its bearing on the therapy of pulmonary tuberculosis.* New York, Springer, 1955.

2. Furesz S et al. Rifampicin: a new rifamycin. 3. Absorption, distribution, and elimination in man. *Arzneimittelforschung*, 1967, 17:534–537.
3. Mitchison DA. Bacteriological mechanisms in recent controlled chemotherapy studies. *Bulletin of the International Union Against Tuberculosis*, 1970, 43:322–331.
4. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1960, 23:535–585.

22. What is the role of host factors in the pathogenesis, prevention, and treatment of tuberculosis?

M. Iademarco[1] *& M. Reichler*[2]

There is a constant, lifelong interplay between the environment, health status, and genetics. For tuberculosis, important host factors in this dynamic process include age, nutritional status, emotional and physical stress, concurrent disease, social circumstances, access to health care, and possibly host genotype (including sex).

In the pre-chemotherapy era, treatment of tuberculosis was necessarily directed toward strengthening the host's resistance (*1*, *2*). Special diets and rest were believed to improve the patient's immune response. By imposing strict bed-rest and using collapse techniques such as artificial pneumothorax, pneumoperitoneum, thoracoplasty, and plombage, clinicians attempted to restrict disease progression and promote healing. With the advent of chemotherapy, these methods have mostly become forgotten history. In addition, many scientific advances have extended our understanding of the biological principles governing the human immune response to tuberculosis.

An individual's health status may be the most important single determinant of risk of progression to tuberculosis disease. Table 25 shows the incidence of disease in persons with a positive tuberculin test followed prospectively. Table 26 shows the relative risk of developing disease among persons with selected clinical conditions. Adult males are at an increased risk of developing tuberculosis, which may reflect a combination of biological and social causes (*3*). Stress and nutrition may also be important influences on the clinical course of the disease (*4*, *5*).

Physical and chemical properties of the upper and lower respiratory tree form the first line of defence against inhaled mycobacteria. If these fail and the mycobacteria reach the alveoli, macrophages are the next line of defence. If the macrophages fail to kill the mycobacteria, the bacilli multiply intracellularly. The ensuing infection may result in dissemination of viable organisms via the bloodstream, which results in the recruitment of lymphocytes, repeated antigen presentation, the elaboration of lymphokines, and subsequent tubercle formation. Although an antibody response is seen

[1] Associate Director for Science, Division of Tuberculosis Elimination, National Center for HIV, TB and STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.
[2] Medical Officer, Division of Tuberculosis Elimination, National Center for HIV, TB and STD Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Table 25
Incidence of tuberculosis disease in persons with a positive tuberculin test, by selected risk factors[a]

Risk factor	Tuberculosis cases/1000 person-years
Recent tuberculosis infection	
infection <1 year past	12.9
infection 1–7 years past	1.6
Tuberculosis infection >2 years past	0.7
HIV infection	35.0–162
Injection drug use	
HIV-seropositive	76.0
HIV-seronegative or unknown	10.0
Silicosis	68
Radiographic findings consistent with old tuberculosis	2.0–13.6
Weight deviation from standard	
underweight by 15% or more	2.6
underweight by 10–14%	2.0
underweight by 5–9%	2.2
within 5% of standard	1.1
overweight by 5% or more	0.7

[a] Source: reference *8*, reprinted with permission.

Table 26
Relative risk[a] ***of developing active tuberculosis, by selected clinical conditions***[b]

Medical condition	Relative risk
Solid organ transplantation:	
renal	37
Silicosis	30
Jejunoileal bypass	27–63
Solid organ transplantation:	
cardiac	20–74
Carcinoma of head or neck	16
Chronic renal failure/haemodialysis	10.0–25.3
Gastrectomy	2–5
Diabetes mellitus	2.0–4.1

[a] Relative to control population; independent of known exposure to tuberculosis and tuberculin test status.
[b] Source: reference *8*, reprinted with permission.

in tuberculosis (*6*), the T-lymphocyte-mediated response is probably the most important immunological determinant of the patient's ability to resist progression from tuberculosis infection to disease (*7*).

Two acquired immune processes act to contain tuberculosis infection. In the first, macrophages that have been activated by lymphokines kill intracellular organisms. In the second, cytolytic T-cells destroy macrophages infected with *Mycobacterium tuberculosis*. This latter mechanism is a delayed-type hypersensitivity reaction and is also responsible for the host response to the intradermal injection of a purified protein derivative of *M. tuberculosis* in an infected person. The balance between organism growth and host response over time dictates whether the infection progresses to clinical illness (*9*).

HIV infection has demonstrated the critical role played by host defences in preventing progression from tuberculosis infection to tuberculosis disease. The susceptibility of HIV-infected patients to tuberculosis and the clinical presentation of the disease closely follows their immune status. Early in the course of HIV infection, patients tend to have cavity formation and positive sputum smears, related in large part to the effort of their own immune systems to contain the infection, which results in destruction of lung parenchyma and pooling of large numbers of bacilli in the cavities thus created. As HIV infection progresses and CD4 cells are depleted, the host immune response becomes less effective, cavity formation and hence sputum smear positivity are less common, and disseminated forms of tuberculosis are more common. HIV infection increases both the risk and the pace of progression from tuberculosis infection to disease; among hospitalized AIDS patients, the median incubation time from exposure to smear-positive tuberculosis and development of tuberculosis disease was found to be 12 weeks (*10*).

Epidemiological evidence suggests that there may be a genetic component to the host immune response to tuberculosis. A 1978 study among monozygotic and dizygotic twins provided the first strong evidence that susceptibility to tuberculosis may be inherited (*11*). A number of candidate susceptibility genes have been recently identified. These include the genes coding for natural-resistance-associated protein-1, interferon-gamma receptor, vitamin D receptor, and human leukocyte antigen (HLA) DQB1 (*11–16*). HLA genotype has also been associated with an increased risk of progression to severe tuberculosis disease and with failure to respond to antituberculosis treatment (*14*).

These observations regarding the host immune response provide the foundation for renewed efforts to develop innovative approaches to tuberculosis diagnosis, treatment, and eventually, vaccination.

References

1. Fox W. The John Barnwell Lecture. Changing concepts in the chemotherapy of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1968, 97:767–790.
2. Tyrrell WF. Bed rest in the treatment of pulmonary tuberculosis. *Lancet*, 1956, 1:821–823.

3. Holmes CB, Hausler H, Nunn P. A review of sex differences in the epidemiology of tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:96–104.
4. Cegielski JP, Kohlmeier L, Cornoni-Huntley J. Malnutrition and tuberculosis in a nationally representative cohort of adults in the United States, 1971–1987. *American Journal of Tropical Medicine and Hygiene*, 1995, 53:152–157.
5. Scrimshaw NS, Taylor CE, Gordon J. *Interactions of nutrition and infection*. Geneva, World Health Organization, 1968:60–144 (WHO Monograph Series, no. 57).
6. Hussain R et al. Selective increases in antibody isotypes and immunoglobulin G subclass responses to secreted antigens in tuberculosis patients and healthy household contacts of the patients. *Clinical and Diagnostic Laboratory Immunology*, 1995, 2:726–732.
7. Ellner JJ. Review: the immune response in human tuberculosis – implications for tuberculosis control. *Journal of Infectious Disease*, 1997, 176:1351–1359.
8. American Thoracic Society and Centers for Disease Control and Prevention. Targeted tuberculin testing and treatment of latent tuberculosis infection. *American Journal of Respiratory and Critical Care Medicine*, 2000, 161:S221–S247.
9. Orme IM. Induction of nonspecific acquired resistance and delayed-type hypersensitivity, but not specific acquired resistance in mice inoculated with killed mycobacterial vaccines. *Infection and Immunity*, 1988, 56:3310–3312.
10. Centers for Disease Control and Prevention. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons – Florida and New York, 1988–1991. *Morbidity and Mortality Weekly Report*, 1991, 40:585–591.
11. Comstock GW. Tuberculosis in twins: a re-analysis of the Prophit survey. *American Review of Respiratory Disease*, 1978, 117:621–624.
12. Bellamy R et al. Variations in the *NRAMP*1 gene and susceptibility to tuberculosis in West Africans. *New England Journal of Medicine*, 1998, 338:640–644.
13. Bellamy R et al. Tuberculosis and chronic hepatitis B virus infection in Africans and variation in the vitamin D receptor gene. *Journal of Infectious Diseases*, 1999, 179:721–724.
14. Brahmajothi V et al. Association of pulmonary tuberculosis and HLA in South India. *Tubercle*, 1991, 72:123–132.
15. Goldfeld AE et al. Association of an HLA-DQ allele with clinical tuberculosis. *Journal of the American Medical Association*, 1998, 279:226–228.
16. Newport MJ et al. A mutation in the interferon-γ-receptor gene and susceptibility to mycobacterial infection. *New England Journal of Medicine*, 1996, 335:1941–1949.

23. What is the therapeutic effect and what is the toxicity of antituberculosis drugs?[1]

T. Frieden[2] *& M. Espinal*[3]

It is difficult to determine and measure the efficacy or toxicity of a particular drug, since antituberculosis drugs are almost invariably administered in combination regimens of several drugs. However, if two or more drugs are taken simultaneously, synergistic as well as antagonistic interactions may occur between the drugs and the host, generally making it impossible to say what is due to what. Although valuable knowledge has been gained from experimental work, there is still no suitable in vitro or animal model from which information can be unequivocally applied to humans.

Isoniazid

Isoniazid is the hydrazide of isonicotinic acid – a chemical compound first synthesized in Prague in 1912. However, its effectiveness in treating tuberculosis was demonstrated only in 1952. Since then, it has ranked among the most powerful antituberculosis agents. Isoniazid is effective only against the tubercle bacillus, not against other bacteria. It penetrates rapidly into all tissues and lesions, and its activity is not influenced by the pH of the environment. Because of its potency, infrequent toxicity, small bulk, and low cost, isoniazid is widely used in the treatment of tuberculosis. It is also used in preventive treatment to reduce the risk of progression from tuberculosis infection to disease (see "What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?", page 220).

Isoniazid is administered orally, the dosage for daily regimens being 5 (range 4–6) mg/kg, i.e. usually 300 mg. In thrice-weekly regimens the dosage is 10 (8–12) mg/kg, i.e. about 450–600 mg given in a single dose for patients weighing 40–60 kg, and in twice weekly regimens the dose is 15 (13–17) mg/kg. The drug should not be given in divided doses: it has been shown that a high peak concentration in the serum is more important than a continuously inhibitory level (*1*).

---

[1] Based on the chapter in the previous edition by K Toman.

[2] Medical Officer, Stop TB Unit, World Health Organization Regional Office for South-East Asia, New Delhi, India.

[3] Medical Officer, Communicable Diseases, Stop TB, World Health Organization, Geneva, Switzerland.

The time during which an adequate isoniazid level is maintained in the tissues and body fluids depends also on the rate of inactivation of the drug. It is metabolized mainly by acetylation, at a rate that varies from one individual to another but is consistent in the same individual. The rate of inactivation is determined mainly by genetic factors, and patients can generally be divided into two groups: slow and rapid inactivators (acetylators) of isoniazid.

Adverse reactions

The most common toxic manifestation of isoniazid treatment is peripheral neuropathy. Tuberculosis patients infected with HIV are at higher risk of peripheral neuropathy. The earliest symptom is paraesthesia, followed by pricking pain and burning sensation in the feet and later in the hands. If untreated, the symptoms worsen and cause distress to the patient. The frequency of neuropathy increases with the dose. The condition is more common in slow inactivators, patients with diabetes or uraemia, malnourished patients, and daily users of alcohol.

Isoniazid neurotoxicity can be prevented by pyridoxine (vitamin B_6) in rather small doses (10 mg/day). Pyridoxine also has a therapeutic effect on isoniazid-induced neurotoxicity, but high doses – though effective – may reduce the bactericidal activity of isoniazid (*2*). Some patients complain of light-headedness, lethargy, and fatigue, particularly with the higher intermittent doses. These effects generally subside with time and reassurance.

Isoniazid can also give rise to hepatotoxicity, most frequently in adults above 35 years of age, particularly when other potentially hepatotoxic agents are administered. Isoniazid-induced hepatotoxicity is reversible if the drug is stopped early. However, it can be fatal (*3*, *4*). Infrequently, toxic psychosis and generalized epileptic convulsions may occur in both slow and rapid inactivators.

Isoniazid increases the serum concentrations of phenytoin and carbamazepine. Its absorption is impaired by antacids containing aluminium hydroxide.

Rifampicin

Rifampicin, a semisynthetic antibiotic first synthesized in 1965, is highly active against tubercle bacilli. In vitro and in vivo studies have demonstrated the exceptional bactericidal effect of rifampicin and its suitability for intermittent use (*5–7*). Since nontoxic oral doses produce a serum concentration about 100 times as high as levels that inhibit growth of *Mycobacterium tuberculosis*, rifampicin raised hopes from the outset that it would reduce the duration of treatment (*8*). In wild strains of the bacillus, the proportion of rifampicin-resistant mutants ($1:10^8$) was found to be substantially lower than that of isoniazid-resistant mutants ($1:10^6$).

Rifampicin is a key component of modern tuberculosis treatment and is the single most important drug in short-course treatment. It is given orally and the usual dose is 10 (range 8–12) mg/kg (maximum 600 mg), three or two times weekly. It

should preferably be given at least 30 minutes before the patient eats, since absorption is reduced when the drug is taken with food.

Adverse reactions

Rifampicin is well tolerated by most patients at the currently recommended dosages. Unlike other drugs, rifampicin produces some adverse reactions more frequently with intermittent than with daily regimens. Moreover, the risk of adverse effects increases with the interval between doses: thus toxicity is high if treatment is taken only once a week.

With currently recommended regimens, reactions are uncommon and generally minor. Rarely, serious hepatotoxicity, generally with a cholestatic pattern, may occur. Rifampicin causes orange-red discoloration of body secretions such as urine, faeces, tears, and sweat, and may result in permanent discoloration of soft contact lenses.

Reactions most frequently observed with intermittent regimens are as follows:

- A cutaneous syndrome consisting of flushing and/or pruritus, with or without rash, involving particularly the face and scalp, often with redness and watering of the eyes.
- An abdominal syndrome consisting of pain and nausea, sometimes accompanied by vomiting or, less commonly, diarrhoea.
- A "flu" syndrome consisting of attacks of fever, chills, malaise, headache, and bone pains.
- A respiratory syndrome (uncommon) characterized by shortness of breath, rarely associated with collapse and shock.
- Purpura and other rare reactions, such as acute haemolytic anaemia, shock, and renal damage with or without impaired kidney function or failure.
- Elevated serum levels of transaminase (quite common but transient, even when treatment is continued), and hepatotoxicity.

The first four of these syndromes typically begin 2–3 hours after the single, morning dose of rifampicin. Many patients exhibit more than one syndrome simultaneously. Cutaneous syndromes usually start during the first month, and gastrointestinal symptoms are spread over the first 6 months. The "flu" syndrome, observed only with intermittent regimens, generally begins in the third to fifth month of treatment (*5*).

Management of adverse reactions to rifampicin (*9–11*)

About half of the patients who experience adverse reactions require no major modification of their regimens. The cutaneous syndrome is often self-limiting and requires symptomatic treatment only. It is rarely necessary to change the regimen, unless other adverse effects, such as generalized hypersensitivity reactions, occur simultaneously. The abdominal syndrome requires only symptomatic treatment provided that it occurs alone. If the patient has been taking the drug on an empty stomach – as is recommended – reactions can usually be stopped by giving the drug during a small meal.

The "flu" syndrome, which is usually mild, requires no change of treatment; it is probably of an immunological nature. If it persists, a change to daily administration may be necessary.

Caution is required in patients with the respiratory syndrome, because shock may develop, with a sudden fall in the systolic blood pressure and anuria. Such cases require immediate hospital care. If shock is followed by renal failure (rare), rifampicin must be stopped and never given again. This also applies if haemolytic anaemia develops.

In summary, adverse reactions to rifampicin – when not self-limiting – can usually be controlled by reducing either the dosage or the interval between doses, e.g. from three times weekly to daily. These measures generally stop the episodes or render them so minor or infrequent that they are no longer of concern (see "What are the most common adverse drug events to first-line antituberculosis drugs, and what is the procedure for reintroduction of drugs?", page 152).

If purpura occurs, rifampicin is stopped and not given again, even in a small test dose. The platelet count then returns to normal within a few days.

Asymptomatic rises in serum transaminase levels are common in patients receiving rifampicin and generally resolve spontaneously. Rarely, patients develop overt hepatitis. When a patient develops treatment-induced hepatotoxicity, all potentially hepatotoxic drugs should be stopped until clinical and biochemical hepatitis resolves. Non-hepatotoxic drugs, including streptomycin, ethambutol, and fluoroquinolones (except ciprofloxacin, which is excreted by the liver) can be used if necessary. After hepatitis resolves, the antituberculosis drugs can be reintroduced in a phased manner.

Rifampicin accelerates the hepatic cytochrome p450 pathway and reduces the serum levels of many drugs, including antifungal agents, corticosteroids, warfarin, and oral hypoglycaemic agents. Rifampicin also reduces the levels of protease inhibitors and non-nucleoside reverse transcriptase inhibitors used to treat HIV (*12*). This interaction may lead to rapid development of resistance in HIV strains to the protease inhibitors. Rifampicin reduces the effectiveness of oral contraceptives (*13*) and patients should be advised to use non-hormonal contraception during, and for one month after, treatment with rifampicin-containing regimens.

Newer rifamycin derivatives related to rifampicin have been developed. Rifabutin has similar activity against *Mycobacterium tuberculosis*, but it has a longer half-life than rifampicin and less effect on the pharmacokinetics of some antiretroviral drugs (*14*).

Rifapentene is a rifamycin derivative with a long half-life and has similar activity against *M. tuberculosis* (*15*). Studies are under way to evaluate its effectiveness. Mycobacterial strains that are resistant to rifampicin are usually, but not always, resistant to rifabutin and rifapentene.

Pyrazinamide

Pyrazinamide has been shown to have a sterilizing effect inside macrophages where organisms grow slowly because of the acid pH of the environment. Thus, pyrazi-

namide is able to kill tubercle bacilli that cannot otherwise be attacked effectively by other currently available drugs.

Because it reduces the required duration of treatment, pyrazinamide is an integral component of short-course treatment. It is given orally, and the usual daily dose is 25 (range 20–30) mg/kg. In intermittent regimens, the dosage is 35 (30–40) mg/kg three times a week or 50 (40–60) mg/kg twice weekly.

Adverse reactions

At currently recommended doses, pyrazinamide rarely causes serious toxicity, but hepatotoxicity can occur at high dosages. Joint pain is a common adverse effect, occurring more commonly with daily than with intermittent pyrazinamide-containing regimens. Arthralgia can be successfully managed with acetylsalicylic acid or other analgesic, anti-inflammatory agents, and does not require withdrawal of the drug. Classic gout is rarely seen; if it develops it can be treated with colchicine. Serum concentrations of uric acid are often elevated in patients receiving pyrazinamide; asymptomatic increase in serum uric acid does not require any treatment.

Severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide are used (*16*).

Hypersensitivity, including fever, rash, and other cutaneous reactions, may occasionally occur.

Ethambutol

Ethambutol is a synthetic compound unrelated to other antituberculosis drugs. It is effective against *M. tuberculosis* and some other mycobacteria, e.g. *M. kansasii*, but it is ineffective against other bacteria or fungi. Ethambutol is mainly bacteriostatic.

Ethambutol is given orally and the usual dose is 15 (range 15–20) mg/kg daily, 30 (25–35) mg/kg three times weekly, and 45 (40–50) mg/kg twice weekly.

Adverse reactions

Ethambutol may produce retrobulbar neuritis, characterized by impairment of vision, with a reduction in visual acuity, red–green blindness, blurring, central scotomas, and peripheral field defects. Ocular toxicity seems to be dose-dependent and occurs only rarely if no more than 15 mg/kg is given daily (*17*, *18*). Patients receiving ethambutol should be warned that an ocular examination should be undertaken if visual symptoms occur. Vision usually returns to normal within a few weeks if the drug is stopped, but the optic nerve may be permanently damaged if ethambutol is continued. Ethambutol should generally not be given to young children who cannot reliably report or be tested for impaired visual acuity.

Because it degrades rapidly in tropical climates, ethambutol must be manufactured and stored in such a way as to prevent absorption of moisture.

Streptomycin

Isolated by Waksman from a soil organism in 1943, streptomycin is now used in the form of streptomycin sulfate and is dispensed as a dry powder in vials. It is administered by intramuscular injection. The usual dose is 0.75–1 g (12–18 mg/kg), daily, two or three times a week, given in a single injection. In older patients and patients weighing less than 35 kg, a dose of 0.5 g is equally effective and less toxic.

The serum concentration of streptomycin reaches maximum 1 hour after administration, and remains above inhibitory levels for many hours.

Streptomycin does not penetrate cell walls or normal biological membranes, such as the meninges or the pleura, unless inflammatory changes have taken place (see also "How does tuberculosis treatment work?", page 102). The drug is excreted almost entirely via the kidneys and, in patients with impaired renal function, may therefore accumulate and cause increased toxicity.

Adverse reactions

Apart from hypersensitivity reactions such as fever and rash (see also "What are the most common adverse drug events to first-line antituberculosis drugs, and what is the procedure for reintroduction of drugs?", page 152), the main toxic effect of streptomycin is vestibular damage and potential ototoxicity. The risk increases with dose and age (over 40 years). Toxicity is manifested as vertigo and ataxia, tinnitus, and loss of hearing. The simplest way of demonstrating ataxia is to ask the patient to walk along a straight line with closed eyes. If the patient walks more unsteadily than with open eyes, ataxia is present. If a patient complains of dizziness and the drug is stopped or the dosage reduced, the dizziness may disappear. If treatment continues, vestibular damage and hearing loss may worsen and may become permanent; this risk is particularly high in patients with impaired renal function. Renal damage may also occur, particularly in patients with pre-existing renal disease, although it is often fully reversible if streptomycin is discontinued promptly.

Transient and minor adverse effects, such as circumoral numbness and tingling, may occur soon after injection.

Streptomycin is contraindicated in pregnant women because of the risk of impairing development of the eighth cranial nerve of the fetus. Streptomycin also potentiates neuromuscular blocking agents used during anaesthesia and should be avoided in patients with myasthenia gravis.

As with all injecting procedures, sterile needles should be used and subsequently disposed of safely.

Thioacetazone

The efficacy and toxicity of thioacetazone are discussed in detail elsewhere (see "What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?", page 159). Thioacetazone is

given orally at the usual dose of 2.5 mg/kg daily; it is not effective when given intermittently. Thioacetazone administered as a single dose of 150 mg has about the same toxicity as PAS. Its adverse effects include rash, jaundice, and reversible bone-marrow suppression. Cutaneous reactions appear to be more serious than with other drugs, and exfoliative dermatitis or Stevens–Johnson syndrome may occur if the drug is not stopped. Most of the serious adverse reactions have been observed within the first 4–6 weeks of treatment.

Thioacetazone was investigated in a large, controlled, double-blind, toxicity trial (see "What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?", page 159). It was poorly tolerated by the Chinese population of Singapore and Hong Kong Special Administrative Region of China, but was well tolerated in East African countries.

In HIV-positive individuals, the risk of major, potentially fatal cutaneous reactions caused by thioacetazone is unacceptably high (*19*). Thioacetazone should therefore never be used in patients who may be HIV-positive or in areas where HIV infection is common.

Reserve drugs (*20*)

Reserve drugs include aminoglycosides (kanamycin, amikacin), polypeptides (capreomycin), thioamides (ethionamide and protionamide), fluoroquinolones (e.g. ofloxacin and ciprofloxacin), cycloserine, and PAS (*20*). They can be classified as follows (*21*, *22*):

— drugs with bactericidal activity: aminoglycosides, capreomycin, and thioamides
— drugs with low bactericidal activity: fluoroquinolones
— drugs with bacteriostatic effect: cycloserine and PAS.

Kanamycin and amikacin

Kanamycin and amikacin are bactericidal agents of the aminoglycoside class; their efficacy and adverse reactions are similar to those of streptomycin. The usual dose is 0.75–1 g (12–18 mg/kg) in a single injection.

Adverse reactions

Intramuscular administration of these drugs is much more painful than streptomycin or capreomycin. Local measures (warm soaks, massage) provide some relief. Cross-resistance between kanamycin and amikacin appears to be complete. Vertigo, ototoxicity, and deafness may occur. Nephrotoxicity may also occur but is reversible. In patients with impaired renal function, the daily dose should be reduced and/or the intervals between doses increased to avoid accumulation of these drugs. In addition, the renal function of such patients should be monitored regularly during use of the drugs. Amikacin and kanamycin should not be used in pregnant women except as a last resort.

Capreomycin

Capreomycin is a bactericidal agent of the polypeptide class and is obtained from *Streptomyces capreolus*. Its bactericidal effect is valuable in patients with bacilli resistant to streptomycin, kanamycin, and amikacin: there is no cross-resistance with the aminoglycosides. The usual dose is 0.75–1 g (12–18 mg/kg) in a single injection.

Adverse reactions

Adverse effects are similar to those of streptomycin, namely mainly tinnitus and vertigo, but possibly with a lesser risk of deafness. Kidney damage may occur. Hypokalaemia, hypocalcaemia, and hypomagnesaemia have also been reported. Eosinophilia and rash are not uncommon and generalized cutaneous reactions and hepatitis may occur rarely. There may be pain and swelling at injection sites if the drug is not given by deep intramuscular injection. Capreomycin should if possible be avoided in patients with impaired hearing or renal function. Serum urea and electrolytes should be monitored during treatment. This drug should also not be used in pregnant women except as a last resort.

Ethionamide (or protionamide)

Ethionamide and protionamide are bactericidal agents from the thioamide class. Although ethionamide is chemically related to isoniazid and pyrazinamide (all are derivatives of isonicotinic acid), there is little cross-resistance among these drugs. The chemical structure of ethionamide resembles that of thioacetazone, with which there is frequent and partial cross-resistance (bacilli resistant to thioacetazone are often susceptible to thioamides, but the reverse is seldom the case). Before the rifampicin era, ethionamide (or protionamide) was a basic component of the re-treatment regimen for tuberculosis patients with bacilli resistant to isoniazid and streptomycin. The maximum optimum daily dosage of ethionamide is 15–20 mg/kg, i.e. 0.5–1 g daily depending upon body weight and patient tolerance. For patients who are receiving directly observed treatment and are unable to tolerate a single dose, a daily dose of 750 mg can be administered as 500 mg under direct observation and 250 mg self-administered later in the day.

Adverse reactions

Ethionamide is one of the most unpleasant of all antituberculosis drugs for patients to take. The principal adverse effects are gastrointestinal – anorexia, salivation, nausea, metallic taste, abdominal pain, and diarrhoea. The drug can cause hypothyroidism, especially when given in combination with PAS, as well as hypoglycaemia in diabetic patients which, although rare, can be dangerous. Some adverse effects result from the action of the drug on the central nervous system, and are difficult to control. Hepatitis has also been reported. Patients with diabetes, liver disease, alcoholism, or psychiatric illness should be very carefully monitored if given this drug. An important factor

that can influence tolerance of ethionamide is patients' determination not to give up treatment, but that requires strong support and persuasion by clinical and nursing staff, as well as sound organization. Effective organization is essential in order to provide convenient therapeutic and social services to patients under re-treatment, many of whom may have serious social problems. Ethionamide may be teratogenic and should not be used in pregnancy.

Other rare adverse effects include gynaecomastia, menstrual disturbance, impotence, acne, headache, and peripheral neuropathy.

Fluoroquinolones

Both ofloxacin and ciprofloxacin have a bactericidal effect in vitro against *M. tuberculosis*; newer fluoroquinolones may be more active. Although these drugs have not been studied extensively in controlled clinical trials, evidence suggests that ofloxacin and ciprofloxacin have roughly the same therapeutic efficacy. There is no cross-resistance with other antituberculosis agents, but there is complete cross-resistance between ofloxacin and ciprofloxacin (and between the other fluoroquinolones such as levofloxacin, which is the L-isomer – active moiety – of ofloxacin). The usual daily dose of ofloxacin is 7.5–15 mg/kg (maximum 800 mg); ciprofloxacin has been used at a daily dose of 1000–1500 mg. Levofloxacin is more active and less toxic, but is currently more expensive. Fluoroquinolones, when used together with other antituberculosis drugs, are moderately effective for the treatment of multidrug-resistant tuberculosis (*23*, *24*). They are also useful if standard tuberculosis drugs are not tolerated, as in patients with severe liver disease.

Adverse reactions

Adverse reactions are uncommon but consist of gastrointestinal disturbance (anorexia, nausea, vomiting) or central nervous system symptoms (such as dizziness, headache, mood changes, and rarely, convulsions). A caffeine-like effect is not uncommon. Very rarely, spontaneous rupture of the Achilles tendon may occur. These drugs should not be used in pregnant women or growing children because they may impair growth and cause damage to growing cartilage. Because of drug interaction, patients taking fluoroquinolones should avoid antacids, iron, zinc, sucralfate, and didanosine (DDI).

Cycloserine (or terizidone)

Cycloserine, a structural analogue of the amino acid D-alanine, has a relatively weak antituberculosis effect. Terizidone is a combination of two molecules of cycloserine. Cycloserine is used only in reserve regimens. It is given orally in doses of 0.5–1 g daily, divided into two or three doses, although a dose of 1 g per day is rarely tolerated. Cross-resistance to any of the other antituberculosis drugs has not been reported; however, drug susceptibility testing of cycloserine may be unreliable. Cycloserine was

valuable in preventing resistance to ethionamide in the re-treatment regimens (ethionamide, cycloserine, and pyrazinamide or kanamycin) that were used before the rifampicin era. Nowadays, its value lies primarily in preventing resistance to other reserve drugs.

Adverse reactions

The main toxic effects concern the central nervous system. Cycloserine may cause headaches, confusion, depression, seizures, and changes of behaviour, and may sometimes even provoke suicide. Very rarely there may be a generalized hypersensitivity reaction or hepatitis. Monitoring for central nervous system reactions is therefore essential when cycloserine is prescribed. To prevent minor adverse reactions such as insomnia, administration of small doses of a tranquillizer is sometimes recommended, and pyridoxine may reduce central nervous system effects. Health care workers in charge of treatment of inpatients, as well as the families of outpatients, should be warned to report immediately any undue depression or personality change. Cycloserine (and terizidone) should be avoided in patients with a history of epilepsy, mental illness, or alcoholism, and should be used very cautiously in patients with renal failure. Cycloserine and terizidone must be stored carefully.

p-Aminosalicylic acid

p-Aminosalicylic acid (PAS) was designed by Lehmann and first used in 1944. The usual dose for adults is 10–12 g orally per day in two or three doses; lower doses, e.g. 6–8 g, may be effective (*25*). As PAS is rapidly excreted, it must be administered in high doses, several times a day, in order to maintain the required high blood levels. It is bacteriostatic and prevents the emergence of isoniazid-resistant organisms when used in combination with isoniazid. This drug is now being used in reserve regimens to treat multidrug-resistant tuberculosis.

PAS is supplied in the form of tablets, powder, or granules, but some preparations do not keep well in tropical conditions. Other disadvantages are the large size of the sachets, the large number of tablets to be taken, and the unpleasant taste. Potassium salts and enteric-coated preparations may be better tolerated, although they are currently more expensive.

Adverse reactions

Apart from hypersensitivity reactions, such as fever, rash, and pruritus, the main adverse effects of PAS are gastrointestinal. Anorexia, nausea, vomiting, and abdominal discomfort are more common than diarrhoea. The side-effects may be lessened by administering the drug after food or with milk. The reported frequency varies with the country and the observer. However, patients can often be persuaded to put up with adverse effects, and in only 1–2% of cases is it necessary to stop the drug.

Gastrointestinal disturbances can be reduced by taking PAS with or immediately after food. Hepatitis and jaundice are rare complications, in which case the drug must be stopped. Hypothyroidism may occur with long-term administration, but reverses when the drug is stopped. Hypokalaemia may occur. The sodium salt form of PAS can result in sodium overload and this form of the drug should be used with caution in patients for whom restricted sodium intake is indicated. In the old tablet preparation of PAS, an excipient (bentonite) impaired the absorption of rifampicin. The new preparation, however, in the form of granules, does not interfere with rifampicin absorption, may be slightly better tolerated, and can be given twice (as opposed to three or four times) a day without loss of efficacy.

References

1. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1960, 23:535–585.
2. McCune R, Deuschle K, McDermott W. The delayed appearance of isoniazid antagonism by pyridoxine in vivo. *American Review of Tuberculosis and Pulmonary Disease*, 1957, 76:1100–1105.
3. Black M. Isoniazid and the liver. *American Review of Respiratory Disease*, 1974, 110:1–3.
4. Girling DJ. The hepatic toxicity of antituberculosis regimens containing isoniazid, rifampicin and pyrazinamide. *Tubercle*, 1978, 59:13–32.
5. Singapore Tuberculosis Service/British Medical Research Council. Controlled trial of intermittent regimens of rifampin plus isoniazid for pulmonary tuberculosis in Singapore. The results up to 30 months. *American Review of Respiratory Disease*, 1977, 116:807–820.
6. Dutt AK, Moers D, Stead WW. Short-course chemotherapy for tuberculosis with mainly twice-weekly isoniazid and rifampin. Community physicians' seven-year experience with mainly outpatients. *American Journal of Medicine*, 1984, 77:233–242.
7. Singapore Tuberculosis Service/British Medical Research Council. Clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1985, 132:374–378.
8. Fox W, Mitchison DA. Short-course chemotherapy for pulmonary tuberculosis. *American Review of Respiratory Disease*, 1975, 111:325–353.
9. Aquinas M et al. Adverse reactions to daily and intermittent rifampicin regimens for pulmonary tuberculosis in Hong Kong. *British Medical Journal*, 1972, 1:765–771.
10. Girling DJ. Adverse reactions to rifampicin in antituberculosis regimens. *Journal of Antimicrobiology and Chemotherapy*, 1977, 3:115–132.
11. Girling DJ, Hitze KL. Adverse effects of rifampicin. *Bulletin of the World Health Organization*, 1979, 57:207–212.
12. Centers for Disease Control and Prevention. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis in HIV-infected persons taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. *Morbidity and Mortality Weekly Report*, 2000, 49:185–189.

13. Skolnick JL et al. Rifampin, oral contraceptives, and pregnancy. *Journal of the American Medical Association*, 1976, 236:1382.
14. Blaschke T, Skinner M. The clinical pharmacokinetics of rifabutin. *Clinical Infectious Diseases*, 1996, S15–S21.
15. Dickinson JM, Mitchison DA. In vitro properties of rifapentene (MDL473) relevant to its use in intermittent chemotherapy of tuberculosis. *Tubercle*, 1987, 68:113–118.
16. Update: Fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations. United States, 2001. *MMWR Morbidity and Mortality Weekly Report*, 2001; 50:733–735.
17. Carr RE, Henkind P. Ocular manifestations of ethambutol toxicity. *Archives of Ophthalmology*, 1962, 67:566–571.
18. Fledelius HC et al. Ocular ethambutol toxicity. A case report with electrophysiological considerations and a review of Danish cases 1972–81. *Acta Ophthalmology (Copenhagen)*, 1987, 65:251–255.
19. Nunn P et al. Cutaneous hypersensitivity reactions due to thioacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*, 1991, 337:627–630.
20. *Guidelines for the management of drug-resistant tuberculosis*. Geneva, World Health Organization, 1997 (documents, WHO/TB/96.210, 1997).
21. Grosset J. *XVII Congrés National de la Tuberculose et des Maladies Respiratoires, Clermont-Ferrand*. Paris, Masson, 1974.
22. Truffot-Pernot C, Ji B, Grosset J. Activities of pefloxacin and ofloxacin against mycobacteria: in vitro and mouse experiments. *Tubercle*, 1991, 72:57–64.
23. Gillespie SH, Kennedy N. Fluoroquinolones: a new treatment for tuberculosis? *International Journal of Tuberculosis and Lung Disease*, 1998, 2:265–271.
24. Yew WW et al. Outcomes of patients with multidrug-resistant pulmonary tuberculosis treated with ofloxacin/levofloxacin-containing regimens. *Chest*, 2000, 117:744–751.
25. Lehmann J. Para-aminosalicylic acid in the treatment of tuberculosis. *Lancet*, 1946, 1:15–16.

24. What is the purpose of the initial intensive phase of two-phase treatment?

K. Toman[1]

There is ample experimental and clinical evidence that the initial administration of more than one drug, particularly a three- or four-drug regimen, greatly improves the efficacy of treatment. Early work by Mitchison (*1*), Canetti (*2*), and others in the 1960s showed that at least two drugs given concurrently were required for the treatment of active tuberculosis; field trials had shown that monotherapy led to high treatment failure and relapse rates. This led to the concept that multidrug treatment would be required to eradicate the tubercle bacilli in patients with active disease.

The notion that an intensive phase of treatment with multiple drugs, followed by a continuation phase with fewer drugs, could be implemented and have a successful outcome gained acceptance. However, not every combination of two or three drugs will have this effect. At least two bactericidal drugs, such as isoniazid and streptomycin or isoniazid and rifampicin, are required in the initial phase. Pyrazinamide given in the initial intensive phase allows a reduction in treatment duration from 9 to 6 months. Ethambutol is of benefit when initial drug resistance may be present or if the burden of organisms is high (see "How effective is tuberculosis treatment and what are the needs for the future?", page 253).

The multiplication of susceptible organisms stops during the first days of effective treatment (*1*, *2*), and the total number of bacilli in the sputum decreases rapidly, especially within the first 2 weeks (*3*). The experimental findings from laboratory and controlled studies are summarized below.

- It is crucial for the outcome of treatment, especially in patients harbouring large bacterial populations, to put a rapid stop to bacterial multiplication and ensure that drug-susceptible bacilli are killed as soon as possible ("early kill"), for the following reasons:
  - — To prevent early deterioration and death in the first weeks of treatment.
  - — If the bacterial population is rapidly reduced from, say, 10^8 (a number commonly found in lung cavities) to 10^3, there is little probability that new resistant mutants will appear, even after seven generations of uninhibited multiplication.

[1] Deceased.

Thus the emergence of new resistant mutants can be minimized or stopped by an initial phase of intensive treatment.

— There is good in vitro evidence that, the more rapid the antibacterial effect, the less likely is the emergence of persisters (*4*). The risk of relapse is thus reduced.

- Appropriate multidrug combinations always contain two drugs capable of destroying single-drug-resistant mutants that pre-exist in wild strains. Thus a three- or four-drug regimen will safely prevent these organisms from multiplying. Such multiplication may be particularly dangerous in the early treatment phase because an appreciable number of drug-resistant mutants may be present at the start of treatment. In one million tubercle bacilli (of a wild strain), about 10–50 isoniazid-resistant mutants and about 1–5 streptomycin-resistant mutants may be found. Thus, in a population of 10^8 (a number commonly found in lung cavities), some 5000 isoniazid-resistant and several hundred streptomycin-resistant mutants could be present at the outset (see "How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?", page 203). If these are allowed to multiply, resistance to two drugs can develop rapidly (*5*).
- In patients with initial resistance to a single drug (except rifampicin) the chances of a favourable response to treatment are almost unimpaired if an initial period of treatment with three or four drugs is provided (see "What are the possible consequences of inaccurate drug-susceptibility testing?", page 213). Patients who will benefit from a fourth drug and an intensive initial phase are mainly those who harbour large numbers of tubercle bacilli, i.e. those who are usually positive by direct smear microscopy.

References

1. Mitchison DA. Chemotherapy of tuberculosis: a bacteriologist's viewpoint. *British Medical Journal*, 1965, 1:1331–1338.
2. Canetti G. Host factors and chemotherapy of tuberculosis. In: Barry VC, ed. *Chemotherapy of tuberculosis*. London, Butterworths, 1964:20–38.
3. Mitchison DA. Mechanisms of the action of drugs in short-course chemotherapy. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1985, 60:30–40.
4. Crofton J, Douglas E. *Respiratory diseases*, 2nd ed. Oxford, Blackwell Scientific, 1975.
5. Mitchison DA. Bacteriological mechanisms in recent controlled chemotherapy studies. *Bulletin of the International Union Against Tuberculosis*, 1970, 43:322–331.

25. What are the current recommendations for standard regimens?

A. Harries[1]

The aims of treatment regimens are to: cure the patient, prevent death from active disease or its late effects, prevent the emergence and spread of drug-resistant organisms, minimize relapse, and protect the community from continued transmission of infection.

All treatment regimens have two phases – an initial intensive phase and a continuation phase (*1*, *2*).

Initial intensive phase

The initial intensive phase of treatment is designed to kill actively growing and semi-dormant bacilli. This means a shorter duration of infectiousness, usually with rapid smear conversion (80–90%) after 2–3 months of treatment. The initial phase of rifampicin-containing regimens should always be directly observed in order to ensure adherence. That phase usually involves between three and five drugs. If initial resistance rates are high, use of a three-drug regimen carries the risk of selecting drug-resistant mutants, especially in patients with high bacillary loads, i.e. with smear-positive pulmonary tuberculosis. Use of a four-drug regimen reduces the risk both of drug resistance developing and of failures and relapses. If a patient defaults on treatment after the initial intensive phase, relapse is less likely.

Continuation phase

The continuation phase eliminates most residual bacilli and reduces failures and relapses. At the start of the continuation phase, numbers of bacilli are low and there is less chance of selecting drug-resistant mutants: fewer drugs are therefore needed.

Standard tuberculosis treatment regimens

Treatment regimens recommended by WHO (*1*) are shown in Table 27. Standard codes are used for tuberculosis treatment regimens: each tuberculosis drug is represented by a standard abbreviation and each regimen has two phases. The number

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

Table 27
Recommended treatment regimens for different diagnostic categories[a]

Diagnostic category	Tuberculosis patients	Tuberculosis treatment[b]	
		Initial phase (daily or 3 times per week[c])	Continuation phase (daily or 3 times per week[c])
I	New smear-positive cases; new smear-negative pulmonary TB with extensive parenchymal involvement; severe concomitant HIV disease or severe forms of extrapulmonary TB	2 HRZE[d]	4 HR or 6 HE daily
II	Previously treated sputum smear-positive PTB: – relapse – treatment after interruption – treatment failure[e]	2 HRZES / 1 HRZE	5 HRE
III	New smear-negative pulmonary TB (other than in Category I) and less severe forms of extrapulmonary TB[f]	2 HRZE[g]	4 HR or 6 HE daily
IV	Chronic and MDR-TB cases (still sputum-positive after supervised retreatment)	Specially designed standardized or individualized regimens are suggested for this diagnostic category.	

[a] Source: reference *1*.
[b] H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters indicates the number of months of treatment.
[c] Direct observation of treatment intake is required for the initial phase in smear-positive cases, and always in treatment that includes rifampicin.
[d] Streptomycin may be used instead of ethambutol. In meningitis, ethambutol should always be replaced by streptomycin.
[e] Whenever possible, drug sensitivity is recommended before category II treatment is prescribed in failure cases. In patients with proven MDR-TB, it is recommended that Category IV regimens are used.
[f] Contacts of patients with culture proven MDR-TB should be considered for early culture and sensitivity testing.
[g] Ethambutol in the initial phase may be omitted for patients with non-cavitary, smear-negative pulmonary TB who are known to be HIV-negative, patients who are known to be infected with fully drug-susceptible bacilli, and young children with primary TB.

before a phase is the duration of that phase in months. A subscript number (e.g. $_3$) after a letter or letters in parentheses is the number of doses of that drug or drugs per week. If there is no subscript number, treatment with that drug is on a daily basis. The use of parentheses indicates that the drugs are formulated in fixed-dose combination; this formulation is recommended whenever possible. An alternative drug (or drugs) appears as a letter (or letters) in square brackets.

Examples

- 2(HRZE)/6(HE)
  The initial phase is 2HRZE. The duration of the phase is 2 months. Drug treatment is daily (there is no subscript number after the letters) with isoniazid (H), rifampicin (R), pyrazinamide (Z), and ethambutol (E) in a fixed-dose combination. The continuation phase is 6HE. The duration of the phase is 6 months. Drug treatment is daily with isoniazid (H) and ethambutol (E) in a fixed-dose combination.

- $2(HRZ)_3E_3/4(HR)_3$
  In the initial phase treatment is three times a week (as indicated by the subscript number after the letters) with isoniazid (H), rifampicin (R) and pyrazinamide (Z) in a fixed-dose combination, plus ethambutol (E). The duration of the phase is 2 months. In the continuation phase treatment is three times a week (subscript number after the letters) with isoniazid (H) and rifampicin (R) in a fixed dose-combination. The duration of the phase is 4 months.

New cases of tuberculosis

Treatment regimens consist of an initial (intensive) phase lasting 2 months and a continuation phase usually lasting 4–6 months. During the initial phase, usually involving four drugs, there is rapid killing of tubercle bacilli and infectious patients become non-infectious within a few weeks. Symptoms improve, and many patients become asymptomatic after 4–8 weeks; most patients with sputum smear-positive pulmonary tuberculosis become smear-negative within 2 months. Pyrazinamide is given during the initial phase and has its maximum sterilizing effect within this time. No further benefit is obtained from continuing pyrazinamide for longer in patients with drug-susceptible bacilli, and the drug is therefore not used in the continuation phase. In the continuation phase, two drugs are generally used.

Patients with smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis harbour fewer bacilli in their lesions, so there is less chance of selecting drug-resistant mutants. Short-course treatment regimens with three drugs during the initial phase and two in the continuation phase are of proven efficacy and are recommended by WHO.

Some countries still use a 12-month regimen, particularly in patients with smear-negative pulmonary or extrapulmonary tuberculosis (*2*) (isoniazid and thioacetazone, supplemented with streptomycin and ethambutol for 2 months in the initial phase). A 12-month period of treatment is required because the regimen contains neither of the drugs (rifampicin and pyrazinamide) that sterilize the tuberculous lesions. The regimen therefore relies on semi-dormant bacilli becoming metabolically active during the treatment period and susceptible to the killing effects of isoniazid. Under routine conditions in nearly all countries the cure rates with this regimen are low, and WHO therefore does not recommend it. In addition, thioacetazone has serious

toxicity, particularly in patients infected with HIV, and should be replaced by ethambutol. However, this type of regimen may need to be used while the DOTS strategy package is being expanded to cover an entire country or area.

Re-treatment cases

Previously treated tuberculosis patients are more likely than new patients to harbour and excrete bacilli resistant to at least isoniazid. The re-treatment regimen consists of five drugs initially, with at least three in the continuation phase. In the initial phase the patient should receive at least two drugs that are still effective to reduce the risk of selecting further resistant bacilli.

WHO-recommended treatment regimens

WHO-recommended treatment regimens are shown in Table 27. There are several possible regimens, depending on a country's budget, health coverage by primary health care facilities, capacity for direct observation, and qualifications of staff at peripheral health level. For each patient, the regimen recommended depends on the patient treatment category (see "What are the diagnostic categories and what is the rationale for these categories?", page 128).

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. Enarson DA et al. *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.

26. What are the diagnostic categories and what is the rationale for these categories?

A. Harries[1]

There are four different diagnostic categories of treatment (see "What are the current recommendations for standard regimens?", page 124). Patients are categorized according to priority for treatment, with priorities being based on cure of the patient, prevention of death, prevention of drug resistance, and reduction of transmission in the community. The highest priority is given to patients with new smear-positive pulmonary tuberculosis and other serious forms of the disease. If 100% of new smear-positive tuberculosis cases were detected and cured, the prevalence of tuberculosis would fall very rapidly (see "Can tuberculosis be controlled?", page 301).

Category I

Includes patients with:

- New smear-positive pulmonary tuberculosis, because they are highly infectious and at high risk of death without treatment, and because treatment failure means risk of the spread of drug-resistant organisms to the community. Cure of a high proportion of new smear-positive patients would have the greatest impact on the control of tuberculosis.
- New patients with severe forms of extrapulmonary tuberculosis such as miliary disease, pericardial disease, meningitis, and spinal disease with spinal cord involvement. Although not infectious, these patients are at high risk of death unless treated with effective drug combinations.
- New patients with severe and extensive smear-negative pulmonary tuberculosis; patients with concomitant HIV diseases are at particularly high risk of death.

Category II

Includes patients previously treated for tuberculosis who have developed smear-positive pulmonary tuberculosis; includes patients with relapse, treatment failures, and patients who previously defaulted from treatment. These patients are given multidrug regimens because they are highly infectious and are more likely to have

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe , Malawi.

drug-resistant organisms that can spread to the community unless they are effectively treated. The entire course of treatment in such patients should be directly observed; patients who were treated previously are at much higher risk of default. For many patients, this represents their last real chance for cure.

Category III

Includes patients with smear-negative pulmonary tuberculosis and less serious forms of extrapulmonary tuberculosis such as pleural effusion and lymphadenopathy. These patients are much less infectious than those with smear-positive pulmonary tuberculosis, and there is less risk of development of drug resistance or of death. However, cases of HIV-infected smear-negative pulmonary tuberculosis may be at greater risk of death compared with HIV-infected smear-positive pulmonary tuberculosis cases because the former are more immunocompromised. HIV-infected patients may also be more prone to acquiring drug-resistant disease. Moreover, smear-negative patients may contribute to the spread of tuberculosis in the community. For these reasons, and because the HIV status in most tuberculosis cases is unknown, WHO now recommends that these patients receive the same regimen at Category I, with four initial drugs.

Category IV

Category IV is comprised of smear-positive pulmonary tuberculosis cases who have completed a fully supervised re-treatment regimen, and those who have multidrug-resistant tuberculosis (with resistance to isoniazid and rifampicin documented in a competent laboratory). Treatment of such patients is lengthy, costly, difficult for both patients and staff, and often unsuccessful. Highest priority must always be given to prevention of such cases by effective, directly observed primary treatment regimens. Where resources and expertise permit, treatment of such individual cases is sometimes attempted on humanitarian grounds (see "What reserve regimens are available and what is their place in tuberculosis control programmes?", page 215). In settings where multidrug-resistant tuberculosis is common and many patients are immunocompromised, Category IV treatment may be necessary for rapid control of multidrug-resistant tuberculosis.

27. What is intermittent treatment and what is the scientific basis for intermittency?[1]

T. Frieden[2]

Intermittent regimens are those in which the individual drugs are given at intervals of more than one day, e.g. three times a week.

Originally it was believed that anti-tuberculosis drugs needed to be given every day to maintain drug concentrations continuously at inhibitory levels. However, in vitro studies and animal experiments have demonstrated that certain drugs are also effective when the drug concentration drops temporarily below that level, and indeed even after the drug has disappeared completely from the lesion (*1*) or the medium (*2*).

In vitro experiments have demonstrated that, after a culture of *Mycobacterium tuberculosis* is exposed to certain drugs for some time, it takes several days (the "lag period") before new growth occurs. Table 28 shows the lag period for growth of *M. tuberculosis* after exposure to different drugs for varying times.

There was no lag after exposure to thioacetazone for 24 hours or even 96 hours. Immediately the thioacetazone was removed from the culture medium, growth started again, suggesting that this drug is unsuitable for intermittent treatment; this was confirmed by animal experiments.

For each bactericidal drug there was a maximum lag period (last column) that seems to indicate the practical limit beyond which the interval between two doses should not be extended. Animal studies (*4*) have shown conclusively that the longer the chosen interval between doses, the higher the doses need to be for most of the drugs, with the exception of rifampicin. Thus, for high doses of isoniazid, a 3-day interval proved to be the optimum; extension of the interval to 8 days gave significantly worse results.

A series of experiments in an animal model (*3*) demonstrated that intermittent dosing actually *increased* the efficacy of treatment with isoniazid, rifampicin, and pyrazinamide (Figure 11).

---

[1] Based on the chapter in the previous edition by K. Toman.

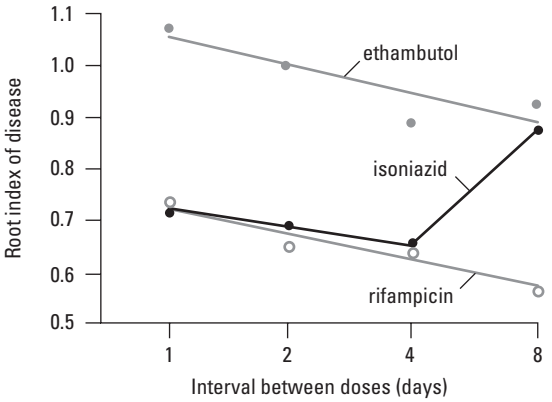
[2] Medical Officer, Stop TB Unit, Who Regional Office for South-East Asia, New Delhi, India.

Table 28
Lag in growth of* Mycobacterium tuberculosis *after temporary exposure to drugs[a]

Drug	Concentration (mg/litre)	Lag (days) after exposure for:	
		6 hours	24 hours
Isoniazid	1	0	6–9
Rifampicin	0.2	2–3	2–3
Pyrazinamide	50	5–40[b]	40[b]
Ethambutol	10	0	4–5
Streptomycin	5	8–10	8–10
Ethionamide	5	0	10
Cycloserine	100	0	4–8
Thioacetazone	10	0	0

[a] Source: reference *2* and *3*.
[b] Depending on the pH of the medium.

Figure 11
Mean root indices of disease related to interval between doses in guinea-pigs treated with isoniazid, ethambutol, or rifampicin[a]



[a] Source: reference 3, reprinted with permission.

Standard intermittent regimens

Although experimental findings cannot be mechanically transferred to humans, these results were promising enough to be explored in clinical studies. The first such randomized controlled clinical trial was undertaken at the Tuberculosis Research Centre, Chennai, India (*5*).

