

Epidemiological Basis of Tuberculosis Eradication

2. Dynamics of Tuberculosis Morbidity and Mortality *

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In most countries there have been signs in recent years of an accelerated decline in tuberculosis, but only the most superficial knowledge exists of what underlies the remarkable changes. It is therefore imperative to document the changing picture of tuberculosis by means of parameters that are not only descriptive but will also serve as guidelines for the development of methods to eradicate the disease.

The authors describe the present system of tuberculosis reporting and control in Denmark, where the requisite conditions for obtaining meaningful statistics are, to a large extent, fulfilled, discussing its potentialities for depicting the forces behind the recent changes and pointing out its inherent deficiencies.

The advantages of the Danish system, in which rates for the prevalence and incidence of respiratory tuberculosis are broken down into those for new cases and those for relapses, are stressed, as is the significance of the recently introduced practice of reporting cures and thus obtaining cure rates on a nation-wide scale.

As an indicator of the lethal effect of tuberculosis in a country, the mortality rate suffers from several limitations, which will play an increasingly important role as the downward trend in tuberculosis continues. The authors suggest that a more objective measure than the specific mortality rate would be the so-called "lethality index" — an index based on all deaths occurring among persons with active tuberculosis, irrespective of whether they were attributed directly to the disease.

INTRODUCTION

For a good many years mortality rates have been the principal and often the only measure of the burden tuberculosis creates for human populations: the calculation of such rates requires only a census count of the population and a system for reporting and classifying deaths according to cause. But just what is meant by deaths from tuberculosis? The difficulties in determining the cause of death are well known to anyone who has struggled with the task of trying to decide what to write on the notification form as the direct and contributing causes of death.

* The first article in this series was unnumbered and appeared, in *Bull. Wld Hlth Org.*, 1959, 21, 5, under the title "Epidemiological Basis of Tuberculosis Eradication in an Advanced Country".—Ed.

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While mortality is an essential index of the most devastating manifestation of tuberculosis, it was realized long ago that much more information about the disease, and its public health significance, could and should be obtained from morbidity rates. The need for more meaningful statistics has become even more urgent since the advent of the chemotherapeutic era, because the great majority of the patients can now be cured. The reason for this change is clear: the usual statistics on mortality are becoming less and less useful as a measure of the present status and trend of tuberculosis. And in many countries, too, the widespread use of BCG means that another, probably the best, index of the tuberculosis problem cannot be used—the rate of new infections based on results of tuberculin tests.

Morbidity rates for tuberculosis are not so simple and straightforward as might appear. Contrary to popular and to some extent professional opinion, it is not easy to diagnose a disease with protean mani-

festations, insidious onset, variable course—sometimes acute, sometimes chronic—and tendency to relapse. Questions which plague the tuberculosis clinician, and the vital statistician and epidemiologist as well, are legion. When can, or should, a person with some of the signs and symptoms of tuberculosis be diagnosed as a “case”, and be reported as having the disease? When, if at all, and by what criteria can a case be considered “cured”, or as having “relapsed”? If the tuberculosis morbidity rate should be based only on “new” cases reported during the year, do new cases include relapses as well as patients reported for the first time? If so, what sort of clinical services, definitions, and reporting systems would be required to furnish reliable counts? Although many countries publish annually what are regarded as tuberculosis incidence and prevalence rates, the interpretation of the rates, and comparisons from one country to another, are difficult, and in some cases impossible, because questions like these often remain unanswered.

In spite of the uncertainties of measuring the extent of the tuberculosis problem, few will doubt its recent accelerated decline in most countries. Just when the decline began may be primarily of academic interest; but one fact is clear and of great practical importance: in many countries, the decline in the past 15-20 years has exceeded all predictions, although only the most superficial knowledge exists of just what has happened, and only guesses about why these changes have come about. And yet, today, it does not seem foolish to consider seriously the possibility of eradication of the disease. To some this may seem unrealistic. To them we say: Who among you could have predicted the phenomenal changes since the Second World War? And who would care to predict that equal or even greater changes may not occur in the next 15 years?

Quite aside from the importance of trying to provide practical information with which it might be possible to hasten the demise of tuberculosis, it would seem equally important to try to document, as clearly and accurately as possible, the changes that occur during what may turn out to be the final phase of the Great White Plague. And if, unexpectedly, the next decades should mark an upturn in tuberculosis, it could be of even greater importance to have tried to document thoroughly the details of just what has happened.

The key to the understanding of the changing tuberculosis picture lies in the development of detailed knowledge of tuberculosis morbidity—what

might be called the dynamics of tuberculosis prevalence and incidence—based on meaningful and interpretable tuberculosis morbidity statistics. It came to light at the European Technical Conference on Tuberculosis Control, organized by the WHO Regional Office for Europe in 1962, that, even among the developed countries, few have established the means by which it would be possible to obtain meaningful morbidity figures within the near future.¹ Denmark is one of the few countries that do offer this possibility.

The purpose of the present paper is first to describe the status of tuberculosis and the control programmes in Denmark, and then to assess briefly the potentialities of its tuberculosis morbidity and mortality statistics for documenting the changing picture of tuberculosis.

BACKGROUND

The years around 1900 marked the real beginnings of the comprehensive tuberculosis control system now in effect in Denmark; as early as 1875 the first treatment centre was established and in 1892 the first legislation on public sickness insurance. The National Association for the Fight against Tuberculosis, soon after its establishment in 1901, set up nine sanatoria in different parts of the country and laid the foundations for today's network of chest clinics by opening small dispensaries in Copenhagen and elsewhere. In 1905, the Government passed two Tuberculosis Acts which provided State support for the building and maintenance of sanatoria and hospitals for treating tuberculosis, pensions amounting to two-thirds of their salaries for teachers, civil servants and other officials dismissed because of infectious tuberculosis, and compulsory notification of pulmonary tuberculosis by the physicians to the health authorities.