Table 29
Results of 12 months' twice-weekly streptomycin/isoniazid (SH) treatment compared with those of daily* p*-aminosalicyclic acid and isoniazid (PH)[a]

Status of disease	SH, twice weekly[b]		PH, daily[c]	
	No. of patients	%	No. of patients	%
Bacteriologically quiescent	68	94	56	85
Bacteriologically active	2	2	9	14
(Death from tuberculosis)	2	3	1	2
Total patients	72	100	66	100

[a] Source: reference *5*.
[b] SH: streptomycin 1 g intramuscular + isoniazid 14 mg/kg body weight.
[c] PH: sodium PAS 10 g + isoniazid 200 mg daily, divided into two equal doses.

A standard oral regimen of isoniazid plus PAS twice daily was compared with a twice-weekly regimen of 1 g of streptomycin given by intramuscular injection plus 14 mg/kg body weight of isoniazid, given orally in a single dose. The oral regimen was dispensed for self-administration. For the intermittent regimens, patients attended the clinic twice a week at intervals of 3–4 days. Treatment was fully supervised, i.e. each patient first took isoniazid tablets in the presence of the staff (who verified that the tablets had actually been swallowed), and then received the injection of streptomycin. The results at 12 months are shown in Table 29.

The intermittent regimen was highly successful and perhaps slightly more effective than the daily regimen. The potency of intermittent treatment is all the more striking as most of the patients admitted to the study had extensive, bilateral cavitary disease with sputum heavily positive by direct smear. This feature was common to all the studies in Chennai (formerly Madras) in which the patients had severe disease. The relapse rates in a 2-year period were 8% for the twice-weekly regimen and 12% for the daily regimen; after 4 years, they were 12% and 15% respectively. In 4 out of 5 patients who relapsed on the intermittent regimen, the bacilli were susceptible to both isoniazid and streptomycin. This suggests that, had there been an intensive phase at the start of treatment, the susceptible bacilli would probably have been eliminated.

In another study, also undertaken in outpatients in Chennai, the possibility of increasing the interval between doses to one week was investigated. Four intermittent regimens were studied concurrently but, for the sake of simplicity, only two are described here.

The twice-weekly streptomycin plus isoniazid (S_2H_2) regimen was compared with streptomycin plus isoniazid given once weekly (S_1H_1). The dosage was the same for both regimens: 1.0 g or 0.75 g of streptomycin plus 15 mg/kg of isoniazid. The effect of a lower dose (0.75 g) of streptomycin was studied because it seemed likely this would be suffi-

Table 30
Comparison of results of 12 months' treatment with streptomycin (S) and isoniazid (H) twice and once weekly[a]

Status of disease	S_2H_2[b] twice weekly[c]		S_1H_1[b] once weekly[c]	
	No. of patients	%	No. of patients	%
Bacteriologically quiescent	107	91	82	71
Bacteriologically active	9	8	30	26
(Death from tuberculosis)	1	1	3	3
Total patients	117	100	115	100

[a] Source: reference *6*.
[b] The subscript after the letter refers to the number of doses per week.
[c] SH: streptomycin 0.75–1 g intramuscular + isoniazid 15 mg/kg body weight.

Table 31
Streptomycin plus isoniazid twice weekly (S_2H_2) compared with once weekly (S_1H_1) according to the rate of isoniazid inactivation and the dose of streptomycin[a]

Regimen	Patients with quiescent disease at 1 year (%)			
	Isoniazid inactivation rate		Streptomycin dosage	
	slow	rapid	1 g	0.75 g
S_2H_2 (twice weekly)	91	91	91	92
S_1H_1 (once weekly)	82	60	76	62

[a] Source: reference *6*.

cient and better tolerated, particularly by debilitated or elderly patients, than the usual dose of 1 g. The results of 12 months of treatment are summarized in Table 30.

The twice-weekly regimen again proved to be highly successful; the once-weekly regimen was considerably less effective. Nevertheless, it was impressive that, despite severe disease, 71% of patients on the once-weekly regimen achieved bacteriological quiescence (*6*).

The reasons for the inferiority of the once-weekly regimen were examined, and the findings were both interesting and important. In this analysis, patients were grouped according to the rate of inactivation of isoniazid and the dosage of streptomycin. Table 31 shows that the efficacy of the twice-weekly regimen was influenced neither by the

inactivation rate of isoniazid nor by a 25% reduction in the streptomycin dosage. In contrast, the once-weekly regimen was clearly affected by the rate of isoniazid inactivation and, to a lesser extent, also by the reduction in the streptomycin dosage. The twice-weekly regimen was thus shown to be robust and effective, even without an initial intensive phase.

The isoniazid inactivation rate also influenced the response to other once-weekly regimens investigated concurrently. With currently available medications, intermittency reaches its practical limit of effectiveness when the interval between doses is extended to one week.

The following conclusions may be drawn from the experience gained with intermittent treatment without rifampicin.

- Twice-weekly regimens containing isoniazid in high dosage (14–15 mg/kg) and streptomycin (0.75–1 g) are highly effective, whether given from the outset or after an initial intensive phase of treatment. Their efficacy in slow and rapid inactivators of isoniazid is similar. These regimens can be highly effective in patients with extensive disease and in populations with a high frequency of rapid inactivators.
- A once-weekly regimen of isoniazid (15 mg/kg) and streptomycin (1 g), after 4 weeks' initial daily therapy with isoniazid and streptomycin, approached the efficacy of the twice-weekly regimen; however, unlike the latter, it was substantially inferior in rapid inactivators and therefore cannot be recommended.

Short-course intermittent regimens

The development of rifampicin and pyrazinamide prompted studies of intermittent short-course regimens. At first, investigators studied regimens with a daily intensive phase followed by an intermittent continuation phase. The risk of relapse is the key indicator of the effectiveness of a regimen. Many regimens achieve nearly 100% cure; relapse should be less than 5%. A series of studies has demonstrated that intermittent treatment following a daily intensive phase – which may be as short as two weeks – is highly effective, provided that treatment observation is ensured (Table 32).

Fully intermittent treatment has also been found to be highly effective (Table 33). The fully oral regimen of 2 months of isoniazid, rifampicin, pyrazinamide, and ethambutol, followed by 4 months of isoniazid and rifampicin, has been studied in daily, partially intermittent, and fully intermittent regimens. Fully intermittent regimens, which make treatment observation more convenient and feasible for health workers and patients, achieve high levels of treatment success with low relapse rates (*16*). Such regimens have now been widely used, with good results. A twice-weekly, 6-month, rifampicin-containing regimen following 2 weeks of daily treatment has also been shown to be highly effective (*17*). However, a single missed dose will result in once-weekly treatment, which is less effective and potentially more toxic because of immunologically mediated adverse effects. Adverse reactions to rifampicin are more frequent in once-weekly treatment.

Table 32
Studies using partially intermittent short-course treatment

Country or area	Year of study	Regimen[a]	No. of patients assessed for relapse	Relapse in 2-year follow-up (%)	Reference number
Madras[b], India	1974	$2HRZS/3H_2Z_2S_2$	129	5[c]	*7*
		$2HRZS/5H_2Z_2S_2$	132	0[c]	
	1974	$2HRZS/4H_2Z_2S_2$	87	7	*8*
Hong Kong[d]		$2HRZS/6H_2Z_2S_2$	87	3	
Madras	1977	$3HRZS/2H_2Z_2S_2$	187	4	*8*
Singapore	1978	$2HRZS/4H_3R_3$	97	1	*10*
		$1HRZS/5H_3R_3$	94	1	
		$2HRZ/4H_3R_3$	109	1	
Poland	1982	$2SHRZ/4H_2R_2$	85	0	*11*
Singapore[e]	1983	$2(HRZS)/4H_3R_3$	46	7	*12*
		$2HRZS/4H_3R_3$	47	0	
		$1(HRZS)/5H_3R_3$	42	5	
		$1HRZS/5H_3R_3$	46	2	
		$2(HRZ)/4H_3R_3$	40	8	
		$2HRZ/4H_3R_3$	44	2	
Poland	1984	$2HRZ/4H_2R_2$	116	4	*13*
		$2HRZS/4H_2R_2$	56	2	
Zaire	1989	$2HRZE/4H_2R_2$	119 (HIV-infected)	9	*14*
		$2HRZE/9H_2R_2$	121 (HIV-infected)	2	
		$2HRZE/4H_2R_2$	180 (HIV-uninfected)	5	
United States[f]	1993	$0.5HRZE/1.5H_3R_3Z_3E_3/4H_2R_2$	293 (HIV-infected)	0	*15*
		$0.5HRZE/1.5H_3R_3Z_3E_3/7H_2R_2$	50 (HIV-infected)	1	

[a] H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.
[b] Now Chennai.
[c] 18 months follow-up.
[d] Now Hong Kong Special Administrative Region of China.
[e] The drug letters between parentheses indicate a fixed-dose combination; letters with no parentheses indicate single drugs.
[f] Half of the patients also received levofloxacin during the intensive phase.

The World Health Organization Collaborating Centre for Tuberculosis Chemotherapy, Prague, reported excellent results (99–100% efficacy) in a study of which an important feature was the flexibility of the treatment organization(*25*, *26*). Each patient could choose to receive treatment at the most convenient place, such as a chest clinic, physician's office, factory dispensary, health centre, or a hospital on the

Table 33
Studies using fully intermittent short-course treatment

Country or area	Year of study	Regimen[a]	No. of patients assessed for relapse	Relapse in 2-year follow-up (%)	Reference number
Hong Kong[b]	1974	$4H_3R_3Z_3S_3/2H_2Z_2S_2$	71	6	*8*
		$4H_3R_3Z_3S_3/4H_2Z_2S_2$	83	1	
South Africa	1975	$6H_2R_2Z_2S_2$	279	6	*18*
Hong Kong[b]	1977	$6H_3R_3Z_3E_3S_3$	152	1	*19*
		$6H_3R_3Z_3S_3$	151	1	
		$6H_3R_3E_3S_3$	166	8	
		$6H_3R_3Z_3E_3$	160	2	
Hong Kong[b]	1979	$2H_3R_3Z_3S_3/4H_3R_3S_3$	220	3	*20*
		$2H_3R_3Z_3S_3/$ $2H_3R_3Z_3S_3/2H_3R_3S_3$	205	5	
		$2H_3R_3Z_3S_3/4H_3R_3Z_3S_3$	208	3	
		$2H_3R_3Z_3/4H_3R_3Z_3$	199	6	
Madras[c], India	1980	$2H_3R_3Z_3S_3/4H_2R_2S_2$	111	2	*21*
		$2H_3R_3Z_3S_3/4H_1R_1S_1$	111	5	
		$2H_3R_3Z_3S_3/4R_2H_2$	101	3	
		$2H_3R_3Z_3S_3/4R_1H_1$	116	2	
		$2H_3R_3Z_3S_3/4H_2S_2$	151	3	
		$2H_2R_2Z_2S_2/4H_2R_2S_2$	108	3	
		$2H_2R_2Z_2S_2/4H_1R_1S_1$	117	4	
		$2H_2R_2Z_2S_2/4R_2H_2$	102	6	
		$2H_2R_2Z_2S_2/4R_1H_1$	109	7	
		$2H_2R_2Z_2S_2/4H_2S_2$	155	10	
Canary Islands[d]	1990	$2H_2R_2Z_2(E_2)/4H_2R_2$	80	3	*22*
Madras[c], India	1990	$2H_3R_3Z_3E_3/4H_2R_2$	273	6	*23*
Haiti	1990	$2H_3R_3Z_3E_3/4H_3R_3$	129 (HIV-infected)	5	*16*
		$2H_3R_3Z_3E_3/4H_3R_3$	211 (HIV-uninfected)	2	
China	1991	$2H_3R_3Z_3S_3/4H_3R_3$	300	3	*24*

[a] H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.
[b] Now Hong Kong Special Administrative Region of China.
[c] Now Chennai.
[d] Ethambutol given only to patients with prior history of default.

way to work. If necessary, an outreach worker could visit the patient's home. The area was partly rural and had adequate transport facilities.

The success of the study was due largely to the excellent cooperation of the patients, which was achieved by adapting treatment services to their convenience. This was greatly facilitated by the intermittent treatment regimen. Although the treatment of

tuberculosis in the former Czechoslovakia was almost entirely the responsibility of a rather extensive network of specialized inpatient and outpatient tuberculosis services, the participation of non-specialized health services was of great importance. Moreover, the study demonstrated how general health services can become increasingly involved in the management of tuberculosis patients, and are capable of taking over this responsibility from the specialized services.

References

1. Canetti G, Grumbach F, Grosset J. Long-term, two-stage chemotherapy of advanced experimental murine tuberculosis with intermittent regimes during the second stage. *Tubercle*, 1963, 44:236–240.
2. Dickinson JM, Mitchison DA. *In vitro* studies on the choice of drugs for intermittent chemotherapy of tuberculosis. *Tubercle*, 1966, 47: 370–380.
3. Mitchison DA. Basic mechanisms of chemotherapy. *Chest*, 1976, 6:771–781.
4. Grumbach F et al. Late results of long-term intermittent chemotherapy of advanced, murine tuberculosis: limits of the murine model. *Tubercle*, 1967, 48:11–26.
5. A concurrent comparison of intermittent (twice-weekly) isoniazid plus streptomycin and daily isoniazid plus PAS in the domiciliary treatment of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1964, 31:247–271.
6. A controlled comparison of a twice-weekly and three once-weekly regimens in the initial treatment of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1970, 43:143–206.
7. Santha T et al. Treatment of pulmonary tuberculosis with short-course chemotherapy in South India – 5-year follow up. *Tubercle*, 1989, 70:229–234.
8. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 1979, 60:201–210.
9. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. *American Review of Respiratory Disease*, 1986, 134:27–33.
10. Five-year follow-up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1988, 137:1339–1342.
11. Snider DE et al. Successful intermittent treatment of smear-positive pulmonary tuberculosis in six months. A comparison study in Poland. *American Review of Respiratory Disease*, 1982, 125:265–267.
12. Assessment of a daily combined preparation of isoniazid, rifampicin, and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1991, 143:707–712.
13. Snider DE et al. Supervised six-month treatment of newly diagnosed pulmonary tuberculosis using HRZ with or without streptomycin. *American Review of Respiratory Disease*, 1984, 130:1091–1094.

14. Perriëns J et al. Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *New England Journal of Medicine*, 1995, 332: 779–784.
15. el-Sadr WM et al. Evaluation of an intensive intermittent-induction regimen and duration of short-course treatment for human immunodeficiency virus-related pulmonary tuberculosis. Terry Beirn Community Programs for Clinical Research on AIDS (CPCRA) and the AIDS Clinical Trials Group (ACTG). *Clinical Infectious Diseases*, 1998, 26:1148–1158.
16. Chaisson RE et al. Six-month supervised intermittent tuberculosis therapy in Haitian patients with and without HIV infection. *American Journal of Respiratory and Critical Care Medicine*, 1996, 154:1034–1038.
17. Cohn DL et al. A 62-dose, 6-month therapy for pulmonary and extrapulmonary tuberculosis. A thrice-weekly, directly observed, and cost-effective regimen. *Annals of Internal Medicine*, 1990, 112:407–415.
18. Bechan S et al. Directly observed therapy for tuberculosis given twice weekly in the workplace in urban South Africa. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1997, 91:704–707.
19. Controlled trial of 4 three-times weekly regimens and a daily regimen all given for 6 months for pulmonary tuberculosis. Second report: the results up to 24 months. Hong Kong Chest Service/British Medical Research Council. *Tubercle*, 1982, 63:89–98.
20. Controlled trial of 2, 4, and 6 months of pyrazinamide in 6-month, three-times-weekly regimens for smear-positive pulmonary tuberculosis, including an assessment of a combined preparation of isoniazid, rifampin, and pyrazinamide. Results at 30 months. Hong Kong Chest Service/British Medical Research Council. *American Review of Respiratory Disease*, 1991, 143:700–706.
21. Balasubramanian R. Fully intermittent six month regimens for pulmonary tuberculosis in South India. *Indian Journal of Tuberculosis*, 1991, 38:51–53.
22. Caminero JA et al. Evaluation of a directly observed six-month fully intermittent treatment regimen for tuberculosis in patients suspected of poor compliance. *Thorax*, 1996, 51:1130–1133.
23. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:40–45.
24. Cao JP et al. Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:360–364.
25. A comparative study of daily and twice-weekly continuation regimens of tuberculosis chemotherapy, including a comparison of two durations of sanatorium treatment. 1. First report: the results at 12 months. *Bulletin of the World Health Organization*, 1971, 45:573–593.
26. Polansky F, Vodrazkova A, Viznerova A. International cooperative tuberculosis chemotherapy studies in Czechoslovakia. *Bulletin of the International Union Against Tuberculosis*, 1974, 49:403–408.

28. What is the dosage of drugs in daily and intermittent regimens?

H. Rieder[1]

Table 34 shows the current dosage of anti-tuberculosis drugs as indicated by WHO (*1*), based on mg/kg body weight. However, WHO (*2*) and IUATLD (*3*) do not recommend the use of twice-weekly intermittent treatment because missing one of the doses results in insufficient treatment and a higher risk of toxicity.

In practice, however, it has proved useful to use dosages based on weight ranges to facilitate the prescription of drugs in terms of number of tablets. The weight of

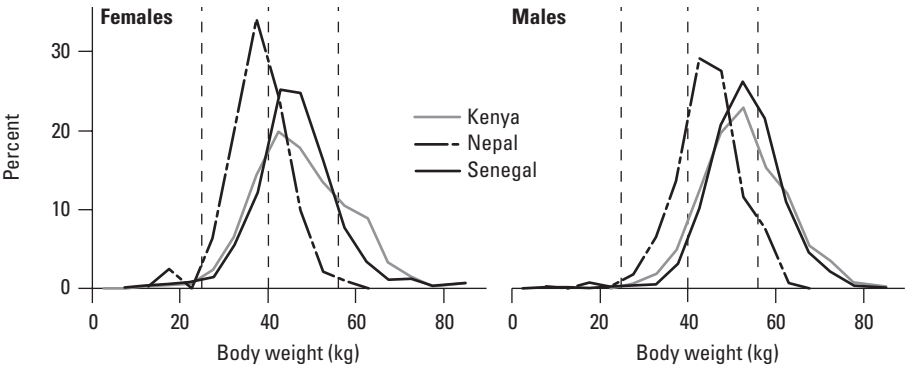
Table 34
Dosages for anti-tuberculosis drugs in mg/kg body weight[a]

Drug	Daily dosage, mg/kg (range)		
	Daily treatment	Treatment three times a week	Treatment twice a week[b]
Isoniazid	5 (4–6)	10 (8–12)	15 (13–17)
Rifampicin	10 (8–12)	10 (8–12)	10 (8–12)
Pyrazinamide	25 (20–30)	35 (30–40)	50 (40–60)
Streptomycin	15 (12–18)	15 (12–18)	15 (12–18)
Ethambutol	15 (13–17)	30 (25–35)	45 (40–50)
Thioacetazone	2.5 (2–3)	NA	NA

[a] Source: references *1, 2*.
[b] Not recommended by WHO and IUATLD because missing a dose results in insufficient treatment and higher risk of toxicity.

[1] Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.

Figure 12
Distribution of body weight among sputum smear-positive patients in Kenya, Nepal, and Senegal[a]



[a] Source: reference *3*.

tuberculosis patients differs in different countries as shown in Figure 12. Weight ranges – shown by the vertical dotted lines – as recommended by the IUATLD (*2*) may thus need adaptation by countries to ensure that the largest possible proportion of patients receive the correct dosage.

Alternatively, a single dosage appropriate for most patients can be used, as in the India Revised Tuberculosis Programme (*4*). Children and patients with very low body weight receive individually adjusted dosages, and patients with high body weight are given extra pills. This permits the use of prepacked treatment boxes, which facilitates drug management.

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 2nd ed. Geneva, World Health Organization, 1997 (document WHO/TB/97.220).
2. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
3. Enarson DA et al. *Management of tuberculosis: a guide for low-income countries.* Paris, International Union Against Tuberculosis and Lung Disease, 2000.
4. *India 1997. Revised National Tuberculosis Control Programme. Technical Guidelines for Tuberculosis Control*. New Delhi, Central TB Division, Directorate General of Health Services.

29. What is the evidence for tuberculosis drug dosage recommendations?

H. Rieder[1]

Each drug is needed in the minimum concentration that can inhibit growth of *Mycobacterium tuberculosis*. This concentration is called the minimum inhibitory concentration (MIC) of the drug and is determined in vitro by testing numerous wild strains to determine the MIC at which the growth of most of these is inhibited. Because it is an in vitro system, the technique affects the result. Thus, MIC values differ when determined on egg-based, broth, or agar media.

The highest dosage that does not lead too frequently to toxic reactions is determined in vivo. If the maximum concentration that can be achieved in serum without causing toxic reactions is lower than the MIC in vitro, the drug cannot be used. If the maximum serum concentration that can be achieved is far above the MIC, the therapeutic margin is large; if it is only slightly above the MIC, that margin is narrow.

A third important element – in addition to the MIC and the maximum serum concentration – is the length of time during which the serum level of the drug remains above the MIC. This is determined by the half-life of the drug. The serum level of each drug needs to remain above the MIC for a certain minimum time in order to exert its action on *M. tuberculosis*. This minimum time varies from one drug to the next.

More important than the MIC is the minimum bactericidal concentration (MBC) – the concentration at which the organism is killed by the drug. The MBC is always higher than the MIC and the MBC-to-MIC ratio is different for different drugs.

The maximum tolerable dosage of a drug, and thus the maximum serum concentration, is determined in clinical practice; the actual therapeutic effect of the drug is established in controlled clinical trials. The challenge is to determine the lowest dosage (to reduce the frequency of toxic reactions) that results in a serum concentration above the MIC (or better the MBC).

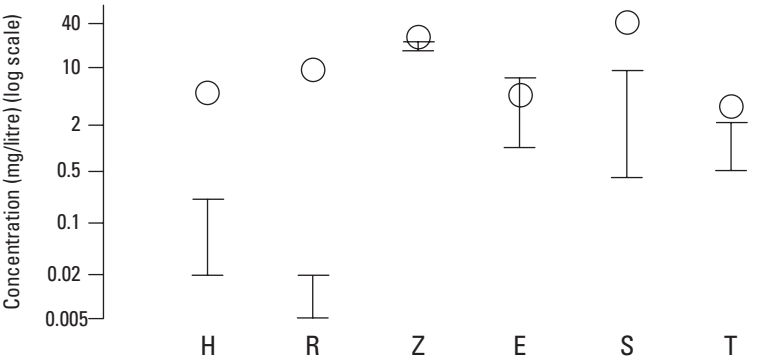
For example, a trial in East Africa studied whether increasing the dosage of isoniazid from 300 mg to 450 mg in combination with thioacetazone improved the efficacy of the regimen (*1*). It did not. Moreover, although isoniazid-attributable toxicity did

[1] Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.

Figure 13

Minimum inhibitory concentrations (MICs) and maximum serum concentration of isoniazid (H), rifampicin (R), pyrazinamide (Z), ethambutol (E), streptomycin (S), and thioacetazone (T)[a]

Circles indicate the maximum serum concentration in vivo, lines the range of the MICs determined in vitro in different studies.



[a] Source: references *3–8*.

not differ for the two dosages in this study, information obtained elsewhere indicates that isoniazid toxicity increases with increasing dosages. The optimum daily dosage of isoniazid was determined to be 300 mg. The optimum dosage of streptomycin was also determined (*2*): for long-term treatment, 0.75 g of streptomycin proved to be as effective as 1.0 g. The lower dosage was equally potent in preventing emergence of resistance to isoniazid and ensuring sputum conversion, but caused vestibular damage less frequently. This type of evaluation – finding a balance between toxicity and maximum therapeutic range – has been done for all anti-tuberculosis drugs and forms the rational basis for the current dosage recommendations.

A summary of the relation between MIC and the maximum serum concentration for the six essential anti-tuberculosis drugs shows that the therapeutic range is large for isoniazid and rifampicin, and smaller for the others (Figure 13) (*3–8*).

References

1. Isoniazid with thiacetazone (thioacetazone) in the treatment of pulmonary tuberculosis in East Africa. Fourth investigation: the effect of increasing the dosage of isoniazid. *Tubercle*, 1966, 47:315–339.
2. Johnston RN et al. Prolonged streptomycin and isoniazid for pulmonary tuberculosis. *British Medical Journal*, 1964, 1:1679–1683.
3. Peloquin CA et al. Pharmacokinetics of isoniazid under fasting conditions, with food, and with antacids. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:703–710.

4. Acocella G. Clinical pharmacokinetics of rifampicin. *Clinical Pharmacokinetics*, 1978, 3:108–127.
5. Pähkla R et al. Comparative bioavailability of three different preparations of rifampicin. *Journal of Clinical Pharmacy and Therapeutics*, 1999, 24:219–225.
6. Davidson PT, Hanh LQ. Antituberculosis drugs. *Clinics in Chest Medicine*, 1986, 7:425–438.
7. Grosset J, Benhassine M. La thiacétazone (TB1): données expérimentales et cliniques récentes. [Thiacetazone (Tb-1): recent experimental and clinical data.] *Advances in Tuberculosis and Respiratory Diseases*, 1970, 17:107–153.
8. Zierski M. Pharmacology, toxicology and clinical use of pyrazinamide. *Praxis und Klinik der Pneumologie*, 1981, 35:1075–1105.

30. What is the optimum duration of treatment?[1]

T. Santha[2]

Short-course regimens achieve smear and culture conversion within 2–3 months in most patients. Many regimens achieve a favourable response, as defined by culture negativity at the end of treatment, of 97–100%. The challenge, however, has been to identify practical regimens that have low (<5%) relapse rates.

Sputum-positive pulmonary tuberculosis

Several studies have shown that a 6-month regimen containing rifampicin throughout and pyrazinamide in the intensive phase is highly effective in the treatment of sputum-positive tuberculosis (Table 35).

These regimens are nearly 100% effective at the end of treatment in patients with initially drug-susceptible organisms; the relapse rate over a 2-year follow-up period was 0–7%.

East African studies have shown that, if rifampicin is given only in the intensive phase, the regimen should be implemented for 8 months (Table 36): 6-month regimens with a continuation phase that does not contain rifampicin have a relapse rate of 7–18%, whereas 8-month regimens have relapse rates of 0–7%. A similar relapse rate (5%) has been reported with daily isoniazid and ethambutol for 6 months in the continuation phase (*12*).

In the initial studies, drugs were given daily throughout or at least during the initial intensive phase at least. Studies conducted at the Tuberculosis Research Centre, Madras (now Chennai), and in Hong Kong (now Hong Kong SAR) (*3*) have shown that fully intermittent regimens are equally effective, with near 100% efficacy at the end of treatment, followed by a relapse rate of 2–7%, and that the reduction in adverse reactions is significant (Table 37).

As indicated from the studies summarized here, treatment of newly diagnosed smear-positive patients should be daily or intermittent for 6–8 months; treatment for 8 months is required if rifampicin is not used in the continuation phase of treatment (*5*). The intensive phase should last for at least 2 months.

---

[1] Based on the chapter in the previous edition by K Toman.

[2] Deputy Director, Tuberculosis Research Center, Chennai, India.

Table 35
Duration of treatment for sputum-positive pulmonary tuberculosis with rifampicin in the continuation phase

Country or area	Year of study	Regimen[a]	Duration of treatment (months)	No. of patients assessed	Relapse rate up to 2 years (%)	Reference
Africa	1972	$2HRZS/4H_2Z_2S_2$	6	159	4	*1, 2*
	1978	2HRZS/4HR	6	166	3	*3, 4*
Hong Kong[b]	1974	$2HRZS/4H_2Z_2S_2$	6	87	7	*5, 6*
Singapore	1973	2HRZS/4HRZ	6	78	0	*7–9*
		2HRZS/4HR	6	80	2	
	1978	$2HRZS/4H_3R_3$	6	97	1	*10, 11*
		$2HRZ/4H_3R_3$	6	109	1	

[a] H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
[b] Now Hong Kong Special Administrative Region of China (Hong Kong SAR).

Table 36
Duration of treatment for smear-positive pulmonary tuberculosis when rifampicin is not used in the continuation phase[a]

Country or area	Year of study	Regimen[b]	Duration of treatment (months)	No. of patients assessed	Relapse rate up to 2 years (%)	Reference
Africa	1972	2HRZS/4HT	6	179	7	*1, 2*
	1974	2HRZS/4HT	6	75	13	*13, 14*
		2HRZS/6HT	8	81	0	
		1HRZS/5HT	6	79	18	
		1HRZS/7HT	8	58	7	
Madras[c], India	1997	2HRZE/6HE	8	305	5	*12*

[a] Source: reference *12*.
[b] H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment.
[c] Now Chennai.

Smear-negative pulmonary tuberculosis

The optimum duration of treatment for smear-negative patients was investigated in a study in Hong Kong. Patients with five smears negative for acid-fast bacilli and X-rays suggestive of tuberculosis were treated for 2 or 4 months with an HRZS regimen (Table 38). Relapse rates were higher with 2–3 months of treatment and the study

Table 37
Intermittent short-course chemotherapy[a]

Country or area	Year of study	Regimen[b]	Duration of treatment (months)	No. of patients assessed	Relapse rate after 2 years (%)	Reference
Hong	1974	$4H_3R_3Z_3S_3/2H_2Z_2S_2$	6	71	6	*5, 6*
Kong[c]		$2H_3R_3Z_3S_3/4H_3R_3S_3$	6	220	3	
Madras,[d]	1980	$2H_3R_3Z_3S_3/4H_2R_2S_2$	6	111	2	*15, 16*
India		$2H_3R_3Z_3S_3/4R_2H_2$	6	101	3	
		$2H_2R_2Z_2S_2/4H_2R_2S_2$	6	108	3	
		$2H_2R_2Z_2S_2/4R_2H_2$	6	102	6	
	1995	$2H_3R_3Z_3E_3/4H_2R_2$	6	519	7	

[a] Source: reference *3*.
[b] H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
[c] Now Hong Kong SAR.
[d] Now Chennai.

Table 38
Duration of treatment for initially smear-negative pulmonary tuberculosisin Hong Kong[a,b]

Year of study	Initial culture status	Regimen[c]	Duration of treatment (months)	No. of patients assessed	Relapse rate after 2 years (%)	Reference
1976	Negative	No treatment	–	176	40	*17–19*
		2HRZS	2	165	4	
		3HRZS	3	162	2	
		$3PHS/H_2S_2$	12	160	0	
	Positive	2HRZS	2	72	15	
		3HRZS	3	69	9	
		$2PHS/H_2S_2$	12	68	0	
1978	Negative	3HRZS	3	364	1	*20*
		$3H_3R_3Z_3S_3$	3	345	1	
		$4H_3R_3Z_3S_3$	4	325	1	
	Positive	4HRZS	4	157	3	
		$4H_3R_3Z_3S_3$	4	136	3	
		$6H_3R_3Z_3S_3$	6	166	4	

[a] Source: references 18–20.
[b] Now Hong Kong SAR.
[c] H = isoniazid, P = protionamide, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.

concluded that smear-negative patients require at least 4 months of treatment. However, for consistency and a margin of safety, WHO recommends 6-month regimens for smear-negative pulmonary tuberculosis.

Results of further shortening the duration of treatment

Two groups of investigators in France and India, in search of a shorter duration of treatment for pulmonary tuberculosis, tried daily regimens of 3 months' duration (90 doses of HRZS) (Table 39). A regimen of HRZS given daily for 3 months in India achieved almost 100% culture conversion at 3 months, but 20% of patients had bacteriologically confirmed relapse (*23*). When fewer doses were given over a longer period – three times weekly for 2 months (27 doses) followed by twice weekly for 4 months (36 doses), making a total of 63 doses in 6 months – relapse rates were 4–6%. Thus, it is the period over which the drugs are given that is important, rather than the number of doses (*15*, *16*).

Similarly, 4-month regimens studied in Singapore also had high relapse rates (8–16%) (*7–9*). Two 5-month regimens (2HRZS/3HZS and 3HRZS/$2H_2Z_2S_2$) tried in Madras were effective and had low relapse rates (4–5%). However, this is the only study that investigated 5-month regimens and acceptable results were achieved only by using streptomycin for the entire 5 months of treatment.

Thus, there is at present no practical regimen of less than 6 months' duration that has given acceptable results in smear-positive tuberculosis.

Table 39
Shorter duration of treatment for smear-positive pulmonary tuberculosis

Country or area	Year of study	Regimen[a]	Duration of treatment (months)	No. of patients assessed	Relapse rate after 2 years (%)	Reference
Singapore	1973	2HRZS/2HRZ	4	79	11	*7–9*
		2HRZS/2HR	4	77	8	
Africa	1976	2HRZS/2HRZ	4	104	16	*21*, *22*
		2HRZS/2HR	4	104	11	
Madras,[b]	1977	3HRZS	3	200	20	*23*, *24*
India	1974	2HRZS/$3H_2Z_2S_2$	5	129		*25*, *26*
	1977	3HRZS/$2H_2Z_2S_2$	5	187	4	*23*

[a] H = isoniazid, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
[b] Now Chennai.

What is the optimum duration of standard, non-rifampicin-containing treatment?

There are situations in which rifampicin is either unavailable or rifampicin and pyrazinamide cannot be given to a patient. Before rifampicin and pyrazinamide became available, patients were treated for prolonged periods. For patients with initially sputum smear-positive tuberculosis, practically all effective regimens achieve bacteriological quiescence within 6 months of the start of treatment. However, relapse occurs in about a quarter of patients treated with streptomycin, isoniazid, and thioacetazone daily for 6 months (Table 40).

On the other hand, there is satisfactory evidence that more than 18 months of good treatment produces little, if any, additional benefit in terms of treatment success or prevention of relapse (*6*).

In studies in East Africa, addition of an initial supplement of streptomycin to the basic regimen of thioacetazone plus isoniazid daily for 8 weeks yielded a success rate of 96%; emergence of resistance was rare among patients who failed treatment. Two weeks of initial intensive treatment resulted in a failure rate of 10%, all with organisms resistant to isoniazid. Bacteriological response in patients who received an initial streptomycin supplement for 4 weeks was only slightly (2%) less favourable than in patients given the supplement for 8 weeks (Table 41).

The investigators concluded that it was desirable to supplement the daily thioacetazone–isoniazid regimen with streptomycin, preferably for the first 8 weeks of treatment; if this could not be achieved, the aim should be to give the streptomycin supplement for the first 4 weeks.

Other studies, in Madras and Singapore, showed that adding 2 weeks of initial

Table 40
Duration of treatment when rifampicin is not used

Country or area	Year of study	Regimen[a]	Duration of treatment (months)	No. of patients assessed	Relapse rate after 2 years (%)	Reference
East Africa	1970	6HTS	6	104	22	*27*, *28*
		6HS	6	112	29	
		2HTS/16HT	18	133	3	*28*
Madras,[b] India	1962	12HT	12	72	19	*29*
		12HP	12	454	17	
		12EHE	12	107	16	
		$12H_2S$	12	199	9	

[a] H = isoniazid, P = protionamide, R = rifampicin, Z = pyrazinamide, S = streptomycin. The number before the letters refers to the number of months of treatment; the subscript after the letters refers to the number of doses per week.
[b] Now Chennai.

Table 41

Response to treatment with streptomycin plus isoniazid and thioacetazone (STH) daily for 2, 4, or 8 weeks, followed by isoniazid plus thioacetazone in the continuation phase: assessment at 1 year[a]

Country or area	Duration of initial phase (STH)	No. of patients treated	Percentage of patients showing: favourable bacteriological response	isoniazid resistance	Reference
East Africa	8 weeks	162	96	3	*30*
	4 weeks	159	94	5	
	2 weeks	161	90	10	
	None[b]	147	88	10	

[a] Source: reference *1*.
[b] Thioacetazone plus isoniazid, without initial supplement.

intensive phase did not add any further benefit to the overall results of the regimens (*31*, *32*). A study in Czechoslovakia (*33*) investigated the role of three drugs during the intensive phase in a fully intermittent regimen and found there was no advantage in extending the phase to 13 weeks (98% and 99%, respectively). Thus the optimum duration of intensive phase in a conventional long-term treatment is 8 weeks.

References

1. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. East African–British Medical Research Councils. *Lancet*, 1974, 2:237–240.
2. Controlled clinical trial of four 6-month regimens of chemotherapy for pulmonary tuberculosis. Second report. Second East African/British Medical Research Council Study. *American Review of Respiratory Disease*, 1976, 114:471–475.
3. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis. *Tubercle*, 1983, 64:153–166.
4. Controlled clinical trial of 4 short-course regimens of chemotherapy (three 6-month and one 8-month) for pulmonary tuberculosis: final report. East and Central African/British Medical Research Council Fifth Collaborative Study. *Tubercle*, 1986, 67:5–15.
5. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis. First report. *American Review of Respiratory Disease*, 1978, 118:219–228.
6. Controlled trial of 6-month and 8-month regimens in the treatment of pulmonary tuberculosis: the results up to 24 months. *Tubercle*, 1979, 60:201–210.
7. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1979, 119:579–585.
8. Long-term follow-up of a clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1986, 133:779–783.

9. Clinical trial of six-month and four-month regimens of chemotherapy in the treatment of pulmonary tuberculosis: the results up to 30 months. *Tubercle*, 1981, 62:95–102.
10. Five-year follow-up of a clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1988, 137:1147–1150.
11. Clinical trial of three 6-month regimens of chemotherapy given intermittently in the continuation phase in the treatment of pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1985, 132:374–378.
12. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Tuberculosis Research Centre. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:509–517.
13. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis: first report. Third East African/British Medical Research Councils study. *American Review of Respiratory Disease*, 1978, 118:39–48.
14. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis. Second report. Third East African/British Medical Research Council Study. *Tubercle*, 1980, 61:59–69.
15. Balasubramanian R. Fully intermittent 6 months regimen for pulmonary tuberculosis in South India. *Indian Journal of Tuberculosis*, 1991, 38:51–53.
16. Tuberculosis Research Centre. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:40–45.
17. Sputum-smear-negative pulmonary tuberculosis: controlled trial of 3-month and 2-month regimens of chemotherapy. *Lancet*, 1979, 1:1361–1364.
18. A controlled trial of a 2-month, 3-month, and 12-month regimens of chemotherapy for sputum smear-negative pulmonary tuberculosis: the results at 30 months. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *American Review of Respiratory Disease*, 1981, 124:138–142.
19. A controlled trial of 2-month, 3-month, and 12-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 60 months. *American Review of Respiratory Disease*, 1984, 130:23–28.
20. A controlled trial of 3-month, 4-month, and 6-month regimens of chemotherapy for sputum-smear-negative pulmonary tuberculosis. Results at 5 years. Hong Kong Chest Service/Tuberculosis Research Centre, Madras/British Medical Research Council. *American Review of Respiratory Disease*, 1989, 139:871–876.
21. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. First report of 4th study. East African and British Medical Research Councils. *Lancet*, 1978, 2:334–338.
22. Controlled clinical trial of five short-course (4-month) chemotherapy regimens in pulmonary tuberculosis. Second report of the 4th study. East African/British Medical Research Councils Study. *American Review of Respiratory Disease*, 1981, 123:165–170.
23. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and

National Tuberculosis Institute, Bangalore. *American Review of Respiratory Disease*, 1986, 134:27–33.

24. Balasubramanian R et al. Five year results of a 3-month and two 5-month regimens for the treatment of sputum-positive pulmonary tuberculosis in South India. *Tubercle*, 1990, 71:253–258.
25. Study of chemotherapy regimens of 5 and 7 months' duration and the role of corticosteroids in the treatment of sputum-positive patients with pulmonary tuberculosis in South India. *Tubercle*, 1983, 64:73–91.
26. Santha T et al. Treatment of pulmonary tuberculosis with short course chemotherapy in South India – 5-year follow up. *Tubercle*, 1989, 70:229–234.
27. Controlled clinical trial of four short-course (6-month) regimens of chemotherapy for treatment of pulmonary tuberculosis. Third report. East African-British Medical Research Councils. *Lancet*, 1974, 2:237–240.
28. Results at 5 years of a controlled comparison of a 6-month and a standard 18-month regimen of chemotherapy for pulmonary tuberculosis. *American Review of Respiratory Disease*, 1977, 116:3–8.
29. Tripathy SP. Relapse in tuberculosis. *Indian Journal of Tuberculosis*, 1981, 28:45–57.
30. Isoniazid with thiacetazone (thioacetazone) in the treatment of pulmonary tuberculosis in East Africa–fifth investigation. A co-operative study in East African hospitals, clinics and laboratories with the collaboration of the East African and British Medical Research Councils. *Tubercle*, 1970, 51:123–151.
31. Controlled comparison of oral twice-weekly and oral daily isoniazid plus PAS in newly diagnosed pulmonary tuberculosis. *British Medical Journal*, 1973, 2:7–11.
32. Lee SK. A Singapore study of intermittent regimens plus isoniazid for pulmonary tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1976, 51:109–113.
33. Polansky F, Vodrazkova A, Viznerova A. International cooperative tuberculosis chemotherapy studies in Czechoslovakia. *Bulletin of the International Union Against Tuberculosis*, 1974, 49:403–408.

31. What are the most common adverse drug events to first-line tuberculosis drugs, and what is the procedure for reintroduction of drugs?

A. Harries[1]

Isoniazid (*1–3*)

Adverse effects

- Skin rash.
- Sleepiness and lethargy.
- Peripheral neuropathy (paraesthesia, numbness and limb pain).
- Hepatitis.

Rare adverse effects

- Convulsions, pellagra, arthralgia, anaemia, lupoid reactions.

Management

- For skin reactions – see below.
- For lethargy – reassurance.
- For peripheral neuropathy – this may be prevented by giving vitamin B6 (pyridoxine), 10 mg daily, or vitamin B complex. For established peripheral neuropathy, pyridoxine should be given at a larger dose of 50–75 mg daily.
- For hepatitis – see below.

Rifampicin

Adverse effects

- Gastrointestinal reactions (abdominal pain, nausea, vomiting).
- Hepatitis.
- Generalized cutaneous reactions.
- Thrombocytopenic purpura.
- On intermittent dosage, "flu syndrome".

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

Rare adverse effects

- Osteomalacia, pseudomembranous colitis, pseudoadrenal crisis, acute renal failure, shock, haemolytic anaemia.

Rifampicin may cause gastrointestinal symptoms such as anorexia, nausea, abdominal pain, and vomiting. These symptoms occur soon after administration and can last several hours. In contrast, the "flu syndrome" consists of fever, chills, malaise, headache, and bone pains.

Rifampicin is a powerful enzyme inducer and may therefore reduce serum concentrations of other drugs that the patient is taking. This is of particular importance in women taking oral contraceptives. Patients should be warned that rifampicin colours all body secretions (urine, tears, semen, and sweat) red or orange.

Management

- For gastrointestinal reactions, the patient should be reassured. If gastrointestinal intolerance is severe enough to risk interruption of treatment, suspension of rifampicin for 3 or 4 doses, use of medications that provide symptomatic relief (e.g. metoclopramide to counteract vomiting), or, as a last resort, giving rifampicin with small amounts of food may allow continued use of the drug in almost all patients (*1*). Although concomitant ingestion of food reduces absorption of rifampicin slightly, this is far preferable to complete discontinuation of rifampicin.
- For hepatitis and skin reactions – see below.
- For adverse effects such thrombocytopenic purpura, shock, acute renal failure, or haemolytic anaemia the drug must be immediately withdrawn and never used again.
- For the "flu syndrome", changing from intermittent to daily rifampicin administration can stop the reaction.

Pyrazinamide

Adverse effects

- Arthralgia.
- Hepatitis.

Rare adverse effects

- Gastrointestinal reactions, cutaneous reactions, sideroblastic anaemia.

Pyrazinamide may cause arthralgia by inhibiting renal tubular excretion of uric acid, and high concentrations of uric acid can lead to gout. Severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide are used for latent tuberculosis infection.

Management

- For joint involvement, simple treatment with analgesics usually minimizes symptoms. Indomethacin may be used for more severe joint involvement. If frank gout occurs, treatment with colchicine is required. Arthralgia is much less common with thrice-weekly treatment. Asymptomatic elevation of serum uric acid levels is expected and does not require either a change in medication or administration of other medications.
- For hepatitis – see below.

Ethambutol

Adverse effects

- The main adverse effect is retrobulbar neuritis.

Rare adverse effects

- Generalized cutaneous reactions, arthralgia, peripheral neuropathy, and – very rarely – hepatitis.

Note: Ethambutol may produce impairment of vision – red–green colour blindness, blurring, and decrease in visual acuity. However, the toxicity is dose dependent and occurs rarely when 15 mg/kg body weight is given daily or 25 mg/kg body weight is given three times a week.

Management

- It is good practice to carry out a basic examination of visual acuity before starting treatment with ethambutol. All patients should be warned that an ocular examination should be undertaken if visual symptoms occur. Impaired vision usually returns to normal within a few weeks of stopping the drug. Some programmes conduct monthly tests for red–green colour blindness (e.g. Ishihara tests), although the utility of this has not been demonstrated.

Streptomycin

Minor adverse effects

- Pain, rash, induration at injection site.
- Numbness around the mouth and tingling soon after the injection.

Major adverse effects

- Cutaneous hypersensitivity.
- Vestibular and auditory nerve damage to the patient and, in a pregnant woman, also to the fetus.
- Renal damage.

Management

- For minor adverse effects the patient can be reassured.
- For cutaneous hypersensitivity – see below.
- For vestibular, auditory, and renal damage, the risk increases with dose and age. The dose should not exceed 15–20 mg/kg and should be reduced in patients aged 45 years or more. Damage to the vestibular and auditory system usually occurs in the first 2 months and is manifested by ringing in the ears, giddiness, ataxia, and/or deafness. The condition is reversible if the drug dosage is reduced or the drug is stopped. Intermittent dosages (e.g. three times a week) are less likely to cause serious toxicity.

Thioacetazone

Common adverse effects

- Skin rash, sometimes with mucosal involvement.

Rare adverse effects

- Acute hepatic failure, agranulocytosis. Exfoliative dermatitis, which may be fatal, is more common in HIV-infected individuals.

Management

- If a rash or other sign of hypersensitivity develops, all treatment should be withdrawn and thioacetazone should not be used again. It can be replaced by ethambutol after the symptoms disappear. Because of the much higher frequency of toxicity in HIV-infected individuals, thioacetazone should not be used in patients suspected of being infected with HIV or in areas with high prevalence of HIV infection (see "What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?", page 159). For management of cutaneous sensitivity see below.

Cutaneous and generalized hypersensitivity reactions to TB drugs

Skin reactions

Itching with no rash or with a mild rash

If the patient (not receiving thiacetazone, see above) complains of itching without a rash or itching with a mild rash, symptomatic treatment with antihistamines may be tried and tuberculosis treatment continued. However, the patient must be monitored with each subsequent dose of antituberculosis drugs.

Itching with a moderate/severe rash

If a moderate or severe rash develops, all treatment should be stopped.

Management of severe rash

If the rash is severe, or if there is evidence of mucosal involvement, hypotension, or severe illness, corticosteroid treatment should be instituted. Oral prednisolone, 40–60 mg, should be given daily until there is a response; the dose should then be reduced gradually in the following days according to the patient's response. Tuberculosis treatment should be withheld until the reaction has completely subsided.

Reintroduction of antituberculosis drugs

Once the reaction has subsided, drugs can be reintroduced according to the schedule below.

Day	Drug, dose
1	Isoniazid 50 mg
2	Isoniazid 300 mg
3	Rifampicin–isoniazid (RH) (half tablet)
4	Rifampicin–isoniazid (RH) (one tablet)
5	Rifampicin–isoniazid (RH) (full dose)
6	Day 5 regimen + pyrazinamide (half tablet)
7	Day 5 regimen + pyrazinamide (one tablet)
8	Day 5 regimen + pyrazinamide (full dose)
9	Day 8 regimen + ethambutol (half tablet)
10	Day 8 regimen + ethambutol (one tablet)
11	Day 8 regimen + ethambutol (full dose)
12	Full dose of Rifampicin–isoniazid + pyrazinamide + ethambutol

Isoniazid and rifampicin are the least likely to cause a reaction and should be reintroduced first. The drugs at the bottom of the table are more likely to cause a reaction. If the initial cutaneous reaction was severe, smaller initial challenge doses should be given. If the patient is restarted on an adequate tuberculosis treatment regimen (e.g. isoniazid, rifampicin, and pyrazinamide), re-challenging with the implicated drug (e.g. streptomycin) is not advisable.

Drug-induced hepatitis

Features that indicate the need to stop medication

Transient, asymptomatic increases in serum liver transaminases occur during the early weeks of treatment. There is no need to interrupt or change treatment unless there is anorexia, malaise, vomiting, or clinically evident jaundice. Clinical features of concern include protracted vomiting, mental changes, and signs of bleeding – all of which suggest impending acute liver failure and require immediate discontinuation of antituberculosis medications.

Management of jaundice and other severe features

If jaundice or any of the clinical features suggestive of acute liver failure develop, all drugs must be stopped until the jaundice or hepatic symptoms have resolved and the liver enzymes have returned to baseline levels. If liver enzymes cannot be measured, it is advisable to wait 2 weeks after the jaundice has disappeared before starting tuberculosis treatment. Other causes of hepatitis must be sought.

Reintroduction of antituberculosis drugs

Once hepatitis has resolved, the same drug regimen can be reintroduced, either gradually or all at once. However, if hepatitis has been life-threatening and was not of viral origin, it is probably safer to use the regimen of streptomycin, isoniazid, and ethambutol.

Symptom-based approach to the management of drug reactions

Minor adverse effects not requiring stoppage of treatment

Symptoms	Drug	Management
Abdominal pain, nausea	Related to rifampicin	Reassure the patient
Burning of the feet	Related to isoniazid peripheral neuropathy	Continue isoniazid, and give pyridoxine 50–75 mg daily; large doses of pyridoxine may interfere with the action of isoniazid
Drowsiness	Related to isoniazid	Reassure patient
Gastrointestinal upset	Any oral medication	Reassure patient; give drugs with less water; give drugs over a longer period of time (e.g. 20 minutes); give drugs with a small amount of food; If these measures fail, provide antiemetic if appropriate
Joint pains	Related to pyrazinamide	Continue pyrazinamide; use aspirin or non-steroidal anti-inflammatory drug; use intermittent directly observed treatment, if possible
Red urine	Related to rifampicin	Reassure the patient
Women on rifampicin	Rifampicin may reduce the effectiveness of oral contraceptive pills	Alternative method of contraception should be provided

Major adverse effects requiring stoppage of treatment

Symptoms	Drug	Management
Loss of hearing	Related to streptomycin	Auroscopy to rule out wax. **Stop** streptomycin if no other explanation; use ethambutol instead
Dizziness	If true vertigo and nystagmus, related to streptomycin	**Stop** streptomycin. If just dizziness with no nystagmus, try dose reduction for one week; if there is no improvement stop streptomycin and use ethambutol instead
Generalized reactions including shock, purpura	May be due to rifampicin, pyrazinamide, and/or streptomycin	**Stop** all medication; use different combination of drugs
Jaundice	May be due to drug-induced hepatitis	**Stop** all antituberculosis drugs until jaundice resolves and liver enzymes revert to baseline levels (see text)
Moderate–severe skin rash	Related to all tuberculosis drugs	**Stop** tuberculosis drugs (see text)
Visual impairment	Related to ethambutol	Visual examination. **Stop** ethambutol
Vomiting/confusion	Suspect drug-induced hepatitis	Urgent liver enzyme tests. If liver enzymes tests unavailable, **stop** tuberculosis drugs and observe

References

1. Girling DJ. Adverse effects of tuberculosis drugs. *Drugs*, 1982, 23:56–74.
2. Harries AD, Maher D. *TB/HIV: a clinical manual.* Geneva, World Health Organization, 1996 (document WHO/TB/96.200).
3. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2002.313).

32. What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?[1]

H. Rieder[2]

Thioacetazone is one of the oldest known antituberculosis drugs. When it was introduced in the late 1940s, there was good evidence of its efficacy, but the relatively high dosages used in those days meant that adverse effects and toxicity were frequent. Thus, with the advent of isoniazid a few years later, thioacetazone was quickly forgotten.

In the early 1960s, thioacetazone was reinvestigated as a companion drug to isoniazid. The intention was to find an alternative to *p*-aminosalicylic acid (PAS) that would prevent the development of resistance to isoniazid equally well and be less bulky (as well as less expensive). Many pilot studies were conducted to establish the optimum dosage of both drugs. The result was the introduction of a regimen containing 150 mg of thioacetazone and 300 mg of isoniazid, given in one dose daily, which proved to be as effective as the PAS–isoniazid combination.

Thioacetazone plus isoniazid with an initial supplement of streptomycin

Several trials investigated the influence of a three-drug initial phase on the thioacetazone–isoniazid regimen. An initial supplement of streptomycin improved the results, with 4 and 8 weeks of streptomycin giving almost the same results.

In many low-income countries, thioacetazone-containing regimens have been used widely because they offer the following advantages:

- They are convenient for patients because only one tablet a day is required.
- They are the least expensive efficacious treatment regimen.
- The tablets have a long shelf life. Thioacetazone is stable even in tropical climates.

Effectiveness of thioacetazone with isoniazid in routine practice

The results obtained in a trial in Kenya were compared with those in a group of patients treated by the routine tuberculosis service (*1*) and provided valuable information. Both groups received the same regimen, i.e. three drugs (300 mg of isoniazid,

[1] Based on the chapter in the previous edition by K Toman.

[2] Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.

150 mg of thioacetazone, and 1 g of streptomycin) daily for 2 months, followed by two drugs (150 mg of thioacetazone plus 300 mg of isoniazid, in a single tablet) daily for 10 months. Bacteriological quiescence was achieved in 96% of patients in the Kenyan study at 12 months, compared with only 76% in the "routine" group (*1*). Analysis of the records showed clearly that the results were dependent upon the regularity and duration of treatment after the initial intensive phase. Patients who took treatment irregularly or stopped their treatment early did poorly; those who took treatment regularly and continued for the full year did well. There was considerably more irregularity in the group of routinely treated patients than in the trial group. Irregularity of treatment in the continuation phase may nullify the benefits of an initial intensive phase. As long as a high level of regularity cannot be ensured, even first-rate regimens will produce inadequate results.

Thioacetazone plus isoniazid in the continuation phase following rifampicin-containing intensive phase

A regimen consisting of 2 months of isoniazid, rifampicin, pyrazinamide and streptomycin, followed by 6 months of thioacetazone plus isoniazid (2HRZS/6HT) was investigated in East Africa (*2*). Results are summarized in Table 42.

This became the main treatment regimen for sputum smear-positive patients without a history of prior treatment in many national tuberculosis programmes with limited resources. Its advantages are:

- It is the least expensive short-course regimen, with high efficacy in patients with fully susceptible organisms.
- Directly observed treatment can be organized during the intensive phase, with a self-administered continuation phase. The probability of selecting rifampicin-resistant mutants is low, even in the presence of initial isoniazid resistance.
- In a patient for whom the above regimen fails, the possibility of cure with a re-treatment regimen based solely on first-line drugs is preserved, as the patient will

Table 42
Treatment outcome in patients treated with 2HRZS/6HT[a]

Outcome	Pretreatment strain susceptibility to isoniazid	
	Susceptible	Resistant
Treatment failure	0/81	1/8
Relapse	0/81	1/7

[a] Source: reference *2*.

always receive at least two drugs (rifampicin and ethambutol) to which the organism is likely to be susceptible.

Thioacetazone and HIV infection

Cutaneous reactions are among the most important adverse side-effects of thioacetazone. A cutaneous reaction may present first as itching; this may be followed by a rash that may then quickly develop further into toxic epidermal necrolysis, with a case-fatality of 20–30%. An elegant study in Kenya demonstrated the causal relationship between adverse cutaneous reactions, thioacetazone, and HIV infection (*3*). The association is so strong and the harmful effects so serious that there is universal agreement that patients known or suspected to have HIV infection should never be given thioacetazone. Furthermore, patients receiving thioacetazone who develop any form of cutaneous reaction should be promptly taken off the drug and never receive it again.

Because tuberculosis patients in most settings where HIV and tuberculosis are common are not routinely offered HIV testing, and their HIV status is therefore unknown, thioacetazone should not be used in areas where prevalence of HIV infection is high.

The closest alternative regimen uses ethambutol and isoniazid in the continuation phase, for the same duration; it is well tolerated and has a similar high efficacy (*4*). Its drawback, in addition to the higher cost and the shorter shelf-life of ethambutol, is that, for patients with true treatment failure, the standard WHO-recommended re-treatment regimen may be less effective because ethambutol resistance may have emerged. This may increase the risk of rifampicin resistance, particularly in patients with HIV infection (*5*).

References

1. Kent PW et al. The therapy of pulmonary tuberculosis in Kenya: a comparison of the results achieved in controlled clinical trials with those achieved by the routine treatment services. *Tubercle*, 1970, 51:24–38.
2. Controlled clinical trial of four short-course regimens of chemotherapy for two durations in the treatment of pulmonary tuberculosis. Second report. Third East African/British Medical Research Council Study. *Tubercle*, 1980, 61:59–69.
3. Nunn P et al. Cutaneous hypersensitivity reactions due to thioacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*, 1991, 337:627–630.
4. A controlled clinical trial of oral short-course regimens in the treatment of sputum-positive pulmonary tuberculosis. Tuberculosis Research Centre. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:509–517.
5. Vernon A et al. Acquired rifamycin monoresistance in patients with HIV-related tuberculosis treated with once-weekly rifapentine and isoniazid. *Lancet*, 1999, 353:1843–1847.

33. How does management of extrapulmonary tuberculosis differ from that of pulmonary tuberculosis?

R. Balasubramanian,[1] *R. Rajeswari*[1] *& T. Santha*[1]

Challenges in diagnosis

The treatment of extrapulmonary tuberculosis differs from that of pulmonary tuberculosis in several ways. This is largely because of the difficulty of diagnosis, which often leads to empirical treatment without pathological or bacteriological confirmation. However, diagnosis made only on clinical grounds leads to over-diagnosis and unnecessary treatment of a large number of patients (*1*). In developing countries, the problems of diagnosis are compounded by a lack of diagnostic resources. Tuberculosis may not be considered at all in the differential diagnosis, resulting in delay or deprivation of treatment (*2*). Extrapulmonary forms of tuberculosis occur in all age groups, adding to diagnostic and treatment difficulties.

Treatment and management of extrapulmonary tuberculosis

Extrapulmonary tuberculosis is usually paucibacillary, and any treatment regimen effective in pulmonary tuberculosis is likely to be effective in the treatment of extrapulmonary tuberculosis as well. For the purposes of treatment, extrapulmonary tuberculosis can be classified into severe and non-severe forms. Severe forms include meningeal tuberculosis, spinal tuberculosis, neuro-tuberculosis, abdominal tuberculosis, bilateral pleural effusion, pericardial effusion, and bone and joint tuberculosis involving more than one site. Extrapulmonary tuberculosis of other sites is classified as non-severe.

There are few reports of the use of short-course chemotherapy in the treatment of extrapulmonary tuberculosis (*3*). The difficulty of defining a clear-cut "end-point" for assessing the efficacy of treatment of extrapulmonary tuberculosis has led to varying durations of treatment, and there have been relatively few controlled clinical trials (*4*). The principles involved in the diagnosis and management of extrapulmonary tuberculosis have therefore evolved mainly from experience gained in randomized controlled clinical trials on pulmonary tuberculosis. However, studies on extrapulmonary tuberculosis (tuberculosis of the spine, tuberculous lymphadenitis, abdominal tuber-

[1] Deputy Director, Tuberculosis Research Centre, Chennai, India.

culosis, and brain tuberculoma) have clearly established the efficacy of short-course treatment (6–9 months) in both children and adults (*5*), with the overall favourable response varying from 87% to 99% (Table 43). Intermittent regimens have been shown to be as effective as daily regimens.

For the severe forms, it is preferable to treat with four drugs in the initial intensive phase and, if required, the total duration of treatment can be extended to 9 months, especially in tuberculous meningitis and neuro-tuberculosis. Steroids should be given in case of tuberculous meningitis with neurological impairment, massive pleural effusion, or tuberculous pericarditis. Lymph nodes can enlarge, persist, and become superinfected with bacteria in the course of tuberculosis treatment. Generally, no modification or prolongation of the tuberculosis treatment regimen is indicated.

Even though treatment gives good results in most forms of extrapulmonary tuberculosis, there are a few exceptions, such as meningitis and spinal tuberculosis (Pott's disease), in which the outcome depends on early diagnosis. In tuberculous meningitis, even with short-course treatment the outcome is related to the stage of the disease at the time treatment is started; only a minority of patients with severe disease recover completely (*11*). Predictors of poor outcome are younger age and advanced stage; neurological sequelae are directly related to the stage of the disease and the duration of symptoms before admission. Similarly, in patients with spinal tuberculosis, the time taken for neurological recovery is not related to the type of treatment regimen but appears to be influenced by factors such as initial motor power, presence or absence of bed sore, and duration of kyphosis (*11*).

The long-term efficacy of short-course treatment regimens of 6–12 months' duration in various forms of extrapulmonary tuberculosis has been studied (*5*). Patients were followed up systematically for 5–10 years. Relapse rates during long-term follow-up were less than 4% in all studies reviewed, demonstrating the adequacy of short-course treatment regimens for extrapulmonary tuberculosis.

Role of surgery

The introduction of short-course treatment for extrapulmonary tuberculosis has made surgery less important. It may be required for diagnosis (biopsy) and management of complications such as tuberculosis empyema and chronic constriction or destroyed kidney or lung with recurrent infections. The roles of surgery and drug treatment in the management of patients with tuberculosis of the spine were investigated in trials by the British Medical Research Council (*12*). It was concluded that operative procedures were generally unnecessary; ambulatory short-course treatment regimens were highly effective, and surgery was indicated only in patients aged less than 15 years and having an initial angle of kyphosis more than 30° (*13*). When surgery is indicated, anterior and posterior fusion are recommended to reduce kyphosis and improve function of the spine (*14*).

Table 43

Efficacy of treatment regimens in different forms of extrapulmonary tuberculosis

Studies	Treatment regimen[a]	Duration (months)	No. of patients	Follow-up period (months)	Overall favourable response (%)	Reference
Spinal tuberculosis	6HR + modified Hong Kong surgery	6	78	120	90	*6*
	6HR	6	78	120	94	
	9HR	9	79	120	99	
Pott's disease	Radical surgery + 2HERS/7H_2R_2	9	20	60	90	*7*
	2HERS/7H_2R_2	9	11	60	73	
Tuberculous lymphadenitis	2$H_3R_3Z_3S_3$/4H_2S_2	6	168	36	97	*8*
Abdominal tuberculosis	2HRZ/4HR	6	85	60	94	*9*
	EHS/HE	12	93	60	87	
Brain tuberculoma	3HRZ/3H_2R_2	9	47	24	89	*10*
	3$H_3R_3Z_3$/6H_2R_2	9	44	24	91	

[a] H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin. The number before the letters refers to the number of months of treatment. The subscript after the letters refers to the number of doses per week.

References

1. Ramanathan M et al. Abdominal tuberculosis: a presumptive diagnosis. *Singapore Medical Journal*, 1997, 38:364–368.
2. Ormerod LP. The management of extra-pulmonary tuberculosis. In: Gangadharam PRJ, ed. *Mycobacteria*. New York, Chapman & Hall, 1997:236–278.
3. Dutt AK, Moers D, Stead WW. Short-course chemotherapy for extra-pulmonary tuberculosis. Nine years' experience. *Annals of Internal Medicine*, 1986, 104:7–12.
4. Short course chemotherapy for tuberculosis of lymph nodes: a controlled trial. British Thoracic Society Research Committee. *British Medical Journal (Clinical Research)*, 1985, 290:1106–1108.
5. Balasubramanian R, Ramachandran R. Management of non-pulmonary forms of tuberculosis: review of TRC studies over two decades. *Indian Journal of Pediatrics*, 2000, 67: S34–S40.
6. Short course chemotherapy for tuberculosis of the spine. A comparison between ambulant treatment and radical surgery – 10-year report. *Journal of Bone and Joint Surgery. British Volume*, 1999, 81:464–471.
7. Rajeswari R et al. Short-course chemotherapy in the treatment of Pott's paraplegia: report on five-year follow-up. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:152–158.
8. Jawahar MS et al. Short course chemotherapy for tuberculous lymphadenitis in children. *British Medical Journal*, 1990, 301:359–362.
9. Balasubramanian R et al. Randomised controlled clinical trial of short course chemotherapy in abdominal tuberculosis: a five-year report. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:44–51.
10. Rajeswari R et al. A controlled clinical trial of short-course chemotherapy for tuberculoma of the brain. *Tubercle and Lung Disease*, 1995, 76:111–117.
11. Alvarez S, McCabe WR. Extrapulmonary TB revisited: a review of experience at Boston city and other hospitals. *Medicine*, 1984, 63:25–55.
12. Thirteenth report of MRC working party on TB of spine. *Journal of Bone and Joint Surgery. British Volume*, 1998, 80:456.
13. Parthasarathy R et al. Short course chemotherapy for tuberculosis of spine. A comparison between ambulant and radical surgery. *Journal of Bone and Joint Surgery. British Volume*, 1998, 81:464.
14. Upadhyay SS et al. Longitudinal changes in spinal deformity after anterior spinal surgery for tuberculosis of the spine in adults. A comparative analysis between radical and debridement surgery. *Spine*, 1994, 19:542–549.

34. How does treatment of tuberculosis differ in patients with pregnancy, liver disease, or renal disease?

A. Harries[1]

Treatment in pregnant women (*1, 2*)

The four basic antituberculosis drugs – isoniazid, rifampicin, pyrazinamide, and ethambutol – are not teratogenic and are safe to use in pregnant women. Streptomycin and other aminoglycosides are potentially ototoxic to the fetus, and therefore should not be used in pregnancy: ethambutol can be used instead. *p*-Aminosalicylic acid has been used safely.

Ethionamide and protionamide are teratogenic and can induce premature labour, and should not be used in pregnancy. Fluoroquinolones are teratogenic in laboratory animals.

Active tuberculosis in pregnancy must be treated because the disease will do more harm than the drugs. It is important that pregnant women understand that successful treatment of tuberculosis with one of the recommended standard regimens is important for a successful outcome of the pregnancy.

Treatment in a breastfeeding woman and her baby

A woman who is breastfeeding and has tuberculosis should receive a full course of tuberculosis treatment. All the antituberculosis drugs are compatible with breastfeeding, and a woman taking them can safely continue to breastfeed her baby. The mother and baby should stay together and the baby should continue to breastfeed in the usual way. However, the concentrations of the drugs in breast milk are insufficient to prevent or treat tuberculosis in infants.

In children, tuberculosis is most severe in those under the age of 6 years and, in particular, in those aged 3 years and under. A child who is in close contact with people who have tuberculosis should be brought to a health unit to be evaluated for symptoms of the disease. Children who have no symptoms should receive preventive treatment for latent tuberculosis infection regardless of whether they have been vaccinated with BCG. Preventive treatment consists of administration of isoniazid (5 mg/kg body weight) daily for 6–9 months.

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

If a tuberculin skin test is available, it should be administered after 3 months:

- If the induration from the tuberculin test is less than 6 mm in diameter, preventive treatment should be stopped and the child should be vaccinated with BCG (if this has not been done previously).
- If the induration is 6 mm or more in diameter, preventive treatment with isoniazid should continue for another 3–6 months.

Treatment in patients with liver disorders (*1–4*)

Patients with the following conditions can receive the usual short-course treatment regimens:

Established chronic liver disease

Isoniazid plus rifampicin plus one or two non-hepatotoxic drugs such as streptomycin and ethambutol can be used for a total treatment duration of 8 months. If there is concern about the extent of liver damage, e.g. the patient has ascites with evidence of portal hypertension, an alternative regimen is streptomycin plus isoniazid plus ethambutol in the initial phase, followed by isoniazid and ethambutol in the continuation phase, for a total treatment duration of 12 months. Patients with established chronic liver disease should not receive pyrazinamide. Recommended regimens are therefore 2HRES/6HE, 2HRE/6HE, or 2HSE/10HE.

Acute hepatitis

It is uncommon for a patient to contract tuberculosis and acute viral hepatitis at the same time. However, it is not uncommon for patients to develop acute viral hepatitis during the course of tuberculosis treatment; in many settings, it is a common cause of jaundice during treatment (*5*). In some cases, it is possible to defer tuberculosis treatment until the hepatitis has resolved; in others it may be necessary to continue to treat tuberculosis. In the latter case, a combination of streptomycin and ethambutol for a maximum of 3 months is the safest option until the hepatitis has resolved. The patient can then receive the continuation phase of treatment with isoniazid and rifampicin for 6 months (6HR). In cases of extensive tuberculosis, a fluoroquinolone such as ofloxacin can be considered in conjunction with streptomycin and ethambutol as an interim non-hepatotoxic regimen, that is generally well tolerated.

Treatment of patients with renal failure (*3, 4*)

Isoniazid, rifampicin, and pyrazinamide can be given in normal dosage to patients with renal failure because these drugs are either almost entirely eliminated by biliary excretion or are metabolized into non-toxic compounds. In severe renal failure, patients receiving isoniazid should also receive pyridoxine to prevent peripheral neuropathy; pyrazinamide can compound the hyperuricaemia that occurs in renal failure.

Ethionamide and protionamide are also excreted almost entirely by non-renal routes, and can be given in the normal dosage in renal failure.

Streptomycin and ethambutol are excreted by the kidney. In the presence of renal failure, doses of both drugs must be reduced. Where facilities are available to monitor renal function, dosage can be adjusted appropriately. Thioacetazone is excreted partially in urine, but the margin between therapeutic and toxic dose is so narrow that patients with renal failure should not receive this drug. The safest regimen for patients with renal failure is 2HRZ/4HR.

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003. (WHO/CDS/TB/2003.313).
2. Chan SL, Yew WW. Chemotherapy. In: Davies PDO, ed. *Clinical tuberculosis*, 2nd ed. London, Chapman & Hall, 1998:243–264.
3. Mitchell I et al. Anti-tuberculous therapy and acute liver failure. *Lancet*, 1995, 345:555–556.
4. Thompson NP et al. Anti-tuberculous medication and the liver: dangers and recommendations in management. *European Respiratory Journal*, 1995, 8:1384–1388.
5. A controlled clinical trial of 3- and 5-month regimens in the treatment of sputum-positive pulmonary tuberculosis in South India. Tuberculosis Research Centre, Madras, and National Tuberculosis Institute, Bangalore. *American Review of Respiratory Disease*, 1986, 134:27–33.

35. How does treatment of tuberculosis differ in persons infected with HIV?

A. Harries[1]

Treatment categories and treatment regimens

In general, tuberculosis treatment is the same for HIV-infected as for HIV-negative tuberculosis patients, with the exception of the use of thioacetazone. Thioacetazone is associated with a high risk of severe, and sometimes fatal, skin reactions in HIV-infected individuals (*1*). Ethambutol should therefore be used instead of thioacetazone in patients known or suspected to have HIV infection (see "What are the merits of thioacetazone as a companion drug to isoniazid, and what is the efficacy of the regimen of isoniazid plus thioacetazone?", page 159).

Some countries may not have the resources to substitute ethambutol for thioacetazone. Where the use of thioacetazone cannot be avoided, it is essential to warn patients about the risk of severe skin reactions. Patients must be advised to stop thioacetazone immediately if a skin reaction occurs and report to the nearest health facility.

Streptomycin remains a useful drug provided that adequate sterilization and safe disposal of syringes and needles can be ensured. Some countries with a high prevalence of HIV infection may not be able to ensure adequate sterilization of syringes and needles and should therefore not use streptomycin.

Response of tuberculosis patients infected with HIV to tuberculosis treatment

Response in patients who complete treatment

Patients who complete treatment show the same clinical, radiographic, and microbiological response to short-course treatment whether they are HIV-infected or HIV-negative (*2*, *3*).

Case-fatality

HIV-infected patients have a much higher mortality during and after tuberculosis treatment compared with HIV-negative patients (*2*, *3*). In sub-Saharan Africa, approx-

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

imately 30% of HIV-positive, smear-positive tuberculosis patients die within 12 months of starting treatment, and about 25% of those who complete treatment die during the following 12 months. In the pre-HIV era, smear-negative pulmonary tuberculosis was a disease with a good treatment outcome. Evidence is slowly accumulating that in some areas HIV-infected, smear-negative pulmonary tuberculosis patients may have a worse prognosis than HIV-positive patients with smear-positive pulmonary tuberculosis. The larger number of deaths in HIV-infected tuberculosis patients during and after treatment is due partly to tuberculosis itself but largely to other HIV-related problems.

Case-fatality is lower in HIV-infected tuberculosis patients treated with short-course regimens than in those treated with standard 12-month regimens that do not include rifampicin (*4*, *5*). This is partly because short-course treatment is more effective, but may also be related to the fact that rifampicin has broad-spectrum antibacterial activity as well as antituberculosis activity. Rifampicin may thus reduce deaths due to HIV-related bacterial infections during tuberculosis treatment. Adjunctive treatments given with antituberculosis drugs may reduce case-fatality rates.

There is evidence that direct observation of treatment is even more important for HIV-infected tuberculosis patients. In a multivariate analysis, Alpert et al. (*6*) found that self-administration of treatment was associated with higher case-fatality rates among HIV-infected tuberculosis patients, even when all other factors were controlled for. Similarly, Alwood et al. (*7*) found a case-fatality rate of 15% in HIV-infected tuberculosis patients treated with direct observation of treatment, compared with 43% in patients who received similar treatment regimens under self-administration.

Relapse

The tuberculosis relapse rate is low in HIV-infected tuberculosis patients who complete a full rifampicin-containing short-course treatment regimen. Extending the duration of the treatment regimen from 6 to 12 months in such patients further reduces the frequency of relapse (*8*). However, this difference is marginal and, given the expense, toxicity, and difficulty of longer treatment, most programmes treat HIV-infected patients for 6, or at most 9, months. The relapse rate is higher in HIV-infected than in HIV-negative tuberculosis patients treated with the standard regimen or a short-course regimen that uses ethambutol and isoniazid during the continuation phase (*9*–*11*).

TB treatment and antiretroviral therapy

Antiretroviral (ARV) drugs are increasingly available to persons living with HIV/AIDS, many of whom also have latent tuberculosis infection or active tuberculosis disease. Effectively given, ARVs lead to a gradual increase in host immunity, which in principle should reduce the risk of progression from latent tuberculosis infection to active tuberculosis disease. Paradoxically, ARVs can sometimes lead to the development of active TB in HIV-positive persons with latent infection, this development

being part of the immune reconstitution syndrome. Of the currently licensed ARV drugs, most protease inhibitors and non-nucleoside reverse transncriptase inhibitors interact with rifampicin and therefore should not be taken with rifampicin-based regimens, although they may be able to be given safely with rifabutin (*12–15*).

THe optimal ARV regimens for use with anti-TB treatment and the best time to start ARV therapy in patients with TB have still to be worked out. Among patients on treatment for tuberculosis who are begun on ARVs, there can be paradoxical worsening of symptoms, presumably related to improved inflammatory response (*16–17*).

It is likely that ARV therapy will reduce HIV-related morbidity and mortality during and after anti-TB treatment, and may also reduce the risk of recurrent TB in HIV-positive persons who have successfully completed anti-TB treatment.

References

1. Nunn P et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*, 1991, 337:627–630.
2. Raviglione MC et al. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11:S115–S123.
3. Harries AD. Tuberculosis in Africa: clinical presentation and management. *Pharmacology and Therapeutics*, 1997, 73:1–50.
4. Okwera A et al. Randomised trial of thiacetazone and rifampicin-containing regimens for pulmonary tuberculosis in HIV-infected Ugandans. *Lancet*, 1994, 344:1323–1328.
5. Elliott AM et al. The impact of human immunodeficiency virus on mortality of patients treated for tuberculosis in a cohort study in Zambia. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1995, 89:78–82.
6. Alpert PL et al. A prospective study of tuberculosis and human immunodeficiency virus infection: clinical manifestations and factors associated with survival. *Clinical Infectious Diseases*, 1997, 24:661–668.
7. Alwood K et al. Effectiveness of supervised, intermittent therapy for tuberculosis in HIV-infected patients. *AIDS*, 1994, 8:1103–1108.
8. Perriëns JH et al. Pulmonary tuberculosis in HIV-infected patients in Zaire. A controlled trial of treatment for either 6 or 12 months. *New England Journal of Medicine*, 1995, 332:779–784.
9. Perriëns JH et al. Increased mortality and tuberculosis treatment failure rate among human immunodeficiency virus (HIV) seropositive compared with HIV seronegative patients with pulmonary tuberculosis treated with "standard" chemotherapy in Kinshasa, Zaire. *American Review of Respiratory Disease*, 1991, 144:750–755.
10. Hawken M et al. Increased recurrence of tuberculosis in HIV-1-infected patients in Kenya. *Lancet*, 1993, 342:332–337.
11. Elliott AM et al. The impact of human immunodeficiency virus on response to treatment and recurrence rate in patients treated for tuberculosis: two-year follow-up of a cohort in Lusaka, Zambia. *Journal of Tropical Medicine and Hygiene*, 1995, 98:9–21.
12. Burman WJ, Gallicano K, Peloquin C. Therapeutic implications of drug interactions in the treatment of human immunodeficiency virus-related tuberculosis. *Clin Infect Dis* 1999, 28:419–430.

13. US Department of Health and Human Services, Centers for Disease Control and Prevention. Prevention and treatment of tuberculosis among patients infected with human immunodeficiency virus: principles of therapy and revised recommendations.
14. Morbid Mortal Wkly Rep 1998, 47(RR-20):1–58.
15. Burman WJ, Jones BE. Treatment of HIV-related tuberculosis in the era of effective antiretroviral therapy. *Am J Respir Crit Care Med* 2001, 164:7–12.
16. Narita M, Ashkin D, Hollender ES, Pitchenik AE. Paradoxical worsening of tuberculosis following antiretroviral therapy in patients with AIDS. *Am J Resp Crit Care Med* 1998, 158:157–161.
17. Navas E, Martin-Davila P, Moreno L, Pintado V, Casado JL, Fortun J, et al. Paradoxical reactions of tuberculosis in patients with the acquired immunodeficiency syndrome who are treated with highly active antiretroviral therapy. *Arch Intern Med 2*002, 162:97–99.

36. What were the main findings of the Madras study comparing home and sanatorium treatment?

K. Toman[1]

Objectives of the trial

The study was designed to assess the relative merits of home and sanatorium treatment. It focused on the effect of physical activity, diet, and accommodation on the outcome of treatment in terms of radiographic and bacteriological response. Of particular interest was the problem of infectivity of patients treated at home, i.e. the frequency of disease in close family contacts.

Study design

Persons living in Madras (now Chennai), up to about 8 km from the Tuberculosis Chemotherapy Centre (now the Tuberculosis Research Centre), who were more than 12 years of age, had a sputum smear and/or culture positive for tubercle bacilli, and had received no previous tuberculosis treatment (or for not longer than 2 weeks), were eligible. Most patients had far-advanced cavitary disease. Those with tuberculosis resistant to isoniazid or *p*-aminosalicylic acid (PAS), or with serious concomitant disease such as leprosy or diabetes, or in need of emergency medical action, or known to be pregnant were excluded. Almost all the patients lived in the poorest section of Madras.

Drug regimen

Every patient received isoniazid and PAS (sodium salt), the standard treatment at the time of the trial in the late 1950s.

Home regimen

Patients allocated to home treatment were asked to take their drugs at home and were expected to attend the Centre once a week to collect a week's supply of drugs. In addition, each patient was visited by a health visitor and on certain occasions a "surprise" pill count was done, and a specimen of urine was collected to test whether the patient

[1] Deceased.

was taking the medicine as prescribed. Patients' families received a free supply of milk powder monthly.

Sanatorium treatment

Patients allocated to treatment in a sanatorium were admitted to the main sanatorium in Madras, which was well staffed and had complete diagnostic and nursing facilities. Every patient was seen weekly by the medical staff of the centre, by a health visitor, and by a social worker.

Physical activity

Patients admitted to the sanatorium remained in bed (with bed-pan facilities) for 3–4 months. After that period they were allowed to be up for 2, and later for 4, hours daily. After 6 months, those considered to be sufficiently fit were permitted to go home once a month, but had to return the same evening.

Patients allocated to home treatment were advised to take rest and to return gradually to their previous physical activity or work only when medically fit. However, most of them were ambulatory much of the time. Female patients generally had to continue their usual work at home, and many male patients returned to work well before they could be considered fit; some refused to stop work at all. Those who had no regular jobs often went for long walks.

At least once a week the home patients had to travel to the Centre – a distance of up to 8 km each way – usually on foot because they were poor.

Most male patients were craftsmen, unskilled labourers, domestic servants, or street vendors, and they usually had to work very long hours in tropical conditions.

Diet

The patients in the sanatorium received a rich diet in terms of calories, fats, proteins (including animal proteins), minerals, and vitamins (*1*). The diet of home patients was inferior: for example, only 8% of them had a daily intake of 30 g or more animal protein, whereas all sanatorium patients had at least that much. The difference in the diet is magnified by the fact that the home patients had much less rest and soon resumed their previous activities.

Accommodation

Whereas sanatorium patients were treated in clean, well-ventilated wards, most home patients lived in overcrowded conditions with a floor space of less than 4.5 m^2 per person.

Allocation of treatment

Allocation was based on random numbers. For every patient eligible for the study, a sealed envelope was opened, and the random number on a slip of paper inside it was

decoded by the Centre's statistical unit (see "What are the principles and requirements of a controlled clinical trial?", page 285).

Neither the Centre's staff (medical and non-medical) nor anyone else had prior knowledge of the treatment that any patient was to receive.

Despite the randomization, by chance the patients treated at home – especially females – were at a certain disadvantage with respect to the severity of the disease, i.e. they had greater cavitation, lung involvement, and bacterial content of sputum.

Results and conclusions

Clinical response

There were three deaths from tuberculosis – two were patients treated in the sanatorium and one had been treated at home. (One death not due to tuberculosis, the result of electrocution at work, occurred in a home patient.)

The sanatorium patients gained more weight than those treated at home.

Radiological response

Radiological progress in terms of reduced cavity size or cavity closure was similar in both groups. When patients with corresponding pretreatment lesions were compared, progress in the two series showed even greater similarity.

Bacteriological response

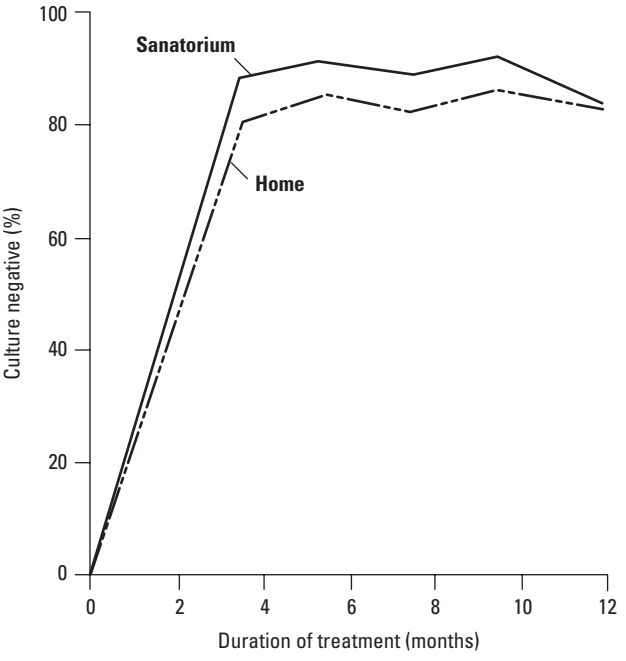
There was rapid bacteriological progress in both groups (Table 44, Figure 14). Sputum positivity declined at almost the same rate in home and sanatorium patients. At 4 months, about 90% had achieved sputum conversion, i.e. multiple specimens examined monthly were negative on culture. Although some individual changes occurred

Table 44
Sputum conversion (all cultures negative) at 2-month intervals, in home and sanatorium patients[a]

Months	Percentage of home patients	Percentage of sanatorium patients
2	45	49
4	89	93
6	91	96
8	89	95
10	92	95
12	90	92

[a] Source: reference *2*.

Figure 14
Sputum conversion in patients treated at home or in a sanatorium (multiple culture-negative specimens)



later, the high level of sputum conversion was maintained until the end of 12 months of treatment.

Quiescence of disease and relapses

The assessment of quiescence of the disease was based on very stringent criteria, i.e. 7–9 cultures examined during the last 3 months had all to be negative. In 75 (92%) of 81 sanatorium patients and 71 (86%) of 82 home patients, the disease was classified as quiescent (Table 45) (*2*).

The frequency of bacteriological relapse was studied in 126 patients whose disease was quiescent at the end of one year of treatment (*3*). Thus, 69 sanatorium patients and 57 home patients were followed up for up to 5 years (Table 46). During that observation period, 11 relapses occurred: 7 (10%) in the sanatorium patients and 4 (7%) in the home patients. The small differences observed at one year (see preceding paragraph) were clearly levelling out. Of the 11 patients who relapsed, eight did so in the first year of follow-up.

Table 45
Quiescence of disease at 1 year in patients treated at home or in sanatorium[a]

Place of treatment	No. of patients	Quiescence at 1 year	
		No.	%
Home	82	71	86
Sanatorium	81	75	92

[a] Source: reference *2*.

Table 46
Relapses in 126 patients with quiescent disease after 1 year of treatment in a sanatorium or at home and followed up for a further 4 years[a]

Status	Home	Sanatorium	Total
Quiescent	57	69	126
Relapsed			
in 2nd year	2	6	8
in 3rd–5th year	2	1	3
Total relapsed	4	7	11
% relapsed	7	10	9

[a] Source: reference *3*.

Risk to family contacts

The close family contacts of the patients admitted to the study were carefully followed for 5 years. The main study of the attack rate (*4*, *5*) was undertaken in families whose only infectious member was the index case. In this way a comparison could be made between the "sanatorium" family contacts (whose infectious index was isolated for a year in sanatorium) and the "home" contacts (who remained exposed to their index cases, living in the same household throughout the treatment). In addition, both contact groups were equally exposed to the risks of the general urban environment of Madras.

All contacts who had radiographic lesions suggesting tuberculosis were excluded; the rest were subdivided into tuberculin non-reactors and reactors (0–4 mm and ≥5 mm induration, respectively, to 5 TU of tuberculin given intradermally).

Table 47
Frequency of tuberculosis in family contacts of patients treated at home or in a sanatorium[a]

Initial tuberculin status	Contact group	No. of persons at risk	Cases occurring in observation year					Total cases in 5-year period	
			1	2	3	4	5	No.	%
Non-reactors	Home	86	7	0	1	1	0	9	10.5
	Sanatorium	87	7	1	2	0	0	10	11.5
Reactors	Home	159	5	4	4	1	1	15	9.4
	Sanatorium	177	13	4	7	2	2	28	15.8

[a] Source: reference *5*.

As Table 47 shows, the frequency of disease in the non-reactor group was almost equal in the home contacts and in the sanatorium contacts. (Among the reactors –a less homogeneous group than the non-reactors– the frequency of disease was higher in the sanatorium contacts.)

Another important finding was that most of the contacts who developed disease during the first year of observation did so within the first 3 months, irrespective of whether the index case was treated at home or in a sanatorium. This was a strong indication that these contacts were probably already infected with *Mycobacterium tuberculosis* when first examined, i.e. it is very likely that they had already been infected before the index case was discovered and treated.

Cooperation of the patients

In spite of a very active welfare service for the patients and their families, 12 of the sanatorium patients discharged themselves from treatment, four being readmitted later. Only one of the patients treated at home was lost through self-discharge.

With regard to the regularity of drug intake, sanatorium patients occasionally, or during certain periods, also failed to ingest the prescribed medicines. This may be because sanatorium supervision was not always sufficient to ensure that every patient actually took every dose.

Social problems

A careful social record was kept for each family. Major problems arose in eight families of home patients and in 20 families of sanatorium patients. The difficulties were usually more serious in the latter and often resulted in disruption of the family.

Summary

In a controlled clinical trial, the effect of treatment was compared in two groups of patients – one group treated under good conditions in a sanatorium, the other under poor conditions at home.

The results in the sanatorium patients, despite good accommodation, nursing care, rich diet, and prolonged bed rest, were not superior to those in patients treated in overcrowded homes, who had a poor diet, much less rest, and often very long working hours. Radiographic changes, such as the reduction of cavity size and cavity closure, were very similar in both groups, particularly when patients with similar pretreatment lesions were compared. The proportion and speed of sputum conversion to negativity were similar in the two groups. After about 4 months, around 90% of the home and sanatorium patients produced multiple specimens that were all negative by culture, and this level was maintained throughout the remainder of the treatment year.

Results for quiescence of the disease at 1 year and relapses in the subsequent 4 years showed few, if any, differences between home and sanatorium patients. Thus, sanatorium treatment did not increase the likelihood of cure or reduce the likelihood of relapse. This study used conventional treatment; short-course treatment makes ambulatory management of tuberculosis patients particularly practical.

The risk to close family contacts was studied for 5 years. There was no difference in the incidence of disease between the contacts of patients treated at home and those of sanatorium patients, and exposure to the index case under effective treatment appeared to present no major risk to contacts. Thus domiciliary treatment did not entail any special danger that might have been prevented by sanatorium treatment.

The study indicated that the major risk to contacts lay in exposure to the infectious index case before diagnosis and the start of treatment. At that point, all the harm the index case could do to family contacts had already been done, so that subsequent isolation in a sanatorium was of little benefit.

The disadvantage of sanatorium treatment is the sacrifice it demands from patients: it is difficult to keep a patient in the sanatorium, separated from family for a long time and maintaining sanatorium discipline. A further social disadvantage is the disruptive effect on family life. Indeed, in this study, 12 patients discharged themselves from treatment (though four were later readmitted), compared with one self-discharge from treatment among home patients.

In addition, the study showed that treatment in a sanatorium is no safeguard against irregularity of drug taking unless the patient is seen to swallow every dose.

This study brought about the dramatic switch from institutional to ambulatory treatment as a general policy (see "What were the main landmarks in the development of tuberculosis treatment?", page 99, and "When should tuberculosis patients be hospitalised, and how infectious are tuberculosis patients while on treatment?", page 274).

References

1. Ramakrishnan CV et al. The role of diet in the treatment of pulmonary tuberculosis. An evaluation in a controlled chemotherapy study in home and sanatorium patients in South India. *Bulletin of the World Health Organization*, 1961, 25:339–359.
2. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1959, 21:51–145.
3. Dawson JJY et al. A 5-year study of patients with pulmonary tuberculosis in a concurrent comparison of home and sanatorium treatment for one year with isoniazid plus PAS. *Bulletin of the World Health Organization*, 1966, 34:533–551.
4. Andrews RH et al. Prevalence of tuberculosis among close family contacts of tuberculosis patients in South India, and influence of segregation of the patient on the early attack rate. *Bulletin of the World Health Organization*, 1960, 23:463–510.
5. Kamat SR et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. *Bulletin of the World Health Organization*, 1966, 34:517–532.

37. How frequently do patients stop taking treatment prematurely?

J. Sbarbaro[1]

The failure to take medications as prescribed is a universal and perplexing phenomenon that must always be taken into consideration in any efforts to treat patients or control disease in a community. The powerful and negative impact on public health programmes of deeply ingrained cultural and personal beliefs has been clearly demonstrated in the failure of patients to complete prophylaxis programmes for leprosy, filariasis, and rheumatic fever (*1*). Many studies have shown that *one out of every three patients will prematurely stop taking their medication* (*2*). Similar default rates have been documented among patients being treated for tuberculosis (*1*, *3–5*). Unfortunately this behaviour is not limited to the ambulatory patient or to the home setting –measurements of drug serum levels and urine metabolites have repeatedly shown that even patients being treated in a hospital will hide and throw away medication delivered to them at the bedside (*3*).

Medication default rates as high as 65% have been documented for a broad spectrum of disease conditions, from hypertension and diabetes to arthritis, asthma, and congestive heart failure. These latter diseases confirm that even the presence of serious symptoms does not ensure patient adherence to a medication regimen. The disappearance of symptoms, however, leads to a further increase in the rate of medication default. Severity of illness, duration of illness, functional impairment, and the number of concurrent diseases do not influence compliance with medical recommendations.

Numerous efforts to pinpoint markers or characteristics that could distinguish compliant from non-compliant patients have been unsuccessful. Studies have found that age, sex, ethnicity, racial origin, socioeconomic status, educational level, marital status, cultural background, and religious belief are of no help in identifying who is or will be compliant with treatment. Unannounced home visits and pill counts have established that regular attendance at clinic does not ensure that patients are actually taking their medication. Intense educational efforts and even reliance on close family members, such as mothers, to ensure the ingestion of medication have proved equally ineffectual.

[1] Professor of Medicine and Preventive Medicine, University of Colorado Health Sciences Center, Denver, CO, USA.

Nevertheless, many health workers remain convinced that they can distinguish the reliable from the unreliable patient, especially if they have known the patient over a long period of time. Again and again, however, studies have demonstrated that even these professionals are unable to predict their patients' compliance any better than by chance variation (*3*).

Not unexpectedly, even good adherence to treatment deteriorates over the weeks and months. The expense of treatment, in terms of both time and money, is a further deterrent to patient compliance. Complicated regimens are associated with even higher default rates.

Treatment interruption can be reduced by a well functioning tuberculosis programme (*6*) that reduces the barriers to treatment compliance (see "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185). Preventing irregularity is the main reason to adopt direct observation of treatment, one of the key elements of the DOTS strategy.

References

1. Fox W. Self-administration of medicaments. A review of published work and a study of the problems. *Bulletin of the International Union Against Tuberculosis*, 1961, 32:307–331.
2. Davis MS. Variations in patients' compliance with doctors' orders: analysis of congruence between survey responses and results of empirical investigations. *Journal of Medical Education*, 1966, 41:1037–1048.
3. Sbarbaro JA. The patient–physician relationship: compliance revisited. *Annals of Allergy*, 1990, 64:325–332.
4. Chaulk CP, Kazandjian VA. Directly observed therapy for treatment completion of pulmonary tuberculosis: Consensus Statement of the Public Health Tuberculosis Guidelines Panel. *Journal of the American Medical Association*, 1998, 279:943–948.
5. Davidson BL. A controlled comparison of directly observed therapy vs self-administered therapy for active tuberculosis in the urban United States. *Chest*, 1998, 114:1239–1243.
6. Broekmans JF. Control strategies and programme management. In: Porter JDH, McAdam KPWJ, eds. *Tuberculosis: back to the future*. Chichester, Wiley, 1994:171–188.

38. What are the advantages of direct observation of treatment?[1]

J. Sbarbaro[2]

Even when innovative efforts to improve tuberculosis control services result in increased patient satisfaction and willingness to cooperate, non-adherence to medication recommendations continues to be a serious problem. Effective treatment of tuberculosis requires multiple drugs to be taken over a prolonged period by patients whose symptoms rapidly disappear, resulting in a renewed sense of well-being – factors that contribute to patient non-adherence to treatment. Tuberculosis control programmes that are committed to the health of their patients must therefore address and overcome this universal trait of non-adherence throughout the full course of treatment.

The main advantage of directly observed treatment is that treatment is carried out entirely under programme supervision. Only when a second person *directly observes* a patient swallowing the given medication can there be certainty that the patient is actually receiving the prescribed treatment regimen. No concealed irregularity can occur, as it can in self-administered regimens. The treatment observer ensures that medicines are taken at the correct intervals and in the correct dosages – and with that certainty come benefits both for the patient and for the community. Perhaps the most immediately apparent is the high cure rate associated with assured completion of treatment. Equally important is the dramatic reduction in the development of drug resistance, because direct observation eliminates the patient's ability to intentionally or unintentionally discontinue one or more drugs, with the subsequent emergence of drug-resistant organisms (see "How does drug resistance develop?", page 193). Moreover, because there is close and continuing contact between the patient and the health worker, adverse effects and treatment complications can be quickly identified and addressed, especially during the critical initial phase of treatment. In addition, the frequency of contact with the treatment provider reduces the time between treatment interruption and action to retrieve the patient, from more than a month in self-administered treatment to just a day in directly observed treatment. Confirmed

[1] Based on the chapter in the previous edition by K Toman.

[2] Professor of Medicine and Preventive Medicine, University of Colorado Health Sciences Center, Denver, CO, USA.

adherence to treatment further reduces the spread of infection in the community and thereby the burden of disease and development of new cases of tuberculosis.

Multiple analyses have demonstrated that the higher personnel and programme expenditures associated with directly observed treatment are more than offset by the savings in the costs of re-treatment, the costs of treating drug resistance and the costs associated with the treatment of the new cases of tuberculosis (many with drug resistance) which arise if treatment is not directly observed (*1–3*). Patients who are reluctant to continue treatment are immediately identified, allowing the community to develop alternative plans for their care. It is essential that health workers ensure that each patient actually ingests the drugs provided. The patient should therefore be given a glass of water or tea to help swallowing. It is also good practice to talk to the patient for several minutes after the medicines have been taken; this strengthens the bond between patient and provider and also ensures that the tablets have actually been swallowed. Directly observed treatment means that *every dose* is administered under direct observation, and convenience to the patient is essential for success.

References

1. Weis SE et al. The effect of directly observed therapy on the rates of drug resistance and relapse in tuberculosis. *New England Journal of Medicine*, 1994, 330:1179–1184.
2. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.
3. Moore RD et al. Cost-effectiveness of directly observed versus self-administered therapy for tuberculosis. *American Journal of Respiratory and Critical Care Medicine*, 1996, 154: 1013–1019.

39. Why does treatment fail and what can be done to avoid poor treatment outcome?[1]

F. Luelmo[2]

Tuberculosis patients have an excellent chance of being cured, especially if they have not received antituberculosis drugs in the past and are not infected with HIV. Short-course treatment regimens can achieve more than 95% cure in previously untreated patients. In practice, however, this success rate is rarely achieved. The main reasons for failure are premature cessation of treatment (default) and irregularity in taking drugs, prescription of inadequate regimens, drug resistance, delay in starting treatment, death from AIDS, and drug toxicity.

Early interruption of treatment and irregularity of drug intake

By far the most important causes of poor treatment outcome are early interruption of treatment and irregularity of drug intake. These are most commonly the result of:

- poor access to health facilities (geographical, economic, limited or inconvenient hours, unfriendly service providers) and the resulting loss of income for the patient;
- irregular supply of drugs, leading to monotherapy and loss of confidence in the health facility;
- poor patient orientation regarding the duration of treatment; and
- the inevitable tendency of patients to forget drug intake and to stop treatment when they are feeling better (see "How frequently do patients stop taking treatment prematurely?", page 181).

A variable proportion of patients have associated problems such as alcohol and drug dependence, which interfere with treatment adherence and require special strategies adapted to each patient (*1*).

Inadequate regimens

Inadequate regimens, which are more commonly prescribed in private clinical practice (*2*), increase the risk of treatment failure and relapse. Only treatment regimens

[1] Based on the chapter in the previous edition by K Toman.
[2] Consultant, Tuberculosis control programmes, Geneva, Switzerland.

that have proved successful in controlled clinical trials and are appropriate to the operational conditions – in terms of the combination of drugs, dosage, periodicity and length of application – should be used (*3*).

Drug resistance

In most settings, drug resistance is not the most important cause of treatment failure. For example, even in a poorly performing programme with a 10% rate of primary multidrug resistance, inability to cure patients most commonly arose from default among patients without multidrug-resistant tuberculosis (*4*). In settings that have recently improved the management of tuberculosis, drug resistance can be an important cause of failure and death, particularly when the strains are resistant to the two main bactericidal drugs isoniazid and rifampicin (multidrug-resistant strains). Drug resistance develops as a result of inadequate or irregular regimens and is a consequence of poorly organized programmes (see "What are the causes of drug-resistant tuberculosis?", page 207). Multidrug resistant strains can be transmitted in the community or in closed environments and replace susceptible strains, making first-line regimens inadequate for achieving high cure rates.

Diagnostic delay

Delay in diagnosis and initiation of treatment increases the severity of disease and the risk of death. Delays are usually due to poor access to health care and barriers to care (such as wage loss, costs of consultation, diagnostic tests and treatment, and the need for multiple visits by the patient), lack of information on or of recognition of symptoms, lack of awareness of availability of services, and delayed diagnostic response of the health system (laboratory results, medical decision, etc.).

AIDS

Infection with HIV increases the probability of patients dying during treatment, often from causes other than tuberculosis (see "How does treatment of tuberculosis differ in persons infected with HIV?", page 169). Prognosis depends on the degree of immunosuppression. Associated diseases in patients with AIDS, as well as antiretroviral treatment, may complicate tuberculosis treatment, and the deterioration and poor prognosis associated with HIV infection may reduce the patient's motivation to continue tuberculosis treatment, leading to irregularity and default. Good coordination between the providers of tuberculosis care and HIV/AIDS care is required to address tuberculosis as one of a number of HIV-related diseases that complicate the course of HIV infection.

Drug toxicity

Drug toxicity can result in treatment failure and sometimes death if adequate care is not provided promptly. Changes in treatment necessitated by toxicity can prolong the

duration of treatment, especially in older patients. An episode of hepatitis or hypersensitivity can also complicate management of tuberculosis.

Preventing poor outcomes of treatment

Unsuccessful treatment may be reduced by:

- Decentralization of treatment to local health facilities and to the community, through health staff or trained and supervised community volunteers, as close to the patient's home or workplace as possible and at convenient times. The patient should be given the opportunity to choose who will directly observe treatment, and where. It is the responsibility of the health system to facilitate the patients' access to treatment; to educate patients regarding the duration of treatment and what to do should they change address; also to ensure that patients are found rapidly and brought back to the health facility if they do not attend for treatment. A system must be maintained to transfer patients from diagnostic to treatment facilities, from hospitals to outpatient care, and from one geographical area to another, and to monitor their arrival and the outcome of treatment.
- Regular supply of good-quality drugs, free of charge to the patient, with sufficient reserve stocks. Packages containing the drugs for the entire treatment of a particular patient prevent use of drugs for other patients in case of stock-out, which would result in interruption of treatment.
- Direct observation of drug intake to ensure that the patient takes all the drugs, to increase contact between patients and the health system, and to reduce the time from treatment interruption to recovery actions (see "What are the advantages of direct observation of treatment?", page 183).
- Use of adequate standard regimens, including by private sector providers. Treatment regimens should start with four drugs in new patients (or three drugs in smear-negative pulmonary and non-severe extrapulmonary tuberculosis) and with at least five drugs in previously treated patients. Governments should choose national standardized treatment regimens based on efficacy data and operational experience, and ensure that they are used by both public and private providers, and that the regimens are followed and achieve the expected outcomes (see "How can the emergence of drug resistance be prevented?", page 209).
- Use of fixed-dose combinations, which ensure that the patient takes "all or none" of the drugs, facilitates prescription and improves patient acceptance.
- Reduction of diagnostic delay through community information regarding symptoms, improved access to care, efficient procedures for collection and reporting of smear results, and case detection among patients with respiratory symptoms who attend health facilities for any reason.
- Prevention of HIV infection, and early diagnosis and adequate management of HIV-infected tuberculosis patients (*5*).

Thus, the key to treatment success is to be found in the organization of the delivery and adequate administration of treatment (*6*). Even the best available regimen will have a low success rate if treatment services are not focused on facilitating patient access to care and ensuring regular drug intake.

References

1. *WHO Expert Committee on Tuberculosis. Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
2. Upplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*, 2001, 358:912–916.
3. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
4. Primary multidrug-resistant tuberculosis – Ivanovo Oblast, Russia, 1999. *Morbidity and Mortality Weekly Report*, 1999, 48:661–664.
5. Harries AD, Maher D. *TB/HIV: a clinical manual.* Geneva, World Health Organization, 1996 (document WHO/TB/96.200).
6. Fox W. General considerations on the choice and control of chemotherapy in pulmonary tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1972, 47:51–71.

40. What are the advantages and disadvantages of fixed-dose combinations of antituberculosis drugs?

K. Laserson[1] *& M. Iademaco*[2]

An essential element of effective tuberculosis control is a reliable supply of good-quality drugs provided to patients free of charge. Fixed-dose combinations (FDCs), incorporating two or more antituberculosis drugs into one tablet in fixed proportions, have been used since the late 1980s and are registered in more than 40 countries (*1*). Combinations of isoniazid and thioacetazone have long been used, and a combination of isoniazid and ethambutol is also commonly used. For short-course treatment, the two most common FDC preparations are isoniazid, rifampicin, and pyrazinamide, used in the intensive phase of treatment, and isoniazid and rifampicin, often used in the continuation phase. A four-drug FDC containing isoniazid, rifampicin, pyrazinamide, and ethambutol is being used increasingly (*2*); the WHO Model List of Essential Drugs includes FDCs in specific formulations.

Potential advantages of FDCs include the following (*2–4*):

- Drug resistance may be less likely to emerge since multiple drugs are incorporated into the FDC (*5–7*). The use of FDCs prevents treatment of tuberculosis with a single drug (monotherapy). Further, if treatment is interrupted (through default or because of inadequate drug supply), *all* drugs will be stopped, which should prevent resistant organisms being selected.
- The use of FDCs involves fewer products and will result in more accurate prescribing practices by clinicians. This might be especially helpful for clinicians less familiar with national tuberculosis treatment guidelines. Moreover, because the amount of each drug in an FDC is invariable, there may be fewer dosage errors.
- Procurement, management, and distribution of drugs are simplified by the use of FDCs. Fewer tablets need to be ordered and managed, and distribution and storage at the local level may be easier. Thus, the use of FDCs may result in increased efficiency.

[1] Epidemiologist, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

[2] Associate Director for Science, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

- A treatment regimen using FDCs is simpler for the patient (fewer tablets), and may result in increased adherence to treatment (*8*, *9*).
- Rifampicin is often used to treat other infections and is sold without prescription in many countries. The use of rifampicin in FDCs may reduce inappropriate use of the drug for other infections, thus preserving its effectiveness for treating tuberculosis.

Nevertheless, the use of FDCs guarantees neither that a patient will ingest the correct number of tablets, nor that a patient will complete treatment. Effective case management is still essential, including directly observed treatment within the DOTS strategy (*2*, *3*).

Potential disadvantages of FDCs include (*2–4*):

- Bioavailability (the amount of an ingested drug absorbed into the blood) of rifampicin may decrease when it is combined with other drugs in the FDC (*10–13*). Use of FDCs, particularly in three- and four-drug combinations, could therefore result in lower plasma levels of rifampicin, with consequent treatment failures, relapses, and/or emergence of rifampicin-resistant strains of *Mycobacterium tuberculosis* (*14*). However, if FDCs are produced according to good manufacturing practices (GMP), they will be equivalent to administration of the constituent drugs as single-drug preparations (*15–17*). Only FDCs for which bioavailability studies have been undertaken in human subjects should be used (*7*, *18*). Demonstrated bioavailability should be a requirement for national registration (*17*, *19*). However, although there may be proven bioavailability during the approval or tender process, there is often no systematic mechanism to ensure that all subsequent batches of FDCs also have adequate bioavailability. The regulatory structure required to adequately monitor GMP and ensure bioavailability standards for FDCs (either imported or domestically manufactured) is inadequate in most countries of the world (*20*). In addition, few laboratories in the world have been officially certified to perform bioavailability testing (*21*).
- The optimal operational efficiency from using FDCs may not be achieved because the doses required for treatment are not the same for all patients. Adjustments for weight are often necessary: the WHO-recommended dosage forms for FDCs allow for easy adjustment of dosage by weight. Adverse effects may also necessitate changes in the dosage. Hence, any tuberculosis control programme using FDCs must also supply single drugs to be used by tuberculosis specialists in particular circumstances.
- There are a number of different formulations of FDCs, involving different drug combinations and different dosages; confusion and incorrect dosing may arise if a country uses more than one FDC formulation. The formulations recommended by WHO and IUATLD should be the only ones used in a country. The national tuberculosis programme should attempt to have the registration of other formulations withdrawn by the national drug regulatory authority.