By 1945 the entire country was covered by chest clinics run by the local authorities and supported by the State. In 1949 an improved Public Assistance Act was passed that provided sufficient public funds to enable the patient and his family to maintain the usual standard of living and not merely to exist at subsistence level; moreover, the 1949 Act stipulated that the patient receiving such assistance must follow the directions of the chest clinic, otherwise the payments stopped. This unique legislation tends to ensure that practically all patients are known and

¹ Unpublished document EURO—84.2.

kept under supervision. The system is further strengthened because examinations and treatment in the chest clinics as well as treatment in the hospitals and sanatoria are free, or nearly so; and this applies to everyone, including the relatively few who are not members of State-approved sickness-benefit associations.

Over the years the public has been kept keenly aware of tuberculosis and informed of the importance of early diagnosis, adequate treatment, and prolonged follow-up. Moreover, the medical profession has turned over the diagnosis, treatment, and follow-up of patients with respiratory tuberculosis to the publicly employed specialists. In each of the 22 counties there is one treatment centre for in-patients; and the counties' central chest clinics (many with branch clinics) function as centres for routine screening of the general population, diagnostic examination of persons referred by practising physicians and general hospitals, examination and follow-up of active cases of tuberculosis, and the treatment and follow-up of ambulatory patients.¹ Practically all of the newly diagnosed patients start treatment in institutions devoted to the treatment of tuberculosis. After several months of hospitalization the patient is discharged and referred to his local chest clinic to continue treatment and follow-up as an out-patient. Close co-operation between the tuberculosis hospitals and chest clinics, which is so necessary for this type of programme, is facilitated because the same chief physician generally directs the work of both.

Although the role of research in tuberculosis has long been appreciated in Denmark, the importance of epidemiological research was emphasized by an official step taken in 1950. Touched off by a desire to take full advantage of a nation-wide mass examination for tuberculosis planned to begin in 1950, the National Health Service, in co-operation with the WHO Tuberculosis Research Office, created an epidemiological-statistical institution, the Danish Tuberculosis Index (hereafter referred to as

DTI).² The DTI was visualized primarily as a research office whose main task would be long-range nation-wide studies of the epidemiology of tuberculosis. To ensure that the data collected in the mass survey would be suitable for such research, the DTI was given technical responsibility for the campaign, so that records and procedures, tuberculin testing, photofluorography, etc., would be as accurate and uniform as possible. Another task of the DTI was revision of the Central Tuberculosis Register and improvement of the bases for the tuberculosis statistics.

Diagnosis of active and cured cases of respiratory tuberculosis

The staff in the chest clinics generally decide whether or not a patient has active respiratory tuberculosis. The routine diagnostic procedures include a medical history, physical examination, tuberculin test, photofluorogram (and roentgenogram, if indicated), and bacteriological examination of sputum, gastric washings or other appropriate specimens. While it is recognized that a clear-cut definition of what constitutes a "case" of active tuberculosis does not exist, the culturing of tubercle bacilli from a clinical specimen is generally, though not always, considered necessary for the diagnosis of active disease. In some cases the diagnosis is based on the appearance and course of the X-ray lesion, the response to chemotherapy, the clinical symptoms, etc. Among the 1221 active cases reported in 1960, for example, tubercle bacilli were cultured from 825 (68%); in the remaining 396 cases, the diagnosis was based on other findings, apparently without bacteriological confirmation. These abacillary cases reflect the variations in diagnostic criteria employed by the different chest clinics: some reported no abacillary cases, while for others as many as half of their reported cases were abacillary.

The need to distinguish, among the new cases reported each year, those that are diagnosed for the first time and those that are relapses of "cured" cases requires a practicable definition of what can be called a "cured" case. The chiefs of all the chest clinics agreed, in 1950, to adopt Lassen's rule (Lassen, 1941) as the criterion for cure, and to report when a patient could be considered cured. According to this rule, a patient is considered cured when

¹ In 1960, there were, in all, 104 chest clinics, employing a total of 79 doctors and 150 registered nurses. The 45 institutions devoted primarily to the treatment and care of in-patients, i.e., sanatoria and special departments in the general hospitals, provided 2250 beds (or 49 per 100 000 population) and had an average of 1558 in-patients per day, which is slightly less than 70% of full capacity. A total of 979 000 persons, of whom 170 000 were children, was examined at the chest clinics in 1960, 2.3% because of previous tuberculous disease, 9.1% because of symptoms, 3.2% because of contact, 78.9% in the course of routine screening examinations, and the remaining 6.5% for other reasons.

² The DTI is supported jointly by: Grant No. CC 00016 from the Public Health Service of the US Department of Health, Education, and Welfare; the World Health Organization; and the Government of Denmark.

tubercle bacilli or other signs of activity, including regressive roentgenological changes, have not been found for three consecutive years during which there has been no treatment. It was presupposed that patients were kept under supervision with regular, periodic examinations, including bacteriological examinations. This supervision is done by the chest clinics; and when a patient changes his place of residence, the new clinic is provided with all of the pertinent findings so that follow-up examinations can be continued.

The most important point in Lassen's criterion of cure was absence of tubercle bacilli, and clinical experience seemed to indicate that most patients fulfilling this requirement would not show other signs of activity. However, in applying Lassen's rule, difficulties were encountered when patients became and remained abacillary but still had some symptoms which might be caused by active disease. It was therefore proposed in 1954 to simplify the criterion for cure by requiring only the absence of tubercle bacilli for three consecutive years after termination of treatment. Again, acceptance of this modified rule for reporting cases as "cured" implied that bacteriological examinations would be made at least twice a year during the follow-up period after treatment was stopped.

Aside from the uncertainty created when this definition of cure is applied to cases with inadequate or incomplete follow-up examinations, there is the even greater uncertainty that arises in connexion with cases diagnosed as active despite the absence of tubercle bacilli; as mentioned earlier, in 1960, about one-third of the newly reported active cases were abacillary at the time of diagnosis.

Initially, too, there were discrepancies in the reporting of patients who had both pulmonary and extrapulmonary disease. Some chest clinics felt that both kinds of lesions should be considered healed before a report of cure was made, while others considered only the pulmonary lesion. Since about 1955, however, it has been generally agreed that the reporting of cure refers only to pulmonary (respiratory) disease.