- There is a theoretical risk that the availability of three- and four-drug FDCs over the counter, as may happen in many countries, would result in more widespread inappropriate use of tuberculosis drugs. In some areas, FDCs have been promoted as an alternative to effective tuberculosis control, potentially with adverse effects for the programme. Taking fewer than the recommended number of FDC tablets may expose bacilli to sub-inhibitory concentration of multiple drugs. In a study that compared patients treated with self-administered FDC with patients given single-drug preparations under direct observation, relapse rates were higher in the group using self-administered FDC (*22*).
- When three- or four-drug FDCs are used in the intensive phase of treatment, a different two-drug FDC is used in the continuation phase. Patient and physician confusion and error may occur.
- Small local manufacturers may not be able to produce FDCs, particularly four-drug FDCs, which may reduce competition and raise prices unless there is international procurement of drugs. A country that uses FDCs will need to provide additional training in drug procurement, treatment recommendations, and patient and provider education (*3*).

Although there are potential advantages to using FDCs, the benefits may be difficult to demonstrate given existing operational, programmatic and regulatory constraints. FDCs are likely to become more widely used, particularly in countries that import antituberculosis drugs, which suggests that measuring their impact is imperative. Each country must carefully weigh the advantages, disadvantages, and appropriate role of FDCs within its programme.

References

1. Norval P et al. Estimate of the global market for rifampicin-containing fixed-dose-combination tablets. *International Journal of Tuberculosis and Lung Disease*, 1999, 3: S292–S300.
2. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2002.313).
3. *Fixed-dose combination tablets for the treatment of tuberculosis: report of an informal meeting held in Geneva, Tuesday 27 April 1999*. Geneva, World Health Organization, 1999 (document WHO/CDC/CPC/TB/99.267).
4. Blomberg B et al. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. *Bulletin of the World Health Organization*, 2001, 79:61–68.
5. Mitchison DA. How drug resistance emerges as a result of poor compliance during short-course chemotherapy for tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:10–15.
6. Moulding T, Putt A, Reichman L. Fixed-dose combinations of tuberculosis medications to prevent drug resistance. *Annals of Internal Medicine*, 1995, 122:951–954.
7. The promise and reality of fixed-dose combinations with rifampicin. A joint statement of the International Union Against Tuberculosis and Lung Disease and the Tuberculosis Programme of the World Health Organization. *Tubercle and Lung Disease*, 1994, 75:180–181.

8. Acceptability, compliance, and adverse reactions when isoniazid, rifampin, and pyrazinamide are given as a combined formulation or separately during three-times-weekly antituberculosis chemotherapy. Hong Kong Chest Service/British Medical Research Council. *American Review of Respiratory Disease*, 1989, 140:1618–1622.
9. Wolde K et al. Fixed dose combination short course chemotherapy in the treatment of pulmonary tuberculosis. *Ethiopian Medical Journal*, 1992, 30:63–68.
10. Acocella G. Human bioavailability studies. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1989, 64:38–40.
11. Acocella G. Studies of bioavailability in man. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1989, 64:40–42.
12. Fox W. Drug combinations and the bioavailability of rifampicin. *Tubercle*, 1990, 71: 241–245.
13. Pillai G et al. Recent bioequivalence studies on fixed-dose combination anti-tuberculosis drug formulations available on the global market. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S309–S316.
14. Long MW, Snider DE, Farer LS. US Public Health Service cooperative trial of three rifampicin–isoniazid regimens in treatment of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1979, 119:879–894.
15. Acocella G et al. Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in tuberculosis chemotherapy. I. Single-dose study. *American Review of Respiratory Disease*, 1988, 138:882–885.
16. Acocella G et al. Comparative bioavailability of isoniazid, rifampin, and pyrazinamide administered in free combination and in a fixed triple formulation designed for daily use in antituberculosis chemotherapy. II. Two-month, daily administration study. *American Review of Respiratory Disease*, 1988, 138:886–890.
17. Panchagnula R et al. Evaluation of rifampicin bioequivalence in fixed-dose combinations using the WHO/IUATLD recommended protocol. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:1169–1172.
18. Assuring bioavailability of fixed-dose combinations of anti-tuberculosis medications. A joint statement of the International Union Against Tuberculosis and Lung Disease and the World Health Organization. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S282–S283.
19. Fourie PB. Proposed minimum registration requirements for fixed-dose combination anti-tuberculosis drugs. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S362–S367.
20. Trébucq A, Caudron JM, Pinel J. Requirements for anti-tuberculosis drug tender requests. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S358–S361.
21. Ellard GA. The evaluation of rifampicin bioavailabilities of fixed-dose combinations of anti-tuberculosis drugs: procedures for ensuring laboratory proficiency. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:S322–S324.
22. Assessment of a daily combined preparation of isoniazid, rifampicin and pyrazinamide in a controlled trial of three 6-month regimens for smear-positive pulmonary tuberculosis. Singapore Tuberculosis Service/British Medical Research Council. *American Review of Respiratory Disease*, 1991, 143:707–712.

41. How does drug resistance develop?

K. Toman[1]

Thanks to clinical and laboratory observations and to comprehensive experimental studies, much is known about how drug resistance develops, its clinical and epidemiological significance, and how it can be prevented or controlled.

The phenomenon of resistance was detected soon after the introduction of streptomycin for the treatment of human tuberculosis. When the drug was given alone, a striking improvement in the patient's symptoms was observed at first, together with a rapid decrease in the number of bacilli in the sputum. Usually, the number of bacilli soon rose again and the patient's condition deteriorated. Bacilli isolated from the sputum of patients who had received streptomycin alone for a few months were drug-resistant, i.e. the bacilli, instead of being killed, continued to grow in vitro in the presence of high concentrations of the drug.

A simple experiment soon provided an explanation (*1*). Sputum from patients who had never received any streptomycin was inoculated on media containing various concentrations of the drug. In many of the cultures, a few colonies appeared in media containing an inhibitory concentration of streptomycin (5–10 µg/ml). It was obvious that some of the bacilli present in the bacterial population must have been resistant to streptomycin, although they had never been in contact with the drug before. It was also observed that, the larger a bacterial population, the higher was the probability that resistant cells (mutants) were present.

Furthermore, it was noticed that, during the treatment of patients with streptomycin alone, the proportion of resistant bacilli rapidly increased. After 12 weeks of treatment, the number of colonies in media containing 100 or 1000 µg/ml of streptomycin approached the number of colonies in the control media without streptomycin.

This experience showed that large bacterial populations contain a minute proportion of organisms that are barely susceptible, if at all, to a particular drug, even before administration of that drug. The susceptible bacteria are killed by the drug, the few resistant organisms survive and multiply, and their non-susceptible descendants,

[1] Deceased.

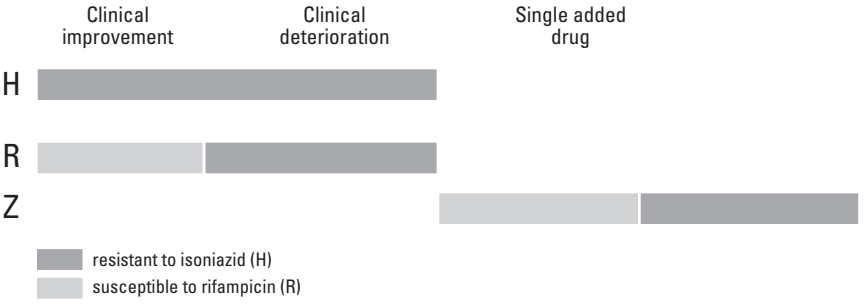
generation by generation, replace the susceptible organisms. Clinically relevant drug resistance is thus the result of a selective process.

In a patient infected with an initially isoniazid-resistant strain, treatment with isoniazid and rifampicin alone during the intensive phase may allow the selective growth of the few organisms that have or that may develop resistance to rifampicin. Thus, treatment with a single effective drug alone may cause a patient's strain to become increasingly drug-resistant, as illustrated Figure 15.

Figure 15

Treatment that is effectively monotherapy in a patient whose isolate was initially resistant to isoniazid (H) and susceptible to rifampicin (R)

Inappropriate treatment with only two drugs (H and R) led to the development of resistance to rifampicin, followed by clinical deterioration. Inappropriate addition of a single drug (pyrazinamide, Z) to a failing regimen led to the emergence of resistance to pyrazinamide.



Reference

1. Pyle MM. Relative numbers of resistant tubercle bacilli in sputa of patients before and during treatment with streptomycin. *Proceedings of the Staff Meetings of the Mayo Clinic*, 1947, 22:465–473.

42. Why are special precautions needed to protect rifampicin?

A. Vernon[1]

Rifampicin must be protected because it is the key sterilizing drug in short-course treatment of tuberculosis (*1*). With rifampicin, treatment for drug-susceptible disease can be completed in 6–9 months, depending on companion drugs, with combined rates of failure and relapse of less than 5%. Without rifampicin, treatment must generally be given for at least 12 months to achieve low rates of failure and relapse. Resistance to rifampicin results in a substantial increase in the rate of failure and relapse when standard three- or four-drug regimens are used (*2*). In trials by the British Medical Research Council, initial resistance to rifampicin was associated with a failure rate of 45% during treatment; moreover, half of the remaining patients relapsed, giving an overall rate of unfavourable treatment outcome of 72% (*3*). This is in striking contrast to the experience of patients with initial resistance to isoniazid and/or streptomycin as shown in table 48.

When there is rifampicin resistance, the minimum required duration of tuberculosis treatment with a feasible regimen is 12–15 months. If resistance to isoniazid is also present (i.e. multidrug resistance), the duration of treatment necessary is likely to be at least 18–24 months.

Resistance to any tuberculosis drug (including rifampicin) is predictable if the drug is used alone. This was first described with streptomycin in 1947 as the "fall and rise" phenomenon (see "What is the 'fall and rise' phenomenon and the 'sequential regimen' mechanism?", page 200). Such resistance can develop after relatively brief periods of single-drug treatment, especially in patients with large numbers of actively replicating bacilli (e.g. in patients with extensive active disease or with severe immunosuppression such as that caused by AIDS). Similar resistance would be expected if only one drug in a regimen were effective (because of pre-existing resistance to the other agents in the regimen). Development of resistance due to the addition of a single drug to a failing regimen has also been well described (*4*).

Most rifamycin resistance involves mutations in critical domains of the *rpoB* gene in *Mycobacterium tuberculosis* (*5*). Resistance to all rifamycins is mediated by this

[1] Epidemiologist, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Table 48
Response of patients with initial resistance to rifampicin, with initial resistance to isoniazid and/or streptomycin only, or with no initial drug resistance[a]

Initial resistance	Failures during treatment		Relapses after treatment	
	assessed	failed	assessed	relapses
Rifampicin[b]	11	5 (55%)	6	3 (50%)
Isoniazid and/or streptomycin	246	5 (2%)	360	24 (7%)
No resistance	1361	0 (0%)	2322	94 (4%)

[a] Source: reference *3*.
[b] One patient resistant to R alone, one to HR, and seven to HRS.

common mechanism and, to date, it appears that resistance to any rifamycin implies resistance to all members of the class.

Isolated use of one drug is most common when that drug is freely available and can thus be prescribed by inexperienced practitioners or used in self-medication by patients. Rifampicin resistance has also rarely occurred in AIDS patients taking rifabutin as prophylaxis against *Mycobacterium avium intracellulare* (*6*). These problems can be prevented by:

— restricting availability of rifampicin and related drugs (rifabutin, rifapentine) to tuberculosis control programmes (as is done in some developing countries with well-functioning programmes) or to licensed or experienced practitioners (as is done in many developed and some developing countries); and/or
— making rifampicin available exclusively as a fixed-drug combination in products that include isoniazid, so that the rifampicin component cannot be administered alone (see "What are the advantages and disadvantages of fixed-dose combinations of tuberculosis drugs?", page 189) (*7*).

The consequences of restriction of rifamycins are minimal, because rifampicin and related drugs have few other indications for which they are the preferred drugs. Rifampicin is occasionally indicated for the treatment of some deep-seated staphylococcal infections, and in prevention of meningococcal disease. Rifabutin is a useful secondary drug for the prevention and treatment of AIDS-related disseminated *Mycobacterium avium intracellulare* infections. Rifamycins should remain available for these other indications.

References

1. Mitchison DA. Basic concepts in the chemotherapy of tuberculosis. In: Gangadharam PRJ, Jenkins PA, eds. *Mycobacteria. Vol. 2, Chemotherapy*. New York, Chapman & Hall, 1998:15–50.

2. Espinal MA et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *Journal of the American Medical Association*, 2000, 283: 2537–2545.
3. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1986, 133:423–430.
4. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis: common errors and their association with acquisition of drug resistance. *Journal of the American Medical Association*, 1993, 270:65–68.
5. Miller LP, Crawford JT, Shinnick TM. The *rpo*B gene of *Mycobacterium tuberculosis*. *Antimicrobial Agents and Chemotherapy*, 1994, 38:805–811.
6. Bishai WR et al. Rifampin-resistant tuberculosis in a patient receiving rifabutin prophylaxis. *New England Journal of Medicine*, 1996, 334:1573–1576.
7. Blomberg B et al. The rationale for recommending fixed-dose combination tablets for treatment of tuberculosis. *Bulletin of the World Health Organization*, 2001, 79:61–68.

43. What are the different types of drug resistance?[1]

M. Espinal[2]

Primary resistance is due to infection with a resistant strain, originating from a patient who has acquired resistance as a result of inadequate treatment. Thus the patient with primary resistance to a drug has never taken this drug in the past, but the original source of infection must have done so. Acquired resistance occurs when a patient is exposed to a single drug through failure of the programme to ensure adherence to treatment, or because of selective drug intake, irregular drug supply, poor drug quality, inappropriate prescription, or, rarely, erratic absorption of medications. The growth of bacilli susceptible to that drug is suppressed, but multiplication of resistant organisms continues.

In surveys of the frequency of primary resistance, as well as in clinical practice, it is difficult to determine whether resistance is primary, since the patients themselves may not know, or may deny, that they have had previous treatment for tuberculosis. It is therefore better to use the expression "drug resistance among new tuberculosis cases". This is defined as the presence of resistant strains of *Mycobacterium tuberculosis* in patients who have never received tuberculosis drugs or have received them for less than 1 month.

The term "acquired drug resistance" implies that the patient initially had a drug-susceptible organism that developed resistance during the course of treatment. In practice, in most areas of the world where tuberculosis is common, reliable pretreatment drug susceptibility results are not available. Further, epidemiological evidence suggests that, in some contexts, most previously treated patients with drug resistance initially had primary drug resistance (*1*). Thus, unless pretreatment drug susceptibility testing results are available, drug resistance in previously treated patients should simply be described as such, i.e. "drug resistance in previously treated patients".

A "natural" drug-resistant strain is a wild strain that is resistant to a particular drug without ever having been in contact with it: neither the patient with naturally resistant bacilli nor the source of infection has received treatment with that drug in the

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.

past. This type of drug resistance is of little practical importance. Wild strains rarely possess sufficient natural resistance to affect the response to standard treatment. An exception is thioacetazone, to which natural resistance may be common in some areas (*2*). Natural resistance to pyrazinamide is also a characteristic of *Mycobacterium bovis* (*3*).

References

1. Frieden TR et al. The emergence of drug-resistant tuberculosis in New York City. *New England Journal of Medicine*, 1993, 328:521–526.
2. Thomas KL et al. Identification of tubercle bacilli from Indian patients with pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1961, 25:747–758.
3. Zhang Y et al. Role of acid pH and deficient efflux of pyrazionic acid in unique susceptibility of *Mycobacterium tuberculosis* to pyrazinamide. *Journal of Bacteriology*, 1999, 181: 2044–2049.

44. What is the "fall and rise" phenomenon and the "sequential regimen" mechanism?[1]

M. Espinal[2]

Figure 16 illustrates, for isoniazid, the "fall and rise" phenomenon frequently observed in patients who are inadequately treated (*1*, *2*).

The first pair of columns represents a bacterial population before the start of treatment. The patient's sputum is positive by direct smear and the total number of bacilli is 100 million (10^8) or more, as is common in medium-sized cavities. A small proportion (perhaps several hundred bacilli) are mutants resistant to, say, isoniazid at concentrations usually found in cavities (see "How does drug resistance develop?," page 193, and "How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?", page 203).

After the start of treatment, the total number of bacilli decreases rapidly (second pair of columns). However, it is the drug-susceptible part of the population (white bars) that diminishes, whereas the resistant part (black bars) remains practically unaffected. In the second month (third pair of columns), the total number of bacilli has decreased further at the expense of the susceptible organisms.

In the subsequent period (fourth pair of columns), the total number of bacilli remains about the same; however, the structure of the population has changed fundamentally because the resistant mutants have gained the upper hand.

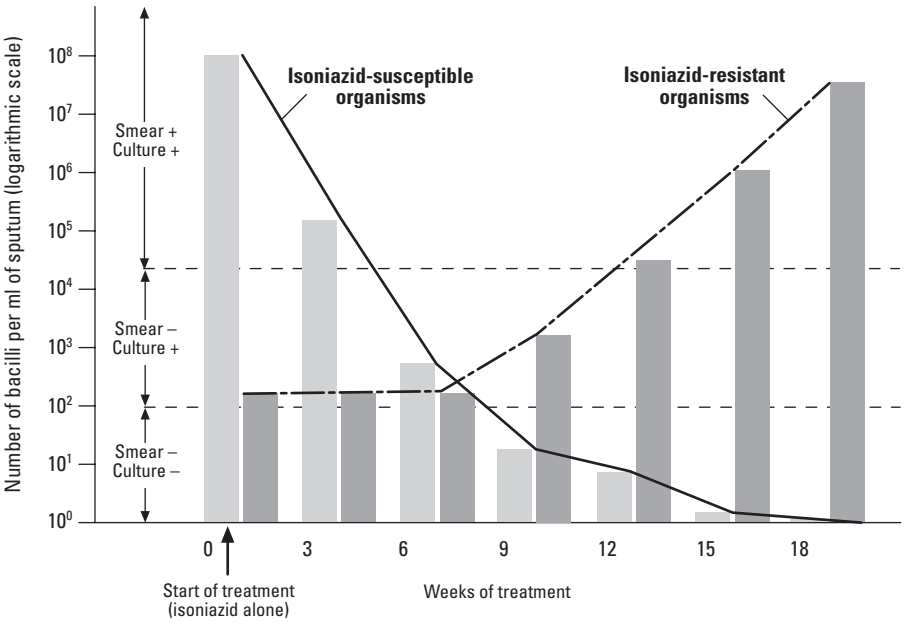
During the next period, the resistant bacilli, now with a biological advantage, rapidly outgrow the remaining drug-susceptible bacilli (fifth pair of columns). After about the fourth month (sixth pair of columns), the mutant organisms have completely replaced the susceptible organisms: the strain has become fully resistant, and the total number of bacilli is approaching the original number (seventh pair of columns).

Thus the sputum, containing enormous numbers of bacilli, was smear-positive at the beginning. After the start of treatment, the bacillary content of the sputum decreased markedly until it was close to the borderline of demonstrability by direct microscopy – marked in the figure by a horizontal line between 10^4 and 10^5. (To find about 10 acid-fast bacilli in about 100 oil-immersion fields, the number of bacilli per

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.

Figure 16
The "fall and rise" phenomenon[a]



[a] Source: references *1, 2*.

millilitre of sputum must be around 50 000, i.e. between 10^4 and 10^5. See Table 2 in the section "How reliable is smear microscopy?", page 14.) Thereafter, the bacillary content dropped further: the sputum became negative by smear microscopy and positive only by culture – the "fall". After a certain time, the bacillary content increased again, the sputum again being positive by direct smear – the "rise". What occurs, in fact, is the "fall" of the susceptible bacilli and the "rise" of the resistant mutants of the strain.

The "fall and rise" phenomenon is prevented by the use of appropriate multidrug regimens in the treatment of tuberculosis. Treatment regimens consisting of four drugs during the initial phase and two during the continuation phase reduce the risk of selecting resistant bacilli. The main principle of multidrug regimens is that mutants resistant to drug A (e.g. rifampicin) are killed by drug B (e.g. isoniazid) and mutants resistant to drug B (isoniazid) are killed by drug A (rifampicin) (*3*).

The emergence of multidrug resistance as a result of several sequences of inappropriate treatment has been recently called the "sequential regimen" mechanism (*4*). It is postulated that resistance may arise because of treatment irregularity, without monotherapy. Selection of resistant mutants could take place after different regimens have been administered, during which several cycles of killing and regrowth of

resistant organisms occur. Resistance could arise first to one of the drugs in the combination, followed by the development of resistance to the other drugs, to produce a multidrug-resistant strain.

References

1. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. *British Medical Journal*, 1948, 2:1009–1015.
2. Mitchison DA. Sensitivity testing. In: Heaf F, Rusby NL, eds. *Recent advances in tuberculosis*. London, Churchill, 1968.
3. Iseman MD. Treatment and implications of multidrug-resistant tuberculosis for the 21st century. *Chemotherapy*, 1999, 45:34–40.
4. Mitchison DA. How drug resistance emerges as a result of poor compliance during short course chemotherapy for tuberculosis. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:10–15.

45. How many drug-resistant tubercle bacilli can be found in the sputum of patients who have never received treatment for tuberculosis?[1]

A. Pablos-Mendez[2]

Genetic mutations that confer drug resistance occur spontaneously, and isolated resistant bacilli are present in wild strains, i.e. in normal bacterial populations that have never been exposed to tuberculosis drugs. This phenomenon was demonstrated soon after the discovery of streptomycin (*1*) and was later found to occur with other tuberculosis drugs (*2–5*) (see "How does drug resistance develop?", page 193).

The demonstration of pre-existing resistant mutants is relatively easy. A wild strain of *Mycobacterium tuberculosis* is inoculated on media containing concentrations of, say, isoniazid, ranging from 0 to 5 µg/ml of medium. Abundant growth develops after about 14 days on the medium containing no isoniazid or as little as 0.05 µg/ml. The tubes containing higher concentrations of the drug remain clear initially, but some growth of colonies appears after about 3 weeks. Over the next few weeks the number of these colonies increases and can reach several hundred, depending on the drug concentration. Each colony, as a rule, originates from one resistant bacillus pre-existing in the original (wild) strain.

The frequency of drug-resistant mutants in a wild strain depends on the origin of the strain, the type and concentration of drug, and, to a large extent, the total number of bacilli. As shown in Table 49, the probability that mutants are present decreases substantially as the bacterial population diminishes. Thus, for example, in a population of one million (10^6) tubercle bacilli, the number of mutants resistant to 0.05 µg/ml isoniazid ranges from 20 000 to 40 000; in a population of 100 (10^2), the number of resistant organisms is proportionally smaller (only 0–4 at the same drug concentration). This quantitative or numerical dependence is a factor of great practical importance.

Thus, drug-resistant mutants will be present before treatment starts, especially in lesions that harbour large numbers of tubercle bacilli, e.g. in the pulmonary cavities of untreated patients. The number of bacilli commonly found inside cavities (about 2.5 cm in diameter) is of the order of 100 million (10^8). As a rule of thumb, the average frequency of resistant mutants is ~1 in 10^6 to isoniazid and ~1 in 10^8 to rifampin.

---

[1] Based on the chapter in the previous edition by K. Toman.

[2] Associate Director, The Rockefeller Foundation, New York, NY, USA.

Table 49

Average numbers of mutants resistant to various drugs found in wild bacterial populations of varying size – based on the number of colonies after 28 days and observations made on more than 50 wild strains of human tubercle bacilli in Löwenstein–Jensen medium containing drugs[a]

Drug concentration (μg/ml)	Number of bacilli in bacterial population exposed to the drug[b]			
	10^8	10^6	10^4	10^2
Isoniazid				
0.05	–	20 000–40 000	0–400	0–4
0.1	4 000	0–200	0–2	0
0.2	500	0–40	0	0
1.0	330	0–10	0	0
5.0	–	0–10	0	0
Rifampicin				
5	~20 000	–	–	~2
10	~750	–	–	0
20	0–1	–	–	0
40	0	–	–	0
80	0	–	–	0
Ethambutol				
1.0	–	0–15 000	–	–
1.5	–	0–120	–	–
2.0	–	0–2	–	–
3.0	–	0	–	–
Pyrazinamide				
10.0	–	0–1 000 000	0–10 000	0–100
50.0	–	0–30 000	0–300	0–3
Streptomycin				
1.0	–	1000–200 000	10–2 000	0–20
4.0	–	0–100	0–1	0
10.0	–	0–10	0	0
100.0	–	0–1	0	0

[a] Source: references *4–7*.
[b] Studies with rifampicin require a much higher number of bacilli given the lesser frequency of spontaneous resistance.

Doubly resistant mutants, expected in ~1 in 10^{14} bacilli, are extremely unlikely. The number of bacilli resistant to any drug is much lower during latency, in patients without cavitary lesions, and after the intensive phase of treatment.

Table 50 shows the estimated number of resistant mutants in two bacterial populations: one containing 100 million (10^8) and the other 100 000 (10^5) bacilli growing

Table 50
Estimated numbers of resistant mutants in populations of 10^8 and 10^5 TB bacilli[a]

Regimen	Intra-cavitary drug concentration (μg/ml)		No. of resistant bacilli in a population of:	
	Isoniazid	Streptomycin	10^8	10^5
Isoniazid alone	1.0	–	330	0
	0.2	–	500	0
	0.1	–	4 000	4
Streptomycin alone	–	20	40	0
	–	4	4 000	4
	–	2	>500 000	>500
Isoniazid plus streptomycin	1.0	20	0	0
	1.0	4	0	0
	1.0	2	>1.6	0
	0.2	20	0	0
	0.2	4	0	0
	0.2	2	>2.5	0
	0.1	20	0	0
	0.1	4	0	0
	0.1	2	>20	0

[a] Source: reference *4*.

at drug concentrations such as are attained in cavities. The numbers in Table 50 acquire greater practical importance when applied to actual situations. For example, a patient with cavitary tuberculosis heavily positive by smear microscopy might be treated with isoniazid alone. As Table 50 shows, the number of isoniazid-resistant mutants present at the outset of treatment would be substantial. At an intra-cavitary isoniazid concentration as high as 1 μg/ml, there might be about 300 resistant organisms; at a concentration of 0.2 μg/ml, the number of resistant mutants might be of the order of 500, and at a very low concentration of 0.1 μg/ml, they might number 4000.

Thus, in large intra-cavitary populations there are appreciable numbers of drug-resistant bacilli that are capable of multiplying and that will not be affected by a single drug, e.g. isoniazid. This finding accounts for the frequent failures observed with monotherapy of patients with large numbers of bacilli in their sputum (see "What is the 'fall and rise' phenomenon and the 'sequential regimen' mechanism?", page 200; "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185).

However, when the patient is treated with two active drugs, e.g. isoniazid and streptomycin, the situation is quite different (see the lower part of Table 50). Mutants resistant to one drug are, as a rule, susceptible to the other, and vice versa. Only mutants

resistant to both drugs simultaneously are a cause for concern. As can be seen in the lower part of the table, such doubly resistant mutants are present, if at all, only when the drug concentration is exceptionally low. Fortunately, such situations are rare.

Another important finding was that, when the bacterial population diminishes from, say, 10^8 to 10^5, as usually happens after the start of effective treatment (see the final column of Table 50), there is little likelihood that any mutants resistant to only one drug are present and virtually no likelihood of the presence of doubly resistant mutants.

These findings indicated that treatment with two or more effective drugs would most probably destroy any existing resistant mutants. Proper drug treatment, particularly with an initial intensive phase, could so markedly reduce the total bacterial population that the risk of the emergence of new resistant mutants would become minimal. Thus, after an initial intensive phase, treatment could continue less aggressively, e.g. switching from four drugs to two drugs. This hypothesis was supported by experimental evidence in murine tuberculosis and has became the basis of the two-phase treatment regimens in use today.

References

1. Crofton J, Mitchison DA. Streptomycin resistance in pulmonary tuberculosis. *British Medical Journal*, 1948, 4:1009–1015.
2. Canetti G, Saenz A. Sur l'apparition tardive de variantes bacillaires résistantes au cours du titrage de la streptomycino-sensibilité du bacilli tuberculeux. [Late finding of resistant bacilli during testing of tubercle bacilli sensitivity to streptomycin.] *Annales de l'Institut Pasteur*, 1949, 77:611–619.
3. Cohn ML, Middlebrook G, Russell WF Jr. Combined drug treatment of tuberculosis. I. Prevention of emergence of mutant populations of tubercle bacilli resistant to both streptomycin and isoniazid in vitro. *Journal of Clinical Investigation*, 1959, 38:1349–1355.
4. Canetti G, Grosset J. Teneur des souches sauvages de *Mycobacterium tuberculosis* en variants résistants a l'isoniazide et en variants résistants a la streptomycine sur milieu de Loewenstein-Jensen. [Percentage of isoniazid-resistant and streptomycin-resistant variants in wild strains of *Mycobacterium tuberculosis* on Loewenstein-Jensen medium]. *Annales de l'Institut Pasteur*, 1961, 101:28–46.
5. Canetti G, Le Lirzin M. Some comparative aspects of rifampicin and isoniazid. *Tubercle*, 1968, 49:367–376.
6. Rist N. La resistance de bacilli tuberculeux à la rifampicine. [Resistance of tubercle bacilli to rifampicin.] *Revue de Tuberculose et Pneumologie (Symposium Rifadine)*, 1969, 33bis:33–38.
7. Le Lirzin M, Djurovic V. Étude sur milieu de Loewenstein-Jensen de la composition des souches sauvages de *Mycobacterium tuberculosis* en variants résistants a la rifampicine et en variants résistants al l'éthambutol. [A study of the composition of rifampicin- and ethambutol-resistant variants of wild strains of *Mycobacterium tuberculosis*, cultivated on Loewenstein–Jensen medium]. *Annales de l'Institut Pasteur*, 1971, 120:531–548.

46. What are the causes of drug-resistant tuberculosis?

M. Espinal[1] *& T. Frieden*[2]

Drug-resistant tuberculosis is a man-made problem. Human error is the principal factor associated with the generation of drug-resistant strains of *Mycobacterium tuberculosis* (*1*, *2*). Resistance to tuberculosis drugs is the result of spontaneous, independent, chromosomal mutations; treatment regimens involving several drugs therefore prevent drug resistance (*3*). The development of drug resistance is almost always a consequence of inadequate drug therapy, which may in turn be due to physician error (health provider-related factors), lack of drug availability (management-related factors), or failure of the tuberculosis control programme to address patient adherence (*4*–*7*).

The most common cause of drug-resistant tuberculosis is undoubtedly the lack of a properly organized system to ensure effective treatment (i.e. national tuberculosis programmes), and particularly the lack of effectively implemented directly observed treatment. In addition, errors that can select resistant bacilli are the prescription of inadequate treatment (*8*, *9)* and the addition of one extra drug in the case of a failing regimen, effectively resulting in monotherapy. Management errors include the lack of availability of a standardized therapeutic regimen; difficulty experienced by poor patients in obtaining all the drugs that they need; shortages of tuberculosis drugs; and use of drugs (or drug combinations) of unproven bioavailability.

A basic principle of tuberculosis control is that the health system, not the patient, is responsible and accountable for ensuring complete treatment of all patients who start treatment. The ethical and pragmatic argument for this position is that tuberculosis control in general – and prevention of drug-resistant tuberculosis particularly – is a *public good*. This public good benefits not only individuals (by curing their disease), but also the community at large, by preventing cases of tuberculosis and preventing the emergence of drug resistance. Thus, tuberculosis programmes must accept that adherence to self-administered medication is unpredictable, and that treatment observation accessible and acceptable to the patient and accountable to the health system must be provided to ensure cure (see "What are the advantages of direct obser-

[1] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
[2] Medical officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

vation of treatment?", page 183). Put simply, if patients develop drug resistance because of incorrect ingestion of medication, this is the legal and ethical fault and responsibility of the treatment system for failing to organize treatment, including direct observation, effectively. A high rate of drug resistance is thus correctly seen as a symptom of poor programme performance in the past.

Once patients acquire resistance to a single drug, they become increasingly likely to acquire further resistance from poor treatment. Thus, strains of tubercle bacilli become sequentially resistant to other agents and may develop multidrug resistance (i.e. resistance to at least isoniazid and rifampicin).

The best way to prevent drug resistance is to ensure the provision of effective regimens of directly observed short-course treatment with first-line drugs for all newly diagnosed tuberculosis cases. This should be implemented within the framework of a well-structured tuberculosis control programme.

References

1. Crofton J. Possible causes of the failure of the treatment of pulmonary tuberculosis; how to avoid them. *Bulletin of the International Union Against Tuberculosis*, 1980, 55:93–101.
2. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. Common errors and their association with the acquisition of drug resistance. *Journal of the American Medical Association*, 1993, 270:65–68.
3. Cohn ML, Middlebrook G, Russell WF Jr. Combined drug treatment of tuberculosis. I. Prevention of emergence of mutant populations of tubercle bacilli resistant to both streptomycin and isoniazid in vitro. *Journal of Clinical Investigation*, 1959, 38:1349–1355.
4. Barnes PF. The influence of epidemiologic factors on drug resistance rates in tuberculosis. *American Review of Respiratory Disease*, 1987, 136:325–328.
5. Crofton J et al. *Guidelines for the management of drug-resistant tuberculosis*. Geneva, World Health Organization, 1997 (document WHO/TB/96.210).
6. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. *American Review of Respiratory Disease*, 1993, 147:1311–1320.
7. Pablos-Mendez A et al. Nonadherence in tuberculosis treatment: predictors and consequences in New York City. *American Journal of Medicine*, 1997, 102:164–170.
8. Uplekar M, Pathania V, Raviglione M. Private practitioners and public health: weak links in tuberculosis control. *Lancet*, 2001; 358:912–916.
9. Uplekar M, Pathania V, Raviglione M. *Involving private practitioners in tuberculosis control: issues, interventions and emerging policy framework.* Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.285).

47. How can the emergence of drug resistance be prevented?

T. Frieden[1]

Drug resistance can be prevented by the use of appropriate treatment regimens, and by ensuring that these regimens are taken correctly.

An appropriate regimen always includes at least two drugs to which the patient's organism is susceptible. Several additional considerations must be taken into account. Pyrazinamide is relatively ineffective in preventing the emergence of drug resistance to companion drugs (*1*). Thus, treatment with a regimen of isoniazid and pyrazinamide may lead to the emergence of isoniazid-resistant (and, subsequently, pyrazinamide-resistant) organisms, even if the isolate was initially susceptible to both isoniazid and pyrazinamide. During the initial phase of treatment, when the bacterial load is high and organisms are multiplying rapidly, use of multiple drugs to which the patient's organism is susceptible is particularly important. In the continuation phase of treatment, emergence of resistance is much less likely. Because of the essential role of rifampicin in the treatment of individual cases and control of disease in the community (see "Why are special precautions needed to protect rifampicin?", page 195), appropriate regimens that minimize the risk of acquisition of resistance, particularly to rifampicin, should always be used.

Choice of an appropriate regimen should be made by national authorities based on international recommendations, scientific evidence from controlled clinical trials, and knowledge of the drug susceptibility pattern of the community in which treatment regimens are being organized.

Optimal regimens maximize chances of cure while minimizing complexity, toxicity, cost and risk of development of additional drug resistance. However, even an optimal regimen will have no value unless it is used correctly. An "ideal" regimen is of little use – and may be counterproductive – if it is not widely accepted and applied. Widespread use of appropriate standard regimens will greatly reduce the risk of drug resistance. For this purpose, many countries involve professional organizations (e.g. thoracic societies) and public health authorities in reaching a consensus on standard regimens that are recommended for all patients.

[1] Medical officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

Correct use of a regimen means that the drugs are taken in the right dosages, at the right times, and for the right duration. High dosages increase toxicity without a commensurate increase in efficacy; low dosages may reduce efficacy and allow emergence of resistance. First-line drugs should be taken as a single dose. Splitting first-line drugs into several doses per day lowers the peak drug concentration and therefore reduces efficacy and may increase the risk of emergence of drug resistance (*2*, *3*).

Fixed-dose combinations of tuberculosis drugs may prevent the emergence of drug resistance by ensuring that a single drug can never be taken in isolation (see "What are the advantages and disadvantages of fixed-dose combinations of antituberculosis drugs?", page 189). However, taking fewer than the recommended number of tablets of a fixed-dose combination drug may expose a patient's organisms to sub-inhibitory concentrations of multiple medications. In addition, there are potential problems with the bioavailability of fixed-dose combinations. Use of fixed-dose combinations has not been proved to reduce the risk of drug resistance.

The only means of ensuring the prevention of drug resistance is the use of direct observation of an appropriate treatment regimen. Properly implemented, direct observation ensures that drugs are taken at the right dosage, at the right intervals, and for the required duration. (See "What are the advantages of direct observation of treatment?", page 183.)

Areas that have implemented directly observed, standardized treatment regimens have prevented the development of drug resistance, even in the context of high rates of HIV infection (*4*–*6*).

References

1. Mitchison DA. Basic mechanisms of chemotherapy. *Chest*, 1979, 76:S771–S781.
2. Tuberculosis Research Centre, Indian Council of Medical Research. Low rate of emergence of drug resistance in sputum positive patients treated with short-course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:40–45.
3. Tuberculosis Chemotherapy Centre, Madras. A concurrent comparison of isoniazid plus PAS with three regimens of isoniazid alone in the domiciliary treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1960, 23:535–585.
4. Zhang LX et al. Trend of initial drug resistance of tubercle bacilli isolated from new patients with pulmonary tuberculosis and its correlation with the tuberculosis programme in Beijing. *Tubercle and Lung Disease*, 1995, 76:100–103.
5. Kenyon TA et al. Low levels of drug resistance amidst rapidly increasing tuberculosis and human immunodeficiency virus co-epidemics in Botswana. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:4–11.
6. Churchyard GJ et al. Drug-resistant tuberculosis in South African gold miners: incidence and associated factors. *International Journal of Tuberculosis and Lung Disease*, 2000, 4: 433–440.

48. How reliable are drug susceptibility tests?[1]

M. Espinal[2]

It is difficult to perform susceptibility testing accurately even when skilled personnel are available and laboratory facilities are of a high standard. In countries where skilled manpower and adequate facilities for such tests are scarce, accuracy is even more difficult to achieve.

Much has been learned about the reliability of drug susceptibility testing in the past decade. An international initiative led by WHO and the IUATLD has improved our knowledge of the performance of international and national reference laboratories, including many in resource-limited countries (*1*, *2*). This initiative, known as the Supranational Reference Laboratory Network, was established to improve the quality of susceptibility testing of national reference laboratories and to validate data obtained in surveys carried out within the WHO/IUATLD Global Project on Drug Resistance Surveillance.

Five rounds of proficiency testing were carried out annually between 1994 and 1998 as part of this initiative. A coordinating laboratory sent reference strains of *Mycobacterium tuberculosis* to all participating supranational laboratories. The laboratories were asked to test the susceptibility pattern of the reference strains using their habitual methods and classify the cultures as resistant or susceptible. The results were compared with a "gold standard" that was derived from the judicial results (i.e. the majority). The strains were also redistributed by some supranational laboratories to several national reference laboratories (sub-networks) around the world.

Overall cumulative sensitivity for drug resistance was 95%, specificity 95%, and reproducibility 96% (*3*). In 1998, overall sensitivity for resistance to isoniazid and rifampicin was 100% and overall specificity was 99% and 100%, respectively. However, three supranational laboratories and some national reference laboratories produced results that were below the standard (lower specificity), suggesting that misclassification of susceptible strains as resistant is still an issue of concern, even in highly qualified laboratories and in the context of carefully performed proficiency testing. (Proficiency testing overestimates laboratory accuracy when compared with routine

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.

practice, since laboratories generally give special attention to panels of samples analysed for proficiency testing.)

While the improvement of susceptibility testing has been remarkable, it is important to highlight that the WHO/IUATLD initiative applies to surveillance and not to clinical practice. Surveys are carried out every 3–5 years. Information for clinical action on the basis of susceptibility tests in resource-limited settings is still very scarce. Additional limitations are the difficulty and unreliability of testing susceptibility to reserve drugs. Furthermore, there is usually only one national reference laboratory in each resource-limited country. It is clear that only on very limited occasions would these laboratories be able to cope with susceptibility testing for clinical purposes. Finally, it is worth keeping in mind that clinical action based on unreliable susceptibility testing can be harmful to the patient (see "What are the possible consequences of inaccurate drug-susceptibility testing?", page 213). Thus, is often wise to limit the use of susceptibility testing to patients who fail standard short-course treatment under directly observed treatment, as the risk of drug resistance is higher in these patients.

Newer culture techniques using liquid media give more rapid results, but may increase the risk of cross-contamination of cultures in the laboratory and are generally expensive. In the future, it is possible that molecular or rapid growth-based techniques will be able to identify patients with rifampicin resistance – those whom standardized regimens would be unlikely to cure. At present, however, such techniques identify less than 80% of rifampicin-resistant isolates and are costly and unproven.

References

1. Laszlo A et al. Quality assurance programme for drug susceptibility testing of *Mycobacterium tuberculosis* in the WHO/IUATLD Supranational Laboratory Network: first round of proficiency testing. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:231–238.
2. Pablos-Mendez A et al. Global surveillance for antituberculosis-drug resistance, 1994–1997. *New England Journal of Medicine*, 1998, 338:1641–1649.
3. *Anti-tuberculosis drug resistance in the world. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. Report No. 2: prevalence and trends.* Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.278).

49. What are the possible consequences of inaccurate drug-susceptibility testing?[1]

M. Espinal[2]

The possible consequences of inaccurate susceptibility testing include:

- misclassification of strains;
- unnecessary changes of treatment;
- use of reserve drugs; leading to:
  - more toxicity
  - less chance of cure
  - more difficult management
  - the need for hospitalization
  - more laboratory work
  - more staff needed
  - higher costs.

Resistant strains may be misclassified as susceptible, and vice versa. If susceptible strains are reported as resistant, regimens may be changed unnecessarily and reserve drugs, if available, may be introduced. However, such drugs are usually more toxic, less effective, and more costly than the drugs used for primary treatment (*1*). In a review of 14 studies that included sputum cultures of more than 100 patients, false-positive cultures were identified in 13 (93%) of them (*2*). False-positive cultures may occur because of contamination of clinical devices, clerical errors, and laboratory cross-contamination. Of the 236 patients with false-positive cultures reported in sufficient detail, 158 (67%) were treated, some of whom experienced toxicity from treatment, as well as unnecessary hospitalization, tests, and contact investigations. Clearly, laboratory mistakes are not rare but they are infrequently recognized by laboratory and clinical personnel.

The management of ambulatory patients receiving reserve drugs may be difficult. Such patients often have to be hospitalized for a long time, which is many times more expensive than domiciliary treatment and risks the spread of tuberculosis in hospital. More staff will be needed, in particular for the additional laboratory work required

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.

(repeated tests of kidney and liver function, blood examinations, and close bacteriological follow-up), and this will add to the cost of hospital treatment. Thus, there may be a heavy drain on resources allocated to therapeutic services, merely as a consequence of inaccurate susceptibility tests.

It cannot be emphasized too often that, whatever the stage of development of a country's laboratory services, no laboratory should embark on drug susceptibility testing and re-treatment with reserve drugs as long as there are deficiencies in case detection and primary treatment. In such cases, resources should be used to improve the treatment, with standard treatment, of persons in whom tuberculosis has been newly diagnosed. That is still the most effective way of avoiding the development of drug resistance – a man-made problem.

References

1. Fox W. General considerations on the choice and control of chemotherapy in pulmonary tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1972, 47:51–71.
2. Burman WJ, Reves RR. Review of false-positive cultures for *Mycobacterium tuberculosis* and recommendations for avoiding unnecessary treatment. *Clinical Infectious Diseases*, 2000, 31:1390–1395.

50. What reserve regimens are available and what is their place in tuberculosis control programmes?[1]

M. Espinal[2]

Reserve regimens are used for patients with multidrug-resistant tuberculosis (see "How does drug resistance develop?", page 193). Since such resistance is the result of inadequate treatment, the need for re-treatment with reserve regimens is avoidable. Before the various reserve regimens are reviewed, some principles of the management of re-treatment will be discussed. Without an organizational framework such as the one suggested in the DOTS strategy (See "What is DOTS?", page 241), and without knowledge of the operational requirements of treatment with reserve regimens, there is little chance of success. This has been shown even in high-resource settings where lack of an effective organizational framework allowed a rapid increase in both tuberculosis and drug resistance (*1*).

The provision of reserve regimens may prove to be an intolerable drain on resources, particularly in countries with limited financial resources, health facilities, and staff, in which annual government expenditure on health may be less than US$ 1 per head. It would be irrational for any country to divert resources to re-treatment with reserve regimens as long as a large proportion of new infectious cases remain untreated or ineffectively treated and short-course treatment with first-line drugs has not reached its full therapeutic potential (*2*). A large requirement for reserve drugs reflects inadequately managed short-course treatment. The vicious cycle shown in Figure 17 can occur all too easily.

Management of re-treatment

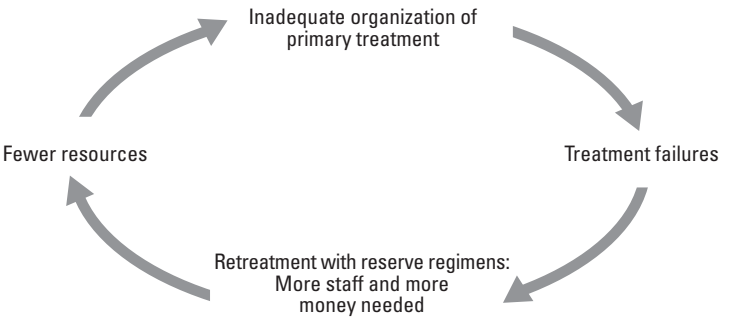
The treatment of patients whose organisms are resistant to the standard drugs or who do not tolerate those drugs presents many difficulties. These difficulties are caused by the drugs themselves and, to a great extent, by the attitudes of the health staff.

With few exceptions, reserve drugs are not highly effective. They often produce toxic reactions that are not only unpleasant but also sometimes dangerous. This may necessitate reducing the dosage, with the result that efficacy is reduced. Moreover,

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.

Figure 17
Cycle of treatment programme failure



reserve drugs are expensive and several are unstable in tropical climates. Intermittent dosing is generally not possible, and several reserve drugs may have to be taken several times a day, further complicating their administration.

A significant proportion of patients with drug-resistant disease belong to groups whose cooperation is not easy to achieve, including those who are alcohol- or drug-dependent, prisoners, and homeless people. Special efforts are needed to persuade such patients to complete the long and arduous treatment regimen. Many authorities therefore recommend that treatment with reserve drugs should be started in hospital to facilitate close observation for toxic effects and the supervision of regularity. Only after tolerance of the drug regimen has been ascertained, and a patient's cooperation has been secured, is ambulatory treatment given. However, patients often dislike hospital discipline and not infrequently discharge themselves from the hospital. Considerable efforts are then required to persuade a patient not to stop the treatment, which, with all its discomforts, is usually the only means of preventing the patient's death. If the health staff are convinced of this, they can sometimes induce a patient to cooperate, but this will mean that every dose of pills must be swallowed under the direct observation of a dedicated health worker.

Because of the highly specialized biochemical and microbiological follow-up examinations needed, it is evident that the organization of re-treatment with reserve drugs demands special measures. These are a heavy drain on skilled staff time, hospital beds, and financial resources. Data on the cost of treating a patient with multidrug-resistant tuberculosis in a resource-poor setting are scarce, but the full cost of treating such a patient in the United States of America has been estimated at up to US$ 100 000 (*3*). Encouraging evidence is emerging on the use of reserve regimens under carefully selected programme conditions (*4*). In resource-poor settings, it may be possible to greatly limit the use of hospitalization; this has many advantages both for the patient and for the health care system. WHO and several partners are testing a new strategy for managing cases of multidrug-resistant tuberculosis in low- and middle-income

countries, using reserve drugs within the DOTS strategy and maximizing ambulatory treatment. The aim is to assess the feasibility and cost-effectiveness of using such drugs under the overall supervision of national tuberculosis programmes (*5*). This initiative is not appropriate for settings where effective tuberculosis control, i.e. DOTS, is not in place.

Re-treatment regimens for patients with organisms resistant to the standard drugs

Certain principles must be followed in designing a reserve regimen. The drugs should not have been used before: in many cases, prescribing a drug that has been used before offers no advantage. The initial regimen should include at least three drugs to which the bacilli are likely to be fully susceptible. Drugs should not be kept in reserve: the most likely effective regimen should be prescribed. If drug susceptibility testing is not available and resources are limited, standard re-treatment regimens with reserve drugs can be used (*6*). It is important to take into account the regimens the patient has received previously, whether they were fully administered under direct observation, and for how long. Even if susceptibility testing is unavailable, every effort should be made to obtain an accurate susceptibility testing profile of patients failing a standard regimen with first-line drugs, particularly if the treatment was actually given under direct observation.

If susceptibility results are not available, at least three drugs never before used for the patient, such as an aminoglycoside, ethionamide, and ofloxacin, should be used, as well as an injectable antibiotic such as capreomycin, amikacin, or kanamycin. Any reserve regimen should be given daily and directly observed. Bacteriological results (smear and, if possible, culture) should also be monitored. Pyrazinamide and ethambutol could be added as the fourth and fifth drugs of choice (even if used previously, because of the low probability of resistance). Another option is to replace ethambutol by cycloserine (or *p*-aminosalicylic acid). An intensive phase of 3–6 months should be followed by a continuation phase of 15–18 months with two or three of the most active and best-tolerated drugs.

If susceptibility test results are available, designing a regimen will depend on a number of factors, such as the drugs to which the strain of *Mycobacterium tuberculosis* is resistant. WHO recommends 3–4 oral drugs plus 1 injectable drug to which the isolate is susceptible for 3–6 months, and then at least 3 effective oral drugs for 15–18 more months. Examples of potentially useful reserve regimens are given in Table 51; all are daily regimens (*6*). There is some evidence that a longer duration of aminoglycoside treatment is associated with a higher success rate (*7*).

Dosages and adverse effects of reserve drugs are discussed elsewhere (see "What is the therapeutic effect and what is the toxicity of antituberculosis drugs?", page 110).

The response of patients with multidrug-resistant strains to second-line drugs is variable. A 56% cure rate that increased to 85% after the addition of surgery was

Table 51
Summary of reserve regimens[a]

Initial phase		Continuation phase	
Drugs[b]	Rhythm and period of administration	Drugs	Rhythm and period of administration
Susceptibility results unavailable:			
KAN[c] + ETH + OFL + Z + E	Daily (3–6 months)	ETH + OFL + E (up to 18 months)	Daily
Susceptibility test results available:			
Resistant to H and S:	Daily	R + E (ETH)[d]	Daily
R + KAN[c] + Z + E	(3 months)	(up to 6 months)	
Resistant to at least H and R:	Daily	All except injectable	Daily
3–4 orals and 1 injec	(3–6 months)[e]	(15–18 months)	

[a] Source: reference *5*.
[b] H = isoniazid, R = rifampicin, E = ethambutol, Z = pyrazinamide, S = streptomycin, ETH = ethionamide, KAN = kanamycin, OFL = ofloxacin. (For dosages, see "What is the therapeutic effect and what is the toxicity of antituberculosis drugs?", page 110)
[c] Amikacin or capreomycin could also be used.
[d] Use ETH instead of E if there is resistance to H, E and S.
[e] Drugs to which isolate is susceptible must be used. Minimum initial phase should be 3 months, but can be extended until there is smear or culture conversion.

reported in patients with chronic disease (*8*). It appears that multidrug-resistant tuberculosis patients without a history of prior treatment respond better to treatment than similar patients who have been treated previously. Indeed, several series of patients without previous treatment courses reported cure rates of 75–96% (*9–11*). These series, however, are from high-income countries or have been obtained with extensive clinical, laboratory, and programme support, and used tailored treatment regimens. Data at programmatic level are needed from resource-limited countries (*12*). The challenge for many resource-limited settings would be the countrywide implementation of tailored regimens with reserve regimens.

References

1. Frieden TR et al. The emergence of drug resistant tuberculosis in New York City. *New England Journal of Medicine*, 1993, 328:521–526.
2. *WHO Expert Committee on Tuberculosis. Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
3. Mahmoudi A, Iseman MD. Pitfalls in the care of patients with tuberculosis. *Journal American Medical Association*, 1993, 270:65–68.
4. *Tuberculosis en el Perú – Informe [Tuberculosis in Perú – Report]*. Lima, Ministerio de Salud, Programa Nacional de Control de la Tuberculosis, 1999.

5. *Guidelines for establishing DOTS-PLUS pilot projects for the management of multidrug-resistant tuberculosis* (*MDR-TB*). Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.279).
6. Crofton J et al. *Guidelines for the management of drug-resistant tuberculosis*. Geneva, World Health Organization, 1997 (document WHO/TB/96.210).
7. Frieden TR et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *Journal of the American Medical Association*, 1996, 276:1223–1228.
8. Iseman MD et al. Surgical intervention in the treatment of pulmonary disease caused by *Mycobacterium tuberculosis*. *American Review of Respiratory Disease*, 1990, 141:623–625.
9. Telzak EE et al. Multidrug-resistant tuberculosis in patients without HIV infection. *New England Journal of Medicine*, 1995, 333:907–911.
10. Park SK, Kin LT, Song SD. Outcome of chemotherapy in 107 patients with pulmonary TB resistant to isoniazid and rifampicin. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:877–884.
11. Geerligs WA et al. Multidrug-resistant tuberculosis: long-term treatment outcome in the Netherlands. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:758–764.
12. Espinal MA et al. Rational "DOTS Plus" for the control of MDR-TB. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:561–563.