Finally, differences still exist between clinics in respect of what is meant by "treatment" in applying the cure rule. For example, some do not consider preventive chemotherapy as treatment *sensu stricto*. If, for instance, drugs are administered prophylactically to a woman who becomes pregnant during the three-year period "after termination of treatment", some clinics report such a patient as cured

three years after completing the initial treatment, while others wait for three years after completion of the prophylactic course of drug.

Central tuberculosis laboratory

The Tuberculosis Department of the State Serum Institute, in Copenhagen, serves as a central bacteriological laboratory for the entire country. The generally accepted policy is that sputum specimens, gastric washings, pleural fluid and other types of specimens are as a matter of routine sent to and examined by culture at the Institute, regardless of whether the microscopic examination is positive or negative for acid-fast bacilli. All positive findings on specimens sent in by physicians or hospitals other than the chest clinics are reported to the local clinic. Figures for the year 1960 illustrate the number of specimens examined at the Institute, and their source. Out of 51 700 sputum specimens, 54% were sent in by chest clinics, 28% by general hospitals, 17% by tuberculosis hospitals and sanatoria, and 1% by general practitioners. Among a total of 15 600 gastric washings, the corresponding percentages were 39, 30, 31 and 0.

In 1940 a filing system was worked out and has been kept up to date at the State Serum Institute. A main roster consists of a name file, as well as a file by year of birth, for all persons whose specimens have ever been positive for tubercle bacilli. Results of the current examination are entered on the main file cards, so a cumulative record for each individual is available. This file is used not only for the Institute's work, but also by the DTI and the local chest clinics as well.

Reporting system

Since the turn of the century it has been obligatory for doctors to report active cases of pulmonary tuberculosis.¹ The notification form, one for each patient, requires identification data, including name, date of birth, and place of residence. In 1940, the forms were revised to include a brief description of the extent and type of involvement, as well as the result of bacteriological examinations. Regular statistical processing of the notifications of new cases was begun in 1920, at which time a central register was set up in the National Health Service. Provision was made to remove deaths from tuber-

¹ Extrapulmonary tuberculosis did not become reportable until 1951 and for many years it was (and still is) diagnosed and treated by specialists in other fields rather than by the tuberculosis specialists, who generally deal only with the respiratory forms of the disease.

culosis from the register each year, but no provision was made to remove deaths from other causes or cases that became "cured", so the register continued to grow in size. In 1930 it was therefore decided to remove cases 8 years after the first notification as arbitrarily "cured", as 8 years was thought to represent the average duration of active disease. In 1950, one criterion for "cure" was generally agreed upon by the chest clinics, and patients considered cured should then be reported.

In close co-operation between the Statistical Unit of the National Health Service and the DTI, the Central Register was revised in 1949-51 by matching, county by county, the cards in the chest clinics' registers with those in the Central Register. Because of the 8-year criterion for cure, and because not all deaths had actually been removed, many cases in the Central Register could not be found in the clinic registers, and *vice versa*. All cases not considered active by the local clinics were removed from the Central Register, classed as cured, and set aside to form the basis for a File of Previous Cases.¹ To this file cases that were reported cured could be added over the coming years. Finally, cases that the clinics knew had died were taken out and put into a third main file, the File of Deceased Cases. Thus, the revision of the Central Register resulted in three files: Active Cases, Previous Cases, and Deceased Cases. The three files, still referred to as the Central Register, were transferred to the DTI in 1953 and have been kept up to date by reports on new cases, cures, and deaths to provide the official tuberculosis statistics for Denmark, as well as to serve as basic material for the research work of the DTI.

The burden of reporting cases of active respiratory tuberculosis falls mainly on the chest clinics: 80% of the first-timers and 95% of the relapses reported in 1960 were diagnosed in the chest clinics.² The notifications are sent by the clinics at regular intervals to the DTI *via* the National Health Service. At the DTI, the information is checked for completeness; compared with the records of bacteriological examinations done at the State Serum Institute; and

finally coded and transcribed on to punch cards. In processing each incoming card, the files are searched to check whether or not any one of them already contains a record for the same person. If no previous card is found, the patient is classed as a first-timer. If a card is found in the File of Previous Cases, he is classed as a relapse; the old card is then removed from the file and the new information is coded and punched on the card. The cards for all new cases reported during a year are kept separately until the end of the year, and then, after being counted, are transferred either to the File of Active Cases or to the File of Deceased Cases.

The duty to report cure rests only with the chest clinics. Each year, the clinics prepare and send to the DTI a special list giving the name and other identification data of patients considered cured as well as those removed from the clinics' registers of active cases for other reasons, such as failure to report for follow-up examinations. The card for each patient so reported is searched for in the File of Active Cases, the information on cure and year of cure (or other reason for removal from the clinic's register of active cases) is added, and the card is transferred to the File of Previous Cases.

All death certificates on which tuberculosis is mentioned, whether the disease was considered active or inactive, the "direct" or a "contributing" cause of death, are sent from the National Health Service to the DTI, where the files are searched for records of the persons concerned. When a card is found, the date and cause of death are copied on to the card, which is then transferred to the File of Deceased Cases. If no card is found, the appropriate chest clinic is asked for information about the person, and an ordinary notification form is made out for him. In 1960, for example, no records were found in the DTI files for 18 of the 174 persons whose deaths were attributed to pulmonary tuberculosis. Copies of the death certificates are sent by the DTI to the chest clinics so that their registers can be kept up to date. In turn, the clinics send the DTI any information they may have about deaths occurring among the tuberculosis patients in their districts, whether or not tuberculosis was considered a cause of death. Copies of death certificates for those persons are then obtained from the National Health Service, and processed as described.

REALITIES OF THE DANISH TUBERCULOSIS STATISTICS

From the above description, it would seem that most of the elements needed to document changes

¹ On account of the special studies to be undertaken in connexion with the mass survey in 1950-52, the file was supplemented with cards for all patients not known to have died who had been reported since 1937; and for all persons born in 1900 or later who had been reported for tuberculosis since 1920 and had attended the mass survey.