51. What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?

M.E. Villarino[1]

WHO recommends (*1*, *2*) that tuberculosis programmes provide treatment for latent tuberculosis infection (LTBI) – also called preventive treatment – for:

- **Children under 5 years of age who are household contacts of smear-positive patients**
  Infants and young children with latent *Mycobacterium tuberculosis* infection are at high risk of rapidly developing disease. Infants 2 years of age or younger are at particularly high risk of developing life-threatening tuberculous meningitis or miliary tuberculosis (*3*).

- **Persons infected with both HIV and *M. tuberculosis***
  The annual risk among HIV infected, tuberculin-positive persons of developing tuberculosis (estimated to be 6–16%) is much higher than that of HIV-uninfected, tuberculin-positive persons, whose lifetime risk of developing tuberculosis is estimated to be no greater than 10%. When tuberculosis develops in an HIV-infected person, the course of immunosuppression in that person is accelerated; the treatment outcome depends both on the person's degree of immunosuppression and on the use of appropriate tuberculosis treatment given under direct observation (*4*).

For persons in either of these high-risk categories, LTBI treatment can potentially reduce the risk of developing active tuberculosis, increase life expectancy, and reduce overall medical costs. However, this intervention strategy may not substantially reduce tuberculosis morbidity in the larger communities in which these persons reside (see "What is the epidemiological impact of treatment of latent tuberculosis infection?", page 226). LTBI treatment programmes are costly, difficult to implement on a large scale, and carry a risk of drug toxicity. In addition, unless active tuberculosis is ruled out, patients with unrecognized active disease who are treated for LTBI may be harmed because they may develop drug resistance as a result of exposure to a drug regimen that is inadequate for treatment of tuberculosis.

[1] Chief, Diagnostic and Therapeutic Studies Section, Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Before a decision is made to incorporate LTBI treatment into a tuberculosis control programme, the following factors must be considered since they limit its application and effectiveness:

— hepatotoxicity (increases with age; is potentiated by other drugs, especially alcohol; is very rare in young children);
— non-adherence (a major factor in limiting effectiveness);
— drug resistance (LTBI regimens may be ineffective for drug-resistant infections);
— operational problems in implementation (need for tuberculin skin testing, for voluntary HIV counselling and testing programmes, etc.);
— the difficulty and cost of excluding tuberculosis and the risk of creating drug resistance if such exclusion is not effective; and
— the costs per se.

In many industrialized countries where incidence of tuberculosis has fallen to record low levels, it is believed that most new cases of tuberculosis disease occur in persons who were infected in the remote past, contained their infection, and then subsequently developed tuberculosis. Although efficient detection and treatment of persons with active tuberculosis remain the highest priority activities for all tuberculosis control programmes, these measures alone will not prevent the new cases that arise from the pool of individuals infected a long time ago. In low-prevalence countries, therefore, the treatment of persons with LTBI who are at high risk of developing active disease is an important component of tuberculosis control.

A regimen of isoniazid for 6–12 months has been the mainstay of treatment for LTBI for more than 30 years. However, the acceptability of isoniazid for LTBI has been limited by the poor patient adherence that results from the relatively long duration of treatment required, and by concerns about toxicity. Consequently, there has been interest in the development of shorter regimens as alternatives to isoniazid for the treatment of LTBI. In recent years, several studies of "short-course" treatment of LTBI have been undertaken in persons infected with HIV (*5*).

The identification of persons with LTBI is a prerequisite for a treatment programme, and guidelines for administering and interpreting the tuberculin skin test are therefore required. The tuberculin test is indicated only for persons at highest risk of tuberculosis and is discouraged for those at low risk. Persons at increased risk of tuberculosis include those who have had recent infection with *M. tuberculosis* and those who have clinical conditions associated with an increased risk of progression from LTBI to active tuberculosis (*5*). Except in community surveys of risk of infection, the tuberculin test should be given only to persons who, if found to be tuberculin-positive, would receive treatment for LTBI. Thus, except in some community surveys, *a decision to administer a tuberculin test is a decision to treat if LTBI is found, irrespective of the age of the person tested.*

Many clinical guidelines use a rating system to grade the strength of the recommendation (A, B, or C) and the quality of evidence supporting the recommendation

Table 52
Rating system for grading the strength of the treatment recommendation

Drugs	Duration	Interval	Rating[a] (evidence[b])	
			HIV–	HIV+
Isoniazid	9 months	Daily	A (II)	A (II)
		Twice weekly	B (II)	B (II)
Isoniazid	6 months	Daily	B (I)	C (I)
		Twice weekly	B (II)	C (I)
Rifampicin + pyrazinamide	2 months	Daily	B (II)	A (I)
	2–3 months	Twice weekly	C (II)	C (I)
Rifampicin	4 months	Daily	B (II)	B (III)

[a] A: preferred, B: acceptable alternative, C: offered when A and B cannot be given.
[b] I: randomized clinical trial data, II: data from clinical trials that are not randomized or were conducted in other populations, III: expert opinion.

(I, II, or III), as shown in Table 52. Four regimens are recommended for the treatment of adults with LTBI. For children, the only recommended treatment continues to be a 6–12-month regimen with isoniazid alone.

Prospective, randomized trials in HIV-negative persons indicate that preventive treatment with isoniazid for 12 months is more effective than 6 months' treatment. However, a daily isoniazid regimen for 9 months is recommended in many countries – in subgroup analyses of several trials, the maximum beneficial effect of isoniazid was achieved by 9 months' treatment, with minimal additional benefit gained by extending treatment to 12 months (*6*). When compared with placebo, both 6-month and 12-month regimens are effective in HIV-positive patients; however, these regimens have not been compared with each other in randomized trials. Although a 9-month regimen of isoniazid is preferred for the treatment of LTBI, a 6-month regimen also provides substantial protection and has been shown to be superior to placebo in both HIV-negative and HIV-positive persons. In some situations, treatment for 6 months rather than 9 months may provide a more favourable outcome from the standpoint of cost-effectiveness; based on local conditions, tuberculosis programmes or providers may opt for a 6-month rather than a 9-month course of isoniazid. Both the 9- and 6-month isoniazid regimens may be given intermittently (i.e. twice weekly).

A 2-month daily regimen of rifampicin and pyrazinamide is recommended on the basis of the results of a prospective randomized trial of LTBI treatment in HIV-infected persons. The trial showed the 2-month regimen to be similar in safety and efficacy to a 12-month regimen of isoniazid (*7*). However, severe hepatotoxicity has been observed when regimens containing rifampicin and pyrazinamide have been used for LTBI (*8*). Twice-weekly rifampicin and pyrazinamide for 2 or 3 months may

Table 53
Management of children exposed to an adult with infectious (smear-positive) tuberculosis

If:	And:	Then:	
The child has symptoms of tuberculosis	A physician determines that the child has tuberculosis	A full course of tuberculosis treatment should be given	
The child does not have symptoms of tuberculosis	A tuberculin test is **not** available	The child should receive treatment for LTBI	
	A tuberculin test is available	The child should receive 3 months of treatment for LTBI and a tuberculin test should then be done	
		If:	Then:
		The child's induration to the tuberculin test is positive	Continue treatment of LTBI for a full course (i.e. 6–12 months of 5 mg/kg of isoniazid)
		The child's induration to the tuberculin test is negative	Stop the preventive treatment and give BCG vaccination (if there has been no previous vaccination)

be considered when alternative regimens cannot be given. This intermittent regimen should be administered as directly observed treatment. Some experts recommend that the 2-month regimen of daily rifampicin and pyrazinamide also be given under direct observation, which can consist of five observed and two self-administered doses each week. When rifampicin cannot be used (e.g. in HIV-infected persons receiving protease inhibitors), rifabutin may be substituted (*9*). Rifampicin given daily for 4 months is recommended on the basis of the efficacy of such a regimen in a prospective randomized trial of tuberculin-positive persons with silicosis and a non-randomized trial in persons exposed to isoniazid-resistant tuberculosis (*10*, *11*). This option may be especially useful for patients who cannot tolerate isoniazid or pyrazinamide.

Before treatment of LTBI is started, active tuberculosis must be ruled out by clinical history, physical examination, chest X-ray, and, when indicated, bacteriological studies. The WHO-recommended protocol for evaluation and treatment of childhood contacts of active tuberculosis is summarized in Table 53 (*12*).

In high-prevalence countries that implement a policy of LTBI treatment for con-

tacts of smear-positive patients, a chest X-ray should be done to rule out active tuberculosis before the start of treatment in at least all HIV-infected persons. All HIV-infected persons who have cough, fever, or other symptoms compatible with tuberculosis should be subjected to careful evaluation, including bacteriological studies, before LTBI treatment is started. Children who have symptoms that are potentially compatible with tuberculosis (e.g. fever, cough, failure to thrive) must also undergo an X-ray before the start of treatment. Ideally, this should apply to all children but, if X-ray is unavailable, LTBI treatment may be given unless a child is symptomatic. For pregnant, HIV-negative women, isoniazid given daily or twice weekly for 9 or 6 months is the recommended regimen for LTBI. A chest X-ray to evaluate the possibility of active tuberculosis should be undertaken in pregnant women (with appropriate shielding precautions) when required, even during the first trimester of pregnancy. For women at risk of progression from LTBI to disease, especially those who are HIV-infected or who have probably been recently infected with *M. tuberculosis*, start of treatment should not be delayed on the basis of pregnancy alone, even during the first trimester. When the risk for active tuberculosis is lower, some experts recommend waiting until after delivery to start treatment for LTBI.

Baseline laboratory testing is not routinely indicated for all patients at the start of LTBI treatment. Patients whose initial evaluation suggests a liver disorder should have baseline liver function tests of serum AST (SGOT) or ALT (SGPT) and of bilirubin. Baseline testing is also indicated for patients with HIV infection, women who are pregnant or in the immediate postpartum period (i.e. within 3 months of delivery), persons with a history of or risk factors for chronic liver disease, and persons who consume alcohol regularly. It is not routinely indicated in older persons. Active hepatitis and severe liver disease are relative contraindications to treatment. Routine laboratory monitoring during treatment of LTBI is indicated for persons whose baseline liver enzymes are abnormal and for others with a risk of hepatic disease. Patients should be educated about the adverse effects associated with LTBI treatment and advised to stop treatment and promptly seek medical evaluation if these occur. They should be questioned about adverse effects and monitored for development of jaundice.

The significance of LTBI treatment in countries where tuberculosis incidence is high and growing, and where *M. tuberculosis* continues to be transmitted at high rates, has been questioned. Certainly, an LTBI treatment programme should not be a priority in the overall tuberculosis control strategy in such contexts. The primary strategy for controlling tuberculosis is to minimize the risk of transmission by early identification and complete treatment of patients who have active infectious tuberculosis. Selective LTBI treatment programmes may be feasible and affordable for some middle-income countries, but are always a lower priority than programmes of successful management of tuberculosis cases. In low-income countries with high tuberculosis prevalence, LTBI treatment programmes would have at most a secondary role in tuberculosis control. The use of LTBI treatment as a tuberculosis prevention strat-

egy should be reserved for persons or groups with the highest risk of developing active tuberculosis. In countries experiencing an epidemic of HIV, treatment of LTBI can provide important benefits for the individual. Although such a strategy could theoretically reduce the incidence of tuberculosis and blunt the impact of HIV on tuberculosis epidemiology if widely applied, this would be difficult, if not impossible, to achieve under programme conditions. Even – or especially – in such settings, prompt identification and rapid, complete treatment of patients with smear-positive tuberculosis is the highest priority.

References

1. Harries AD et al. *TB/HIV: a clinical manual.* Geneva, World Health Organization, 1996 (document WHO/TB/96.220).
2. Preventive therapy against tuberculosis in people living with HIV. Policy statement. *Weekly Epidemiological Record*, 1999, 74:385–400.
3. Starke JR, Jacobs RF, Jereb JA. Resurgence of tuberculosis in children. *Journal of Pediatrics*, 1992, 120:839–855.
4. Shafer RW et al. Predictors of survival in HIV-infected tuberculosis patients. *AIDS*, 1996, 10:269–272.
5. Targeted tuberculin testing and treatment of latent tuberculosis infection. *Morbidity and Mortality Weekly Report*, 2000, 49:1–51.
6. Comstock GW. How much isoniazid is needed for prevention of tuberculosis among immunocompetent adults? *International Journal of Tuberculosis and Lung Disease*, 1999, 3:847–850.
7. Gordin F et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. *Journal of the American Medical Association*, 2000, 283:1445–1450.
8. Update: fatal and severe liver injuries associated with rifampin and pyrazinamide for latent tuberculosis infection, and revisions in American Thoracic Society/CDC recommendations. United States, 2001. *Morbidity and Mortality Weekly Report*, 2001; 50:733–735.
9. Updated guidelines for the use of rifabutin or rifampin for the treatment and prevention of tuberculosis in HIV-infected persons taking protease inhibitors or non-nucleoside reverse transcriptase inhibitors. Centers for Disease Control and Prevention. *Morbidity and Mortality Weekly Report*, 2000, 49:185–189.
10. A double-blind placebo controlled trial of three antituberculosis chemoprophylaxis regimens in patients with silicosis in Hong Kong. Hong Kong Chest Service/Tuberculosis Research Center, Madras/British Medical Research Council. *American Review of Respiratory Disease*, 1992, 145:36–41.
11. Villarino ME et al. Rifampin preventive therapy for tuberculosis infection: experience with 157 adolescents. *American Journal of Respiratory and Critical Care Medicine*, 1997, 155: 1735–1738.
12. *Managing tuberculosis at district level: administering treatment*. Geneva, World Health Organization, 1994 (WHO/TB/96.211:AT3119).

52. What is the epidemiological impact of treatment of latent tuberculosis infection?

Z. Taylor[1]

Treatment of latent tuberculosis infection (LTBI) is an important component of tuberculosis control in the USA, but is rarely used outside North America other than for treatment of contacts of infectious cases. Until recently, isoniazid daily or twice weekly for 6–12 months was the only commonly recommended treatment regimen (*1*). This was based on the results of randomized, placebo-controlled trials that established the efficacy of isoniazid in preventing tuberculosis in persons with latent infection (*2*, *3*). The average reduction in the development of active tuberculosis observed in these trials was 60% (*2*). In persons who took more than 80% of their prescribed medication for 12 months, the effectiveness of isoniazid approached 90% (*2*). Isoniazid taken for 6 months was effective, but treatment for 12 months was even more effective (*3*). More recent recommendations include a 2-month regimen of daily rifampicin and pyrazinamide and a 4-month regimen of rifampicin, as an alternative to 6–9 months of daily or twice-weekly isoniazid (*4*). The recommendations were based on controlled clinical trials that found equivalent protection using these regimens compared with isoniazid regimens (*4*).

Most of the reported clinical trials of LTBI treatment involved high-risk populations such as recent contacts, persons in high-risk congregate settings, persons with HIV infection, or persons with untreated, inactive tuberculosis (*2*, *3*, *5*, *6*). The epidemiological impact of these treatment trials depended not only on the effectiveness of treatment, but also on the contribution of the treated groups to the incidence of tuberculosis in their communities. Three clinical trials, conducted in Greenland, Alaska, and Tunisia, attempted to measure the impact of LTBI treatment on the incidence of tuberculosis in a population. The trial in Greenland in 1956 involved 76 villages and 8081 participants (*7*). In each village, all eligible adults were given either isoniazid or placebo, with everyone in any given village receiving the same medication. Medication was administered twice weekly for two 13-week periods, with an intervening 13-week break. The trial in Alaska began in 1957 and involved 30 communities and 6064 participants (*8*). In this trial, households were randomized to receive either isoniazid or placebo. Finally, the Tunisian trial, which started in 1958,

[1] Centers for Disease Control and Prevention, Atlanta, GA, USA.

Table 54
Results of community trials of preventive treatment with isoniazid, 1956–1958[a]

Trial/treatment group	No. of participants	Case rate per 1000 person-years	% reduction
Greenland villagers			
Placebo	3907	13.8	
Isoniazid	4147	9.8	31[b]
Alaskan villagers			
Placebo	3017	7.7	
Isoniazid	3047	3.2	59[b]
Tunisian community			
Placebo	8141	3.1	
Isoniazid	7769	2.3	26[c]

[a] Source: references *2, 7, 8*.
[b] $P < 0.0001$ by chi square statistic.
[c] Statistically insignificant.

was conducted in a poor suburb of Tunis (*2*). Blocks of houses were randomized to receive either isoniazid or placebo; a total of 15 910 persons participated in the trial. The results of these trials are summarized in Table 54.

There is an obvious variation in the results of these trials, with a substantial effect in Alaska, a much smaller effect in Greenland, and the smallest effect in the Tunisian community study The trials in Alaska and Greenland took place in small, isolated villages with populations that supported the interventions. In addition, effective tuberculosis control programmes were in place in both locations. In Greenland, 400–600 mg isoniazid was given twice weekly on consecutive days for 13 weeks, followed by 13 weeks without treatment, and then a further 13 weeks of twice-weekly isoniazid. This is not a standard dosage schedule and is possibly sub-optimal, which may explain the reduced effectiveness observed in this study. In the Tunisian study, there was evidence that adherence to medication was low in the study population.

In the Alaskan communities, after completion of the trial, persons who were on placebo during the trial were offered and treated with isoniazid for 12 months. Although this was not a controlled trial, the investigators observed lower rates of active tuberculosis in persons who took more than 40% of the prescribed isoniazid compared with persons who took no isoniazid or took less than 40% of the prescribed doses (83% reduction in tuberculosis observed) (*9*). Since much of the morbidity occurred in persons with untreated, inactive tuberculosis, the authors estimated that by treating only that portion of the population, 40% of the tuberculosis in the community could be prevented.

In conclusion, the epidemiological impact of the treatment of LTBI may be a 31–59% reduction in active tuberculosis in a community where an effective tubercu-

losis control programme is in place and where the majority of active tuberculosis results from reactivation of latent infection. Theoretically, the reduction could be as much as 80–90% if all cases of active tuberculosis were the result of reactivation of latent infection, all persons with latent infection could be identified, and all persons with latent infection completed treatment. In practice, this combination of circumstances is rarely if ever to be found. Even in a low-incidence, resource-rich country like the USA, a significant proportion of active tuberculosis cases result from recent transmission of infection (*10*, *11*) and completion of treatment for LTBI is often less than 50% (*12*, *13*). The epidemiological impact of the treatment of LTBI is therefore likely to be more modest than the effect estimated by the studies in Alaska and Greenland. Further, the human and financial resources required to identify and treat persons with LTBI on a mass basis exceed the capacity of most tuberculosis control programmes. For well-funded, effective tuberculosis control programmes, treatment of LTBI in contacts, prisoners, persons with both HIV and LTBI, and other high-risk populations may be a viable option. The epidemiological impact will depend on the contribution of the risk group to tuberculosis incidence in the population, the proportion of the group identified treated, and the proportion of persons who complete treatment.

References

1. Treatment of tuberculosis and tuberculosis infection in adults and children. American Thoracic Society. *American Journal of Respiratory and Critical Care Medicine*, 1994, 149: 1359–1374.
2. Ferebee SH. Controlled chemoprophylaxis trials in tuberculosis. A general review. *Advances in Tuberculosis Research*, 1970, 17:28–106.
3. Efficacy of various durations of isoniazid preventive therapy for tuberculosis: five years of follow-up in the IUAT trial. International Union Against Tuberculosis Committee on Prophylaxis. *Bulletin of the World Health Organization*, 1982, 60:555–564.
4. Targeted tuberculin testing and treatment of latent tuberculosis infection. American Thoracic Society and Centers for Disease Control and Prevention. *American Journal of Respiratory and Critical Care Medicine*, 2000, 161:S221–S247.
5. Whalen CC et al. A trial of three regimens to prevent tuberculosis in Ugandan adults infected with the human immunodeficiency virus. *New England Journal of Medicine*, 1997, 337:801–808.
6. Gordin F et al. Rifampin and pyrazinamide vs isoniazid for prevention of tuberculosis in HIV-infected persons. An international randomized trial. *Journal of the American Medical Association*, 2000, 283:1445–1450.
7. Horwitz O, Payne PG, Wilbek E. Epidemiological basis of tuberculosis eradication. 4. The isoniazid trial in Greenland. *Bulletin of the World Health Organization*, 1966, 35:509–526.
8. Comstock GW, Ferebee SH, Hammes LM. A controlled trial of community-wide isoniazid prophylaxis in Alaska. *American Review of Respiratory Disease*, 1967, 95:935–943.
9. Comstock GW, Woolpert SF. Preventive treatment of untreated, nonactive tuberculosis in an Eskimo population. *Archives of Environmental Health*, 1972, 25:333–337.

10. Barnes PF et al. Transmission of tuberculosis among the urban homeless. *Journal of the American Medical Association*, 1996, 275:305–307.
11. Kimerling ME et al. Restriction fragment length polymorphism screening of *Mycobacterium tuberculosis* isolates: a population surveillance for targeting disease transmission in a community. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:655–662.
12. Nazar-Stewart V, Nolan CM. Results of a directly observed intermittent isoniazid preventive therapy program in a shelter for homeless men. *American Review of Respiratory Disease*, 1992, 146:57–60.
13. Marks SM et al. Outcomes of contact investigations of infectious tuberculosis patients. *American Journal of Respiratory and Critical Care Medicine*, 2000, 162:2033–2038.

Monitoring

53. What is the health, social, and economic burden of tuberculosis?

I. Smith[1]

The consequences of tuberculosis on society are immense. Worldwide, one person out of three is infected with tuberculosis – that is, 2 billion people in total. Global estimates of the burden of tuberculosis-related disease and death for 1997 indicated that 8 million people developed active tuberculosis every year and nearly 2 million died (*1*).

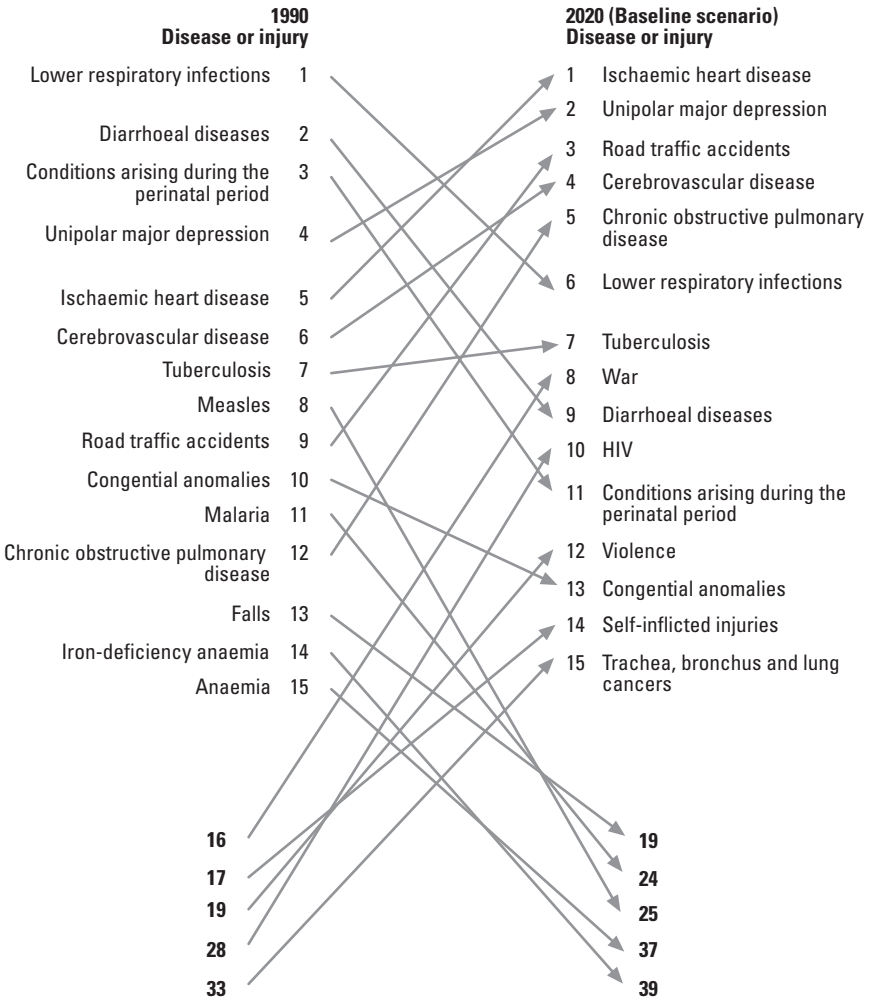
Tuberculosis accounts for 2.5% of the global burden of disease (*2*) and is the commonest cause of death in young women, killing more women than all causes of maternal mortality combined. As illustrated in Figure 18, tuberculosis currently holds seventh place in the global ranking of causes of death, and, unless intensive efforts are made, is likely to maintain that position through to 2020, despite a substantial projected decline in disease burden from other infectious diseases (*3*).

Infection with HIV increases the risk of tuberculosis disease (*4*). Countries with a high prevalence of HIV, particularly those in sub-Saharan Africa, have witnessed a sharp increase in tuberculosis, with reported incidence rates increasing two- to four-fold in the 1990s (*5*).

Drug resistance is an increasing problem in many countries, arising as a result of poor treatment organization. Poorly conceptualized control programmes, irregular drug supplies, and uncontrolled use of tuberculosis drugs in the private sector lead to drug resistance, which can be prevented with effective use of DOTS. WHO and the IUATLD carried out a global survey of drug resistance from 1994 to 1997 in 35 countries (*6*, *7*). Overall, among people with newly diagnosed tuberculosis, there was resistance to at least one drug in 9.9% of cases, and multidrug resistance (resistance to at least isoniazid and rifampicin) in 1.4%. A report on the second round of global surveillance, published in 2000, revealed a similar picture (any drug resistance in 10.7% of new cases, multidrug resistance in 1%). These reports confirm that the strongest risk factor for drug resistance is previous tuberculosis treatment; 23.3% of such cases had resistance to at least one drug, and 9.3% had multidrug-resistant tuberculosis (*8*). Drug resistance reduces the efficacy of the standard

[1] Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland.

Figure 18
Change in rank order for the 15 leading causes of death, world, 1990–2020[a]



[a] Reproduced from reference *3* with permission.

treatment regimens recommended by WHO, with failure rates 15 times higher in patients with multidrug-resistant tuberculosis than in those with drug-susceptible disease (*9*).

Tuberculosis hinders socioeconomic development: 75% of people with tuberculosis are in the economically productive age group of 15–54 years (*10*). Ninety-five per cent of all cases and 99% of deaths occur in developing countries, with the greatest burden in sub-Saharan Africa and south-east Asia. Twenty-three countries together

Table 55
Estimated household costs of tuberculosis

Cost to patient	Bangladesh (11)	India (*12*)	South Africa (*13*)	Uganda (*14*)
Direct costs (US$)	130	41	99	68
Lost work	57%	NA	NA	91%
Time loss	14 months	3 months	4 months	10 months
Lost income (US$)	115	89	272	161
Indirect cost as percentage of annual household income	15	14	NA	NA
Total cost as percentage of annual household income	31	20	NA	NA

account for more than 80% of all cases of tuberculosis. Household costs of tuberculosis are substantial (Table 55).

Although the "direct" costs of diagnosis and treatment are significant for poor families, the greatest economic loss occurs as a result of "indirect" costs, such as loss of employment, travel to health facilities, sale of assets to pay for treatment-related costs, funeral expenses, and particularly lost productivity from illness and premature death. A study from Uganda found that 95% of subsistence farmers with tuberculosis reported a loss in production, and 80% of wage-earners had stopped work (*14*). A review of studies investigating the economic impact of tuberculosis showed that, on average, 3–4 months of work time are lost if an adult has tuberculosis, resulting in the loss of 20–30% of annual household income, and an average of 15 years of income is lost if the patient dies from the disease (*15*).

The relation between tuberculosis and poverty is complex, as the disease impoverishes those who suffer from it, and the epidemic is exacerbated by socioeconomic decline. Poverty results in crowded housing with increased risk of transmission and in poor nutrition with increased risk of breakdown from infection to tuberculosis disease. The break-up of the Soviet Union in the early 1990s and the subsequent economic decline and collapse of health and social support structures have led to a rapid rise in tuberculosis, with rates increasing by 7% per year in the Russian Federation, Ukraine and other countries of the former Soviet Union (*5*). In Cuba over a 3-year period, economic and nutritional hardship resulted in a striking increase (24% per annum) in the tuberculosis notification rate (*16*). A strengthened programme allowed a renewed trend in transmission reduction, resulting in a renewed reduction in incidence.

Negative social consequences, such as stigma, are a particular problem for women in some societies, restricting options for marriage and employment and even leading to divorce. A study in India indicated that 15% of women with tuberculosis (equivalent to 100 000 women per year nationally) faced rejection by their families (*12*).

The negative impact carries over to the next generation, as the coping mechanisms of poor families adversely affect their children. The same study from India found that 8% of rural and 13% of urban children (equivalent to 300 000 nationally) were taken out of school when a parent (usually the father) developed tuberculosis. Other long-term consequences include indebtedness; the Indian study showed that more than two-thirds of households went into debt to cover the costs of tuberculosis; the average family debt was US$ 59, equivalent to 12% of the annual household income. Continued spread of tuberculosis infection condemns the next generation to the avoidable risk of tuberculous illness and death.

References

1. Dye C et al. Global burden of tuberculosis: estimated incidence, prevalence, and mortality by country. *Journal of the American Medical Association*, 1999, 282:677–686.
2. *World Health Report 2000. Health systems: improving performance*. Geneva, World Health Organization, 2000.
3. Murray CJL, Lopez AD, eds. *The global burden of disease: a comprehensive assessment of mortality and disability from diseases, injuries and risk factors in 1990 and projected to 2020*. Cambridge, MA, Harvard School of Public Health on behalf of the World Health Organization and the World Bank, 1996 (Global Burden of Disease and Injury Series, Vol. I).
4. Raviglione MC et al. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11:S115–S123.
5. *Global tuberculosis control. WHO Report 2000.* Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.275).
6. *Anti-tuberculosis drug resistance in the world*. Geneva, World Health Organization, 1997 (document WHO/TB/97.229 WHO).
7. Pablos-Mendez A et al. Global surveillance for antituberculosis drug resistance, 1994–1997. *New England Journal of Medicine*, 1998, 338:1641–1649.
8. *Anti-tuberculosis drug resistance in the world. The WHO/IUATLD global project on anti-tuberculosis drug resistance surveillance. Report No.2: prevalence and trends.* Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.278).
9. Espinal MA et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *Journal of the American Medical Association*, 2000, 283:2537–2545.
10. Knight L. *Tuberculosis and sustainable development*. Geneva, World Health Organization, 2000 (document WHO/CDS/STB/2000.4; Stop TB Initiative series).
11. Croft RA, Croft RP. Expenditure and loss of income incurred by tuberculosis patients before reaching effective treatment in Bangladesh. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:252–254.
12. Rajeswari R et al. Socio-economic impact of tuberculosis on patients and family in India. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:869–877.
13. Floyd K, Wilkinson D, Gilks C. Comparison of cost effectiveness of directly observed treatment (DOT) and conventionally delivered treatment for tuberculosis: experience from rural South Africa. *British Medical Journal*, 1997, 315:1407–1411.

14. Saunderson PR. An economic evaluation of alternative programme designs for tuberculosis control in rural Uganda. *Social Science and Medicine*, 1995, 40:1203–1212.
15. Ahlburg D. *The economic impacts of tuberculosis*. Geneva, World Health Organization, 2000 (document WHO/CDS/STB/2000.5; Stop TB Initiative series).
16. Marrero A et al. Towards elimination of tuberculosis in a low-income country: the experience of Cuba, 1962–97. *Thorax*, 2000, 55:39–45.

54. What are the global targets for tuberculosis control, and what is the basis of these targets?

I. Smith[1]

The global targets for tuberculosis control are to cure 85% of the sputum smear-positive cases detected, and to detect 70% of the estimated new sputum smear-positive cases (*1*). These targets were originally adopted by WHO in 1991. It became clear that the global targets would not be achieved by 2000 as intended, and the target date was put back to 2005 by the World Health Assembly in May 2000.

The numerator for the case detection target is the number of new cases of sputum smear-positive tuberculosis registered in one year, and the denominator is the number of new sputum smear-positive cases estimated to have arisen in the same population over the same period. As the case detection target relies on an estimate for the incidence of tuberculosis, it is difficult to measure accurately in most settings, especially in the context of an epidemic of HIV infection.

The numerator for the cure rate target is the number of patients in a one-year cohort of new cases of smear-positive tuberculosis fulfilling the WHO/IUATLD definition for cure, and the denominator is the number of patients originally registered for treatment in that cohort.

Progress in implementing effective tuberculosis control based on the DOTS strategy has been slow; by 1999, only 40% of estimated new infectious cases were reported to WHO (23% in DOTS programmes, and 17% in non-DOTS programmes) (*2*). Cure rates for patients registered in DOTS programmes in 1998 were much higher than those in non-DOTS programmes – 73% vs 16%. The addition of patients completing treatment without a smear result to confirm cure gave a "treatment success" rate of 84% in DOTS programmes – close to the global target.

Adoption of the targets is based on two principles – impact and feasibility. First, epidemiological modelling has demonstrated that achieving the targets will result in a significant decline in the tuberculosis epidemic, reducing incidence by about 50% in 8–12 years, in the absence of HIV. A 1991 report by Styblo & Bumgarner showed the effect of differing rates of case detection and cure on the prevalence of tuberculosis, and predicted that cure rates in excess of 75% would lead to a substantial reduc-

[1] Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland.

tion in prevalence over time. Increasing case detection without improving cure rates will actually worsen the epidemic (*3*). This work was influential in defining the targets, and has been confirmed by more recent studies, which suggest that countries achieving the global targets would then see a fall in incidence of 8–12% per year (cases reduced by 50% in as little as 6–9 years) and an even faster reduction in mortality of 9–13% per year (50% reduction in 5 years or less) (*4*).

These theoretical figures fit past and current experience. Tuberculosis declined rapidly in much of Europe over the last century, but the fall in incidence of infection accelerated from 4–5% to 12–13% per year following the introduction of effective treatment (*5*). This has been recently confirmed by data from Peru, which suggest that the decline in incidence has reached nearly 8% per year, double the rate before DOTS was introduced (*2*, *6*).

Second, achieving these targets is feasible. Early studies of the sociology and epidemiology of tuberculosis in India revealed that 70% of people with smear-positive tuberculosis had symptoms and sought health care, confirming the feasibility of achieving the target by case detection in health facilities (*7*). Additional experience in IUATLD-supported national tuberculosis programmes of Benin, Malawi, United Republic of Tanzania, and Viet Nam in the late 1980s showed that cure rates exceeding 80% could be achieved and sustained, demonstrating the feasibility of the cure rate target (*8*). A survey in the United Republic of Tanzania suggested that 70% detection of new infectious cases could be achieved under programme conditions. By 2000, seven countries had achieved the global targets, and 43 had reported treatment success rates in excess of 70% with estimated case detection rates of over 50% (*2*).

Significant challenges face the world if the targets are to be met as planned. The tuberculosis epidemic in sub-Saharan Africa is increasing by 10% per year, driven primarily by the HIV pandemic (*2*). The high death rate in people with HIV-related tuberculosis prevents many affected countries from achieving the global cure rate targets. In addition, neither of the targets for case detection or cure takes HIV into account; effective tuberculosis control services cannot at present prevent an increase in tuberculosis in the context of a significant HIV epidemic (see "Can tuberculosis be controlled?", page 301).

A second obstacle to achieving the global targets is inadequate case detection and notification. Although 43% of the global population lived in areas covered by DOTS programmes in 1999, only 23% of people with infectious tuberculosis were treated with DOTS (*2*). Contributing factors are the limited primary health care infrastructure in many countries, the widespread availability of diagnosis and treatment in the private sector in some countries, particularly those of southern Asia that are home to one-third of people with tuberculosis, and the fact that the private sector in developing countries generally does not report diagnosed cases.

Achievement of the global targets depends on the ability of countries to accelerate coverage of the population with DOTS whilst sustaining high cure rates, the effectiveness of strategies to address HIV-related tuberculosis, and the ability of tubercu-

losis programmes to increase case detection through provision of effective services, social mobilization, and involvement of the private sector.

References

1. Revised international definitions in tuberculosis control. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:213–215.
2. *Global tuberculosis control. WHO Report 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).
3. Styblo K, Bumgarner R. Tuberculosis can be controlled with existing technologies: evidence. *Tuberculosis Surveillance Research Unit Progress Report*, 1991, 2:60–72.
4. Dye C et al. Prospects for worldwide tuberculosis control under the WHO DOTS strategy. *Lancet*, 1998, 352:1886–1891.
5. Styblo K. *Selected papers. Vol. 24, Epidemiology of tuberculosis*. The Hague, Royal Netherlands Tuberculosis Association, 1991.
6. *Global DOTS expansion plan: progress in TB control in high-burden countries, 2001*. Geneva, World Health Organization, 2001 (documentWHO/CDS/STB/2001.11).
7. Banerji D, Andersen S. A sociological study of awareness of symptoms among persons with pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1963, 29:665–683.
8. Broekmans JF. Control strategies and programme management. In: Porter JDH, McAdam KPWJ, eds. *Tuberculosis: back to the future*. Chichester, Wiley, 1994.

55. What is DOTS?

I. Smith[1]

DOTS is the internationally recommended strategy to ensure cure of tuberculosis (*1*). It is based on five key principles (see Table 56) that are common to disease control strategies, relying on early diagnosis and cure of infectious cases to stop spread of tuberculosis.

The treatment of infectious cases as a strategy for preventing transmission and thereby controlling tuberculosis was highlighted by Crofton in the early 1960s (*3*), less than 20 years after the first effective drugs were discovered and only 10 years after randomized controlled trials had demonstrated that combined treatment regimens can cure patients and prevent the emergence of drug resistance (*4*).

The package of interventions that eventually became known as the DOTS strategy was first formulated in national tuberculosis programmes supported by the IUATLD under the leadership of Dr Karel Styblo. Initially in the United Republic of Tanzania, and then later in several other countries of Africa and Latin America, Styblo developed the technical and managerial principles of effective tuberculosis control based on the management unit of the district. The district has the staff and resources to organize diagnostic and treatment services, maintain supplies and monitor programme performance for a population of 100 000–150 000. Styblo showed that short-course treatment was essential to reach adequate cure rates on a programme basis, verified the necessity of directly observed treatment, and developed the principles of recording, reporting, and drug management that are also integral to DOTS.

WHO began to promote this strategy in 1991 (*5*), and in 1994 produced a Framework for Effective Tuberculosis Control (*6*) that clearly described the main components of what was later to be known as the DOTS strategy. The Framework was revised and expanded in 2002 (*7*).

The term "directly observed therapy" had been in use for several years before it was modified to "directly observed treatment, short-course" by WHO in 1995, and used to designate a comprehensive strategy to control tuberculosis (*8*). Although "DOTS" appears to emphasize the direct observation component of the strategy, all aspects are

[1] Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland.

Table 56
Principles and components of DOTS[a]

Key principle	Component of DOTS
Organized and sustained intervention	Government commitment to ensuring sustained, comprehensive tuberculosis control activities
Accurate and early identification of infectious cases	Case detection by sputum smear microscopy among symptomatic patients self-reporting to health services
Effective and patient-friendly treatment	Standardized short-course treatment using regimens of 6–8 months, for at least all confirmed smear-positive cases. Effective case management includes directly observed treatment during the intensive phase for all new smear-positive cases, the continuation phase of rifampicin-containing regimens, and the whole re-treatment regimen
Effective drug management	A regular, uninterrupted supply of all essential antituberculosis drugs
Outcome-based monitoring	A standardized recording and reporting system that allows assessment of case detection and treatment results for each patient and of the tuberculosis control programme's overall performance

[a] Source: reference *2*.

essential, and DOTS is no longer an acronym but the "brand name" of the WHO-recommended strategy for TB control.

Government commitment is an essential component of DOTS, and WHO has emphasized advocacy and social mobilization as means of achieving this commitment. Sufficient funds and administrative support to hire staff, purchase essential items (drugs, microscopes, reagents, printed materials, etc.), and contract for services are necessary for the programme to operate.

The rationale for diagnosis primarily by microscopy among patients in health facilities has been reviewed in detail in the first section of this book.

Direct observation of treatment in which "a trained and supervised person observes the patient swallowing the tablets" is fundamental to the DOTS strategy to ensure adherence to treatment (*2*). Early WHO documents emphasized the importance of direct observation by health workers (*9*). Later, experience gained in DOTS programmes around the world demonstrated that trained lay people were at least as effective in observing treatment; these have included community health volunteers in Bangladesh (*10*), storekeepers in South Africa (*11*), religious leaders, lay health workers, and community volunteers. Some recent studies have questioned the necessity of direct observation of treatment (*12*) or proposed reducing the frequency of

observation to once a week (*13*). However, the benefits for health workers and patients of reducing the frequency of observation may be offset by the potential for increasing rates of drug resistance arising from hidden non-adherence. To be effective, a treatment observer must be accessible and acceptable to the patient, and trained by and accountable to the health service.

The requirement of an uninterrupted supply of tuberculosis drugs is clear. In addition, the quality of drugs should be ensured, particularly if they are provided in fixed-dose combinations, which are more susceptible to problems in manufacture (see "What are the advantages and disadvantages of fixed-dose combinations of antituberculosis drugs?", page 189).

The reporting system in DOTS, which allows simple and robust monitoring of patient progress and programme performance, is described in "Why is a recording and reporting system needed, and what system is recommended?" (page 270). DOTS records can be easily checked for internal consistency and for consistency between records, and can also be externally verified by reviewing sputum slides, interviewing patients and health workers, and monitoring consumption of drugs and supplies. Operational research designed to continuously analyse and improve the programme is another aspect of systematic monitoring and evaluation.

Modifications to the DOTS strategy have been proposed – for example, to address specific problems such as HIV-related tuberculosis and multidrug-resistant tuberculosis. These modifications to the basic strategy are usually known as DOTS Plus (*14*). Additional elements that have been proposed for low-incidence countries (Table 57) include active case detection in selected high-risk groups, routine drug susceptibility testing, and expanded use of treatment for latent tuberculosis infection.

Status of DOTS expansion

WHO receives reports on DOTS implementation from national tuberculosis programmes and has published annual global reports on tuberculosis control since 1997. The 2003 report provides information on case detection during 2001 and treatment outcomes for patients registered in 2000. The seven published reports show that the number of countries implementing DOTS has increased from 70 in 1995 to 155 in 2003, with 7.1 million patients reported as treated in DOTS programmes between 1995 and 2000.

By the end of 2002, 61% of the global population had access to DOTS, but only 32% of people estimated to have newly developed sputum smear-positive tuberculosis were registered in DOTS programmes (*15*).

Constraints to rapid DOTS expansion include financial shortages, human resource problems, inadequate health care infrastructure, lack of secure supply of good-quality antituberculosis drugs, and gaps in public information about the danger of tuberculosis (*16*). In order to address these concerns, WHO, jointly with high-burden countries, has developed a Global DOTS Expansion Plan, which describes the actions and resources needed to rapidly expand DOTS to reach the global tuberculosis control

Table 57
DOTS in low-incidence countries[a]

The required components of the DOTS policy package	Additional elements of tuberculosis control for low-incidence countries
Government commitment to sustained tuberculosis control	Government commitment to tuberculosis control, with the aim of elimination: • legal framework including laws on mandatory notification, cohort analysis of treatment results, and drug policy; • tuberculosis control policy based on consensus by national authorities and leading organizations; • maintenance of an efficient network for tuberculosis control by ensuring technical leadership at national level and trained human resources at lower levels.
Sputum smear microscopy to detect infectious cases among people with symptoms of pulmonary tuberculosis attending health care facilities	In the general population, case detection among symptomatic patients. Risk-group management (e.g. active case detection in high-risk groups). Diagnosis confirmed by culture. Drug susceptibility testing, especially in groups at high risk of drug resistance. Outbreak management (e.g. source and contact tracing).
Standardized short-course chemotherapy for all tuberculosis cases, with directly observed treatment for at least the initial 2 months among infectious cases	Directly observed treatment for more than the initial 2 months for high-risk groups and where cure rates are low. Specialized treatment for multidrug-resistant tuberculosis. Preventive treatment for newly infected persons and for some high-risk groups, e.g. HIV-infected individuals.
Regular, uninterrupted supply of antituberculosis drugs (preferably quality-controlled fixed-dose combination drugs)	Regulations on drug use; reserve drugs for drug-resistant tuberculosis available only in highly qualified centres
Evaluation and supervision: use of sputum smear microscopy for evaluation of patient progress towards cure	Surveillance based on a uniform reporting system. Culture and sputum smear examination to assess treatment outcome. Drug resistance surveillance. Quality assurance of tuberculosis control data (e.g. auditing system).

[a] Source: reference *1*.

targets (*17*). Successful implementation of this plan will require increased investment of human and financial resources, as well as new strategies and additional resources to address global and local challenges to tuberculosis control, particularly HIV-related tuberculosis.

References

1. *What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS*. Geneva, World Health Organization, 1999 (document WHO/CDS/CPC/TB/99.270).
2. Revised international definitions in tuberculosis control. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:213–215.
3. Crofton J. The contribution of treatment to the prevention of tuberculosis. *Bulletin of the International Union Against Tuberculosis*, 1962, 32:643–653.
4. The prevention of streptomycin resistance by combined chemotherapy. Medical Research Council. *British Medical Journal*, 1952:1157–1162.
5. Kochi A. The global tuberculosis situation and the new control strategy of the World Health Organization. *Tubercle*, 1991, 72:1–6.
6. *Framework for effective tuberculosis control*. Geneva, World Health Organization, 1994 (document WHO/TB/94.179).
7. *An expanded DOTS Framework for Effective Tuberculosis Control*. Geneva, World Health Organization, 2002 (document WHO/CDS/TB/2002.297).
8. *Global tuberculosis programme. Stop TB at the source: 1995 annual report on the tuberculosis epidemic*. Geneva, World Health Organization, 1995.
9. *Managing tuberculosis at the district level: a training course*. Geneva, World Health Organization, 1994 (document WHO/TB/96.211).
10. Chowdhury AMR et al. Control of tuberculosis by community health workers in Bangladesh. *Lancet*, 1997, 350:169–172.
11. Wilkinson D, Davies GR, Connolly C. Directly observed therapy for tuberculosis in rural South Africa 1991 through 1994. *American Journal of Public Health*, 1996, 86:1094–1097.
12. Walley JD et al. Effectiveness of the direct observation component of DOTS for tuberculosis: a randomised controlled trial in Pakistan. *Lancet*, 2001, 357:664–669.
13. Becx-Bleumink M et al. High cure rates in smear-positive tuberculosis patients using ambulatory treatment with once-weekly supervision during the intensive phase in Sulawesi, Republic of Indonesia. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:1066–1072.
14. Farmer P, Kim JY. Community based approaches to the control of multidrug-resistant tuberculosis: introducing "DOTS-plus". *British Medical Journal*, 1998, 317:671–674.
15. *Global tuberculosis control. WHO Report 2003*. Geneva, World Health Organization, 2003 (document WHO/CDS/TB/2003.316).
16. *Global tuberculosis programme. Report of the ad hoc committee on the tuberculosis epidemic*. Geneva, World Health Organization, 1998 (document WHO/TB/98.245).
17. *Global DOTS expansion plan: progress in TB control in high-burden countries*. Geneva, World Health Organization, 2001 (document WHO/CDS/STB/2001.11).

56. Is DOTS cost-effective?

I. Smith[1]

The relative value of different interventions can be assessed by comparing inputs and outputs. For health interventions, this is usually achieved by combining elements of cost and impact. Assessments of cost-effectiveness are useful for prioritizing different disease-specific interventions, for assessing the relative value of different interventions for the same condition, and as a tool for resource mobilization to promote investment.

Costs are directly comparable, as they are generally measured in the same way. However, the impact of one intervention is not always directly comparable with that of another. For example, disability prevented by polio immunization is not directly comparable with deaths averted by DOTS. Some form of standardization of impact is therefore needed for the comparison of interventions.

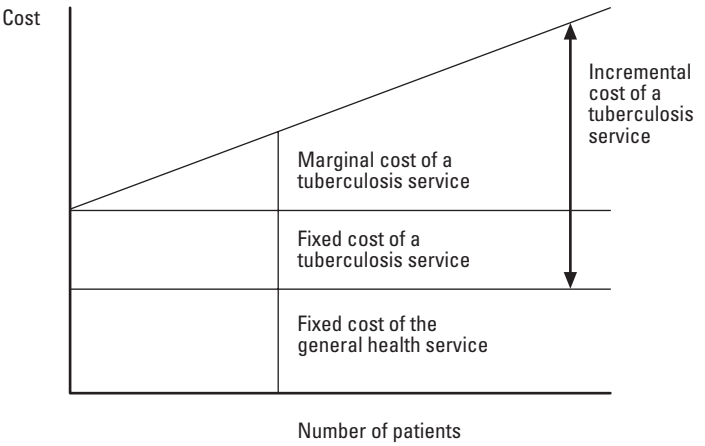
The most widely used analysis of relative efficiency of health care interventions is cost-effectiveness, in which the impact of an intervention is converted to a common health benefit, such as years of potential life saved. However, this indicator may underestimate the value of interventions for diseases that are not life-threatening but that cause considerable disability, such as leprosy. The concept of the disability-adjusted life year (DALY) was therefore developed, as an indicator that incorporates measures of disability and death (*1*). The cost-effectiveness of an intervention can then be measured in terms of the cost of preventing the loss of one disability-adjusted year of life.

The health service costs of tuberculosis control can be divided into four categories (Figure 19):

- fixed costs of general health services;
- fixed costs of tuberculosis control services – the costs of adding a tuberculosis programme to the general health services, which do not change with increasing numbers of patients, for example, staff salaries;
- marginal costs of tuberculosis control services – the costs associated with each additional new patient diagnosed and treated, for example, costs of drugs;
- incremental costs – this measure combines the fixed and marginal costs of tuberculosis control services.

[1] Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland.

Figure 19
Theoretical framework for costing a tuberculosis control service[a]



[a] Source: reference *2*.

Evidence that DOTS is cost effective compared with other health care interventions

In 1993, the World Bank published *Investing in Health*, comparing the cost-effectiveness of different primary health care interventions. The report estimated that effective tuberculosis control cost US$ 20–57 per death averted and US$ 1–3 per DALY saved. Thus, tuberculosis chemotherapy was found to be one of the most cost-effective of all health interventions, along with measles vaccination and vitamin A supplementation (*1*). Since publication of this report, costs of antituberculosis drugs have fallen considerably; a basic course of treatment now costs as little as US$ 10 compared with US $40–60 in the early 1990s (*3*), further increasing the cost-effectiveness of DOTS. However, cost-effectiveness has not been comprehensively reassessed in the context of HIV; by reducing the post-cure survival time of tuberculosis patients, HIV infection is likely also to reduce the cost-effectiveness of DOTS somewhat.

Evidence that DOTS is cost-effective compared with other tuberculosis control strategies

Other strategies for tuberculosis control are BCG vaccination, preventive treatment, and active case detection in the community. Although these strategies are appealing in theory, in practice they are relatively ineffective in controlling tuberculosis compared with DOTS.

BCG vaccination of infants is recommended in high-prevalence countries to prevent serious forms of tuberculosis in children, such as meningitis and miliary tuberculosis. The World Bank estimated that BCG costs US$ 7 per DALY saved, but

the intervention is cost-effective only if the annual risk of tuberculosis infection is high (i.e. more than 1% per year) (*4*). However BCG vaccination, since it primarily prevents noninfectious forms of tuberculosis, has little or no impact on tuberculosis transmission.

The World Bank study did not estimate the cost per DALY of preventive treatment, but concluded that selective screening and treatment in high-risk populations (e.g. household contacts of infectious patients and people with HIV infection) was "suspected to be reasonable", and cautioned that "mass prophylaxis has high cost with limited effectiveness" (*4*).

On a theoretical basis, active case detection in the community may be effective. However, as discussed in "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?" (page 72), such a strategy has severe practical limitations. It would detect prevalent cases primarily, which can be rapidly controlled with DOTS in any case (see "Can tuberculosis be controlled?", page 301). Moreover, patients identified through surveys of this nature tend to be unlikely to complete a full course of treatment.

Evidence that DOTS is cost-effective compared with other tuberculosis treatment strategies

Two early studies comparing the cost-effectiveness of different strategies for providing tuberculosis treatment came from experience in countries of Africa – one from Botswana (*5*), and one each from Malawi, Mozambique and the United Republic of Tanzania (*6*). Each study compared short-course treatment with "long-course" regimens based on streptomycin, isoniazid, and thioacetazone, and also compared fully ambulatory regimens with inpatient care during the intensive phase. Although the drug costs for short-course treatment were more than three times higher than those for standard treatment, improved cure rates made short-course treatment the more cost-effective option, particularly if treatment was provided on an outpatient basis. Further studies have substantiated this finding, and a review of eight cost-effectiveness studies published between 1982 and 1992 showed that the cost per outcome for ambulatory short-course treatment was 19–41% that of long-course treatment with two-month hospitalization (*2*).

The cost savings for countries as they implement DOTS can be substantial. An economic analysis of DOTS in India conducted by WHO in 1996 estimated that an additional investment of US$ 200 million per year would yield an annual return of US$ 750 million through reduced prevalence of disease, deaths averted, and release of hospital beds (*7*).

However, the economic benefits of DOTS are even greater for communities than for governments. In many developing countries, the direct costs of tuberculosis diagnostic and treatment services for government health services are considerably lower than the direct and indirect costs for households. A study in Uganda was one of the first to demonstrate this, revealing that, out of a total cost of US$ 324, the patient con-

tributed US$ 229 in direct and indirect costs (*8*). Of these patient costs, lost income equivalent to 3–4 months of work time usually forms the greatest proportion (see "What is the health, social, and economic burden of tuberculosis?", page 233) (*9*).

Evidence of the potential economic benefit of DOTS for communities comes from a study conducted in Thailand, which showed that for every US$ 1 invested by the government in tuberculosis control, the community gains by US$ 50 over a 20-year period (*10*).

The per capita incremental cost of implementation of DOTS may be as low as US$ 0.05 in some low-income countries (*11*), and would rarely be more than US$ 0.20 in high-prevalence, low-income countries.

In summary, DOTS is a highly cost-effective strategy, producing significant savings for governments and communities. DOTS is a "good buy" for health planners and policy-makers. In resource-poor settings, DOTS should be one of the highest priorities for health services, and it offers significant advantages over other tuberculosis control strategies and methods of treatment.

References

1. World Bank. *Investing in Health: 1993 World Development Report*. Oxford, Oxford University Press, 1993.
2. Fryatt RJ. Review of published cost effectiveness studies on tuberculosis treatment programmes. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:101–109.
3. Stop Tuberculosis Initiative. Report by the Director-General. Geneva, World Health Organization, 1999 (document EB105/13, available at http://www.who.int/gb/EB_WHA/PDF/EB105/ee13.pdf).
4. Jamison D. Disease control priorities in developing countries: an overview. In: Jamison D et al. *Disease control priorities in developing countries*. New York, Oxford University Press, 1993.
5. Barnum HN. Cost savings from alternative treatments for tuberculosis. *Social Science and Medicine*, 1986, 23:847–850.
6. Murray CJL et al. Cost effectiveness of chemotherapy for pulmonary tuberculosis in three sub-Saharan African countries. *Lancet*, 1991, 338:1305–1308.
7. Dholakia R, Almeida J. The potential economic benefits of the DOTS strategy against TB in India. Geneva, World Health Organization, 1997 (document WHO/TB/96.218).
8. Saunderson PR. An economic evaluation of alternative programme designs for tuberculosis control in rural Uganda. *Social Science and Medicine*, 1995, 40:1203–1212.
9. Ahlburg D. *The economic impacts of tuberculosis.* Geneva, World Health Organization, 2000 (document WHO/CDS/STB/2000.5; Stop TB Initiative series).
10. Sawert H et al. Costs and benefits of improving tuberculosis control: the case of Thailand. *Social Science and Medicine*, 1997, 44:1805–1816.
11. *Joint tuberculosis programme review: India, February 2000*. New Delhi, World Health Organization Regional Office for South-East Asia, 2000 (document SEA-TB-224).

57. How can the progress of treatment be monitored?[1]

T. Santha[2]

The three approaches to monitoring progress of patients during treatment are bacteriological, clinical, and radiographic assessment.

Assessment by bacteriology

Bacteriological assessment can be done by smear and culture. Although culture is more specific, it is time-consuming and costly and there is a delay in getting the results. Moreover, appropriate facilities are not universally available. Hence the management of patients is generally based on smear microscopy. Based on smear results, the response to 12-month treatment regimens that do not contain rifampicin can be predicted with 90–92% confidence (*1*). With short-course treatment, the organisms are killed rapidly, but dead bacilli may be excreted for some time, with the result that smears may be positive in some patients even when they are responding well to treatment (*2*).

On monthly sputum examination, one of the four patterns shown in Table 58 could be observed. It is evident that, if culture results are not available, serial smears alone clearly show all the different courses. Thus, in monitoring treatment, culture examinations are merely confirmatory. It is exceptional for patients receiving treatment to be consistently negative on smear yet positive on culture: the patient who is smear-positive initially either attains culture negativity or reverts to smear positivity.

It is not necessary to examine the sputum every month. WHO and IUATLD recommend monitoring progress during treatment in smear-positive patients though sputum smears on three occasions: at two months, during the fifth month, and at the end of treatment (*3*, *4*). This allows decisions on treatment management to be made with a minimum of tests.

A laboratory report that states "sputum not obtainable" or "patient does not expectorate" by no means implies sputum smear negativity; it is important that such a report is regarded as unsatisfactory. In patients who do not produce sputum despite careful instruction, tickling the throat with a laryngeal swab or inducing sputum with

[1] Based on the chapter in the previous edition by K. Toman.

[2] Deputy Director, Tuberculosis Research Centre, Chennai, India.

Table 58
Interpretation of the results of sputum examination by smear and culture during tuberculosis treatment

Month	Smear	Culture	Smear	Culture	Smear	Culture	Smear	Culture
0	++	+++	++	+++	++	+++	++	+++
1	++	+	++	+	++	+++	++	+++
2	0	0	+	0	++	++	++	++
3	0	0	+	0	0	+	++	++
4	0	0	0	0	0	+	++	+++
5	0	0	0	0	++	+	+++	+++
6	0	0	0	0	++	++	+++	+++
Response	Favourable		Favourable		Fall and rise		Failure	

saline can provoke a clearing cough and sputum suitable for smear examination. Smear positivity alone, especially if the degree of positivity is declining, need not be cause for alarm.

Clinical assessment

Clinical assessment of progress is largely subjective. Disappearance of clinical symptoms, general well-being, ability to resume normal activities, and weight gain are all pointers to clinical progress. Persistence or reappearance of symptoms plus weight loss – i.e. objective clinical deterioration – indicates the need for further investigations by sputum microscopy. Erythrocyte sedimentation rate and other tests are unreliable and unnecessary in monitoring progress. Clinical assessment is often the only means available for judging progress in extrapulmonary and smear-negative pulmonary tuberculosis: weight gain is a valuable indicator in such cases.

Assessment by radiography

Serial radiography is still preferred by many physicians. However, several studies have demonstrated that this can be very misleading for assessing the progress and eventual outcome of treatment. Patients may show radiographic improvement yet still discharge tubercle bacilli. Bacteriologically quiescent disease may be classified as treatment failure because of residual lesions on the X-ray, including cavitation. Patients with persisting bacteriological negativity could show radiographic changes that would be interpreted as deterioration by expert assessors. In a study of 112 patients with bacteriologically quiescent disease, followed up by bacteriology and radiography for 4 years, radiographic changes in 35 patients (31%) were classified as deterioration. In 12 patients (11%), an increase in cavitation or appearance of cavitation was recorded. Clearly, assessment by radiographic changes alone can be very misleading (*5*).

Summary

Microscopic examination of the sputum smear is a reliable and inexpensive method for assessing the results of treatment in initially smear-positive patients. Radiographic and clinical evaluations are unsatisfactory for assessing progress. Smear microscopy is also a valuable guide to progress and outcome: Examination of smear-positive patients at 2 months, 5 months, and at the end of treatment will give a good indication of the success of treatment in large-scale treatment programmes. Follow-up smears provide reliable information about patient progress and programme performance. However, the individual patient benefits from bacteriological assessment only if, in the event of treatment failure, another course of treatment with an effective regimen can be provided.

References

1. Devadatta S et al. Comparative value of sputum smear examination and culture examination in assessing the progress of tuberculosis patients receiving chemotherapy. *Bulletin of the World Health Organization*, 1966, 34:573–587.
2. Al-Moamary MS et al. The significance of the persistent presence of acid-fast bacilli in sputum smears in pulmonary tuberculosis. *Chest*, 1999, 116:726–731.
3. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (document WHO/CDS/TB/2002.313).
4. Enarson D et al. *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
5. Fox W. The chemotherapy of tuberculosis in developing countries. In: Heaf F, Rugbsy NL, eds. *Recent advances in respiratory tuberculosis*. London, Churchill, 1968:127–159.

58. How effective is tuberculosis treatment and what are the needs for the future?[1]

T. Santha[2]

The introduction of effective antituberculosis drugs brought about a revolution in the management of tuberculosis. From the era of bedrest, good food, and fresh air in a sanatorium – the best that the pre-chemotherapy era had to offer to a selected few – tuberculosis can now be treated effectively in the patient's home, without interfering with normal life or work (see "What were the main findings of the Madras study comparing home and sanatorium treatment?", page 173). Currently recommended regimens can achieve 90–95% relapse-free cure rates, not only in controlled clinical trials but also under programme conditions.

In previously untreated patients who take treatment regularly and completely the following results can be achieved:

- Standard treatment for 18 months, with three initial drugs for 2 months but without rifampicin, has a potential cure rate of 96% and a relapse rate of less than 3%. However, it has generally not been possible to implement this regimen on a mass basis (see "What is the optimum duration of treatment?", page 144).
- Short-course chemotherapy of 6–8 months' duration, including rifampicin at least in the intensive phase, can achieve cure rates of 97–99% and a relapse rate of less than 6% (see "What is the optimum duration of treatment?", page 144).
- Patients who have relapsed can achieve more than 80–90% cure if treated for 8–9 months with five drugs, including rifampicin, during the intensive phase and three drugs in the continuation phase, since more than 80% of the relapses occur with drug-susceptible organisms (*1*).
- In patients who had incomplete prior treatment, response will depend upon the drugs and dosages given during the prior treatment and the duration of treatment since these factors influence subsequent drug susceptibility (*2*). In well-performing programmes, 70–80% of these patients are cured (*3*).
- Smear-positive patients who have failed a directly observed short-course treatment or re-treatment regimen have a low probability of cure with regimens that include

[1] Based on the chapter in the previous edition by K. Toman.

[2] Deputy Director, Tuberculosis Research Centre, Chennai, India.

only first-line drugs, as the probability of resistance to several of the drugs is high. Treatment of these patients with reserve drugs for a long period (18–24 months) can achieve relapse-free cure in two-thirds of them at best (see "What reserve regimens are available and what is their place in tuberculosis control programmes?", p. 215).

On the whole, the efficacy of current treatment regimens is high: a patient who adheres to treatment has a greater than 98% chance of cure, generally with only one course of treatment. Most patients who default or relapse can be cured with a retreatment regimen. Thus, there is little potential for new drugs to increase cure rates. However, new drugs could promote tuberculosis control by reducing the duration or frequency of treatment.

Lack of treatment success in practice is most often due to failure to ensure correct treatment, rather than to failure of correctly applied treatment (see "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185, and "How frequently do patients stop taking treatment prematurely?", page 181). In poorly organized programmes, more than 30% of patients default. Treatment irregularity is common, particularly if drug intake is not observed and if drug supply is not regular, free of charge, and easily accessible to the patient. Death during treatment (all causes) may be high because of HIV infection or delayed diagnosis.

Much can be gained by improving operational aspects of tuberculosis control programmes (see "What is DOTS?", page 241). However, development of new drugs could substantially facilitate programme implementation. A longer period between intermittent doses (see "What is intermittent treatment and what is the scientific basis for intermittency?", page 130) would reduce the frequency of patient visits and facilitate observation of drug intake – but two or three highly effective drugs with the same efficacy and half-life are required. More effective drugs, in addition to isoniazid and rifampicin, could shorten the initial intensive phase, overcome drug resistance, and reduce the risk of death during the initial weeks of treatment.

The principal problem remaining today is that available drugs have little or no action on quiescent bacilli (see "How does tuberculosis treatment work?", page 102). The purpose of the second phase of treatment is to eliminate bacilli that reproduce slowly or occasionally, much like the effect of preventive treatment in persons infected with *Mycobacterium tuberculosis* who do not have disease. A drug capable of acting on latent tubercle bacilli, or an immunomodulator able to improve the capacity to destroy those bacilli, would shorten treatment duration. Shorter treatment would reduce default and increase cure rates and also reduce the work and cost of maintaining patients on treatment.

These are some of the areas of research now being explored. However, with the present technology and good programme organization, most tuberculosis patients can be cured, most sources of tuberculosis infection can be rendered noninfectious in a few days or weeks of treatment, and most tuberculosis patients can be cured. If a

sufficient proportion of the sources of infection in the community are detected and treated, the prevalence and transmission of tuberculosis, and the resulting mortality, can be reduced rapidly.

References

1. Cao JP et al. Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:360–364.
2. Datta M et al. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. *Tubercle and Lung Disease*, 1993, 74:180–186.
3. *Global tuberculosis control. WHO Report 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).

59. Is primary drug resistance a menace to the control of tuberculosis?[1]

M. Espinal[2] *& T. Frieden*[3]

In the early days of chemotherapy, regimens were often inadequate, irregularity of treatment was common, and failure rates were high. As a result, the prevalence of patients with chronic pulmonary tuberculosis discharging drug-resistant organisms increased. It was generally feared that these patients would infect the community to such an extent that primary drug resistance (see "What are the different types of drug resistance?", page 198) might become an epidemiological and clinical problem similar to that of penicillin resistance in staphylococcal disease. Alarming figures of drug resistance in 50% or more of newly attending patients were reported, mainly from developing countries, where, in fact, most of these patients had (concealed) treatment failure and thus had acquired – not primary – resistance.

It was not possible to compare the data from different clinical reports or surveys, mainly because of the considerable differences in laboratory techniques, criteria of drug resistance, and methods of selecting groups of patients for examination.

The WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance overcame these methodological concerns. Epidemiological surveys were conducted between 1994 and 1999 in more than 72 countries/areas using stringent methods, including population-based representative sampling, careful differentiation between new and previously treated cases, standard laboratory methods, and an international proficiency testing programme (*1*). Trends were available from 28 countries/areas.

Of 65 of the countries/areas surveyed, 11 showed a relatively high prevalence of multidrug-resistant tuberculosis (see Figure 20). The remaining sites surveyed showed no signs of a major problem, suggesting that multidrug-resistant tuberculosis is far from universal. While a high prevalence of streptomycin resistance was documented in many countries, this finding is of limited significance as the use of streptomycin is being abandoned for treatment of new patients by many of these countries (*2*). A high prevalence of resistance to isoniazid – but not to rifampicin or ethambutol – was also documented.

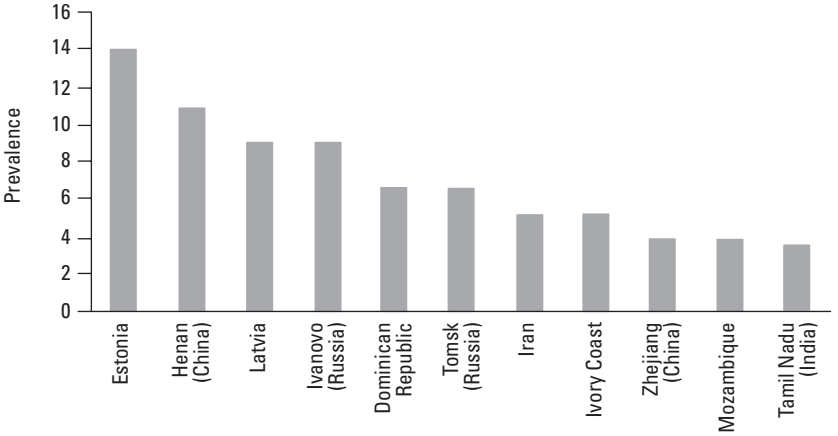
---

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Communicable Diseases, World Health Organization, Geneva, Switzerland.
[3] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

Figure 20

Countries/areas with the highest prevalence of multidrug-resistant tuberculosis within the WHO/IUATLD Global Project on Antituberculosis Drug Resistance Surveillance[a]



[a] Source: reference *1*.

Table 59 gives information on the distribution of resistance among new cases of tuberculosis.

Information from 28 countries/sites that had conducted two or more comparable surveys showed no evidence of increasing drug resistance among new cases (i.e. primary resistance) between 1994 and 1999. As far as trends can be observed, there is an indication that the levels are fairly stable in most areas.

Systematic surveillance and mathematical models suggest that the number of new tuberculosis cases found to be drug-resistant, especially multidrug-resistant, will remain low in most parts of the world (*4*). This prediction follows from the assumption that multidrug-resistant strains of *Mycobacterium tuberculosis* have a relatively low genetic fitness (either less transmissible or less likely to cause infectious tuberculosis if transmitted) compared with drug-susceptible strains. Relative fitness is measured by dividing the odds of finding a resistant strain in a restriction-fragment length polymorphism cluster by the odds of finding a susceptible strain in a cluster. With low relative fitness, multidrug-resistant strains would be, on average, less likely to persist in self-sustaining transmission cycles, and new multidrug-resistant cases are generated mainly as the by-product of low cure rates among drug-susceptible or monoresistant cases.

High default rates can lead to high rates of multidrug-resistant tuberculosis among new cases as seen, for example, in Estonia, Latvia, and parts of the Russian Federation. Under these circumstances, the main remedy is to ensure high cure rates for drug-susceptible or mono-resistant disease. Reserve drugs would be needed to treat

Table 59
Resistance to one or more drugs in 58 countries/settings surveyed between 1996 and 1999 among newly diagnosed, previously untreated patients[a]

Strains	Median	(Minimum, maximum)
Total examined	474	(41, 12 063)
Total resistant	10.7%	(1.7, 36.9)
Resistant to any one drug	7.0%	(1.3, 17.9)
Resistant to isoniazid	3.0%	(0, 7.9)
Resistant to rifampicin	0.2%	(0, 2.0)
Resistant to streptomycin	2.5%	(0, 14.5)
Resistant to ethambutol	0.5%	(0, 3.0)
Resistant to two drugs	2.5%	(0, 11.9)
Resistant to three drugs	0.6%	(0, 7.3)
Resistant to four drugs	0.1%	(0, 8.5)
Multidrug resistance[b]	1.0%	(0, 14.1)

[a] Source: reference *3*.
[b] Resistance to at least isoniazid and rifampicin.

individual multidrug-resistant tuberculosis cases, but whether they would be needed to contain an epidemic of multidrug-resistant strains will depend on the relative fitness of the specific strains, the characteristics of the host population, and environmental factors (e.g. crowding) that influence transmission dynamics. In an extreme case, a highly fit strain of multidrug-resistant tuberculosis has been reported as having spread rapidly and extensively among severely immunosuppressed AIDS patients hospitalized under conditions of inadequate infection control (*5*). Similarly, it is likely that certain strains of multidrug-resistant tuberculosis could spread widely among malnourished prisoners housed in overcrowded conditions (*6*). In such settings, reserve drugs might well be needed to contain an epidemic of multidrug-resistant tuberculosis. In contrast, it is far from certain that strains of multidrug-resistant tuberculosis could cause a self-perpetuating community-wide epidemic, particularly in the absence of significant immunocompromise.

There is now adequate evidence that, with standard treatment, the prognosis for patients with primary resistance to one drug – provided that it is not rifampicin – is almost as favourable as that for patients with susceptible organisms (*7*). Only a very high level of primary drug resistance in a population can substantially reduce the overall success rate of standard two-phase treatment including an initial phase of four drugs daily. There is thus no reason to assume that primary drug resistance is becom-

ing a greater danger to the community than the current danger of exposure to infection with drug-susceptible organisms.

References

1. *Anti-tuberculosis drug resistance in the world. The WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance. Report 2, Prevalence and trends*. Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.278).
2. Rabarijaona L et al. Replacement of streptomycin by ethambutol in the intensive phase of tuberculosis treatment: no effect on compliance. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:42–46.
3. Espinal MA et al. Global trends in resistance to antituberculosis drugs. *New England Journal of Medicine*, 2001, 344:1294–1303.
4. Dye C, Espinal MA. Will tuberculosis become resistant to all antibiotics? *Proceedings of the Royal Society of London. Series B. Biological Sciences*, 2001, 268:45–52.
5. Frieden TR et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *Journal of the American Medical Association*, 1996, 276:1229–1235.
6. Kimerling ME et al. Inadequacy of the current WHO re-treatment regimen in a central Siberian prison: treatment failure and MDR-TB. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:451–453.
7. Espinal MA et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *Journal of the American Medical Association*, 2000, 283: 2537–2545.

60. What are the keys to cure?

K. Toman[1]

How is it that cure rates in many areas are still low, despite the extraordinary potency of present-day treatment?

Some physicians believe that high success rates can be achieved only in certain outstanding treatment centres and that success rates will remain low unless more effective drugs are introduced. This is a rather superficial view. For more than 25 years, there have been drugs from which nearly 100% effective, inexpensive, non-toxic, and accessible regimens can be composed. Thus, the key to cure lies not in the introduction of new and better drugs or regimens but elsewhere (see "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185).

An important technical requirement for successful treatment is the prescription of adequate regimens, i.e. only those whose efficacy has been established by controlled trials. A regimen should contain at least two drugs to which the patient's bacilli are susceptible. The chosen drug should be given in the same dosage, at the same rhythm (daily or intermittently), and for the same period as was done in controlled trials. Deviations from this rule that have no scientific basis and that cannot be clearly justified should be regarded as malpractice.

Another technical, almost axiomatic, prerequisite is the regularity of drug intake. Since the advent of treatment, many changes have taken place. Drug combinations and dosages have been varied and the rhythm of administration and duration of treatment have changed, but the need for regularity of drug intake persists. No new regimen or drug has been able to overcome the necessity of long-term regularity, and interruption of the regular rhythm of treatment increases the risk of failure. It must be borne in mind that the main reason for treatment failure is not drug resistance but the irregularity of drug ingestion.

It is illusory to expect that new drugs will solve the main problem of treatment, unless a regimen can be found that needs to be administered in one injection or only for a few days. The success of treatment is determined as much by operational as by technical factors.

[1] Deceased.

Even the most effective regimens currently available, irrespective of the drug combination or duration of treatment, may fail if not administered regularly. Thus, today it is not the lack of knowledge about adequate treatment but its adequate administration (*1*) that is the crux of the matter (see "Why does treatment fail and what can be done to avoid poor treatment outcome?", page 185). This is one of the problems that can be solved not by technical or medical means but mainly by organizational measures. Ensuring regular drug intake is a managerial task *par excellence*, and it has rightly been stated that the control of tuberculosis is basically a management problem. Nearly all attempts to ensure adherence through health education – for example, by thoroughly instructing patients about the importance of regularity and the poor prognosis in case of irregularity – have been insufficient to motivate patients to take their drugs regularly as prescribed (see "How frequently do patients stop taking treatment prematurely?", page 181). Verbal motivation of patients is rarely successful unless applied in an adequate organizational framework satisfying certain operational requirements.

Operational requirements

Treatment services must be easily accessible. Patients who feel very ill may be willing to travel long distances in order to be seen by a reputed physician. However, they can rarely repeat such travel or stay at the place of treatment for a long time. Treatment services should therefore be within easy reach and be free of charge (*2*, *3*).

Treatment services should be acceptable to and utilized by the community. Health staff should be able to communicate with patients in their own language and should be sympathetic to their complaints and needs. Patients should be helped to handle the problems causing default. Services must be compatible with local beliefs, traditions, and habits, and should also be efficient. In short, they should inspire confidence (see "What is the significance of default (treatment interruption) in the treatment of tuberculosis?", page 263).

Drugs should always be available in sufficient quantities. When patients have to be turned away because drugs are out of stock, the effect on treatment regularity is bound to be detrimental.

Treatment should be directly observed. This means that each dose should be administered under the direct observation of a trained, accountable individual. It is particularly important when rifampicin is included in the regimen, and especially in the intensive phase of treatment when the bacterial load is highest. However, it is not always easy to organize such treatment for every patient. In many instances, individual arrangements for treatment observation will have to be made. Sometimes the observation of treatment will have to be delegated to other institutions or individuals, e.g. to a hospital or health post located close to the patient's workplace or home.

In summary, treatment must be organized with a view to the patient's convenience rather than to the convenience of the treatment service.

At present, the key to cure is to be found in the organization of treatment delivery. The success rate of even the best available regimen will be low if treatment

services are not focused on the cooperation of patients. On the other hand, even a second-best regimen may be highly successful if treatment is delivered with adequate organization.

References

1. Fox W. General considerations on the choice and control of chemotherapy in pulmonary tuberculosis. *Bulletin of the International Journal of Tuberculosis and Lung Disease*, 1972, 47:51–71.
2. *WHO Expert Committee on Tuberculosis. Eighth report*. Geneva, World Health Organization, 1964 (WHO Technical Report Series, No. 290).
3. *WHO Expert Committee on Tuberculosis. Ninth report*. Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).

61. What is the significance of default (treatment interruption) in the treatment of tuberculosis?[1]

N. Bock[2]

The most important cause of tuberculosis *treatment failure* among detected patients is non-completion of treatment, or default. The most important cause of tuberculosis *programme failure* is a low rate of treatment completion, as defaulting patients continue to transmit tuberculosis in the community, sometimes with acquired drug resistance. Treatment success rates of at least 70–85% are necessary to ensure a substantial reduction in the incidence of tuberculosis (*1*). Systematic cohort analysis frequently reveals that less than half of patients who start treatment actually complete it.

Treatment regimens capable of curing almost every tuberculosis patient have been available for more than 40 years, yet a large proportion of the patients detected have not been successfully treated. In a 1964 report of a community-based tuberculosis treatment programme in southern India using a regimen of isoniazid plus *p*-aminosalicylic acid (PAS), only 64% of 123 patients were culture-negative after 12 months although the regimen was capable of a 90% cure rate (*2*). The low level of success was attributed to failure of the health delivery services to maintain patient adherence to treatment. By the end of the 12-month period 27% of patients had refused treatment, 10% had died or moved, and fewer than half of the remainder had collected at least 80% of their medication.

A comparison of the results of a triple-drug treatment regimen (streptomycin + thioacetazone + isoniazid) in routine health delivery services versus controlled clinical trials, both in Kenya, indicates the importance of both default in treatment failure and organization of treatment services in treatment success (*3*). The triple regimen achieved culture negativity at 1 year in 96% of patients in controlled clinical trials, but in only 76% of those in routine health delivery services. The proportion of patients completing 12 months of continuation-phase treatment in the well-organized clinical trial programmes was 91%, compared with 51% of those receiving routine services.

---

[1] Based on the chapter in the previous edition by K. Toman.

[2] Medical Officer, Research and Evaluation Branch, Division of Tuberculosis Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Treatment interruption is a major challenge in almost all areas. In New York City, for instance, only 11% of patients who started on treatment as inpatients in one hospital in 1988, before improvement in the tuberculosis control programme, were shown to have completed treatment (*4*). Failure to achieve high completion rates was a factor underlying both the striking increase in tuberculosis in New York City and the emergence of drug resistance in the USA in the late 1980s and early 1990s (*4–6*). Patient factors that have been associated with default range from inadequate understanding of the treatment regimen (*7*) and fear of discrimination due to the stigma associated with tuberculosis (*8*) to financial burden or travel distance to the clinic (*9*). Health system factors include unreliable drug supply, inconvenient clinic hours, inadequate patient education and support by staff, and poor staff motivation (*10*).

After 1 or 2 months of effective treatment, the patient feels symptom-free. From that moment it seems pointless to the patient to take medication that may be unpleasant and give rise to minor adverse effects that cause more discomfort than the disease itself. It is only natural to enjoy the recovery and stop taking medication.

Discontinuation of treatment has also been observed in a number of other conditions that require prolonged drug ingestion, such as cardiovascular diseases, rheumatic fever, leprosy, epilepsy, diabetes, and malaria prophylaxis. It is also true of the self-administration of oral contraceptives.

The dictionary definition of default is failure to do something required by duty or law. When default might cause harm to the individual or community, corrective or preventive action should be taken. In the case of a tuberculosis patient, irregularity or premature cessation of treatment usually has serious consequences not only for the patient but also for the community as a whole. It is the moral, if not the legal, duty of the health services to take the necessary precautions. However, since the interruption or self-termination of treatment is a common feature of human behaviour, these precautions must be an essential part of the treatment strategy – a built-in element of treatment organization. Prevention and management of default are integral components of treatment and are thus – principally and undeniably – the responsibility of the doctor or person in charge of treatment. The DOTS strategy shifts the ultimate responsibility for patient cure from the patient to the health system. Therefore, if treatment failure is due to default, it is unjust to hold the patient primarily responsible.

As long as the organizers of treatment services do not accept this responsibility, even the most effective drug regimens will fail to produce the high level of therapeutic and epidemiological success of which they are capable.

However, it is easier to identify than to remedy the causes of default. Many health professionals believe that health education of the sick and of the public is all that is needed to ensure compliance with medical instructions. Unfortunately, experience has shown that such efforts, or even detailed instructions by a doctor, are generally insufficient to motivate patients to take the prescribed regimen.

There is far more to motivation than informing and instructing people: it is a matter of human relations and requires an understanding of the patient's non-medical

problems, way of life, work, beliefs, wants, fears, and attitudes towards traditional and modern medicine. Motivation requires a person to speak the patient's "language" and bridge intellectual and social distances, remove cultural barriers, and change attitudes and habits. Positive motivating factors are efficient professional performance, good working morale, compassion, and staff's identification with the community they serve.

In summary, motivation is a problem of human communication, differing from one patient to another and one community to another. That is why no uniform and generally applicable recipe can be given. Failure to communicate with the patient, a patronizing approach, or disrespectful behaviour will alienate the patient and create distrust, resulting in the rejection of treatment.

The only means of ensuring that treatment is taken as prescribed is by direct observation (see "What are the advantages of direct observation of treatment", page 183). In an effective programme of direct observation, each patient's needs and concerns are addressed and a human bond between the patient and the treatment observer is established so that the risk of default is minimized.

Among 725 275 smear-positive cases reported to WHO in the 1998 cohort and receiving standardized short-course treatment in a DOTS programme, the global default rate was 6% (*11*). Considering patients who were not evaluated as defaulting, the default rate among those treated in a DOTS strategy programme was less than one-quarter of that among those treated in non-DOTS programmes (11% vs 58%). Thus, the DOTS strategy, if successfully applied, can address the health system organizational problems that are factors in default.

References

1. Styblo K. *How should a tuberculosis control program be evaluated*? [Unpublished talk at the World Congress on Tuberculosis, Bethesda, MD, 17 November 1992, cited by Hadler JL. Control of tuberculosis. In: Friedman LN, ed. *Tuberculosis: current concepts and treatment*, 2nd ed. Boca Raton, CRC Press, 2001.]
2. Frimodt-Møller J, Acharyalu GS, Pillai KK. A controlled trial of the effect of domiciliary tuberculosis chemotherapy programme in a rural community in South India. *Indian Journal of Medical Research*, 1981, 73:S1–S80.
3. Kent PW et al. The therapy of pulmonary tuberculosis in Kenya: a comparison of results achieved in controlled clinical trials with those achieved in routine services. *Tubercle*, 1970, 51:24–38.
4. Brudney K, Dobkin J. Resurgent tuberculosis in New York City: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Review of Respiratory Disease*, 1991, 144:745–749.
5. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.
6. Meeting the challenge of multidrug-resistant tuberculosis: summary of a conference. *Morbidity and Mortality Weekly Report*, 1992, 41:51–57.
7. Barnhoorn F, Adriaanse H. In search of factors responsible for noncompliance among

tuberculosis patients in Wardha District, India. *Social Science and Medicine*, 1992, 34: 291–306.

8. Liefooghe R et al. Perception and social consequences of tuberculosis: a focus group study of tuberculosis patients in Sialkot, Pakistan. *Social Science and Medicine*, 1995, 41: 1685–1692.
9. Sumartojo E. When tuberculosis treatment fails. A social behavioral account of patient adherence. *American Review of Respiratory Disease*, 1993, 147:1311–1320.
10. Rouillon A. Problems raised by the organization of an efficient ambulatory treatment for tuberculosis patients. *Bulletin of the International Union Against Tuberculosis*, 1972, 47: 68–93.
11. *Global tuberculosis control. WHO Report 2000*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).

62. How important is follow-up and what is the frequency of relapse after the completion of treatment?[1]

T. Santha[2]

Relapse is defined as "a patient previously treated for tuberculosis who has been declared cured or treatment completed, and is diagnosed with bacteriologically positive (smear or culture) tuberculosis" (*1*).

Before the advent of treatment, the complete cure of smear-positive pulmonary tuberculosis was seen only rarely. Pathologists and clinicians maintained that the disease practically never healed in the strict sense of the term, but could only be arrested, become stabilized, or rendered inactive. Since bacilli almost always persisted in the residua of tuberculosis lesions, relapse was common, and that was the reason for the adoption of a policy of lifelong follow-up of patients who had completed treatment. These patients were kept on a register and examined regularly at intervals of several months, or at least once a year. That routine, however, placed a steadily increasing burden on the health services, absorbing a substantial proportion of staff time and financial resources. The dramatic success of treatment called into question the usefulness of indefinite follow-up and prompted demands for the reassessment of this policy. For that purpose, two questions needed to be answered:

- What is the frequency of relapse?
- How is relapse detected?

In a longitudinal survey and analytical studies, it was found that relapse still accounted for about 15–20% of the annual incidence of newly registered infectious cases (*2–4*). Controlled clinical trials in which patients were followed up regularly for 2 years or more have shown that the frequency of relapse is around 3–7% with standardized short-course chemotherapy. Similar results were obtained with either a 6-month regimen using rifampicin throughout the treatment period or 8 months if rifampicin was given only in the initial intensive phase of treatment. Approximately 80% of the relapses occur within the first 6 months of stopping treatment (*5*). More than 80% of relapses occur with organisms susceptible to the tuberculosis drugs used earlier (*6*) and hence their re-treatment does not pose a problem.

---

[1] Based on the chapter in the previous edition by K. Toman.

[2] Deputy Director, Tuberculosis Research Centre, Chennai, India.

It was also found that the individual risk of relapse among persons with a history of bacteriologically confirmed tuberculosis varied substantially and was determined mainly by three factors:

— whether treatment had been received or not (in case treatment was not given, the patient would be considered to have recurrent tuberculosis, not to have relapsed);
— whether or not the regimen given was adequate and regularly taken; and
— the time that had elapsed since smear/culture conversion to negative was achieved.

The highest relapse rate is found in patients who have never received any treatment (about 5% per annum) and the next highest rate (about 2%) in patients with prior inadequate treatment (*7*). After 3–5 years, the risk in both groups diminishes appreciably, to about 1% (*7*).

The most important finding was the striking effect of adequate treatment on relapse, which falls to a few per million per annum (*8*, *9*). Although the risk is still considerably higher than the risk of disease in persons with no history of previous tuberculosis, it does not warrant lifelong follow-up. Moreover, even with active monitoring, relapses were mostly discovered on account of symptoms rather than during routine follow-up examination. In a longitudinal survey lasting 12 years, each person with a history of tuberculosis was examined bacteriologically every 6 months and by X-ray once a year. Less than half of the relapses were discovered through follow-up examinations, despite a stringent research discipline.

In patients who have been adequately treated, the risk of relapse is too small to justify prolonged follow-up (*10*). Thus, routine follow-up examinations are generally unnecessary. This conclusion was reached by the Centers for Disease Control of the Public Health Service in the USA (*11*), as well as by investigators who followed up patients treated in Scotland (*12*). The former stated (*11*): "Tuberculosis patients who complete adequate chemotherapy should be considered cured. They have no need for routine lifetime periodic recall for X-ray examination. Indeed, perpetuating life-time follow-up of such treated patients diverts clinic personnel and resources from the crucial task of providing services for those who really need them."

However, ex-patients should be strongly advised to come for examination without delay if they develop symptoms suggestive of tuberculosis (*10*). General practitioners and physicians who are likely to encounter patients with a history of previous tuberculosis should be informed about the possibility of relapse and the need to promptly evaluate recurrent respiratory symptoms (such as prolonged cough). However, it should also be understood that, among symptomatic ex-patients, cough is more the result of irreversible, bacteriologically quiescent lung damage than of recurrence of active tuberculosis disease (*13*).

References

1. Revised international definitions in tuberculosis control. *International Journal of Tuberculosis and Lung Disease*, 5:213–215.
2. Chan-Yeung M et al. Reactivation of inactive tuberculosis in Northern Canada. *American Review of Respiratory Disease*, 1971, 104:861–865.
3. Steinbruck P et al. The risk of tuberculosis in patients with fibrous lesions radiologically diagnosed. *Bulletin of the International Union Against Tuberculosis*, 1972, 47:144–171.
4. Nakielna EM, Cragg R, Grzybowski S. Lifelong follow-up of inactive tuberculosis: its value and limitations. *American Review of Respiratory Disease*, 1975, 112:765–772.
5. Controlled clinical trial of four 6-month regimens of chemotherapy for pulmonary tuberculosis. Second report. Second East African/British Medical Research Council Study. *American Review of Respiratory Disease*, 1976, 114:471–475.
6. Low rate of emergence of drug resistance in sputum positive patients treated with short course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:40–45.
7. Grzybowski S et al. Reactivations in inactive pulmonary tuberculosis. *American Review of Respiratory Disease*, 1966, 93:352–361.
8. Stead WW, Jurgens GH. Productivity of prolonged follow-up after chemotherapy for tuberculosis. *American Review of Respiratory Disease*, 1973, 108:314–320.
9. Krivinka R et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. Second report (1965–1972). *Bulletin of the World Health Organization*, 1974, 51:59–69.
10. *WHO Expert Committee on Tuberculosis. Ninth report.* Geneva, World Health Organization, 1974 (WHO Technical Report Series, No. 552).
11. Recommendations for health department supervision of tuberculosis patients. *Morbidity and Mortality Weekly Report*, 1974, 23:75–76.
12. Pearce SJ, Horne NW. Follow-up of patients with pulmonary tuberculosis adequately treated by chemotherapy: is this really necessary? *Lancet*, 1974, 2:641–643.
13. Cao JP et al. Two-year follow-up of directly-observed intermittent regimens for smear-positive pulmonary tuberculosis in China. International Journal of Tuberculosis and Lung Disease, 1998, 2:360–364.

63. Why is a recording and reporting system needed, and what system is recommended?

D. Maher[1] *& M. Raviglione*[2]

The recording (patient registration) and reporting system is used to systematically evaluate patient progress and treatment outcome, as well as overall programme performance, and to identify problems that need to be solved (*1*, *2*). It is a fundamental principle of effective tuberculosis control that the programme is responsible for monitoring and reporting outcomes of every patient started on treatment, without exception – "no cheating". It is common for specialized institutions or individual physicians to believe sincerely that a high proportion of the patients they place on treatment are cured, but for systematic evaluation to reveal that only a minority of patients – not infrequently, a small minority – actually complete treatment (*3*).

What is the recommended recording system?

The recommended recording system consists of:

- a tuberculosis laboratory register that includes data from all patients who have had a sputum smear examination;
- patient treatment cards that detail the regular intake of medication and follow-up sputum examinations; and
- the tuberculosis register, which lists *every* tuberculosis patient and monitors individual and collective progress toward cure (*1*, *4*) (some countries register only tuberculosis patients who start treatment).

Tuberculosis laboratory register

The laboratory technician records patient details in the tuberculosis laboratory register with a serial identification number. The results of the sputum examination are then recorded in the general health facility where the patient is registered for treatment. From tuberculosis laboratory registers and routine clinic records, the proportion of outpatients (attending health facilities for any reason) examined and the

[1] Medical Officer, Stop TB Department, World Health Organization, Geneva, Switzerland.
[2] Coordinator, TB Strategy and Operations, Stop TB Department, World Health Organization, Geneva, Switzerland.

proportion of patients examined for diagnosis who are found to be smear-positive can be easily monitored.

Patient treatment card

Each person with a diagnosis of tuberculosis (smear-positive, smear-negative, or extrapulmonary) has a patient treatment card. This card records basic epidemiological data (age, sex, etc.), clinical information (type of patient, category of treatment, smear result, weight), and the administration of drugs. Each card also gives information on the patient's address and treatment centre; this is useful in case the patient does not attend scheduled treatment. The health worker uses the patient treatment card for recording the treatment given and the results of follow-up sputum examinations. During the continuation phase and at the end of treatment, patients submit sputum samples for microscopy to ensure that they become – and remain – negative and are thus declared cured of tuberculosis. These results, along with follow-up patient weight, are also recorded on the treatment card.

Tuberculosis register

The health care worker responsible for supervising each administrative area or institution uses the tuberculosis register to monitor progress and treatment outcome for *all* patients in that district. This provides the district or local health director with rapid, continuous feedback on programme performance in the district. Each patient's address and treatment centre are also recorded, facilitating the tracing of patients who interrupt treatment.

What is cohort analysis?

Cohort analysis refers to the systematic assessment and reporting of standard outcomes of treatment. A cohort of tuberculosis patients consists of patients registered during a certain time period, which is usually a quarter of a year (i.e. 1 January to 31 March, 1 April to 30 June, 1 July to 30 September, and 1 October to 31 December). Sputum smear-positive pulmonary tuberculosis patients (the infectious cases) form a separate cohort from sputum smear-negative and extrapulmonary tuberculosis patients. For smear-positive pulmonary tuberculosis patients, the standard outcomes of treatment reported are cure, treatment completion, treatment failure, death, treatment interruption (default), and transfer out. In smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis patients, cure cannot be assessed systematically because the outcome indicators depend on the sputum smear examination. For these patients, therefore, treatment completion, death, default, failure, and transfer out are recorded in the tuberculosis register. New and previously treated patients form separate cohorts.

Cohort analysis is the key management tool for evaluating the effectiveness of tuberculosis control activities in any area. It enables the identification of problems so

that the programme can institute appropriate action to improve performance. The quarterly report on case detection rapidly identified poor-quality diagnosis, so that diagnostic practices can be promptly improved. The quarterly smear conversion report and quarterly and annual treatment success rates (percentage of patients who are cured plus those who complete treatment) provide any middle- or upper-level manager with timely, concrete indicators of achievements or of problems requiring action. Examples of problems include low cure rate, high default rate, higher-than-expected proportion of sputum smear-negative pulmonary tuberculosis or extrapulmonary tuberculosis, and lower-than-expected case-detection rate.

The recording and reporting system allows for targeted, individualized follow-up to help patients who are not making satisfactory progress, and for rapid managerial assessment of the overall performance of each institution, district, region, or country. The system ensures systematic accountability, and its inherent internal and external cross-checks make false reporting difficult to perform and easy to detect. For example, the laboratory number appears on the tuberculosis laboratory register, the patient treatment card, and the tuberculosis register. These three records are often kept in different health units, which would make false reporting logistically difficult, particularly as the tuberculosis and laboratory registers may contain hundreds or even thousands of records.

What is the recommended reporting and monitoring system?

Monitoring of treatment outcomes by cohort analysis takes place about 3 months after all patients in the cohort should have completed their course of treatment. The tuberculosis officer should perform cohort analysis of treatment outcome every quarter and at the end of every year. Quarterly reports on treatment outcome are forwarded to the intermediate level (e.g. region). The tuberculosis officer at this intermediate level verifies that local reports are correct, complete, and consistent, compiles cohort analysis reports on all patients in the area, and submits the report to the central unit of the national tuberculosis control programme. The national programme compiles cohort analysis reports on all tuberculosis patients registered nationally. The World Health Organization collects and publishes summary, consolidated data annually and, in some regions, quarterly (*5*, *6*).

References

1. *Treatment of tuberculosis: guidelines for national programmes*, 3rd ed. Geneva, World Health Organization, 2003 (WHO/CDS/TB/2003.313).
2. *What is DOTS? A guide to understanding the WHO-recommended TB control strategy known as DOTS*. Geneva, World Health Organization, 1999 (document WHO/CDS/CPC/TB/99.270).
3. Brudney K, Dobkin J. Resurgent tuberculosis in New York City. Human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Review of Respiratory Disease*, 1991, 144:745–749.

4. Enarson D et al. *Management of tuberculosis: a guide for low income countries*, 5th ed. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
5. Raviglione MC et al. Assessment of worldwide tuberculosis control. *Lancet*, 1997, 350: 624–629.
6. *Global tuberculosis control. WHO Report 2001.* Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).

64. When should tuberculosis patients be hospitalized, and how infectious are tuberculosis patients while on treatment?[1]

E.A. Talbot[2] *& C.D. Wells*[3]

For most tuberculosis patients, successful treatment can be given entirely in an outpatient setting, without significant risk of tuberculosis transmission within the community. In situations where this is possible, a policy of routine hospital admission for tuberculosis treatment is unnecessary – and even anachronistic.

There is a solid body of evidence that outpatient treatment is as effective as inpatient treatment, even for patients with extensive disease and living in poor conditions. In the classic Madras study (see "What were the main findings of the Madras study comparing home and sanatorium treatment?", page 173), 163 patients with pulmonary tuberculosis were randomized to care either in their homes or in a sanatorium (*1*). Conditions in the sanatorium included prolonged bedrest, nutritious diet, nursing services, and a well-ventilated and clean environment, which had been advocated as conducive to healing tuberculosis. After 1 year of treatment with isoniazid and *p*-aminosalicylic acid, compliance and clinical, radiographic, and bacteriological responses were equivalent in the two groups. A total of 126 patients were followed for 5 years and no difference in the rate of relapse was observed between the home-treated and sanatorium-treated patients (*1*).

Following this and other controlled trials in both developed and developing settings (*2–4*), there has been increased emphasis on outpatient management of tuberculosis (*5*). Nevertheless, hospitalization of tuberculosis patients remains a common practice in some settings (*6*, *7*), and may even be increasing (*8*, *9*). A reason often cited for initial hospitalization is concern that the patient is infectious and must therefore be isolated from family and community. It is currently impossible to determine exactly when an individual patient becomes non-infectious. However, most patients with disease due to drug-susceptible organisms become non-infectious within several days to weeks after treatment is started, and the risk of infection to contacts is therefore greatly reduced (*10*). During the 5-year follow-up period of the Madras study, close

[1] Based on the chapter in the previous edition by K. Toman.

[2] Director TB/HIV Research, The BOTUSA Project, Division of TB Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

[3] Associate Director for International Activities, Division of TB Elimination, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

contacts of the tuberculosis patients were observed for skin-test conversion and the development of tuberculosis (*11*). The tuberculin-negative contacts of patients treated at home were no more likely to convert to positive than the contacts of those in the sanatorium. Moreover, tuberculosis developed no more frequently in contacts of home-treated patients (10.5%) than in contacts of patients treated in the sanatorium (11.5%). Most cases of tuberculosis developed within the first 3 months, suggesting that infection occurred before the start of treatment (*11*). Additional studies support this landmark finding (*12*, *13*).

There are national and international guidelines that recommend hospitalization for tuberculosis patients who cannot be managed on an outpatient basis (*10*, *14*, *15*).

Occasionally tuberculosis is diagnosed while a patient is in hospital, whether or not symptoms of tuberculosis led to the admission; in other words, tuberculosis may be an incidental finding. The indications for admission to or continued stay in hospital related to tuberculosis are similar to those for any other disease. These include potentially life-threatening conditions such as miliary/meningeal disease, adult respiratory distress syndrome, intravascular coagulation, severe haemoptysis, and severe reaction to drugs. Infectiousness is not now, in itself, an indication for confinement in the hospital, except in rare cases (*16*). However, while it may be appropriate to return a patient to home and family, special circumstances – such as army barracks or crowded correctional facilities – make isolation (in a hospital or elsewhere) advisable until the patient is asymptomatic and has negative or decreasingly positive acid-fast bacilli smears (*17*). Some programmes recommend that, if patients would be discharged to congregate living situations (e.g. shelter, nursing home, jail, prison, or group home), and in other selected situations, they remain in hospital until they are smear-negative (*18*).

In a few select circumstances, hospitalization or institution-based treatment may be preferable to outpatient treatment. For example, there are limited data to determine when patients with isoniazid- and rifampicin-resistant (multidrug-resistant) tuberculosis become non-infectious after the start of appropriate reserve drug treatment. In a series of multidrug-resistant tuberculosis patients who responded to treatment at the National Jewish Hospital, the interval from start of treatment to the first of a series of negative cultures ranged from 1 to 8 months (median 2 months) (*19*). Contacts of infectious multidrug-resistant tuberculosis patients who become infected with multidrug-resistant strains and who develop active disease require longer and more costly treatment, have a lower likelihood of cure, and are at greater risk of death (*20–22*). Given that multidrug-resistant tuberculosis patients may be infectious for longer, hospitalization may have a role in treatment when multidrug-resistant tuberculosis patients are likely to have close contacts, particularly young children and immunocompromised persons.

Good infection control policies and practices must be in place in facilities where such patients are treated (see "What is nosocomial transmission of tuberculosis and how can it be prevented?", page 278). Outbreaks of multidrug-resistant tuberculosis

can occur in hospitals in both developed and developing countries if good infection control policies are not practised (*2–25*). Reported outbreaks, mostly among patients infected with the human immunodeficiency virus, resulted in high mortality.

The American Thoracic Society (*26*) has said: "In summary in this era of chemotherapy, tuberculosis should be treated in whatever setting most appropriately meets the needs of the patient and the community. Some patients can be entirely treated at home. Others may require some short period of hospitalization in a general hospital followed by ambulatory care. Still others may require longer-term care in an institution mainly because of their other medical and social problems. The fact of tuberculosis should not be the primary determinant of the local care, nor should it act as a constraint. Continuity and completion of chemotherapy are the keys to recovery wherever the care is provided."

References

1. Concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1959, 21:51–58.
2. Tyrrell WF. Bed rest in the treatment of pulmonary tuberculosis. *Lancet*, 1956, 1:821–823.
3. Bell JW. The initiation of chemotherapy in pulmonary tuberculosis in West Africans: hospital and ambulant treatment compared using streptomycyclidine–isonicotinic acid hydrazide. *British Journal of Diseases of the Chest*, 1960, 54:247–254.
4. Isoniazid with thiacetazone (thioacetazone) in the treatment of pulmonary tuberculosis – fourth investigation: the effect of increasing the dose of isoniazid. *Tubercle*, 1966, 47: 315–339.
5. *Global tuberculosis control. WHO Report 2000*. Geneva, World Health Organization, (document WHO/CDS/TB/2000.275).
6. Nutini S et al. Hospital admission policy for tuberculosis in pulmonary centres in Italy: a national survey. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:985–991.
7. Taylor A et al. Causes and cost of hospitalization of tuberculosis patients in the United States. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:931–939.
8. Leff DR, Leff AR. Tuberculosis control policies in major metropolitan health departments in the United States. IV: Standards of practice in 1988. *American Review of Respiratory Disease*, 1989, 139:1350–1355.
9. Leff DR, Leff AR. Tuberculosis control policies in major metropolitan health departments in the United States. VI: Standards of practice in 1996. *American Journal of Respiratory and Critical Care Medicine*, 1997, 156:1487–1494.
10. American Thoracic Society. Control of tuberculosis in the United States. *American Review of Respiratory Disease*, 1992, 146:1623–1633.
11. Kamat SR et al. A controlled study of the influence of segregation of tuberculous patients for one year on the attack rate of tuberculosis in a 5-year period in close family contacts in South India. *Bulletin of the World Health Organization*, 1966, 34:517–532.
12. Gunnels JJ, Bates JH, Swindoll H. Infectivity of sputum-positive tuberculous patients in chemotherapy. *American Review of Respiratory Disease*, 1974, 109:323–330.

13. Brooks SM, Lassiter NL, Young EC. A pilot study concerning the infection risk of sputum positive tuberculosis patients on chemotherapy. *American Review of Respiratory Disease*, 1973, 108:799–804.
14. Joint Tuberculosis Committee of the British Thoracic Society. Chemotherapy and management of tuberculosis in the United Kingdom: recommendations 1998. *Thorax*, 1998, 53:536–548.
15. Gruppo di Studio AIPO Tuberculosi. *Gestione di diagnosi, terapia e follow up dei casi. [Management of case diagnosis, treatment and follow-up.]* Rass Pat App Resp Suppl, Pacini Editore, 1994:50–52.
16. American Thoracic Society. Non-drug issues related to the treatment of tuberculosis: hospitalization of patients with tuberculosis. *Chest*, 1985, 87:S125–S127.
17. Noble RC. Infectiousness of pulmonary tuberculosis after starting chemotherapy: review of the available data on an unresolved question. *American Journal of Infection Control*, 1981, 9:6–10.
18. Bureau of Tuberculosis Control. *Clinical policies and protocols,* 2nd ed. New York, Department of Health, 1997:82.
19. Goble M et al. Treatment of 171 patients with pulmonary tuberculosis resistant to isoniazid and rifampin. *New England Journal of Medicine*, 1993, 328:527–532.
20. Iseman MD. Drug therapy: treatment of multidrug-resistant tuberculosis. *New England Journal of Medicine*, 1993, 329:784–791.
21. Espinal MA et al. Standard short-course chemotherapy for drug-resistant tuberculosis: treatment outcomes in 6 countries. *Journal of the American Medical Association*, 2000, 283:2537–2545.
22. Iseman MD, Cohn DL, Sbarbaro JA. Directly observed treatment of tuberculosis – we can't afford not to try. *New England Journal of Medicine*, 1993, 328:576–578.
23. Frieden TR et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *Journal of the American Medical Association*, 1996, 276:1229–1235.
24. Wilkinson D et al. Nosocomial transmission of tuberculosis in Africa documented by restriction fragment length polymorphism. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1997, 91:318.
25. Ritacco V et al. Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires. *Journal of Infectious Diseases*, 1997, 176:637–642.
26. American Thoracic Society. Guidelines for long-term institutional care of tuberculosis patients. *American Review of Respiratory Disease*, 1976, 113:253.

65. What is nosocomial transmission of tuberculosis and how can it be prevented?

P.M. Simone[1]

Nosocomial transmission of tuberculosis is the spread of *Mycobacterium tuberculosis* from a patient with active tuberculosis to other patients or health care workers in a health care setting. Investigation of large outbreaks of multidrug-resistant tuberculosis in hospitals in the USA in the late 1980s and early 1990s (*1–5*) found that transmission occurred because of delays in diagnosis and treatment of patients with active tuberculosis and lack of appropriate infection control measures. In addition, many of the patients were infected with HIV, and there was a very high mortality rate. HIV-infected persons who are exposed to and infected with *M. tuberculosis* may progress rapidly to active tuberculosis. Delays in the diagnosis and treatment of these secondary cases facilitated further transmission and contributed to the poor outcomes in these patients.