² In those instances when tuberculosis is diagnosed in a general hospital or by a private practitioner, the completed notification forms are sent through the local chest clinic, because each clinic keeps a register of all known active cases in its district.

in the picture of respiratory tuberculosis in Denmark are available today. True, the population is not large, only 4 581 000; but it represents a complete and, in a sense, "closed" population. Moreover, tuberculosis was as serious there as in almost any other country not so many years ago; but it has recently run through a course to where it is now considered more or less under control—and this is the present goal of most countries. Other important features for documenting the changing picture are that the population is co-operative and well informed about tuberculosis; almost all cases of the disease are detected, treated, and followed up by specialists; persons who move their place of residence can be readily traced through the municipal population registers; and unique nation-wide systems have been developed for reporting cases and cures, for keeping records, and for analysing tuberculosis statistics. Although theoretically ideal, are the various elements of the problem, as actually carried out, sufficient and adequate? Unfortunately, the answer has to be "almost". Uncertainties and deficiencies, most of them remediable, do exist and the more important ones are discussed in this section of the paper.

As mentioned earlier, the File of Active Cases in the Central Register should provide the data for estimating what may be called the current "burden" of tuberculosis—i.e., the number of active cases in the country at any point in time. This, in technical terms, is the point prevalence. So far as can be judged now, the File of Active Cases is probably complete and accurate; it is undoubtedly the best of the three main files in the Central Register, and, at the present time, probably the best of its kind in the world. Improvement of the file involves more efficient systems for removing cards for patients who have died from causes other than tuberculosis, and more realistic definitions for and reporting of patients who might be considered "cured" of tuberculosis. With the highly effective measures available today for treating tuberculosis, some of the patients carried in the file as active cases, perhaps a fairly large number of them, can hardly be regarded as having active tuberculosis: they are merely waiting out the three-year period until they can "officially" be called cured.

The File of Previous Cases, which is the source of the important group of patients classed as relapses, appears to be a fairly complete numerical record of patients reported cured after 1950-51. Patients who became eligible for inclusion in the file before 1950 are probably highly unrepresentative of all the

patients whose records should be in that file. In 1960, for example, the file contained records for 35 300 persons: about 23 800 were classified as previous cases in or after 1950, and only about 11 500 so classified before that time. If, as one estimate indicates, about one-fifth of a million Danes were diagnosed as having tuberculosis during the first half of the present century, it is unrealistic to believe that only 11 500 of them were still alive in 1960. It is difficult to visualize how this defect in the file could be remedied; perhaps nothing can be done, and as time passes the significance of the defect will become less.

A defect that can be remedied, however, and one that is now being worked on, involves the cards in the File of Previous Cases for persons who have died of causes other than tuberculosis. More efficient and less expensive ways must be found of removing the fairly large number of such cards still in the file.¹ Until this can be done, and kept current, relapse rates based on the present file have to be regarded as underestimates.

Another, less important, defect in the File of Previous Cases concerns patients reported as active cases but who, for one reason or another, have not been kept under observation so their disease status is actually unknown. Such patients should be taken off the clinics' registers of active cases three years after cessation of treatment and reported as lost to follow-up. In the Central Register, cases so reported are transferred from the File of Active Cases to the File of Previous Cases, with appropriate notations added to the cards. The number of such cases is relatively small and, because it seems reasonable to assume that if the persons concerned still had significant disease they would have returned to the clinics for treatment, they are handled as if they no longer had active disease.

The third main file in the Central Register, the File of Deceased Cases, contained about 18 000 cards on 1 January 1960. At present, this file is not much more than a convenient depository for the records of persons, now dead, who once had tuberculosis. And, particularly because it does not contain records for all of the dead persons from the File of Previous Cases, it is incomplete. However, when deaths are cleared from that file, the File of Deceased Cases

¹ Since there are about 45 000 deaths from all causes in Denmark each year, the present task of removing cards amounts to the annual matching of 45 000 cards with the File of Previous Cases which, in 1960, already contained over 35 000 records.

should prove most useful for studying the history and characteristics of that special sample of the general population that once had tuberculosis, particularly those who had the disease after 1950.

In addition to the files themselves, the records of persons who, each year, enter or are removed from each file are a most important source of epidemiological data. It is therefore desirable to consider the completeness and accuracy of such groups at the present time.

First, except for the relatively minor defects already noted, it is believed that removals from the File of Active Cases are adequate for at least preliminary studies of cure rates as well as of mortality rates among persons with active tuberculosis.

Next, the number of new cases entering the File of Active Cases can be considered quite complete. Less reliance, however, can be placed on dividing the gross incidence into the part contributed by persons diagnosed as having tuberculosis for the first time and the part contributed by those classed as relapses. There are several reasons for this uncertainty. Probably the most important is that in the past case-finding was not as efficient as it is today. Many persons with small "primary" and self-limiting lesions in childhood and youth probably were not considered as having active tuberculosis; when, years later, some among them develop active tuberculosis, they will be classed as "first-timers" and not as "relapses". In addition, the deficiency in the File of Previous Cases, mentioned above, will also tend to diminish the actual number of cases classed as relapses. Even at the present time the official Danish tuberculosis morbidity statistics refer only to new cases as persons who are diagnosed for the first time as having the disease; relapses are not included. Today, this does not seem very realistic, but it must be remembered that it has only been in recent years that cures have been reportable and could therefore be removed from the File of Active Cases.

Thus the specific designation of "cure" and the official reporting of cured cases is a relatively new and still not too well developed concept in either the clinical or statistical handling of tuberculosis. Efforts to overcome some of these problems include the expenditure of considerable time in the DTI office in matching all notified or "renotified" case reports with the records in both the File of Active Cases and the File of Previous Cases and with the records of bacteriological examinations in the State Serum Institute. One of the results of this

work is an increase in the number of cases classed as relapses with a corresponding decrease in the number of first-time cases. It should be emphasized, again, that the records in the File of Active Cases can be regarded as quite complete with regard to the *total number* of persons with active tuberculosis in the population; but separation of the active cases into first-timers and relapses is not very accurate, and the results will tend to understate the proportion that should be designated as relapses.

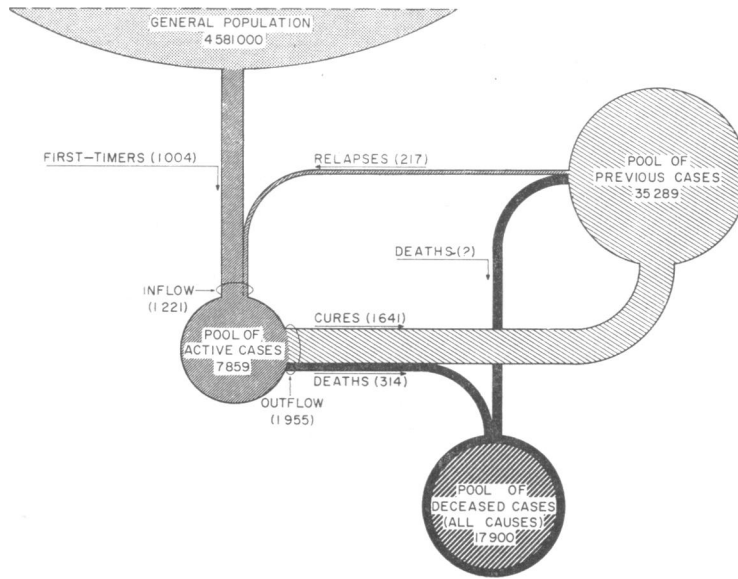
A few general comments about the present status of Danish tuberculosis statistics should probably be added. The clinical and statistical operations as now carried out are the result of many years of co-operative efforts by many workers—and many changes have been and are still being made. Probably none of these operations is as satisfactory or as efficiently carried out as would be desired. It takes time to effect desirable and agreed-upon changes. Outmoded techniques and procedures tend to be continued; omissions and errors in the records are plentiful; and basic documents made many years ago are not comparable with those being made today. Nevertheless, it seems fair to say that, so far as a judgement can be made today, all of the elements needed to document the evolving picture of tuberculosis are now in force in Denmark. In the parlance of the engineers, a complex machine for diagnosing, reporting, and analysis has been built, it works, but there are "bugs" that have to be eliminated. To do so will require careful, co-ordinated work; and that will take time, and be expensive.

DYNAMICS OF THE STATISTICS

A concept of the dynamics of tuberculosis morbidity and mortality—the constantly changing numbers of persons developing the disease, becoming cured, or dying—is illustrated schematically in Fig. 1, the numbers given there referring to the calendar year 1960.

The segment of a large circle shown at the top and to the left of the figure represents the general population of Denmark, about 4.5 million persons with no record in the Central Register of ever having had pulmonary tuberculosis. The darkly shaded circle directly below, the Pool of Active Cases, represents the nearly 8000 persons on record in the File of Active Cases on 1 January 1960. The larger, lightly shaded circle above and to the right is the Pool of Previous Cases; it comprises about 35 300 persons once reported as having active

FIG. 1
DYNAMICS OF TUBERCULOSIS MORBIDITY AND MORTALITY IN DENMARK, 1960



tuberculosis but whose disease is now considered cured or is of unknown status. The black circle at the bottom of the figure represents roughly 18 000 persons, now dead, who at some time in their lives had active tuberculosis.

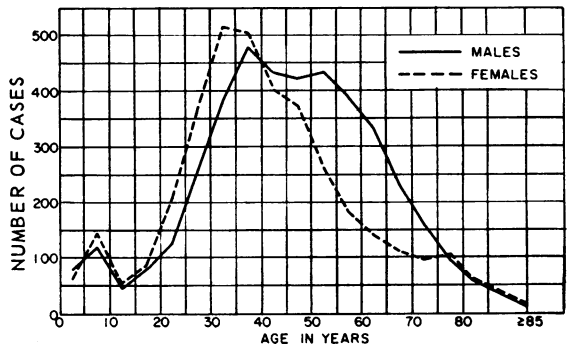
The channels connecting the various pools represent the continuously flowing streams of persons who during the year 1960 were entering the Pool of Active Cases as first-timers from the general population and relapses from the Pool of Previous Cases, and those who became cured and went into the Pool of Previous Cases or died and went to the Pool of Deceased Cases. The numbers of persons in the pools and streams, and the changes in these numbers from year to year, depict the forces which lie hidden in the statistics of tuberculosis prevalence, incidence, and mortality.

It is not possible to predict which of the many indices that may be derived from the material will prove most useful, or what kind of further information might be needed about the cases—both for practical purposes and for a better understanding of the natural history of the disease. Some of the possibilities can, however, be illustrated.

Morbidity—prevalence

As shown in Fig. 1, nearly 8000 persons were in the Pool of Active Cases on 1 January 1960. This number, when related to the total population of Denmark, provides a point-prevalence rate of 172 active cases per 100 000 population. And, since the pool and the general population contained about

FIG. 2
POOL OF ACTIVE CASES, DISTRIBUTED ACCORDING TO SEX AND AGE, AT THE BEGINNING OF THE YEAR 1960



the same proportions of males and females, the prevalence rates for the two sexes were not very different: 183 for males and 161 for females. However, distribution of the active cases by age as well as sex (Fig. 2) shows that there were more females than males in the age-groups up to 40 years, and considerably more males thereafter.

During the year 1960, the streams flowing into the Pool of Active Cases totalled about 1200 persons, but the outflowing streams contained nearly 2000. As a consequence, the prevalence decreased to 156 per 100 000 at the end of the year—a reduction of about 9%, although for females the decrease was nearly 13% while for males it was only about half that figure, i.e., approximately 7%. For both sexes, the reduction in the number of active cases occurred principally in persons between 20 and 50 years of age (Fig. 3).