Several studies have demonstrated an increased risk of nosocomial transmission of *M. tuberculosis* to health care workers in Africa, South America, and Asia (*6–12*). These health care workers included nurses, physicians, nursing and medical students, and laboratory technicians. The risk was greatest among those who had the closest and longest duration of contact with tuberculosis patients. The studies suggest that the greatest risk for nosocomial transmission is from the patient whose tuberculosis has not yet been diagnosed or treated.

Transmission of *M. tuberculosis* can be prevented or reduced by implementing certain infection control measures (*13*). There are three levels of control:

— administrative controls to help reduce exposure of patients and health care workers to *M. tuberculosis*;
— environmental controls to reduce the concentration of organisms in the air; and
— personal respiratory protection to help protect workers in certain settings when the concentration of organisms cannot be sufficiently reduced by administrative and environmental controls.

[1] Chief, Prevention Support Service, Office of the Director, National Center for HIV, STD and TB Prevention, Centers for Disease Control and Prevention, Atlanta, GA, USA.

Administrative controls are by far the most important; environmental controls and personal respiratory protection will be ineffective in the absence of good administrative controls.

Administrative controls should receive the highest priority in any tuberculosis infection control programme. Some basic administrative controls should be implemented in all health care facilities, and additional controls are recommended for larger, referral-level facilities. The most important administrative control in all settings is having appropriate policies and procedures in place to facilitate early diagnosis and treatment. Tuberculosis should be suspected in patients who have symptoms of, or risk factors for, tuberculosis. When tuberculosis is suspected, a diagnostic evaluation should be initiated promptly and the results should be returned in a timely fashion so that treatment can be initiated. Ensuring that all medications are taken under direct observation and that treatment is continued and completed after hospital discharge is essential to prevent disease recurrence and subsequent readmission of patients with infectious tuberculosis.

Additional administrative controls recommended for all settings include:

— assessing the risk for transmission in different areas of the facility;
— developing an infection control plan;
— training health care workers in tuberculosis, its transmission, and their role in implementing infection control measures to reduce the risk of transmission;
— educating patients about the importance of covering their mouths when coughing;
— collecting sputum in well-ventilated areas;
— prioritizing patients with suspected tuberculosis in outpatient settings to reduce exposure in waiting areas; and
— reducing exposure in the laboratory.

In addition, the implementation of these interventions should be evaluated periodically.

For referral-level facilities, additional measures are recommended. One effective way to reduce the risk of transmission in these facilities is to promote outpatient management of tuberculosis patients. Two means of doing this are early discharge and avoidance of hospitalization altogether. Hospitalization can be avoided by ensuring prompt and appropriate referral to outpatient tuberculosis care. When hospitalization cannot be avoided, infectious tuberculosis patients should be placed in a separate ward, area, or (ideally) building of the facility. This can reduce transmission to other patients in the facility, especially when used in conjunction with administrative controls for early diagnosis and treatment. In larger facilities, two wards in a separate building, one for patients with suspected tuberculosis and one for tuberculosis patients on treatment, would be optimal. True isolation is usually not feasible because it requires expensive engineering controls. Policies and procedures for enforcing and discontinuing isolation/separation should be developed and evaluated. Consideration

should also be given to collecting data on the number of health care workers in the facility who are diagnosed with tuberculosis and information about risk factors.

Environmental controls are most appropriate for referral-level facilities. They are used to remove and dilute air contaminated with *M. tuberculosis* in tuberculosis patient areas. The simplest and least expensive environmental control is maximizing natural ventilation through open windows. Obviously, this will not be feasible in some climates. The direction of airflow can be controlled to prevent contaminated air from a tuberculosis ward from reaching other parts of the facility, but this requires more expensive measures such as window fans or exhaust ventilation systems. Ultraviolet germicidal irradiation can clean the air by killing airborne *M. tuberculosis*. Lamps are placed near the ceiling to irradiate the air in the upper part of the room without exposing patients and workers in the rest of the room, but there must be good mixing of air in the room for this to be effective. High humidity may reduce effectiveness, and precautions must be taken to ensure safe installation (*13*).

Respirators are special masks made of material that filters small particles (95% filter efficiency for particles 0.3 µm in diameter) and fit well. Personal respiratory protection is a lower priority than administrative or environmental controls. However, in referral-level facilities, respirators can be used as a supplement to administrative and environmental controls in certain high-risk settings, such as isolation rooms, and rooms where bronchoscopy, sputum induction, spirometry, or autopsies are performed.

These precautions are particularly important where HIV infection is common. Without them, tuberculosis can spread rapidly in AIDS wards and similar settings. HIV-infected health care workers are at risk of tuberculosis, and ideally should not be exposed to infectious tuberculosis patients.

Implementing a tuberculosis infection control programme with an emphasis on administrative controls will help to reduce transmission of *M. tuberculosis* within health care facilities, protecting not only other patients but also health care workers who are vital resources in the fight against tuberculosis.

References

1. Pearson ML et al. Nosocomial transmission of multidrug-resistant tuberculosis: a risk to patients and health care workers. *Annals of Internal Medicine*, 1992, 117:191–196.
2. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons – Florida and New York, 1988–1991. *Morbidity and Mortality Weekly Report*, 1991, 40: 585–591.
3. Coronado VG et al. Transmission of multidrug-resistant *Mycobacterium tuberculosis* among persons with human immunodeficiency virus infection in an urban hospital: epidemiologic and restriction fragment length polymorphism analysis. *Journal of Infectious Diseases*, 1993, 168:1052–1055.
4. Small PM et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *New England Journal of Medicine*, 1993, 328: 1137–1144.

5. Frieden TR et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *Journal of the American Medical Association*, 1996, 276:1229–1235.
6. Aita J et al. Hospital transmission of multidrug-resistant *Mycobacterium tuberculosis* in Rosario, Argentina. *Medicina*, 1996, 56:48–50.
7. Harries AD et al. Delays in diagnosis and treatment of smear-positive tuberculosis and the incidence of tuberculosis in hospital nurses in Blantyre, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1997, 91:15–17.
8. Ritacco V et al. Nosocomial spread of human immunodeficiency virus-related multidrug-resistant tuberculosis in Buenos Aires. *American Journal of Infectious Disease*, 1997, 176: 637–642.
9. Wilkinson D et al. Nosocomial transmission of tuberculosis in Africa documented by restriction fragment length polymorphism. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1997, 91:318.
10. Do AN et al. Increased risk of *Mycobacterium tuberculosis* infection related to occupational exposures to health care workers in Chiang Rai, Thailand. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:377–381.
11. Muzzy de Souza GR et al. Tuberculin conversion among health care workers in a general hospital of Rio de Janeiro, Brazil. Final results. *American Journal of Respiratory and Critical Care Medicine*, 1998, 157: (3) Abstract A 705.
12. Sidibe K et al. Tuberculin skin test reactivity among health care workers and level of exposure to tuberculosis patients in Abidjan, Côte d'Ivoire. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:S103.
13. Granich R et al. Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings. Geneva, World Health Organization, 1999:1–51 (document WHO/CDC/TB/99.269).

66. Where is tuberculosis usually spread and how can spread be reduced?

H. Rieder[1]

The risk of being *exposed* to *Mycobacterium tuberculosis* depends principally on three factors:

— the number of cases capable of transmitting *M. tuberculosis* in a community (principally sputum smear-positive cases);
— the duration of infectiousness of such cases; and
— the number and duration of encounters between a source of infection and susceptible individuals.

The risk of becoming *infected* with *M. tuberculosis*, after exposure, depends on three other factors:

— the number of infectious droplet nuclei produced by an infectious case;
— the volume of air in which these droplets are contained; and
— the period over which a susceptible individual inhales air containing such droplet nuclei.

Spread of *M. tuberculosis* will therefore be most common in communities and population groups in which the prevalence of infectious tuberculosis is high, where cases remain infectious for a prolonged period of time, and where people interact frequently. Transmission is most likely to occur where the concentration of bacilli in the air is high and exposure to that air is prolonged. It will be highest where there is prolonged direct contact between infectious sources and susceptible individuals.

The risk of becoming infected after exposure outdoors differs from that following indoor exposure. Outdoors, infectious droplet nuclei rapidly disperse in an essentially infinite volume of air (and are rapidly killed by sunlight); indoors the droplet nuclei are trapped, particularly if ventilation is poor. Household contacts of an infectious case are thus at higher risk than community contacts, and among household contacts, intimate contacts are at highest risk (*1*).

[1] Medical Officer, Tuberculosis Division, International Union Against Tuberculosis and Lung Disease, Paris, France.

M. tuberculosis is thus most likely to be spread whenever the above conditions are met – in prisons, hospitals, schools, offices, aeroplanes, etc. However, the relevant epidemiological question is what settings are of major public health importance. Household contact is certainly the most frequent event: almost always when a new case emerges, a household member will have been exposed, and often in a closed environment (the house, the bedroom, etc.). At the other extreme, infection on an aeroplane (*2*) will be a rare event because the likelihood of an incident infectious case on board is small, duration of exposure is limited, and ventilation on aeroplanes is usually good (*3*).

Special populations such as health care workers are more frequently exposed to infectious cases than the general community, and are often in close and prolonged contact with cases who have not yet been identified and hence have not yet started treatment. Health care workers are thus at increased risk of tuberculosis (*4*). Similarly, many prisons have a high incidence of tuberculosis. In countries where a substantial proportion of the population might be sentenced to prison, contact is prolonged, the environment closed, and diagnosis of infectious cases often delayed, the transmission risk is high (*5*).

The means of reducing the spread of tuberculosis can be derived from the above principles. With existing technology, little can be done on a mass basis directly to prevent the emergence of incident infectious cases. The duration of infectiousness can be curtailed, however, by prompt identification and complete treatment of such cases through an effective network of diagnostic and treatment services. This is the major intervention for reducing the spread of *M. tuberculosis*. In special settings known to carry an increased risk of spread, such as prisons and health care facilities, administrative and engineering measures to improve ventilation (and thus reduce the concentration of infectious droplets) might be done at affordable cost.

The key intervention for reducing spread is the same, regardless of the setting: tuberculosis cases must be identified as swiftly as possible when they present at health care facilities with respiratory symptoms; they must be placed on effective treatment; and treatment with the required frequency and for the required duration must be ensured, so that cure is effected. This strategy most efficiently reduces the risk of exposure and infection in the community, and leads ultimately to a reduction in the emergence of new infectious cases.

References

1. Lutong L, Bei Z. Association of prevalence of tuberculin reactions with closeness of contact among household contacts of new smear-positive pulmonary tuberculosis patients. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:275–277.
2. Driver CR et al. Transmission of *Mycobacterium tuberculosis* associated with air travel. *Journal of the American Medical Association*, 1994, 272:1031–1035.
3. *Tuberculosis and air travel: guidelines for prevention and control*. Geneva, World Health Organization, 1998:1–45 (document WHO/TB/98.256).

4. *Guidelines for the prevention of tuberculosis in health care facilities in resource-limited settings*. Geneva, World Health Organization, 1999:1–51 (document WHO/CDC/TB/99.269).
5. *Guidelines for the control of tuberculosis in prisons*. Geneva, World Health Organization, 1998:1–87 (documentWHO/TB/98.250).

67. What are the principles and requirements of a controlled clinical trial?[1]

F. Rehman[2]

Conscientious physicians treat patients only with methods in which they have confidence. However, different physicians often treat the same disease in different ways. If patients recover, physicians understandably ascribe the success to their choice of treatment. How subjective and changeable these judgements are can be seen from the large number of treatment methods that are given prominence, praised by sincere advocates, and eventually consigned to oblivion. It may take a long time for the value of a certain treatment method to be determined. Gold salts, for example, had been in use for almost 20 years as a specific treatment for tuberculosis, as recommended in some 200 published papers, before it was recognized that they were useless, if not actually harmful (*1*, *2*).

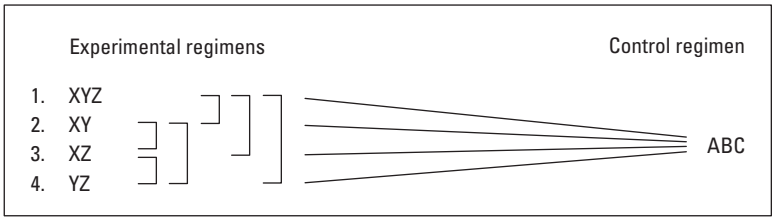
In the first half of the 20th century, innumerable therapeutic methods, diets, and compounds were used in the treatment of tuberculosis – tuberculin, other biological agents such as bacterial extracts, attenuated mycobacteria, antisera, and antitoxins, gold salts, cod-liver oil, vitamin C, calcium injections, creosote, salt-free diets, radiation therapy, and various climates (hot and dry, high altitudes, seaside locations) all had their passionate advocates (*3*). In addition, a host of therapeutic interventions were tried – pneumothorax, diaphragmatic paralysis, pneumoperitoneum, oleothorax, pneumonolysis, plombage, cavity drainage, thoracoplasty, and finally resectional surgery. While this is far from a complete account, it serves as a reminder of the confused of the past.

Determined efforts have been made over the past 50 years to use scientific techniques to evaluate the treatment of tuberculosis. An important advance has been the development of an assessment method known as the controlled trial. Many controlled trials have been carried out and have made it possible to establish the efficacy, toxicity, and applicability of currently recommended treatment regimens. However, some physicians still do not appreciate the value and scope of this method. There are also some authors who refer to their investigations as controlled trials without observing

[1] Based on the chapter in the previous edition by K. Toman.

[2] Senior Research Officer, Tuberculosis Research Centre, Chennai, India.

Figure 21
Example of comparison of treatment regimens in a controlled trial
The new drugs of which the experimental regimens are composed are X, Y, and Z, the symbol for the control regimen being ABC. Four regimens are constructed from different combinations of drugs X, Y, and Z.



the essential requirements. Therefore, it might be worth recalling the main features of the method.

The method

In a controlled trial, two or more equivalent groups of patients are formed. One group – the controls– remains untreated or receives a treatment of known effect, while the other – experimental – groups receive the treatments to be studied. (It is unethical to have an untreated group for a disease if effective treatment is available.)

Nowadays, the control group usually receives a standard robust regimen, with almost 100% efficacy and minimal relapse rates. If a control regimen is not included in the study, the protocol must specify which regimen – of known effectiveness – will be used as the control.

By using certain study schemes known as factorial designs, it is possible not only to measure the effects of the tested regimens, but also to identify the separate contribution of each drug provided that the drugs do not interact (*4*). See Figure 21.

Using such a design, 10 different comparisons can be made. Each experimental regimen can be compared with the control regimen. Comparing the experimental regimens with one another allows the individual contributory effect of each drug or factor, as well as the relationships between them, to be studied in terms of bacteriological and radiographic response, adverse effects, emergence of drug resistance, and relapse rate. The comparisons may also reveal synergistic or antagonistic interactions between the drugs or factors under study.

Ethical considerations

There are critics who reject controlled trials with generalizations such as: "Conducting controlled therapeutic trials is experimenting on people and is thus unethical." However, such statements disregard the fact that the prescribing of any treatment that

is not supported by quantified evidence of the benefits and risks is effectively experimenting on people. Moreover, it is experimentation with a treatment whose effects will remain uncertain. Unless the disease treated is known to be fatal, unavoidable bias may easily result in errors, and it is now widely accepted that it is neither ethical for the doctor nor safe for the patient to use a new treatment that has not been tested in a controlled trial.

There must always be an important reason for a trial, such as the need for a treatment of higher efficacy or acceptability, or for reducing the duration of treatment, the level of toxicity, the relapse rate, or the cost. Furthermore, there must be good justification for taking risks. The possible risks from the experimental treatment should be balanced against the risks to the patient and the community if the disease were left untreated or treated in the usual manner. Doctors participating in the trial should be given the assurance, laid down in the protocol, that they may withdraw a patient from the trial or break the code whenever continuation of the treatment might, in their view, cause serious harm. This must be ensured, even at the risk of nullifying the whole trial. Thus, the administration of a new treatment with strict observance of the principles of the controlled trial safeguards medical ethics and ensures scientific research of a high standard.

The protocol of a controlled trial

An essential requirement of a controlled trial is that it be planned and conducted according to a meticulous plan and working programme – the protocol. After the decision has been made to conduct a controlled trial, the protocol is drafted by a team of experts including not only physicians, but also representatives of other disciplines involved in the trial, e.g. a bacteriologist, a statistician, a nurse, a sociologist, a biochemist, an immunologist, and an administrator. The objectives, methods, working procedures, and schedules, are defined in the protocol, as well as the responsibilities of the parties involved in the trial. Every individual involved in the trial is strictly bound to adhere to the protocol, which should be consulted for instruction and guidance throughout the trial. The slightest deviation from the protocol must have the consent of the coordinating centre, otherwise the whole trial may be seriously impaired or invalidated. Thus, a protocol needs to be prepared with care, expertise, and responsibility. An unplanned trial, i.e. a trial without a protocol, is not a controlled trial, and the results of a trial with a deficient protocol are unconvincing, if not void.

Preliminary test runs

Before a protocol is completed, preliminary (pilot) studies may have to be conducted to obtain information rapidly, e.g. on the feasibility or operational efficiency of certain procedures, on unknown effects, or on the acceptability of certain policies. Sometimes it is useful to have a short test run of the protocol to see whether it contains any flaws.

All the investigators have the right to ask for amendments before participating in the trial and should feel that the protocol is their own, for which they will share responsibility and recognition. The final version of the protocol should be agreed upon by all authorized participants before the trial starts.

In the protocol, instructions and definitions can usually be found under the following headings:

1. Aim of the trial
2. Treatment to be studied (with justifications, ethical considerations, and related studies)
3. Study population and requirements for admission
4. Allocation to treatment groups
5. Management of treatment
6. Monitoring of progress
7. Recording and reporting
8. Analysis of data, assessment, and interpretation of results

Aim of the trial

The problem must be clearly defined and the objective of the study stated, i.e. what is to be proved or how the study is intended to solve the problem.

> ***Example***
>
> *The problem.* Six-monthly treatment regimens are too long for many patients to complete.
>
> *The objective.* To reduce the duration of treatment to 4 months. The study is to prove (or disprove) that this is feasible and that the additional resources required are commensurate with the benefits. The study must be conducted in such a way as to show the advantages of one regimen over the other in clinical, epidemiological, and economic terms.

Although it is theoretically possible to investigate many problems in a single trial, it is wise to address only a few.

Most controlled trials in the field of tuberculosis are designed to explore clinical aspects of treatment, such as duration, efficacy, or the toxicity of various dosages of drugs, or the efficacy, adverse effects, and relapse rate of various drug combinations (see "What is intermittent treatment and what is the scientific basis for intermittency?", page 130). Present knowledge of the treatment of tuberculosis is based almost entirely on controlled trials. Not only is the controlled trial a device for measuring the effects of drugs, but it has also been successfully employed to establish the value of certain policies for treatment and general management of tuberculosis patients. The best-known example is the classic Madras study (*5*) comparing home and sanatorium

treatment (see "What were the main findings of the Madras study comparing home and sanatorium treatment?", page 173).

Thus, controlled trials have a wide spectrum of objectives.

Treatments to be studied

The drugs, dosages, and method of administration used in the trial should be described precisely, so that the treatment can be replicated elsewhere and the results verified. Both the protocol and the report should therefore make clear: the compound that is to be used (e.g. streptomycin = streptomycin 1 g/0.75 g sulfate base powder, diluted with sterile distilled water); the form of preparation (e.g. powder, granules, tablets, enteric-coated granules); the exact quantity per dose; and details of administration (e.g. single dose or divided doses, time of the day, dosage intervals, before or after food, directly observed or not). The control regimen, whether it is a standard regimen or not, must be similarly well described. No doubt or ambiguity should be left on any important point, since that might lead to confusion and potentially harmful errors.

The significance of the research, previous studies, and ethical considerations should be analysed and discussed.

Study population

The criteria for admission to a trial should be laid down clearly and should define not only the types of patients eligible, but also those to be excluded.

> ***Example***
>
> *Eligible for admission:* patients of both sexes, 15 years of age and above, living within 5 km of the treatment centre, with sputum positive for tubercle bacilli by microscopy and culture, and with organisms susceptible to isoniazid and rifampicin.
>
> *Not eligible*: patients who have been treated for tuberculosis before, weigh less than 40 kg, have diabetes or jaundice, are pregnant, or are migrants likely to move out of the area within the next 2 years.

It is useful, for the purpose of assessment, to keep the characteristics (age, sex, severity of disease, etc.) of patients in the various treatment groups as uniform as possible.

The number of patients to be admitted to the trial, based on calculations of required sample size, is an important question. It will depend largely on the nature and objective of the trial, the number of treatment groups, the estimated magnitude of expected differences in results, and the precision required for valid comparison of the results. A competent statistician should be consulted.

A controlled trial does not necessarily require vast numbers of patients. In fact, if strictly comparable groups can be constructed, the statistician may find that groups of 100 or fewer patients are adequate. Large numbers in themselves are often worse than useless if the groups are not comparable – and may create false confidence in potentially invalid results.

However, if large numbers of patients are required, so that the period of intake to the trial would be very long, or if the numbers are larger than one treatment centre can cope with, the trial should be decentralized. It is one of the advantages of a controlled trial that it can be conducted simultaneously in a series of centres in one or more countries or even continents. In this way, the intake period can be substantially shortened and all patients, though treated in different places, can be handled uniformly according to the protocol.

Allocation to treatment groups

The allocation of patients to the various treatment groups is critical for the correct conduct of a controlled trial, the aim being to ensure statistical comparability of the groups. Groups must therefore be similar in every respect except treatment: only then can the differences between results be measured and effects attributable to the various treatments identified.

Allocation must be strictly randomized. Proper randomization procedures – designed by competent statisticians, laid down in the protocol, and rigidly followed – will ensure that group differences in the results obtained will be due only, or probably, to differences in the regimens studied and not to differences (variations) in the groups of patients. If the randomization is deficient, the whole trial may be null and void.

Some randomization procedures still in use leave much to be desired. For instance, randomization by alternation – allocation of every second or third eligible patient to a particular regimen, or allocation according to the year of birth (odd or even number) – is unsatisfactory. The allocated treatment can be easily identified and the investigator or assessor will be biased, consciously or unconsciously. Moreover, allocation by alternation invites manipulation. For instance, if several patients happen to be admitted to the trial at one time, the order of admission can be arranged so that certain of them are allocated to the treatment that is thought preferable by the person in charge.

In many trials the so-called envelope system is used: the investigator is given a number of serially numbered sealed envelopes, each containing an indication of the treatment to be given to a patient admitted to the trial. At admission, a serial number must be assigned to each patient *before* the corresponding envelope is opened; otherwise, if several patients are to be allocated at the same time, the envelopes may be opened first, and treatments could then be allocated according to the investigator's prejudice. Correctly implemented, the envelope system works satisfactorily. The code remains confidential, and can be broken only in case of emergency or for assessment purposes.

A satisfactory randomization method that is frequently used involves a secret list of serial numbers accessible only to a neutral party (usually a statistician) or person with no vested interests in the trial. Each serial number in the list corresponds to a certain treatment, the sequential order of the treatments being arranged according to a table of random sampling numbers. When investigators admit a patient to the trial, they communicate the patient's particulars to the neutral party, and are then informed of the treatment (or coded treatment in double-blinded trials) to be given. Such an arrangement avoids almost all prejudice.

In summary, randomization is essential to avoid biased selection and to obtain equivalent groups in terms of smear positivity, extent of disease, age, sex, etc. Correct random allocation ensures that each person admitted to a study has an equal chance of being allocated to any of the trial groups. Thus, like can be compared with like.

Ideally, trials are double-blinded, meaning that neither the patient nor the investigator knows which treatment the patient is receiving. This is impractical, for example, with trials of daily versus intermittent treatment. However, it could be used in a trial of a vitamin (e.g. pyridoxine) supplement to be given in addition to standard treatment. In this case, a placebo that is physically indistinguishable from the drug to be prescribed would be given; neither the patients nor the investigators know who is receiving the drug and who is receiving the placebo.

Management of treatment

After the requested pretreatment examinations have been carried out as prescribed by the protocol and the necessary forms have been completed, treatment is started and administered precisely as laid down in the protocol. If a patient has to change, interrupt, or stop treatment, this should be done, whenever possible, with the consent of the coordinating centre. Complete protocols will include criteria and procedures for handling most such situations. The centre also decides whether such patients should be excluded from or kept in the trial for follow-up and assessment. Every exclusion for any reason – including "lost sight of the patient" and the refusal of treatment or of important examinations – should be considered carefully, since the results of the trial may be substantially biased through exclusions from assessment.

Monitoring of progress

A special section of the protocol should be devoted to the various monitoring measures and their timing. All routine examinations, as well as special examinations requested only on certain occasions (e.g. in the case of adverse effects), should be described in detail. The uniformity of all monitoring procedures should be ensured. It may be useful for examinations requiring specialist skills and accuracy to be performed in a central (reference) laboratory.

Recording and reporting

The importance of the design of recording forms and of an efficient system for the routing of information is too often underrated. A form (record or report) should be as self-explanatory as possible; its use should not require lengthy instructions. Only questions demanding clear-cut answers, preferably "Yes/No", should be posed.

Before the design of a form is finalized, it may be necessary to test whether the staff concerned find it easy to understand and complete. Sometimes it is advisable to include "trick" questions for cross-checking the correctness of certain recorded data. However, a record should be used only for the collection of information relevant to the operation and assessment of the trial.

Clearly, tuberculosis trials involving long periods of observation require the collection and processing of a huge amount of data, which calls for well organized administrative and clerical procedures.

A continuous check must be kept on the completeness and accuracy of data and reports, and reminders should be sent out promptly to the reporting centres, if necessary. Large-scale multi-centre trials will require computerized data management; all data should be entered in duplicate by two different individuals, the two data sets automatically compared, and all discrepancies investigated and corrected.

Analysis of data and assessment

Before each analysis, whether interim or final, the data should be rechecked for completeness and correctness. An important interim analysis may include, for example, periodic tabulation of bacteriological results and adverse effects according to regimen, duration of treatment, and regularity of drug intake. This provides up-to-date information on the merits of experimental regimens and, occasionally, early warning of the risks involved. If interim analyses are repeated periodically, the final analysis can usually be produced soon after the final data have been entered, thus speeding up completion of the final report.

Analysis, tabulation, and interpretation of results should always be done in close collaboration with the statistician(s). There is generally no disagreement on the factors to be analysed to establish the efficacy of drugs or regimens. However, the classification, and thus the assessment, of response to treatment in bacteriological, radiographic, or clinical terms may easily vary from one centre to another unless clear-cut criteria have been established in the protocol and applied rigidly. Definitions of terms such as "quiescence", "favourable response", "cavity closure", "improvement", "failure", "doubtful", "default", and "relapse" should therefore be foolproof.

If radiographic assessment is required (though this is of minor importance) and the extent of lung involvement (size and number of cavities) at various times has to be compared, the reader(s) should use a uniform nomenclature. Because the interpretation of radiographic findings is unavoidably influenced by individual reading error, the assessment of chest radiographs should be undertaken by a panel of inde-

pendent readers, if possible. However, it is difficult to organize multiple readings in large-scale trials. Therefore, all films are generally read by a single reader who is not otherwise involved in the trial. Such a solution is usually satisfactory since the principal aim is to compare the initial and subsequent radiographic status. In any case, radiographic assessment must be undertaken without knowledge of the patients' particulars or of the treatment that patients have received. Whenever possible, bacteriological and other findings should also be assessed blindly.

The analysis of failures, relapses, and deaths occurring during the entire observation period is just as important as the study of efficacy and success. In addition, all patients whose treatment has been changed because of adverse effects, or who have had major interruptions – even if these seem to have been entirely unrelated to the treatment – should be studied in detail, irrespective of the outcome. Premature cessation of treatment or self-discharge because of drug toxicity may be a shortcoming of the therapy. Often a relatively high frequency of "drop-outs" or irregularity in taking a particular regimen may indicate an acceptability problem that requires special investigation.

Presentation of the report on the trial

In reporting the results of a trial, it is important to provide an overview of the plan and conduct of the study. The report should therefore contain the essentials of the protocol, particularly the criteria for admission, regimens studied, method of randomization, management of patients, and methods of assessing response to treatment. The total number of patients admitted to the study and allocated to the various treatment groups and reasons for exclusion from the main analysis must be specified. All measures taken to eliminate bias should be described so that the reader can judge the validity of the individual decisions.

To show the comparability of the various treatment groups, the report should include tabulated data on the initial status (such as age, sex, weight, bacteriological status, drug susceptibility, radiographic extent of the disease, and cavities) of the patients allotted to the various treatments.

In the evaluation of treatment results, due consideration should be given to the analysis of variables other than the treatment that might have influenced the response or the relapse rate. The authors should give good reasons for ascribing certain effects to the regimens applied and others merely to chance variation.

The report should be presented in such a way that readers can understand what was done and how, and thereby assess the merits of the trial. Readers should be able to draw their own conclusions based on scientifically established facts and findings. That is why the results of well-conducted controlled trials are so convincing and why they are so often readily and widely accepted.

Conclusions

The controlled trial method has not met with universal approval. It is often argued that it is invalid to generalize results because the groups studied are too small, because people are not alike and individual differences may be so great that generalization becomes misleading, or because each individual's response to a drug is variable and therefore unpredictable.

It is true that age, sex, metabolism, genetic and immunological factors, living conditions, physical and mental stress, and a host of other external factors that determine the course and outcome of a disease may differ from one individual to another. On that basis, opponents of the controlled trial conclude that it does not compare like with like, and that such a comparison is invalid. However, this conclusion disregards the very principles of the method.

From biostatistics it is well known (*6*) that variability is an essential characteristic of living matter and, as such, is natural or normal. However, this variability is within a certain range that can be defined by statistical techniques. For instance, when a series of observations is made on a certain variable in a randomized group (sample), it may be found that the values obtained are grouped with increasing frequency around a certain value. The characteristics of this distribution may be expressed in measurable terms, enabling comparisons to be made between one series of observations and another. The information thus obtained is fully valid for the samples studied. In controlled trials, the results obtained are group results, i.e. results valid for the group as a whole. It is impossible to predict precisely from those results how a particular individual will respond to a treatment previously tested in a certain group, but the response of a group similar to the trial group can be stated with reasonable certainty. Only the controlled trial method can neutralize the effects of individual differences between human beings in their illnesses and responses to treatment. Thus, these differences do not invalidate the method but justify it.

On the other hand, it is known that judgements based on personal impressions may often be deceptive. Clinical experience based on personal impressions can undoubtedly be valuable, but an assessment – of a therapeutic regimen, say – based merely on intuitive impressions cannot be accepted without reservation or scepticism.

Many physicians are guided in their daily work by previous clinical impressions of their own or by school doctrines founded on the impressions of others. Such doctrines, particularly when they are perpetuated in textbooks and repeatedly quoted by reputed teachers, can easily become fixed formulas in the minds of some people – just as if they were proven facts. Traditional ways of learning and teaching have meant that authoritarian judgements and statements have come to be respected and adopted without criticism. Graduates or postgraduates frequently accept them without ascertaining whether they have been subjected to scientific test.

The treatment of the sick must be based on the best scientific knowledge available. The past five decades have shown clearly that the controlled trial is by far the quickest way of obtaining conclusive and reliable information on the efficacy and risks of

a new treatment. The dramatic progress made in the treatment of tuberculosis has been due largely to the fact that the regimens currently in use have first been tested by means of controlled clinical trials. These trials have laid the foundation for the standardization, and hence the worldwide application, of tuberculosis treatment.

References

1. Amberson JB et al. A clinical trial of sanocrysin in pulmonary tuberculosis. *American Review of Tuberculosis*, 1931, 24:401–435.
2. Martini P, Resendahl A. Bilanz der Goldtherapie bei der Lungentuberculose; Sanocrysin. *Zeitschrift für Tuberkulose*, 1940, 84:330–340.
3. Pinner M, ed. *Pulmonary tuberculosis in the adult. Its fundamental aspects*. Springfield, IL, Thomas, 1945.
4. Fox W. The scope of the controlled clinical trial, illustrated by studies of pulmonary tuberculosis. *Bulletin of the World Health Organization*, 1971, 45:559–572.
5. A concurrent comparison of home and sanatorium treatment of pulmonary tuberculosis in South India. *Bulletin of the World Health Organization*, 1959, 21:51–144.
6. Hill AB. *Principles of medical statistics*, 8th ed. London, The Lancet Ltd, 1967:12.

68. What is molecular epidemiology and what is its role in tuberculosis control?

K. DeReimer[1] *& P.M. Small*[2]

What is molecular epidemiology?

Molecular epidemiology combines laboratory-based molecular methods for identifying individual strains of bacteria with conventional epidemiological field methods to investigate the determinants and distribution of disease (*1*). DNA fingerprinting of *Mycobacterium tuberculosis*, using techniques such as restriction fragment-length polymorphism (RFLP) analysis, allows investigators to determine the genetic relatedness of clinical isolates. Patients infected with identical strains may have been infected from each other or from a common source. In the context of epidemiological data it is possible to provide evidence for transmission between persons with active tuberculosis.

There are limitations to this technology. It is still not possible to track transmission between persons when a culture of *M. tuberculosis* is not available from each individual. DNA fingerprinting analysis requires a high degree of sustained quality control, consistency, and proficiency in laboratory techniques. More importantly, the hypotheses to be tested, the study design best suited to test the hypotheses, and the sampling schemes need to be clearly stated and correctly implemented. For example, only limited information is gained from DNA fingerprinting analysis of a case series of specimens if complementary epidemiological information is not available.

What is the role of molecular epidemiology in tuberculosis control?

Molecular epidemiological techniques were first used in outbreak investigations of tuberculosis to confirm suspected epidemiological links and to demonstrate the effectiveness of control measures. In an outbreak investigation of tuberculosis in a facility for persons infected with HIV, DNA fingerprinting analysis of the strains from different patients supplemented information from patient interviews and an outbreak curve to unambiguously identify the source case and the chain of transmission. More

[1] Fellow, Division of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford, CA, USA.
[2] Associate Professor, Division of Infectious Diseases and Geographic Medicine, Stanford University Medical Center, Stanford, CA, USA.

importantly, molecular analysis supported recommendations for, and allowed objective monitoring of, the impact of specific, targeted public health interventions such as screening and early detection of cases, their isolation from other susceptible contacts, and the use of preventive treatment of infected contacts. Continued surveillance in the facility, after the initial outbreak was identified and control measures were implemented, demonstrated that the chain of transmission had been interrupted (*2*).

Tuberculosis outbreak investigations in recent years have used DNA fingerprinting techniques to demonstrate new sites and routes of tuberculosis transmission. Molecular epidemiological techniques have demonstrated significant tuberculosis transmission in settings such as commercial bars (*3*), clandestine bars (*4*), crack houses (*5*), prisons (*6–9*), and shelters and other sites used by the urban homeless (*10*, *11*). DNA fingerprinting can also quickly exclude the possibility of an outbreak, thereby avoiding expensive, time-consuming epidemiological investigations and inappropriate interventions. The importance of treating every infectious case of tuberculosis, even "difficult", non-adherent patients, and of implementing rapid, efficient contact-tracing practices was illustrated by mini-epidemics and incident cases linked to index cases detected many years earlier (*12*). These techniques have also been used to demonstrate tuberculosis transmission in health care settings, such as transmission between patients, transmission from patient to health care provider, and transmission from health care providers to patients (*13*, *14*). Tuberculosis transmission by inadequately sterilized equipment, such as bronchoscopes, has also been documented (*15*, *16*). The value of this information is that it points to specific public health and institutional interventions that can be implemented to reduce or stop tuberculosis transmission. Effective interventions can reduce the rates of both transmission and incidence.

Population-based molecular epidemiological studies are difficult, labour-intensive, and expensive. Nevertheless, they provide otherwise unavailable insight and add new knowledge of the dynamics of tuberculosis transmission in a community. For example, a 7-year population-based study of tuberculosis in San Francisco, USA, showed that a decline in tuberculosis transmission rates was partially attributable to specific public health interventions that reduced transmission as demonstrated by a reduced rate of clustering, or shared strains, among the USA-born population (*17*). Although foreign-born cases account for more than 65% of the reported tuberculosis cases in San Francisco, this study demonstrates that there is limited transmission from foreign-born to USA-born persons, and that most of the transmission in the city is among USA-born persons with risk factors such as HIV infection, substance use, and homelessness (*18*). A 5-year, population-based, molecular epidemiological study in southern Mexico showed that incidence rates, degree of recent transmission as measured by clustering, and initial drug resistance levels declined in a high-prevalence area as DOTS was implemented (unpublished observations, García-García M, Instituto Nacional de Salud Pública, Mexico).

Molecular epidemiological techniques can be very useful to illustrate laboratory cross-contamination (*19*), which may account for 1–4% of positive cultures even in otherwise well-performing laboratories. In addition, these techniques have revealed exogenous reinfection (*20*, *21*), and simultaneous infection with more than one strain of *M. tuberculosis* (*22*), phenomena that were thought to occur but were proved only when DNA fingerprint analysis of isolates of *M. tuberculosis* became available. At present, several research sites are trying to determine the amount and role of reinfection in countries with a high prevalence of tuberculosis. The potential impact of public health interventions will be defined by the proportion of tuberculosis that arises from recent infection and reinfection; this can be established by molecular epidemiology.

Molecular epidemiological techniques have also demonstrated that transmission by sputum smear-negative pulmonary tuberculosis cases does occur and can account for as much as one-fifth of the ongoing transmission in a low-prevalence community (*23*). Combined with conventional techniques, such as tuberculin skin testing, molecular epidemiology has pointed to super-infectious and pathogenic strains of tuberculosis (*24*).

How will molecular epidemiology be used in the future?

It is likely that molecular genotyping techniques, such as RFLP analysis, will continue to be used for investigating laboratory cross-contamination and suspected point-source outbreaks, and to differentiate relapse from exogenous reinfection (*25*). However, if preliminary molecular epidemiological analysis confirms that there are strain-specific differences in tuberculosis, it is possible that these differences can be exploited to improve tuberculosis prevention and control efforts, and the role of molecular epidemiology in tuberculosis control may be greatly expanded. For example, molecular epidemiological techniques may be used to identify strain-specific differences in the degree of infectivity and pathogenicity of *M. tuberculosis*. Comparative genomic analysis of *M. tuberculosis* may identify the genetic determinants of bacterial virulence, aerosolization, infectivity, pathogenicity, drug resistance, and other steps in the pathogenesis of tuberculosis. Molecular epidemiology and functional genomics may contribute to established approaches for new diagnostic techniques, drugs, and – eventually – a vaccine.

References

1. Thompson RCA, ed. *Molecular epidemiology of infectious diseases*. New York, Oxford University Press, 2000.
2. Daley CL et al. An outbreak of tuberculosis with accelerated progression among persons infected with the human immunodeficiency virus. An analysis using restriction-fragment-length polymorphisms. *New England Journal of Medicine*, 1992, 326:231–235.
3. Kline SE, Hedemark LL, Davies SF. Outbreak of tuberculosis among regular patrons of a neighborhood bar. *New England Journal of Medicine*, 1995, 333:222–227.

4. García-García M et al. The role of core groups in transmitting *Mycobacterium tuberculosis* in a high prevalence community in Southern Mexico. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:12–17.
5. Leonhardt KK et al. A cluster of tuberculosis among crack house contacts in San Mateo County, California. *American Journal of Public Health*, 1994, 84:1834–1836.
6. March F et al. Predictors of tuberculosis transmission in prisons: an analysis using conventional and molecular methods. *AIDS*, 2000, 14:525–535.
7. Chaves F et al. A longitudinal study of transmission of tuberculosis in a large prison population. *American Journal of Respiratory and Critical Care Medicine*, 1997, 155:719–725.
8. Ferreira MM et al. Tuberculosis and HIV infection among female inmates in Sao Paulo, Brazil: a prospective cohort study. *Journal of Acquired Immune Deficiency Syndrome and Human Retrovirology*, 1996, 13:177–183.
9. Valway SE et al. Outbreak of multi-drug-resistant tuberculosis in a New York State prison, 1991. *American Journal of Epidemiology*, 1994, 140:113–122.
10. Barnes PF et al. Transmission of tuberculosis among the urban homeless. *Journal of the American Medical Association*, 1996, 275:305–307.
11. Gutierrez MC et al. Molecular fingerprinting of *Mycobacterium tuberculosis* and risk factors for tuberculosis transmission in Paris, France, and surrounding area. *Journal of Clinical Microbiology*, 1998, 36:486–492.
12. Chin DP et al. Spread of *Mycobacterium tuberculosis* in a community implementing recommended elements of tuberculosis control. *Journal of the American Medical Association*, 2000, 283:2968–2974.
13. Frieden TR et al. A multi-institutional outbreak of highly drug-resistant tuberculosis: epidemiology and clinical outcomes. *Journal of the American Medical Association*, 1996, 276:1229–1235.
14. Ikeda RN et al. Nosocomial tuberculosis: an outbreak of a strain resistant to seven drugs. *Infection Control and Hospital Epidemiology*, 1995, 16:152–159.
15. Michele TM et al. Transmission of *Mycobacterium tuberculosis* by a fiber optic bronchoscope. Identification by DNA fingerprinting. *Journal of the American Medical Association*, 1997, 278:1093–1095.
16. Agerton T et al. Transmission of a highly drug-resistant strain (strain W1) of *Mycobacterium tuberculosis*. Community outbreak and nosocomial transmission via a contaminated bronchoscope. *Journal of the American Medical Association*, 1997, 278:1073–1077.
17. Jasmer RM et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991–1997. *Annals of Internal Medicine*, 1999, 130:971–978.
18. Chin DP et al. Differences in contributing factors to tuberculosis incidence in U.S.-born and foreign-born persons. *American Journal of Respiratory and Critical Care Medicine*, 1998, 158:1797–1803.
19. Burman WJ et al. The incidence of false-positive cultures for *Mycobacterium tuberculosis*. *American Journal of Respiratory and Critical Care Medicine*, 1997, 155:321–326.
20. van Rie A et al. Exogenous reinfection as a cause of recurrent tuberculosis after curative treatment. *New England Journal of Medicine*, 1999, 341:1174–1179.
21. Small PM et al. Exogenous reinfection with multidrug-resistant *Mycobacterium tuberculosis* in patients with advanced HIV infection. *New England Journal of Medicine*, 1993, 328:1137–1144.

22. Yeh RW, Hopewell PC, Daley CL. Simultaneous infection with two strains of *Mycobacterium tuberculosis* identified by restriction fragment length polymorphism analysis. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:537–539.
23. Behr MA et al. Transmission of *Mycobacterium tuberculosis* from patients smear-negative for acid-fast bacilli. *Lancet*, 1999, 353:444–449.
24. Valway SE et al. An outbreak involving extensive transmission of a virulent strain of *Mycobacterium tuberculosis*. *New England Journal of Medicine*, 1998, 338:633–639.
25. Behr MA, Small PM. Molecular fingerprinting of *Mycobacterium tuberculosis*: how can it help the clinician? *Clinical Infectious Diseases*, 1997, 25:806–810.

69. Can tuberculosis be controlled?[1]

T. Frieden[2]

In some quarters there is a firm belief that tuberculosis, like the weather, can be described but not controlled. Tuberculosis declines if socioeconomic conditions improve (*1*, *2*). This fact has led some observers to conclude mistakenly that tuberculosis can be controlled *only* if living conditions improve. However, it was predicted on theoretical grounds (*3*), and has now been convincingly demonstrated in practice, that tuberculosis can be controlled in almost any socioeconomic circumstances (*4*–*6*).

Five aspects of disease control–disease burden, mortality, prevalence of disease, rate of infection, and incidence of disease – are considered below, in declining order of amenability to control.

Disease burden

The burden of tuberculosis disease – including illness, disability, and direct and indirect costs of the illness – can be reduced rapidly through prompt diagnosis and effective treatment. In addition to the rapid decline in mortality considered below, duration of disease is drastically reduced by effective treatment. Untreated, patients remain ill with tuberculosis for an average of at least 2 years. An effective programme detects most patients within a month of the onset of significant symptoms, and the application of directly observed short-course treatment generally restores complete function within 1 or 2 months. The duration of illness can therefore be reduced from an average of 24 months or more to about 2.5 months – a 90% reduction. If the global target for case detection is met (see "What are the global targets for tuberculosis control and what is the basis of these targets?", page 238), this would result in an overall reduction in tuberculosis morbidity in the community of about two-thirds, even without taking into account the decline in incidence considered below.

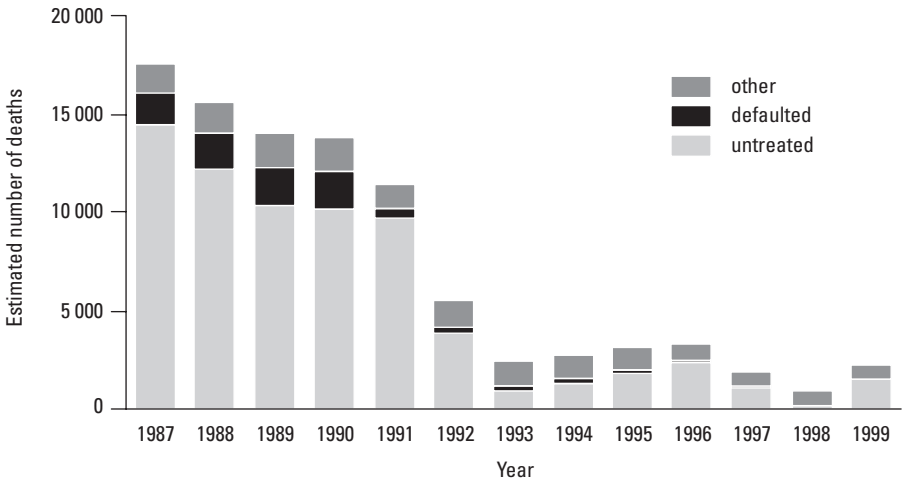
Mortality

Directly observed treatment of tuberculosis rapidly reduces mortality. This was seen even in the first days of tuberculosis treatment: treatment with a single drug resulted

[1] Adapted and reprinted with permission from *International Journal of Epidemiology*, 2002, 31:894–899.

[2] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

Figure 22
Reduction in deaths from tuberculosis Peru, 1990–1999[a]



[a] Source: reference *5*.

in dramatic, albeit fleeting, reductions in mortality. Current regimens, given under appropriate management conditions, are nearly 100% curative for patients with drug-susceptible organisms; the reduction in mortality is dramatic and sustained. Untreated, 50–80% of patients with smear-positive tuberculosis will die of their disease (*7*). In a poorly implemented tuberculosis programme, as many as 30% of patients with smear-positive tuberculosis die (*8*). In contrast, death rates in DOTS programmes throughout the world are generally less than 5%: of 725 275 new smear-positive patients treated in DOTS programmes in 1998, only 3.8% were reported to have died (*9*).

In countries where baseline data exist, it is possible to make a reasonable estimate of the reduction in mortality achieved through DOTS implementation. Peru has been able to implement a highly effective DOTS programme (*5*), with a striking 80% reduction in mortality within just 3 years (Figure 22). This has been achieved by reducing the case-fatality rate among treated patients by prompt diagnosis and effective and directly observed treatment, and because a greater proportion of patients are treated. In India, mortality among smear-positive patients in the previous programme was 20–30%, compared with 4% in the DOTS programme – an approximately sevenfold reduction (*8*). Considering both smear-positive and smear-negative cases, DOTS reduces the case-fatality rate by about 18%, even if neither the increased detection rate nor secondary cases and their mortality are taken into account. By early 2002, the Indian DOTS programme had treated more than 2 million patients, thereby saving more than 350 000 lives. In China, national coverage with DOTS would prevent more than 50 000 deaths per year (*10*).

Prevalence of disease

Prevalence of tuberculosis can also be reduced rapidly. In a poorly functioning tuberculosis control programme, the ratio of incidence to prevalence may be as high as 1 : 3.5 (*11*). Achievement of the global targets for tuberculosis control, even if only a small proportion of prevalent cases are treated each year, will result in a rapid reduction in prevalence. This point is illustrated in a simple model (Figure 23). In this model, there are 100 new smear-positive cases per 100 000 population at the outset and the ratio of incidence to prevalence is 1 : 3.5. The model assumes that targets for case detection (70% of new smear-positive cases) and treatment success (85%) are met, that about half as many prevalent smear-positive cases as incident smear-positive cases are treated each year (*12*), that 85% treatment success is achieved, that the proportion of patients who fail treatment is as per the global averages in DOTS programmes (*9*), and that there is a 5% decrease in incidence per year (see below). As can be seen, prevalence declines very rapidly, being reduced to less than half of its previous level within 3 years.

The validity of this theoretical model has been confirmed under programme conditions in both developed and developing countries. In Kolín, in the former Czechoslovakia, an intensive surveillance and control programme in a population of 100 000 reduced the prevalence of chronic tuberculosis by more than 33% per year – to less than one-fourth of its earlier rate in 3 years (*13*). In New York City, the number of patients with persistently positive cultures fell by two-thirds in 3 years – more than 30% annually (*14*, *15*). This could be documented because the monitoring system identifies almost every patient with bacteriologically proven tuberculosis (*4*). In Beijing, as documented by community surveys, the prevalence of smear-positive cases declined by 87% between 1979 and 1990, from 127/100 000 to 16/100 000 – a 17% annual decrease sustained over 11 years (*16*).

Rate of infection

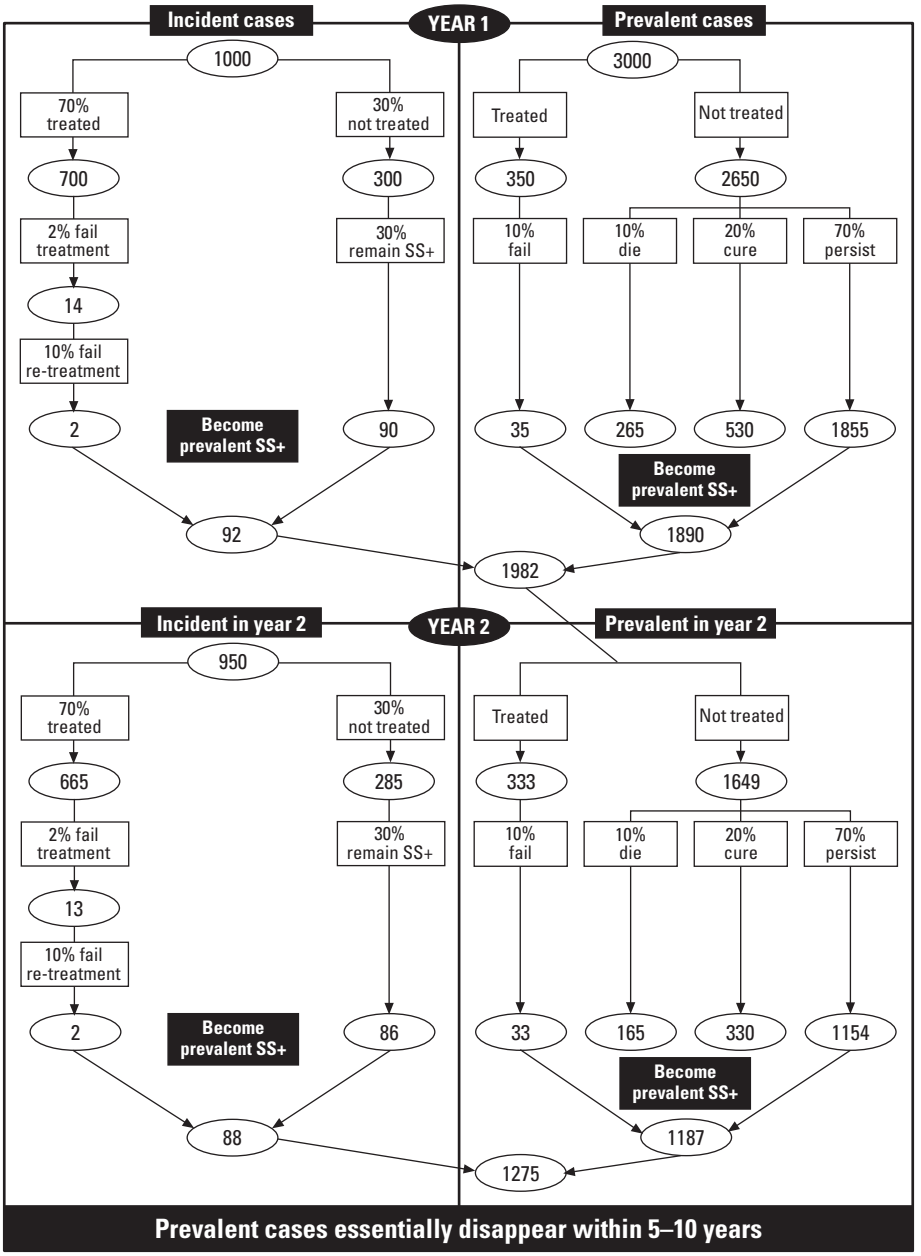
The rate at which individuals become infected with *Mycobacterium tuberculosis* determines the course of the epidemic in a community. For the long-term control of tuberculosis, it is therefore essential that infection rates decline. In industrialized countries, the risk of infection with tuberculosis bacteria declined by approximately 5% or more per year, even before the introduction of chemotherapy. With the introduction of effective treatment, the rate of infection declined by 15% or more per year (*17*). In developing countries, in contrast, there is little or no decline in the annual risk of tuberculosis infection unless effective tuberculosis treatment services are in place.

Effective diagnosis and treatment of tuberculosis can rapidly reduce the risk of infection. On theoretical grounds, it should be possible to reduce the risk of infection even in developing countries by 10% or more per year (*3*). However, few studies have attempted to document this in developing countries. Such studies are logistically

Figure 23
Dynamics of smear-positive tuberculosis if global targets are met

SS+ = sputum-smear positive

(1 million population; incidence of smear-positive tuberculosis = 100/100 000)



difficult and are further complicated by difficulties in the interpretation of tuberculin tests in the same population over time. One such survey in the Republic of Korea found an annual reduction in the risk of tuberculosis infection of 8–14%, even though treatment success did not quite reach 85% (*18*). At a constant rate of BCG vaccination, the incidence of tuberculous meningitis in infants is a reflection of the annual risk of infection. In Beijing, tuberculous meningitis fell from 2.1 to 0.1 per 100 000 between 1986 and 1996, a reduction of 26% per year (*16*). However, some of this reduction may have been the result of improved vaccination practices.