Further analyses for a variety of factors can provide details not only about the characteristics of persons who become active cases but also of those who remain active cases. For example, the Pool of Active Cases can be separated according to whether

tubercle bacilli had or had not been cultured when the cases came into the pool, and further according to the proportion of the initially "positive" persons in the pool who at any point in time are still excreting bacilli; it can also be separated according to severity of disease (roentgenographic findings), place of residence, and so on. Such information should underlie the development of new ways to hasten the decline of the disease.

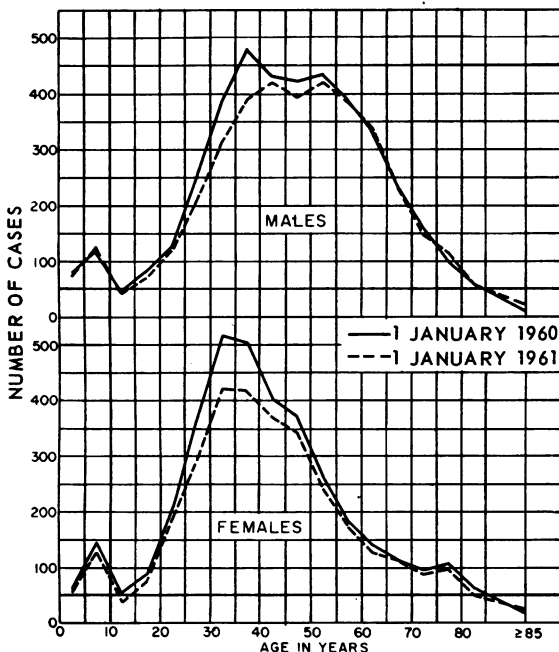
Morbidity—incidence

Incidence rates, as derived from the streams of patients flowing into the Pool of Active Cases, furnish details not previously available on a nationwide basis. As Fig. 1 shows, 1221 cases of active respiratory tuberculosis were diagnosed and reported during the year 1960, giving an incidence rate of 27 per 100 000 general population. This over-all rate, however, should be subdivided according to previous history of tuberculosis: 945 new cases from the general population, classed as "first-timers",—21 per 100 000; 217 from the Pool of Previous Cases, classed as "relapses",—5 per 100 000; and, finally, 59 patients who, although they were first-timers in the sense that they did not have a record in the File of Previous Cases, were undoubtedly really relapses as judged from information available from a variety of sources—1 per 100 000.

Taken all together, it can be seen that relapses are a significant part of the tuberculosis incidence. In fact, registered relapses accounted for 18% of all new cases reported during 1960; and, as mentioned above, there are cogent reasons to believe that this figure is an underestimate and that the proportion (though perhaps not the numbers) of relapses will increase in coming years. At the present time, however, the majority of the cases are first-timers; and from the practical side of the control programme it is essential to know what proportion of these cases are arising as a result of recent infection—primary tuberculosis—and what proportion are arising among persons infected many years ago—post-primary tuberculosis. Suffice it to mention here that the results of the four-year follow-up of the participants in the 1950-52 nation-wide survey for tuberculosis, reported by Groth-Petersen, Knudsen & Wilbek (1959), showed that the vast majority of new cases were occurring in persons already infected at the time of the survey. Preliminary analysis of further follow-up studies indicates much the same situation. This tallies well with the very low infection rate which could be observed among school-

FIG. 3

POOL OF ACTIVE CASES, DISTRIBUTED ACCORDING TO SEX AND AGE, AT THE BEGINNING AND AT THE END OF THE YEAR 1960



children in one of the districts where vaccination with BCG has been postponed until graduation (Groth-Petersen, 1963).

The sex and age composition of the active cases reported in 1960 furnish elementary but important details about tuberculosis incidence. Among the 945 true first-timers, 602 were males and 343 were females, which gives an incidence nearly twice as high in males as in females—27 and 15 per 100 000, respectively. Although other indices, both in Denmark and in other countries, point to an increasing difference between the sexes, one must be cautious in interpreting all of the difference as representing biological factors. Groth-Petersen, Knudsen & Wilbek (1959), for example, called attention to the larger numbers of men than women included in the routine "group examinations" for tuberculosis conducted by the chest clinics among factory and other workers in Denmark.

In striking contrast to the sex difference in the numbers of new cases (first-timers) arising in the general population, no difference was observed for the 217 relapses coming from the Pool of Previous Cases: 110 males and 107 females. Since the Pool of Previous Cases, like the general population, contains about equal numbers of both sexes, the estimated rates are similar for both sexes.

The age composition of the new cases is shown in Fig. 4. The pair of curves for first-timers has one peak in early childhood and one, or more, in the older age-groups. After the age of 15 years the curve for males rises to a peak at about 50 years,

whereas the curve for females seems to run at two levels, the higher between 20 and 50 years and the lower from 50 years onwards. As the figure shows, the higher incidence of new cases among males than among females can be attributed primarily to men in the middle age-groups. The two curves for relapses differ completely from those for first-timers. They seem to be unimodal, with a peak around 45 years, and are nearly the same for both sexes except that the peak occurs in a slightly older age-group in males than in females.

This brief view of the new cases should not be concluded without mentioning the undesirability of limiting tuberculosis incidence rates to cases designated as "new", meaning first-timers, as has been traditional. A relapsed case of tuberculosis is just as much a part of the burden of tuberculosis as a first-timer, and just as much, if not more so, a source of new infections in the community. In fact, tubercle bacilli were cultured from 78% of the relapsed cases, as compared with 65% of the first-timers, reported in 1960.

Mortality from or with tuberculosis—the lethality index

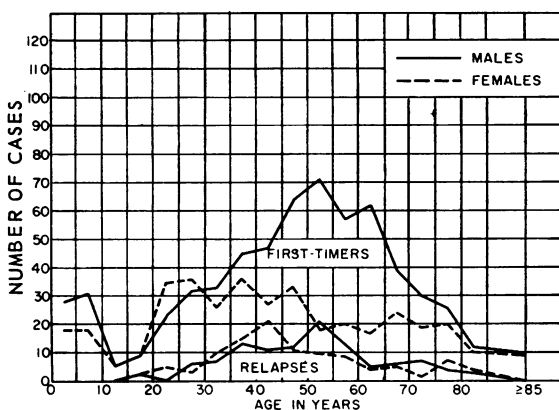
The mortality rate for a specific disease is generally conceived of as a measure of how many persons were killed by the disease. For illnesses such as smallpox this concept seems reasonable; and the same may have applied to tuberculosis in the past, when many deaths, particularly of young people, were obviously the direct result of their having tuberculosis.

However, do the ordinary tuberculosis mortality rates measure the killing effect of tuberculosis today? We believe they do not. And it will be shown below why it is thought they do not and how another index appears to furnish a more realistic and objective measure of the lethal effect of the disease.

According to the official statistics, the tuberculosis mortality rate in Denmark in 1960 was 3.8 per 100 000—174 deaths in 4.5 million people. According to the generally accepted connotation of a mortality rate, those 174 persons died because of their disease. But how and by whom were the decisions made that resulted in the number being 174, not more and not less?

The inclusion or exclusion of a particular disease or condition as a cause of death is the result of a series of decisions by the doctor who fills out the death certificate, the clerk who codes what the

FIG. 4
INFLOW INTO THE POOL OF ACTIVE CASES
DURING 1960, DISTRIBUTED ACCORDING TO SEX
AND AGE



LETHALITY INDEX FOR ACTIVE TUBERCULOSIS IN DENMARK, 1960

Tuberculosis population	Number of cases	Deaths during 1960			Lethality index ^a	Percentage of lethality index
		Observed number	Expected number	Excess (observed—expected)		
Entered the Pool of Active Cases after 1 January 1960, as:						
First-timers	1 004	86	9.5	76.5	1.7	37
Relapses	217	16	1.6	14.4	0.3	7
Already in the Pool of Active Cases on 1 January 1960	7 859	212	96.8	115.2	2.5	56
Total	9 080	314	107.9	206.1	4.5	100

^a Excess number of deaths per 100 000 general population.

doctor wrote on the certificate, and the statistical staff who interpret the official rules that govern the selection of one, and only one, disease as *the* cause of a death. The doctor's is a difficult role, because most deaths in which tuberculosis might be considered a possible cause nowadays occur among older people, many of whom also have other diseases and conditions. The doctor, according to his background and opinions, judges which of them, if any, outweighs tuberculosis as the direct or a contributing cause of death. Moreover, the modern, highly efficient treatment of tuberculosis could unconsciously introduce a significant bias. Since it is now generally accepted that the vast majority of patients can be cured, when a patient dies the doctor may look more carefully than in former years for other diseases or conditions as the cause of death. If this policy were carried to its extreme, tuberculosis could practically disappear as a cause of death.

Further difficulties arise from the necessity, for statistical purposes, to classify deaths according to only one cause. This involves an administrative selection based on rules for what diseases and conditions take precedence over others (World Health Organization, 1957). Partly because tuberculosis no longer kills a great many people, and partly because of the uncertainties in deciding what killed the patient, traditional mortality rates can no longer be considered satisfactory measures of either the status of the tuberculosis problem or of its lethal effect.

The information available in the Danish files furnishes possibilities for another, more objective,

measure of how much tuberculosis contributes to mortality—a measure that cannot be tampered with because it does not involve the difficulties of assigning causes of death to individual persons.

The diagram in Fig. 1 shows that a total of 314 deaths, from all causes, occurred in 1960 among the persons in the Pool of Active Cases. Although not shown in the diagram, 102 were among patients who had entered the pool during the year and 212 were among patients already in the pool at the beginning of the year (see accompanying table). Thus, the number of persons who died *with* the disease—314—is nearly twice the official figure of 174 persons who died *from* the disease.

What does it mean that 314 patients with active tuberculosis died during the year? Some of these patients no doubt died because they had tuberculosis; but some may have died because they had cancer, or cerebral vascular accidents, or almost any other disease. The question, then, is how much did tuberculosis add to the patients' "normal" expectation of death?

To estimate the number of deaths that could have been expected in a similar group in the general population, the death rates for the general population were applied to all patients with active disease in 1960.¹ This showed that 108 deaths were expected. However, 314 deaths were actually observed among the patients, which means that there has been an

¹ Sex- and age-specific (5-year age-groups) mortality rates for deaths from all causes in the general population (Statistisk Departement, 1962) were applied to all patients, with an average period at risk of 6 months for new cases entering the pool during the year 1960 and of 12 months for those already in the pool at the beginning of the year.

excess of 206 deaths. This excess might be considered a result of the patients' tuberculous disease, either directly or indirectly. Admittedly, the patients also differ from the general population in other important respects, such as socio-economic status. In some countries, these factors may be of considerable importance, but we believe at the present time that their significance is not great in Denmark. It is therefore considered reasonable to hold active tuberculosis accountable for most, if not all, of the 206 excess deaths, giving a rate for 1960 of 4.5 deaths per 100 000 general population. This rate, for want of a better term, is called the *lethality index* for active tuberculosis.

The various groups which make up the tuberculosis population contributed differently to the lethality index for 1960, as shown in the table. The relatively small group of 1221 cases that entered the Pool of Active Cases during the year contributed nearly as much to the lethality index as the group of 8000 already in the pool as active cases at the beginning of the year. To reduce the lethality index it might therefore appear, at first glance, most profitable to concentrate on improving methods for earlier case-finding, since the great majority of new cases come out of the general population. Closer examination of the material reveals, however, that it would be more profitable to focus attention on patients already in the Pool of Active Cases and the Pool of Previous Cases, as deaths occurring among them together accounted for two-thirds of the lethality index.

The lethality index for active cases of tuberculosis cannot be considered as measuring all of the possible lethal effects of the disease. To this index should be added the rate found for previous cases of tuberculosis, but unfortunately it is not now known how many deaths actually occurred in the Pool of Previous Cases. However, a rough estimate was obtained from a recent pilot study, which indicated that the observed number of deaths exceeded the expected number. This can only mean that the total burden of tuberculosis, in terms of lives lost, is higher than the estimated 4.5 per 100 000.