Incidence of disease

The incidence of tuberculosis is the combination of:

- recurrent tuberculosis in patients who have had previous episodes of disease;
- rapid progression to tuberculosis disease among individuals infected or reinfected within a relatively short period (e.g. 2 years) of infection; and
- reactivation of tuberculosis infection contracted many years previously.

Recent developments in molecular epidemiology, along with conventional epidemiological investigations, have helped to determine the relative proportion of cases arising from each of these groups – which will vary from population to population, and, within one population, over time. For example, in a comprehensive study of tuberculosis epidemiology in southern India in 1972, only 37% of all smear-positive cases of tuberculosis arose from individuals who had a normal X-ray at the outset of the survey. Within 12 years, this fraction had increased to two-thirds, and the proportion of cases arising from individuals who, at survey outset, had X-rays consistent with tuberculosis with negative cultures decreased from 33% to 8%. This corresponded with a reduction in the annual risk of development of tuberculosis among persons with highly abnormal X-rays from 7.0% per year to 3.2% per year, presumably reflecting the greater likelihood that such patients had received at least some, although partial, tuberculosis treatment (*11*). A recent survey in Norway has shown that fewer than one in five patients developed tuberculosis as the result of recent infection; the overwhelming majority of cases arose from remote infection or recurrent tuberculosis (*19*).

The amenability to control of tuberculosis incidence – with or without HIV infection – depends to a great extent on local epidemiology. At one extreme are situations in which the vast majority of tuberculosis cases arise from remote infection. Most such cases will not be prevented with current technologies. Many individuals with remotely acquired infections will not be candidates for preventive treatment, and, even if preventive treatment is attempted, its success is far from assured (see "What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?", page 220). At the other extreme are populations in which as many as half of all tuberculosis cases arise from infection or reinfection within the preceding 2 years. In such a context, the application of effective tuberculosis control measures can result in a

very rapid decline in tuberculosis cases. In New York City, for example, the incidence of tuberculosis among persons born in the USA declined by 25% annually over the 5-year period 1992–1996; incident cases of multidrug-resistant tuberculosis, which were mostly linked to ongoing transmission in health facilities, declined by 34% annually in the same time period (*20*). Similarly, an elegant study in San Francisco documented that more than one-third of cases resulted from recent transmission. With improved control measures, the overall case rate declined by 7% per year; the rate of clustered cases declined by 15% per year, while non-clustered cases declined by only 5% per year (*21*). In New York City, molecular epidemiological studies similarly documented a 26% annual decline in the estimated incidence of clustered tuberculosis between 1991 and 1997 (*22*; and New York City Department of Health, unpublished data, 1997).

A limited number of representative surveys in developing countries suggest that the proportion of new cases caused by recent infection may range from 29% to 48% (*23–26*). Such cases can be rapidly reduced by effective treatment. In addition, the proportion of cases arising from reactivation of tuberculosis may decline steadily over a longer period of time. Thus, on theoretical grounds, it should be possible to control incidence even in developing countries. This prediction has been borne out by experience.

In developing countries where effective treatment practices have not been implemented, the incidence of tuberculosis remains essentially static (*11*). In contrast, rapid declines in tuberculosis incidence have been documented in the developing world when effective tuberculosis control measures are applied. In Beijing, during a period when the notification rate was believed to be high and constant, a 9% annual decrease in new smear-positive cases was documented between 1986 and 1996 (*16*). In Cuba, with directly observed treatment and efficient treatment organization achieving high rates of treatment success, the rate of new smear-positive cases decreased by 10% annually over a 26-year period (*6*). In Peru, cases of tuberculosis declined by approximately 8% per year (*5*). An 8–10% annual reduction will cut the number of cases by half in 7 years. Thus, in the absence of an HIV epidemic, the incidence of tuberculosis can be significantly reduced even in developing countries.

Tuberculosis control in the context of HIV

The HIV epidemic undermines tuberculosis control. In the context of HIV, the tuberculosis burden of disease, mortality, prevalence, and, possibly, rate of infection can still be controlled by an effective tuberculosis control programme. However, this can be done only with significantly increased effort and with a very low margin for error.

Because of the increased risk of reactivation in patients who are already infected with the tuberculosis bacteria, as well as the risk of rapid and widespread dissemination of tuberculosis in HIV-infected populations, the incidence of tuberculosis will inevitably increase in most areas of the world if the rate of HIV infection in the adult population is 5% or more. However, an effective tuberculosis control programme can

blunt the impact of this increase, and can also prevent the related emergence of multidrug-resistant tuberculosis. Not only is there an increased incidence because of cases arising from infection acquired many years previously, but each individual tuberculosis patient is likely to give rise to an increased number of secondary cases because of immunosuppression in close contacts. Tuberculosis has increased explosively in areas of the world where HIV is endemic; these increases have been significantly less in areas with effective tuberculosis control services (*27*).

Experience in the United Republic of Tanzania is somewhat encouraging in this regard. Although the country is in the midst of a substantial epidemic of HIV, systematic surveys for annual risk of infection over the past 15 years have documented continued stable or even slightly declining (by 2% annually) rates of tuberculosis infection (*28*). This suggests that an effective tuberculosis control programme can, by means of prompt diagnosis and effective treatment, limit the number of secondary infections and cases.

Theoretically, preventive treatment for HIV-infected patients who also have tuberculosis infection could dramatically reduce the impact of HIV on tuberculosis epidemiology. However, since most individuals with HIV infection in developing countries do not know their infection status, and because of the logistic difficulties of giving treatment to a large number of patients who have no clinical symptoms (see "What is the role of treatment of latent tuberculosis infection in a tuberculosis control programme?", page 220), the practical applicability of treatment of latent tuberculosis infection may be limited to individual rather than public health interventions.

New York City demonstrated that it is possible to control an outbreak of tuberculosis even in the context of HIV, and even in an area where multidrug resistance had become common (*4*). This was achieved by ensuring prompt diagnosis, high-quality laboratory work, standardized treatment regimens, direct observation as the standard of care, and rigorous cohort reporting with accountability for every case diagnosed. In addition, the spread of tuberculosis in hospitals was curtailed (see "What is nosocomial transmission of tuberculosis and how can it be prevented?", page 278). However, the prevalence of HIV infection among adults in New York City probably did not exceed 3%, in contrast to the more than 30% among adults in some countries of Africa.

Conclusions

Control is a more modest goal than elimination or eradication. Elimination has been defined arbitrarily as no more than one new case per million population per year, or a prevalence of tuberculosis infection of below 1% in the general population (*29*). This may be achieved in some developed countries even without additional technological advances within the next 20–50 years. However, migration and continued high rates of tuberculosis in many countries may prevent this from occurring unless a concerted effort is made to control tuberculosis in all countries. Eradication, which is applicable to only a small number of disease entities, is defined as the

achievement of a status whereby no further cases of a disease occur anywhere and control measures are unnecessary. Tuberculosis is not currently a candidate for eradication efforts.

Thus, the answer to the question, "Can tuberculosis be controlled?" is "Yes" – if scientific principles are followed, effective clinical and public health management is ensured, and there are committed and coordinated efforts for control from within and outside of the health sector. Tuberculosis control is a winnable battle.

References

1. McKeown T. *The Role of Medicine*. Princeton, Princeton University Press, 1979.
2. Frieden TR. Tuberculosis control and social change. *American Journal of Public Health*, 1994, 84:1721–1723.
3. Styblo K, Bumgarner JR. Tuberculosis can be controlled with existing technologies: evidence. In: *Progress report 1991*. The Hague, Tuberculosis Surveillance Research Unit:60–72.
4. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.
5. Suarez P et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases*, 2001, 184:473–478.
6. Marrero A et al. Towards elimination of tuberculosis in a low-income country: the experience of Cuba, 1962–97. *Thorax*, 2000, 55:39–45.
7. Tuberculosis in a rural population in South India: a five-year epidemiological study. *Bulletin of the World Health Organization*, 1975, 50:90–106.
8. Datta M et al. Critical assessment of smear-positive pulmonary tuberculosis patients after chemotherapy under the district tuberculosis programme. *Tubercle and Lung Disease*, 1993, 74:180–186.
9. *Global tuberculosis control. WHO Report 2001*. Geneva, World Health Organization, 2001 (document WHO/CDS/TB/2001.287).
10. Dye C et al. Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China. *International Journal of Epidemiology*, 2000, 29:558–564.
11. Trends in the prevalence and incidence of tuberculosis in South India. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:142–157.
12. Khatri GR, Frieden TR. The status and prospects of tuberculosis control in India. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:193–200.
13. Styblo K et al. Epidemiological and clinical study of tuberculosis in the district of Kolín, Czechoslovakia. *Bulletin of the World Health Organization*, 1967, 37:819–874.
14. Frieden TR et al. The emergence of drug resistant tuberculosis in New York City. *New England Journal of Medicine*, 1993, 328:521–526.
15. Fujiwara PI et al. A continuing survey of drug-resistant tuberculosis, New York City, April 1994. *Archives of Internal Medicine*, 1997, 157:531–536.
16. Zhang LX, Tu DH, Enarson DA. The impact of directly-observed treatment on the epidemiology of tuberculosis in Beijing. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:904–910.
17. Styblo K. Overview and epidemiologic assessment of the current global tuberculosis situ-

ation with an emphasis on control in developing countries. *Reviews of Infectious Diseases*, 1989, 11:S339–S346.

18. Neuenschwander BE et al. Trends in the prevalence of infection with *Mycobacterium tuberculosis* in Korea from 1965 to 1995: an analysis of seven surveys by mixture models. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:719–729.
19. Heldal E et al. Pulmonary tuberculosis in Norwegian patients. The role of reactivation, reinfection and primary infection assessed by previous mass screening data and restriction fragment length polymorphism analysis. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:300–307.
20. *Tuberculosis information summary – 1999*. New York, New York City Department of Health, 2000.
21. Jasmer RM et al. A molecular epidemiologic analysis of tuberculosis trends in San Francisco, 1991–1997. *Annals of Internal Medicine*, 1999, 130:971–978.
22. Frieden TR et al. The molecular epidemiology of tuberculosis in New York City: the importance of nosocomial transmission and laboratory error. *Tubercle and Lung Disease*, 1996, 77:407–413.
23. Diaz R et al. Molecular epidemiology of tuberculosis in Cuba outside of Havana, July 1994 – June 1995: utility of spoligotyping versus IS6110 restriction fragment length polymorphism. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:743–750.
24. Yang ZH et al. DNA fingerprinting and phenotyping of *Mycobacterium tuberculosis* isolates from human immunodeficiency virus (HIV)-seropositive and HIV-seronegative patients in Tanzania. *Journal of Clinical Microbiology*, 1995, 33:1064–1069.
25. García-García M et al. The role of core groups in transmitting *Mycobacterium tuberculosis* in a high prevalence community in Southern Mexico. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:12–17.
26. Wilkinson D et al. Molecular epidemiology and transmission dynamics of *Mycobacterium tuberculosis* in rural Africa. *Tropical Medicine and International Health*, 1997, 2:747–753.
27. Cantwell MF, Binkin NJ. Tuberculosis in sub-Saharan Africa: a regional assessment of the impact of the human immunodeficiency virus and national tuberculosis control program quality. *Tubercle and Lung Disease*, 1996, 77:220–226.
28. Tuberculosis control in the era of the HIV epidemic: risk of tuberculosis infection in Tanzania, 1983–1998. *International Journal of Tuberculosis and Lung Disease*, 2001, 5:103–112.
29. Styblo K. Eradication of tuberculosis in developed countries in the HIV era. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1989, 64:58–64.

70. Can effective case detection and treatment prevent and reverse drug resistance in a community?

M. Raviglione[1]

The prevalence of multidrug-resistant tuberculosis (MDR-TB) in 35 countries was surveyed by WHO in 1994–1997. The prevalence of MDR-TB was found to be related to the quality of tuberculosis control programmes (*1*). Countries were classified as having "better" or "poorer" tuberculosis control, with better control being defined as full coverage with DOTS, or coverage of at least one-third of the national territory, or a tuberculosis notification rate below 10 per 100 000 population. Any country that had not adopted DOTS or that had a coverage of less than one-third of its territory was defined as having poorer tuberculosis control. The analysis revealed that countries with better control had a lower combined prevalence of MDR-TB than those with poorer control (1.6% vs 3.9%; $P < 0.05$). The prevalence of MDR-TB in countries with better tuberculosis control was also lower among previously treated cases (7.7% vs 17%), while the prevalence of MDR-TB among new cases was similar to that in countries with poorer control.

In a second assessment, the relationship between programme performance and prevalence of drug resistance was studied in countries with reliable data on both drug resistance and treatment outcome (*2*). The treatment success rate, as the best expression of the performance of tuberculosis control programmes, should be inversely related to the prevalence of MDR-TB. Indeed, countries achieving a high rate of treatment success had low primary MDR-TB prevalence, and the relationship was statistically significant ($r^2 = 0.5$, $P = 0.003$). In some countries where treatment success was high at the time of the survey, such as Peru and Viet Nam, MDR-TB prevalence was still moderately high (2–3%). This was probably due to the persistence, after implementation of DOTS, of MDR-TB created by previously weak programmes.

These observations suggest that proper tuberculosis control, as achieved in effective DOTS programmes, minimizes the emergence of MDR-TB where it does not yet exist. African countries such as Benin, Botswana, and Kenya, which started using rifampicin in their standardized short-course treatment regimens at the time of implementation of good tuberculosis control practices (1983, 1986, and 1993, respec-

[1] Coordinator, TB Strategy and Operations, Stop TB Department, World Health Organization, Geneva, Switzerland.

tively) and have achieved high cure rates, have been successful in minimizing the emergence and spread of MDR-TB. Similarly, some Latin American countries, such as Chile, Cuba, and Uruguay, with traditionally excellent control programmes curing most patients, today have very low levels of MDR-TB. On the other hand, countries such as Côte d'Ivoire, Dominican Republic, Estonia, Latvia, Russian Federation, and Thailand, which used rifampicin widely before strengthening their programmes, have a higher prevalence of MDR-TB. Thus, effective tuberculosis control prevents MDR-TB. The situation might be different, however, in settings where MDR-TB is already common.

It is believed by some that adoption of the standard regimens recommended by WHO and the IUATLD for countrywide use will lead to a slow decline in prevalence of MDR-TB. In fact, many patients will be cured even though they are infected with multidrug-resistant strains: some (25–30%) will undergo spontaneous cure as part of the natural history of the disease, and some will die quickly and thus stop infecting others. Available data from the USA (*3*) suggest that specialized and individualized treatment can cure a relatively high proportion of patients with primary MDR-TB, thus removing them from the infectious pool. However, the duration of infectiousness before sputum conversion or death is also high. Therefore, the assumption that a large number of MDR-TB patients are either cured or die quickly (and therefore stop spreading infection) is unwarranted. In the USA, where these assessments were made, expensive individualized regimens and surgery are more readily available than in most other countries. In developing countries using standard short-course treatment as part of DOTS, however, a much larger number of patients are affected. It appears that most cases of tuberculosis resistant to isoniazid or streptomycin alone can be cured using standard first-line regimens in programme settings. The failure rate of 6-month treatment in tuberculosis cases resistant to isoniazid has been reported as only 1%, with a relapse rate of 11% (*4*). Similarly, very low failure rates, 0–2%, were observed in clinical trials when regimens of at least 6 months were used to treat patients with strains resistant to either isoniazid or streptomycin (*5*).

Recent data reported to WHO from national control programmes, as distinct from controlled trials, show that, in patients with strains resistant to a single drug (not including rifampicin) who are treated with short-course regimens, cure rates are not significantly lower than in patients with fully susceptible strains. In Peru, 90% (1029/1145) of patients with susceptible strains and 87% (105/121) with resistance to a single drug were cured with first-line drugs ($P = 0.27$). In the Republic of Korea, the figures were 85% (1668/1968) and 80% (104/129; $p = 0.11$), respectively. These data suggest that standard short-course regimens may cure most cases with monoresistance. Inevitably, however, treatment success rates of rifampicin-resistant and MDR-TB cases are lower. In Peru and the Republic of Korea, success rates of 58% and 56% have been documented in MDR-TB cases, which are significantly lower rates in susceptible cases ($P < 0.001$ in both countries).

In a multi-centre study involving six areas (Dominican Republic, Hong Kong

Special Administrative Region of China, Italy, Peru, and Republic of Korea, and the Ivanovo Oblast in the Russian Federation) average treatment success rate was 52% among new MDR-TB cases, with an average failure rate of 21%. The death rate was generally below 10% (*6*). Thus, some response to standard first-line drugs is indeed possible, although the failure rate is very high. The question remains of whether achieving a treatment success rate of about 50% among new MDR-TB cases and a relatively low case-fatality rate, but allowing a high failure rate, is sufficient to eliminate MDR-TB.

Countrywide trends of MDR-TB prevalence in good DOTS programmes could provide a direct answer to this question. Few data are currently available from developing countries, but trend data from the Republic of Korea are illustrative (*7–9*). The estimated number of all resistant cases fell slowly from 1965 to 1980, and then more steeply from 1980–1985 onwards. The number of MDR-TB cases increased between 1975 and 1985, but was lower in 1990 and 1995. The fall in all resistant cases, and in MDR-TB cases, coincides with a rapid increase in cure rates in the Republic of Korea, especially between 1980 and 1985. This is not sufficient to prove that first-line treatment given in a good programme can reverse MDR-TB, but these data do suggest that effective treatment can influence the decline of MDR-TB by preventing the emergence of new MDR-TB cases.

Drug resistance trends have also been studied in Algeria (*10*). In the region of Algiers, from 1965 to 1990, drug resistance decreased from 15% to 5.2% among new cases and from 81.9% to 21% among re-treatment cases. This decline coincided with two important policy changes: the introduction of standard regimens in the late 1960s and of rifampicin-containing treatment in 1980. However, whether the decline would have occurred regardless of these changes is not known, as there are no data on previous trends. The trend of MDR-TB over time has been reported among cases eligible for a re-treatment regimen: there was no change in either numbers or percentages (11% and 11.5%, respectively) between the periods 1980–1985 and 1986–1990.

Taken together, the experiences from Algeria and the Republic of Korea suggest that MDR-TB can possibly be reduced, but not eliminated, by the use of properly administered regimens with first-line drugs. A recent study from Bobo-Dioulasso, Burkina Faso, shows that introduction of short-course treatment and improved supervision and treatment observation policies in 1989 resulted in a lower prevalence of drug resistance, including rifampicin resistance, in a 1992–1994 survey compared with previous surveys in 1978 and 1986. Unfortunately, no trend data are available for MDR-TB (*11*).

Evidence from the New York City experience suggests that MDR-TB can be rapidly controlled (*12*). Between 1991–1992 and 1994, following the implementation of effective control measures, the total number of MDR-TB cases nearly halved (44% decrease); MDR-TB cases decreased by more than 85% between 1992 and 1997. Control measures included directly observed treatment, which ensured high completion rates; infection control interventions in congregate settings such as hospitals, jails,

and shelters for the homeless; and the adoption of adequate treatment regimens for cases with both susceptible and MDR strains (treated with reserve drugs in order to achieve high success rates).

New York City's experience can be summarized as follows. Well-organized treatment with first-line drugs increased the cure rate among non-MDR cases, "turned off the tap" and stopped the generation of acquired MDR-TB. This reduced the spread of MDR-TB strains, contributing to the decline in primary MDR-TB. In addition, existing MDR-TB cases were cured with reserve drugs ("emptying the pool"). This, combined with effective hospital infection control, dramatically reduced the spread of MDR-TB.

Clearly, without reserve agents it will not be possible to achieve a cure rate substantially above 50% among MDR-TB cases. Unless high cure rates are achieved, it is unlikely that transmission of MDR-TB will stop rapidly or be eliminated within a few years.

In conclusion, the information available today on the efficacy of short-course treatment regimens for tuberculosis demonstrates that the emergence of drug resistance can be minimized by programmes that administer drugs correctly to patients and achieve cure. However, the treatment regimens recommended as part of DOTS cannot rapidly reverse MDR-TB if it has already emerged as a significant problem. The crucial factor for elimination is treatment success: at a high cure rate for both susceptible and multidrug-resistant cases, the emergence of MDR-TB will be reversed. High cure rates of susceptible cases ensure that MDR-TB is not created; as a result, "primary" MDR-TB will also decline. At the same time, an increased cure rate of existing MDR-TB will eliminate the sources of transmission in the community.

References

1. *Anti-tuberculosis drug resistance in the world: the WHO/IUATLD Global Project on Anti-Tuberculosis Drug Resistance Surveillance, 1994–1997*. Geneva, World Health Organization, 1997 (document WHO/TB/97.229).
2. Raviglione MC. DOTS and multidrug-resistant tuberculosis. In: Bastian I, Portaels F, eds. *Multidrug-resistant tuberculosis*. Dordrecht, Netherlands, Kluwer Academic Publishers, 2000:115–131.
3. Telzak EE et al. Multidrug-resistant tuberculosis in patients without HIV infection. *New England Journal of Medicine*, 1995, 33:907–911.
4. Coates ARM, Mitchison DA. The role of sensitivity tests in short-course chemotherapy. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1983, 58:110–114.
5. Mitchison DA, Nunn AJ. Influence of initial drug resistance on the response to short-course chemotherapy of pulmonary tuberculosis. *American Review of Respiratory Disease*, 1986, 133:423–430.
6. Espinal MA et al. Standard short-course chemotherapy for drug resistant tuberculosis. Treatment outcomes in 6 countries. *Journal of the American Medical Association*, 2000, 283:2537–2545.

7. Hong YP et al. The seventh nationwide tuberculosis prevalence survey in Korea, 1995. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:27–36.
8. Kim SJ, Bai SH, Hong YP. Drug-resistant tuberculosis in Korea. *International Journal of Tuberculosis and Lung Disease*, 1997, 1:302–308.
9. Espinal M et al. Rational "DOTS Plus" for the control of MDR-TB. *International Journal of Tuberculosis and Lung Disease*, 1999, 3:561–563.
10. Chaulet P. Tuberculose et transition épidémiologique: le cas de l'Algérie. [Tuberculosis and epidemiological transition: the case of Algeria.] *Annales de l'Institut Pasteur*, 1993, 4:181–187.
11. Ledru S et al. Impact of short-course therapy on tuberculosis drug resistance in South-West Burkina Faso. *Tubercle and Lung Disease*, 1996, 77:429–436.
12. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.

71. What are the indicators of an effective tuberculosis control programme?

F. Luelmo[1] *& T. Frieden*[2]

Indicators can measure process, outcomes, or impact. They measure the essential elements needed to carry out activities, the extent and quality of those activities, and the results, and should be limited to markers of the most important elements of the programme. Since epidemiological (impact) indicators change slowly and are difficult to measure, operational indicators of process and outcomes are often used to assess effectiveness.

Process indicators

The primary aim of the tuberculosis programme is to detect and cure infectious tuberculosis cases in order to reduce transmission, morbidity, and mortality. To achieve this, a programme requires trained staff and supplies such as antituberculosis drugs and microscopes in a network of general health facilities and laboratories accessible to the population. Relevant process indicators of administrative aspects include the coverage of programme activities (such as proportion of population having access to, and the proportion of health facilities implementing, the recommended policies for diagnosis and treatment), availability of supplies (e.g. frequency of drug stock-outs), availability of trained staff, frequency of supervision, completeness of reporting, and quality of interventions (e.g. quality of sputum smear examination, proportion of pulmonary cases confirmed by positive sputum smears among diagnosed pulmonary cases, indicating the use of microscopy as a diagnostic tool). Another important indicator is the proportion of patients identified as smear-positive in the laboratory register who are registered and treated as documented in the tuberculosis register.

Outcome indicators

The main outcome indicator of an effective programme is the cure rate – the proportion of patients cured out of those diagnosed, analysed in cohorts of patients. Since cure can be confirmed only through bacteriology – in most countries sputum

[1] Consultant, Tuberculosis control programmes, Geneva, Switzerland.
[2] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

microscopy – and the priority is the sputum smear-positive sources of infection, the cure rate is analysed mainly in new smear-positive pulmonary tuberculosis cases. Some patients complete treatment with clinical improvement but without bacteriological confirmation of cure (completion rate); this should be a small proportion. A good programme can achieve a cure/completion rate (also called success rate) of more than 85%, except in HIV-endemic areas. In most such areas, at least 10% of patients die before completing treatment (generally of causes other than tuberculosis), making an 85% cure rate practically unattainable. The cure/completion rate and the case detection rate are the main outcome indicators for monitoring programme effectiveness.

Complementary indicators are the proportion of failures (1–2%, usually the result of inadequate regimens or drug resistance), of defaulters (a good programme should have less than 5%), of transfers without information regarding outcome (often influenced by migration), and of death due to any cause (often due to late diagnosis, HIV/AIDS, or non-tuberculosis causes). The same analysis can be done for re-treatment cases as a group, and independently for relapses, defaulters who are re-treated, patients who fail initial treatment, and other cases.

Treatment outcome indicators must include the *entire* cohort of registered cases in a period, usually 3 months, and can be analysed only after giving time for all the patients to complete treatment, usually 1 year. An early proxy for the cure/completion outcome is the proportion of smear-positive cases who have negative smears after receiving 2–3 months of treatment (sputum smear conversion rate). This indicator reflects the capacity of the programme to maintain patients on treatment, obtain follow-up smears, and reduce patients' bacterial population through treatment.

A second operational priority for the programme is to detect infectious cases for treatment, mainly through sputum smear microscopy in outpatients attending general health facilities. The main indicators are the number of new infectious cases detected as a percentage of expected incident cases (case-detection rate), the percentage of outpatient suspects examined by sputum smear, and the percentage of these who are smear-positive. Incidence can be estimated only roughly at country level (on the basis of studies of prevalence of tuberculosis infection, mortality, and notification) and not at all at district or local level. The proportion of outpatients examined by smear microscopy and the trend of notified new smear-positive cases are more useful and practical at district or health centre level. Additional indicators reflecting case-detection activities are the number of patients examined for diagnosis and the proportion of contacts of tuberculosis cases examined, diagnosed, and placed on treatment.

Impact indicators

The epidemiological impact of an effective programme is measured by the reduction of mortality, morbidity, and transmission (*1*). Reduction in tuberculosis mortality can be monitored through death certification trends over several years. However, these data may not always be available, or may often be imprecise so that changes are seen

only after several years. The most evident impact on mortality is the reduction of deaths in patients under treatment (health facility data).

Reduction in the prevalence of tuberculosis in the community can be detected directly through periodic population surveys – which are expensive and complex – or indirectly through a reduction in the prevalence of smear-positive patients attending health facilities, and through a diminishing trend in notifications if case detection is maintained at a constant level. Diminished prevalence reduces transmission, which can be measured through surveys of prevalence of infection in children, repeated every 5 years. Surveys of the prevalence of infection allow the annual risk of tuberculosis infection and its trend to be estimated.

Reduction in incidence is difficult to measure because operational factors affect case detection and notification. At a constant level of case detection, the trend of notification is a proxy for the trend in incidence. The maximum annual reduction in incidence and transmission expected as a result of a good programme is around 12–15% per year (e.g. Germany, Netherlands, New York City); in developing countries 7–10% per year is very good (Brazil/ Rio Grande do Sul, Chile, Cuba, Peru) (*2–6*). Reduction in transmission results in a more rapid decrease of incidence in children and young adults and changes the age and sex distribution of cases. Notified incidence of tuberculosis and of tuberculous meningitis in children under 5 years of age reflects the reduction of transmission as well as the protective effect of BCG vaccination; at constant vaccination coverage these are good indicators of the programme impact on transmission.

Prevalence of drug resistance – particularly multidrug resistance, indicating the negative impact of poor quality treatment programmes – is a complementary indicator. A high rate of primary multidrug-resistant tuberculosis interferes with achievement of high cure rates through an increase of failures (drug resistance) and of case-fatality, besides increasing mortality, prevalence, and transmission.

References

1. Rieder HL. *Epidemiologic basis of tuberculosis control*. Paris, International Union Against Tuberculosis and Lung Disease, 2000.
2. *Global tuberculosis control: WHO Report 2000*. Geneva, World Health Organization, 2000 (document WHO/CDS/TB/2000.275).
3. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.
4. Suarez PG et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases*, 2001; 184:473–478.
5. Rodriguez Cruz R. *Tuberculosis control programme*. Cuba, World Health Organization, 1992 (document WHO/TB/93.172).
6. Cauthen GM, Pio A, ten Dam HG. *Annual risk of tuberculosis infection*. Geneva, World Health Organization, 1988 (document WHO/TB/88.154).

72. What are examples of effective tuberculosis control programmes?

M. Raviglione[1] *& T. Frieden*[2]

An effective tuberculosis control programme detects at least 70% of new sputum smear-positive cases and successfully treats at least 85% of cases detected. An effective programme prevents the creation and spread of drug-resistant forms of tuberculosis by ensuring that cases are detected quickly and placed on proper regimens. A stricter definition of an effective programme, however, should be based on the ultimate capacity of the programme to stop tuberculosis transmission and, as a result, to reduce incidence progressively until tuberculosis is eliminated as a major public health problem. This may not be achieved by curing 85% of detected cases if insufficient cases are detected.

In order to achieve these outcomes, an effective programme ensures guidelines, training, and resources for good tuberculosis case management and gives priority to detection and treatment of the sources of infection. Such a programme monitors both process and impact. Effectiveness is measured indirectly in terms of impact on mortality, morbidity, and transmission; programme quality can be measured directly in terms of case-fatality, cure, and coverage.

As of early 2002, about 155 countries worldwide had adopted a tuberculosis control strategy following the WHO recommendations. However, only 102 of them had achieved full population coverage, thus guaranteeing potential access to all people living in the country. Only fifteen countries had achieved the global targets by early 2002. An additional 54 countries had a detection rate of at least 50% and a treatment success rate of at least 70% (*1*).

Probably one of the best recent examples of a country with an effective tuberculosis control programme is Peru. After implementing a new strategy of tuberculosis control following WHO recommendations, Peru reached the WHO targets in 1995 and has maintained its performance since then. The estimated case detection rate was more than 90% in 1999. Of all cases analysed in 1998, 90% were successfully treated.

[1] Coordinator, TB Strategy and Operations, Stop TB Department, World Health Organization, Geneva, Switzerland.
[2] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

More importantly, there is now evidence of a decline in notification of new pulmonary tuberculosis cases following 2 years of increase immediately after the implementation of the revised programme in 1991. This decline has averaged 7.5% per year nationally, despite a 10-fold increase in diagnostic effort. Compared with previous trends, the implication is that some 16% of expected cases and 70% of expected deaths were averted between 1991 and 1999 (*2*). This was achieved through decentralization of diagnostic capacity to well-equipped health centres around the country and effective case management based on direct observation of treatment. As a result, default rates have been minimized and more than 90% of cases have been cured.

Health services in Peru have been equipped with the necessary diagnostic tools; general health staff have been intensively trained and retrained on tuberculosis case management; an effective supply system has ensured continuous supply of drugs; an adequate information system has allowed programme performance to be monitored and corrective action taken; and a general information campaign has brought knowledge and awareness of tuberculosis to all levels of the community. The programme has been fully supported by the commitment of the government to fight tuberculosis. Local areas monitor standard as well as important locally defined indicators (e.g. delay in diagnosis, causes of default, proportion of symptomatic patients examined). A capable management system has been put in place and maintained over the years at national and regional levels. This is a recipe for effective tuberculosis control in developing countries.

Similar successful programmes were set up in other Latin American countries such as Chile, Cuba, and Uruguay, as well as in Morocco and Viet Nam. Other programmes that have achieved remarkable results in terms of high cure rates are those of Benin, Cambodia, China, Malawi, Nicaragua, and United Republic of Tanzania (*3–10*). In these countries, however, there is no definitive nationwide evidence yet that incidence has decreased as a result of the tuberculosis control efforts.

One of the best-documented effective programmes in a developing country is the tuberculosis control programme of Beijing, China (*11*). This programme has used direct observation of treatment since 1979, and has documented a substantial and progressive decline in tuberculosis cases (87% reduction in prevalence from 1979 to 1990), deaths (80% reduction), and chronic cases. Drug resistance has remained minimal. One interesting aspect of this programme is the systematic, independent verification that treatment is being directly observed as per policy.

Effective tuberculosis control is reflected by the very low notification rates (as a proxy for incidence rates) in many European countries and in the USA (*1*). In the USA, a strengthened notification system, the establishment of clear standards of care, the use of special measures for HIV-infected individuals and recent immigrants, and infection control measures, especially in congregate settings, have all contributed to reversing the increasing trend observed between the mid-1980s and 1992 (*12*). In the USA, one of the best examples of an effective tuberculosis control programme is that of New York City. There, the number of tuberculosis cases rose dramatically in the

1980s until 1992, and began decreasing after the implementation of a revised control programme. The experience in New York City shows that multidrug-resistant tuberculosis can be reduced rapidly even in the context of an HIV epidemic. Within six years, the programme reduced multidrug-resistant cases by 80% and USA-born tuberculosis cases by more than 60%. Control measures included proper short-course regimens and directly observed treatment, which allowed the achievement of high completion rates; infection control interventions in congregate settings, such as hospitals, shelters for the homeless, and correctional institutions; and the adoption of adequate treatment regimens for cases with susceptible and multidrug-resistant strains (*13*).

An ideal programme not only meets the targets for case detection and cure, but also ensures *patient-friendly* services that make patients feel respected and valued, thereby further increasing the likelihood of high detection and cure rates. Furthermore, an ideal programme demands rigorous accountability from health workers while also ensuring their input and involvement in improving the programme. Such a programme also ensures the continuous and accurate analysis of data to allow objective evaluation and progressive improvements in performance, creating a self-sustaining positive feedback loop. Finally, an optimal programme makes efficient use of resources, generates and documents cost savings, and leverages available human and financial resources in order to ensure long-term sustainability.

References

1. *Global tuberculosis control. WHO Report 2003*. Geneva, World Health Organization (document WHO/CDS/TB/2003.316).
2. Suarez PG et al. The dynamics of tuberculosis in response to 10 years of intensive control effort in Peru. *Journal of Infectious Diseases*, 2001; 184:473–478.
3. Gninafon M. The antituberculosis programme of Benin. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 66:57–58.
4. Perez-Stable EJ, Pedraza RO. Tuberculosis in Cuba. *American Review of Respiratory Disease*, 1984, 130:520–523.
5. Arguello L. Results of the tuberculosis control programme in Nicaragua in 1984–1989. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 66:51–52.
6. Nyangulu DS, Nkhoma WN, Salaniponi FM. Factors contributing to a successful tuberculosis control programme in Malawi. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 66:45–46.
7. Chum HJ. The Tanzania National Tuberculosis/Leprosy Programme in the face of HIV infection. *Bulletin of the International Union Against Tuberculosis and Lung Disease*, 1990, 66:53–55.
8. Norval PY et al. DOTS in Cambodia. Directly observed treatment with short-course chemotherapy. *International Journal of Tuberculosis and Lung Disease*, 1998, 2:44–51.
9. Dye C et al. Evaluating the impact of tuberculosis control: number of deaths prevented by short-course chemotherapy in China. *International Journal of Epidemiology*, 2000, 29: 558–564.

10. Results of directly observed short-course chemotherapy in 112,842 Chinese patients with smear-positive tuberculosis. *Lancet*, 1996, 347:358–362.
11. Zhang LX, Tu DH, Enarson DA. The impact of directly-observed treatment on the epidemiology of tuberculosis in Beijing. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:904–910.
12. Tuberculosis morbidity – United States, 1997. *Morbidity and Mortality Weekly Report*, 1998, 47:253–257.
13. Frieden TR et al. Tuberculosis in New York City – turning the tide. *New England Journal of Medicine*, 1995, 333:229–233.

73. What are the relative priorities for a tuberculosis control programme, and what activities should not be undertaken?

F. Luelmo[1] *& T. Frieden*[2]

Priority-setting in a tuberculosis control programme is based on programme objectives, the effectiveness of interventions, and the resources available. The first priority is to identify, cure, and document cure among patients seeking care in health facilities. A reasonable target is 85% cure of new sputum smear-positive patients. Once this is achieved, programmes can expand coverage to detect more cases and to detect cases earlier. These first priorities aim to directly cut the chain of transmission and reduce mortality. This is achieved by accurate and prompt diagnosis, free provision of drugs, regular intake of drugs, and systematic monitoring of successive cohorts of pulmonary smear-positive patients. For this to occur, a programme must ensure:

- Organization of outpatient treatment for tuberculosis patients (all forms, both new and re-treatment), including guidelines, training, supplies, registration, sputum smears, monitoring, and supervision. This includes directly observed treatment decentralized to peripheral health workers and community volunteers who are convenient to the patient.
- Organization of diagnosis, including the laboratory network, publication of guidelines, training, quality control, registration, monitoring, and supervision.
- Implementation of case detection in outpatient health facilities, including training and monitoring. This also includes information to the community regarding free availability of tuberculosis diagnosis and cure and the need for prompt evaluation for diagnosis of persons with prolonged cough.

Secondary priorities, which should be incorporated gradually once the basic package is producing satisfactory results, include:

- Enhanced quality control of drugs.
- Expansion of case detection and treatment to nongovernmental institutions and private practice.

[1] Consultant, Tuberculosis control programmes, Geneva, Switzerland.
[2] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

- Expansion of the laboratory network for culture and development of susceptibility testing at the national laboratory. Use of culture for diagnosis in smear-negative patients suspected of having tuberculosis.
- Formulation and implementation of diagnostic and treatment guidelines for children and extrapulmonary cases, associated tuberculosis and HIV/AIDS, tuberculosis in prisons, migrants and other special groups.
- Surveillance of case notification, drug resistance, tuberculosis/HIV, meningitis in children, prevalence of infection, and mortality (if death registration is available).
- Operational research, with emphasis on descriptive epidemiology; risk factors for delayed diagnosis, default, treatment failure, and death; monitoring of cost-effectiveness of interventions and rationalization of care (hospitalization, surgery, referral system, specialized care, integration with other control activities within general health care).

Depending on availability of resources and the epidemiological context, the following activities may also be undertaken:

- Expanded examination of contacts and high-risk groups for diagnosis and preventive treatment (e.g. those living in congregate facilities, high-prevalence groups, HIV-infected persons, persons with incompletely treated tuberculosis in the past).
- Expansion of the tuberculosis package of care to drug-resistant cases. This activity has a much higher priority in areas with high rates of initial multidrug-resistant tuberculosis that also have large populations of immunosuppressed persons, particularly where there are congregate settings (e.g. AIDS wards, prisons, mines).

Staff and other resources of the tuberculosis programmes and of the health delivery system should *not* be used for activities of low yield and little benefit for the community.

Some examples of unnecessary, inadequate, or damaging interventions

Case detection

- "Active" case detection through mass miniature radiography in the general population (see "What is the role of case detection by periodic mass radiographic examination in tuberculosis control?", page 72).
- Screening – with tuberculin, X-ray, or bacteriology – of low-risk populations such as students, teachers, food handlers, etc.
- Active promotion of services that are not available to the community; for instance, promotion when there are insufficient or irregular supplies of drugs or the treatment services are poorly organized and are achieving low cure rates.
- Use of mobile units specifically for tuberculosis, isolated from permanent health facilities or staff able to provide regular treatment until cure.

- Establishment of tuberculosis diagnostic centres isolated from general health care – most patients with symptoms consult general facilities, without knowing that they have tuberculosis.
- Diagnosis on a clinical basis only, or on the basis of radiology alone. Because of low specificity, many patients without tuberculosis or with healed lesions will be put on treatment unnecessarily, risking harm and wasting resources.
- Request for smears on different successive days, with multiple visits by the patient (three smears can be collected in two visits, spot – early morning – spot).
- Centralized diagnosis or confirmation of diagnosis at specialized institutions (e.g. tuberculosis dispensaries). Most patients with respiratory symptoms first consult the outpatient departments of general hospitals, primary health centres, and private physicians.
- Use of complex inappropriate technology, for instance, use of the polymerase chain reaction in control programmes.

Treatment

- Centralized treatment only at specialized institutions. Although the knowledge of tuberculosis and of clinical complications is usually better and there may be more diagnostic resources, central facilities lose a higher proportion of patients because of greater distance from patients' homes. Except in some urban settings, these facilities should be used only for referral of difficult cases for diagnosis or management of complications, and patients should be referred or transferred to an easily accessible treatment point as soon as possible.
- Asking the patient to buy the missing drugs because of irregular drug supply. This leads to monotherapy and drug resistance, loss of confidence in the service, and treatment default.
- Prolongation of treatment. Very few patients benefit from longer treatment, and there is no justification for extending treatment for all. There is no evidence that longer treatment for meningitis or other forms of tuberculosis is of additional benefit.
- Addition of costly vitamins, nutritional supplements, minerals, and other medication, unless there is a specific deficiency. The nutritional status of the patient improves as a consequence of reduced bacterial load. Nutrition is an important risk factor for breakdown from tuberculosis infection to disease, but has no impact on cure when short-course, high-efficacy regimens are used. Food (for the patient and the family) can, however, be a highly effective incentive to improve treatment adherence.
- Monthly follow-up with X-rays.
- Use of surgical masks by health personnel. These masks are not useful in preventing inhalation of bacilli, they alienate staff from patients, and give the staff a false impression of safety.

Monitoring (including research)

- Monitoring large numbers of process indicators such as number of patients on treatment at any point in time. Standard indicators (diagnostic quality, conversion rate, cure rate, estimated annual detection rate) are revealing and should not be diluted by less important information.
- Extensive monthly reports. Quarterly reporting is generally sufficient for prompt and effective monitoring.
- Combining tuberculosis data collection (quarterly reporting) with the general health information system. On the other hand, quarterly reporting information should be disseminated to as wide an audience as possible – through the general health information system and otherwise.
- Use of excessive resources in pilot projects or operational research, making the tested intervention inapplicable or not sustainable for expansion to the whole country.

74. What is the impact of HIV on the epidemiology of tuberculosis in a community?

A. Harries[1]

HIV infection reduces cell-mediated immunity and is a powerful risk factor for the development of tuberculosis (*1*, *2*). The impact of HIV on the epidemiology of tuberculosis depends on the extent of overlap between the population infected with HIV and that infected or at risk of becoming infected with *Mycobacterium tuberculosis*. At present, about 70% of people in the world co-infected with HIV and *M. tuberculosis* live in sub-Saharan Africa (*3*).

The annual risk of developing active tuberculosis disease in a co-infected person ranges from 5% to 15%, depending on the degree of immunocompromise (*1*). There is also good evidence that HIV infection favours rapid progression from exposure to *M. tuberculosis*, through infection, to active tuberculosis. Among severely immunocompromised patients hospitalized with the complications of AIDS and exposed to infectious patients, the median time between exposure and disease was 12 weeks (*4*).

Impact of HIV

HIV has its greatest impact on tuberculosis in sub-Saharan Africa, although in parts of India, Myanmar, and Thailand the association between these two infections is becoming increasingly apparent. There are many aspects to the impact of HIV, described below.

Tuberculosis case numbers

In the past 10–15 years, tuberculosis case numbers have increased 300–400% in high HIV-prevalent countries of Africa, mainly because HIV increases the risk of disease reactivation in people with latent *M. tuberculosis* (*5*). Along with the increase in case numbers, there has been a disproportionate increase in cases with smear-negative pulmonary tuberculosis and extrapulmonary tuberculosis (*1*).

Increased case numbers place an immense burden on tuberculosis control efforts: more staff are needed, particularly tuberculosis programme officers and laboratory

[1] Technical Adviser, Malawi National Tuberculosis Control Programme, Lilongwe, Malawi.

personnel; there is an increased need for laboratory resources, drugs, sputum containers, and stationery; where patients are hospitalized for the initial phase of treatment, wards become overcrowded, making consistently good nursing care impossible and increasing the risk of nosocomial infection.

Hot spots for tuberculosis transmission

Hot spots for transmission, fuelled by concurrent HIV infection, may occur in places where people are crowded together, such as prisons, refugee camps, mines, health care institutions, and boarding schools. In such situations, active case detection may sometimes be required to curtail tuberculosis transmission.

Increased case fatality

HIV-positive tuberculosis patients experience HIV-related morbidity during tuberculosis treatment. Adverse reactions to antituberculosis drugs, particularly thioacetazone-induced cutaneous reactions, are more frequent, leading to interruptions of treatment and occasional fatalities (*6*). It is not surprising that HIV-infected patients have a much higher mortality during and after tuberculosis treatment compared with HIV-negative patients. In sub-Saharan Africa, approximately 30% of HIV-infected, smear-positive tuberculosis patients will die within 12 months of starting treatment, and about 25% of those who complete treatment will die during the subsequent 12 months (*1*).

The high death rates in HIV-infected, smear-positive tuberculosis patients mean that treatment is less cost-effective in terms of years of life saved than previously calculated for HIV-negative patients. In the pre-HIV era, smear-negative pulmonary tuberculosis was a disease with a good treatment outcome. Evidence is slowly accumulating in sub-Saharan Africa that the prognosis for HIV-infected, smear-negative pulmonary tuberculosis patients may be worse than that for patients with smear-positive pulmonary tuberculosis (*7*).

Recurrence of tuberculosis after completion of treatment

Recurrence rates (defined as return of clinical evidence of active tuberculosis, positive sputum smears, or positive cultures of *M. tuberculosis*) are higher in HIV-infected patients. The use of non-rifampicin-containing regimens and treatment interruptions as a result of drug reactions are associated with an increased risk of recurrence of tuberculosis (*1*). Recurrence includes both true relapse and recurrent disease following reinfection. The proportion of tuberculosis recurrence due to disease reactivation versus reinfection is unknown.

Drug resistance

Outbreaks of multidrug-resistant tuberculosis have been reported from both industrialized and developing countries in patients with HIV infection. HIV itself does not

cause multidrug-resistant tuberculosis, but it fuels the spread of this dangerous condition by accelerating the progression from infection to disease.

Global targets for tuberculosis control

The overall objective of tuberculosis control is to reduce mortality, morbidity, and transmission of the disease. At present, the best way to achieve this is to focus on new cases of smear-positive tuberculosis, curing at least 85% of detected smear-positive cases, and detecting at least 70% of new infectious cases. HIV makes the targets for cure and detection rates difficult to reach. Cure rates of 85% in smear-positive tuberculosis cases are almost impossible to achieve because of high HIV-related mortality. The case detection target of 70% is also impossible to verify because a method for estimating the total number of such cases with certainty (for use in the denominator) has not yet been found, particularly in the context of a high prevalence of HIV.

Implications

HIV inexorably reveals any weakness in a tuberculosis control programme. Low detection rates lead to rapid spread of infection and disease from untreated patients. Low cure rates, if combined with high default rates, may result in the rapid emergence and spread of drug-resistant strains. And ineffective infection control facilitates rapid and potentially extensive institutional spread of tuberculosis. Tuberculosis rates will generally rise for as long as HIV prevalence rises. If the prevalence of HIV in the adult population reaches 5% in a developing country, current technology cannot contain the increase in cases. DOTS can, however, prolong the lives of individual patients, prevent drug resistance, and blunt the increase in cases. Increased cases result from the increased risk of active tuberculosis in HIV-infected patients, hot spots for tuberculosis transmission, and increased recurrence rates. Ultimately, HIV prevalence will reach a plateau, and it is then likely that tuberculosis case notifications will also plateau, although at rates several times higher than those seen in the pre-HIV era. The control of tuberculosis in high HIV-prevalent areas will depend to a large extent on the control of HIV.

References

1. Raviglione MC et al. Tuberculosis and HIV: current status in Africa. *AIDS*, 1997, 11: S115–S123.
2. De Cock KM et al. Tuberculosis and HIV infection in sub-Saharan Africa. *Journal of the American Medical Association*, 1992, 268:1581–1587.
3. Dye C et al. Estimated incidence, prevalence, and mortality by country. *Journal of the American Medical Association*, 1999, 282:677–686.
4. Nosocomial transmission of multidrug-resistant tuberculosis among HIV-infected persons – Florida and New York, 1988–1991. *Morbidity and Mortality Weekly Report*, 1991, 40: 585–591.

5. *Global tuberculosis control. WHO Report 2001.* Geneva, World Health Organization, Communicable Diseases, 2001 (document WHO/CDS/TB/2001.287).
6. Nunn P et al. Cutaneous hypersensitivity reactions due to thiacetazone in HIV-1 seropositive patients treated for tuberculosis. *Lancet*, 1991, 337:627–630.
7. Harries AD et al. Treatment outcome of an unselected cohort of tuberculosis patients in relation to human immunodeficiency virus serostatus in Zomba hospital, Malawi. *Transactions of the Royal Society of Tropical Medicine and Hygiene*, 1998, 92:343–347.

75. How can tuberculosis control services be promoted and sustained?

T. Frieden[1]

Challenges and advantages

Effective tuberculosis control requires sustained political and administrative commitment at national and local levels. An effective tuberculosis control programme must therefore initiate, build, and sustain this commitment – a challenging task. Most tuberculosis patients are economically disadvantaged and exert little political influence. Moreover, the disease tends to alienate patients; tuberculosis patients do not naturally form associations or support groups to lobby for more services and resources. Finally, tuberculosis control is a long-term struggle that requires continued support.

Approximately 2 billion people alive today are infected with tuberculosis bacteria, and at least 100 million of them are likely to develop active tuberculosis at some point in their lives. Thus, even if the spread of tuberculosis could be completely stopped and an effective vaccine to prevent tuberculosis in uninfected persons were discovered and applied widely, tuberculosis control services would be needed for at least another 40–50 years.

In addition, the HIV epidemic has drastically increased tuberculosis caseloads, generally in countries with limited resources. Health services in many developing countries are undergoing reform, raising new challenges for tuberculosis control. Although health sector reform can potentially improve efficiency and increase community involvement, in practice it often translates into user fees, reduced services, and limitations in the ability of specific disease control programmes, such as tuberculosis control, to function effectively (*1*).

Despite these substantial challenges, tuberculosis control programmes have several advantages. First, tuberculosis is a curable disease, and the tuberculosis epidemic is a winnable battle – in contrast to many other health and social problems. Second, tuberculosis control services are highly accountable, and are therefore appealing to many decision-makers. A tuberculosis control programme can track the exact number of patients examined, diagnosed, treated, and cured, make a reasonable estimate of the number of deaths prevented by these activities, and report this information to those

[1] Medical Officer, Stop TB Unit, WHO Regional Office for South-East Asia, New Delhi, India.

who fund and support the programme. Third, tuberculosis control is highly cost effective (see "Is DOTS cost-effective?", page 246). Fourth, many people living in high-prevalence areas recognize tuberculosis as an important cause of sickness and death, and rightly perceive effective tuberculosis control services as a critical indicator of good governance. Fifth, the DOTS strategy can be implemented successfully in almost any context, as it relies on relatively simple interventions. Finally and perhaps most importantly, DOTS is rooted in reliable scientific evidence – including data to support the diagnostic strategy as summarized in the case detection section of this book; randomized controlled clinical trials demonstrating efficacy of practical, short-course treatment regimens reviewed in the treatment section; and a recording and reporting system that allows individual and aggregate evaluation to identify problems rapidly (see "Why is a recording and reporting system needed, and what system is recommended?", page 270).

Promoting tuberculosis control services

In general, effective tuberculosis control services are best promoted at national level by a tuberculosis programme that is adequately staffed and supported. The programme's overall strategy should be to establish sound technical policies, make maximum efforts to involve and convince key decision-makers of the importance of implementing these policies, and engage individuals, groups, and communities from outside the government in promoting effective tuberculosis control. Most programmes require the authority to hire staff, purchase goods and equipment, and contract for services. These functions can be performed effectively only if there is political and administrative commitment from within the country or area.

Sustaining tuberculosis control services

Tuberculosis control is a long-term battle. In several countries, initial success in the control of tuberculosis led to complacency, a subsequent resurgence of cases, and the emergence and spread of drug resistance (*2*, *3*). The term "U-shaped curve of concern" has been used to describe the phenomenon of declining interest, commitment, and support for tuberculosis control, followed by an increase in disease burden resulting from poor programme performance (*4*). The most important strategy to preserve tuberculosis control services is to ensure that they are implemented effectively and that this success is systematically documented and publicized widely to those who allocate funds. Effective implementation requires ongoing analysis of programme data to objectively evaluate and continuously improve services. A key strategy is to identify and maintain the support of key external constituencies within the country. Public sector management tends to be driven by constraints rather than tasks (*5*). To limit the impact of this inevitable tendency, programmes must seek support from individuals, institutions, and nongovernmental groups. In the case of tuberculosis control, these include individuals and groups interested in ensuring that effective tuberculo-

sis control services remain available in the community. Individuals and groups outside government can therefore play a critical role in promoting and sustaining effective tuberculosis control services.

Ultimately, the establishment and maintenance of high-quality tuberculosis control services reflect effective national leadership and service.

References

1. Bosman MC. Health sector reform and tuberculosis control: the case of Zambia. *International Journal of Tuberculosis and Lung Disease*, 2000, 4:606–614.
2. Brudney K, Dobkin J. Resurgent tuberculosis in New York City: human immunodeficiency virus, homelessness, and the decline of tuberculosis control programs. *American Revew of Respiratory Disease*, 1991, 144:745–749.
3. Frieden TR et al. The emergence of drug resistant tuberculosis in New York City. *New England Journal of Medicine*, 1993, 328:521–526.
4. Reichman LB. The U-shaped curve of concern. *American Review of Respiratory Disease*, 1991, 144:741–742.
5. Wilson JQ. *Bureaucracy*. New York, Basic Books, 1989.