This brief analysis suggests that the lethality index for tuberculosis can be a useful guide to one aspect of the progress towards eradication: when the index approaches zero, it could be claimed that at least the lethal effect of the disease has been eliminated.

Potentialities in the Pool of Previous Cases

It was probably not visualized in 1950 either how difficult the task would be, or how significant the

potentialities would be, if a nation-wide file of previous cases of tuberculosis in Denmark could be kept up to date. Despite the imperfections in the present file, it has become evident that the work initiated by the late Dr E. Groth-Petersen represents one of the most significant advances in tuberculosis statistics since the disease was officially declared reportable. One of the major tasks now is to realize some of the potentialities in this Pool of Previous Cases and in the streams of cases entering and leaving it.

Analysis of the yearly stream of cured cases, for example, should make it possible to evaluate the effectiveness of present-day treatment of tuberculosis for the country as a whole. Cure rates approaching 100% have been reported for selected groups of patients treated in particular ways; but, so far as the national picture is concerned, a realistic evaluation of what is actually being achieved must rest on the results obtained for all patients, treated by all hospitals, clinics and physicians throughout the country. How many and what kinds of cases are, in fact, being cured, and with what treatment? Conversely, what cases are not being cured, or die?

As previously mentioned, the File of Previous Cases contains records for nearly 24 000 patients reported cured since 1950. There were 188 relapses in this group during 1960, which gives an incidence rate of almost 800 per 100 000—40 times higher than the incidence in the general population. Actually the difference in rates is even greater, because not all the deaths, regardless of cause, have been removed from the File of Previous Cases. Moreover, the cases cured since 1950 constitute a very small proportion of the total Danish population—certainly no more than 0.5%—but they contributed 15% of all the active cases reported during the year. If practical ways can be found of reducing the incidence of relapse, then it is of enormous advantage that these persons can easily be traced, as identifying data are already available on the cards in the file. Moreover, the information on these cards may also be used to define subgroups among them with the highest risk of relapse, as well as those for whom the risk is so low that continued follow-up is much less profitable.

In a sense, since relapses could be regarded as delayed treatment failures, it will undoubtedly become more and more important to learn, for the country as a whole, what types of cases, given what types of treatment, are most likely to relapse

and to die. Plainly, answers to such questions should make it possible to pin-point those special groups for close surveillance, as their contribution to the burden of tuberculosis for the country will be very great. Moreover, information about such

high-risk groups will provide the bases for devising new and more efficient methods for the eradication of tuberculosis—methods that undoubtedly will be quite different from those used so long for the control of tuberculosis.

RÉSUMÉ

En de nombreux pays des signes d'un déclin rapide de la tuberculose ont apparu mais l'on ne possède qu'une connaissance très superficielle des raisons profondes de ce changement. Il est par conséquent indispensable d'utiliser dans l'étude de la tuberculose des paramètres qui ne soient pas seulement descriptifs mais puissent indiquer les lignes selon lesquelles doit s'ordonner la lutte contre la maladie. Le but de l'article est de décrire la dynamique du problème tuberculeux au Danemark, d'après les données recueillies dans l'index danois de la tuberculose.

La dynamique de la morbidité et de la mortalité peut être représentée par 4 grands compartiments humains reliés par des courants continus. Le plus grand est celui de la population générale indemne de tuberculose; les trois autres, plus petits, contiennent respectivement les malades en cours d'évolution, les anciens malades et les tuberculeux décédés (qu'ils aient été, au moment du décès, en pleine évolution ou d'anciens malades). Deux courants se déversent dans le compartiment des malades en cours d'évolution: l'un est composé de nouveaux cas et provient du compartiment de la population générale, le second provient du compartiment des anciens malades et apporte ceux qui présentent des rechutes; deux courants quittent le compartiment des malades actifs et se rendent respectivement au compartiment des anciens malades (en cas de guérison) ou à celui des tuberculeux décédés. De même le compartiment des anciens malades est alimenté par les cas guéris et se vide dans celui des malades en cours d'évolution (en cas de rechute) et dans celui des tuberculeux décédés.

Les faits, les estimations et autres données nécessaires à l'établissement de statistiques valables sont recueillis à la suite d'observations faites sur toute l'étendue du terri-

toire. La recherche de la tuberculose doit être poussée de telle sorte qu'un nombre négligeable de cas échappe au dépistage. Les malades doivent être systématiquement revus et suivis. Les critères d'activité de la maladie ou de guérison doivent être définis de façon uniforme et précise afin que les taux prennent toute leur signification. La première des choses est, bien entendu, l'établissement d'un registre central et d'un système efficace d'enregistrement des maladies, des guérisons et des décès. Toutes ces conditions sont largement remplies au Danemark; cependant plusieurs défaillances ont été signalées et sont discutées. La plupart des défaillances peuvent et doivent être palliées même s'il faut pour cela du temps et de l'argent.

En partant des données actuelles l'on a obtenu des chiffres précis et véridiques sur la fréquence globale et la fréquence des nouveaux cas, ainsi que sur les rechutes pour l'année 1960. Le système actuel d'enregistrement des guérisons présente un grand intérêt car c'est, semble-t-il, la première fois que les taux de guérison, à court terme comme à long terme, peuvent être connus à l'échelle nationale. Les taux de mortalité par tuberculose sont également fournis, mais ces données sont sujettes à certaines imperfections (médicales, cliniques, administratives) qui joueront un rôle croissant tandis que la courbe générale de la tuberculose continue à descendre. Une mesure plus objective du danger mortel de la tuberculose pour la collectivité comme pour les malades serait l'index de létalité basé sur le chiffre des décès survenant chez les tuberculeux et non, comme c'est l'usage, sur celui des décès *par* tuberculose.

L'auteur fournit d'autres exemples de l'utilisation et l'analyse des chiffres et des taux pour la mise en évidence des facteurs responsables de l'évolution de la tuberculose.

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