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Epidemiological Basis of Tuberculosis Eradication in an Advanced Country

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The first section of the report provides a background for the long-range epidemiological studies being conducted by the Danish Tuberculosis Index. An outline is given of the main indices of tuberculosis and the changing tuberculosis situation in Denmark during the past several decades with respect to prevalence of infection, morbidity and mortality. Difficulties encountered in international comparisons are briefly discussed. The prevalence of tuberculous infection in children and the prevalence of bacillary cases of pulmonary tuberculosis in adults are suggested as the most valuable indices of eradication.

The second section describes the nation-wide mass campaign of 1950-52, which was planned and conducted as a combined service and research programme under the direction of the Danish Tuberculosis Index. With a view to the follow-up studies, details are given of the results of tuberculin tests of the unvaccinated, the documented vaccinated and mixed groups in the population examined. A survey is made of the results of X-ray examination and of the relation between vaccination status, tuberculin reaction and X-ray findings.

The results of the first follow-up period are analysed in the final section of the report in terms of new cases of pulmonary tuberculosis appearing in the adult population. Seventy-five per cent of the new cases appeared among the unvaccinated tuberculin-positive population, and among this population groups of persons with widely different risks of developing tuberculosis could be identified on the basis of X-ray findings and reactions to the intradermal 10 TU tuberculin test. A proposal is made to reduce the number of routine repetitive examinations for adults and to concentrate efforts on preventive measures for the high-risk groups.

INTRODUCTION

Until recently, effective control of tuberculosis —a major health problem of the world—could hardly be called promising. Prevention of the disease was more dependent upon improvement in living standards than upon direct medical and public health procedures. In the course of the last ten years, however, the situation has changed radically with the dramatic discovery and rapid development of potent antituberculous drugs. Now, for the first time, we have the means for a direct attack upon the tubercle bacilli in the human reservoir, and the curative and prophylactic values of these chemotherapeutic agents are high.

In view of recent achievements the time has come to review critically our present tuberculosis programme and to determine how to utilize the discoveries of the past decade to the greatest advantage of both the individual and the community. In countries which already have a very low tuberculosis morbidity and a low tuberculous infection-rate it should now be possible to visualize complete eradication of the disease. A certain reorientation of the existing tuberculosis programme may be necessary and must be based on descriptive as well as on experimental epidemiological studies. Furthermore, the events taking place during the phase of eradication in some countries must be followed, described and measured very carefully, so that the experience gained may help to guide other countries in a reorientation towards eradication.

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Denmark [1] is some years ahead of most other countries in the progress towards the eradication of tuberculous disease; the organization of the tuberculosis service, and the field work, as well as the centralized laboratory service and registration, offer particularly favourable facilities for carrying out the required studies; and a research project, the Danish Tuberculosis Index, established by the Danish National Health Service in collaboration with the WHO Tuberculosis Research Office, has been in operation over a number of years. Among the problems it has taken up for study is the possibility of dividing the general population, on the basis of a single or a few examinations, into groups with markedly different risks of developing tuberculosis. The study demonstrates that even such simple examinations as tuberculin testing and chest radiography may result in a definition of large low-risk groups and permit a reduction of the enormous number of routine examinations of the population. In the same way, it may be possible to define high-risk groups on which frequent observation and preventive efforts must be concentrated.

The report is divided into three sections. The first discusses briefly the main indices of tuberculosis and outlines the tuberculosis situation in Denmark during the past several decades as a background to the work of the Danish Tuberculosis Index. The purpose of the second section is twofold: (1) to describe how the Danish tuberculosis mass campaign of 1950-52 was planned both as a community health service and in the interests of research; and (2) to set forth the findings of the campaign as far as they may be of interest in the follow-up studies. The final section is concerned solely with the new cases of tuberculosis appearing over the subsequent four-year period in the adult population who were deemed healthy with regard to tuberculosis at the time of the campaign.

THE BACKGROUND FOR THE STUDIES: TUBERCULOSIS IN DENMARK

Tuberculosis morbidity and mortality rates in Denmark have been among the lowest in the world for some decades, and the goal of eradication is nearer than in most other countries. Yet despite such a favourable situation, Danish tuberculosis specialists strongly advocated a nation-wide mass BCG vaccination campaign; and late in 1949 plans were being made for a programme which would include tuberculin testing and X-raying as well as vaccination of large segments of the population. It was recognized that the results of examinations conducted carefully and with uniform procedures would provide basic material for prospective epidemiological studies.

Information which would characterize the population as regards pertinent criteria for the campaign against tuberculosis and pinpoint the sources of infection in the present phase of the campaign could, it was believed, be of great value not only to Denmark but to other countries soon to enter the eradication phase of tuberculosis control.

INDICES OF TUBERCULOSIS

The indices which are used to describe the tuberculosis situation in a population are tuberculosis mortality and morbidity rates and the prevalence of tuberculous infection (WHO Study Group on Tuberculosis Control, 1956).

For many years tuberculosis mortality has been the only reasonably good measure for international comparisons and for some parts of the world it is still the only available index. However, in an increasing number of countries deaths from tuberculosis are now so few, particularly in the younger age-groups, that mortality rates are no longer satisfactory. They do not give a proper picture of the morbidity trends and are affected too much by random fluctuations.

The use of morbidity statistics for international comparisons is complicated by differences in the definition of the term " tuberculous disease ", in the case-finding activities and in the systems of reporting cases. Through the years the conception " tuberculous disease " has been constantly widened to keep abreast of advances in diagnosis, therapy and public health facilities. As tuberculosis is generally a chronic disease some patients will live for many years with such slight or bearable symptoms that medical attention is not sought and the disease remains unrecognized. Nevertheless such chronic cases are of public health significance because, *inter alia*, they may be periodic or constant sources of infection; but they will only be discovered if examina-

[1] Total population on 1 July 1955 : 4 440 000

tion, including adequate bacteriological examination, is required by the public health service. Morbidity statistics will therefore be influenced by the proportion of the population examined without respect to symptoms.

Undoubtedly the diversity in the systems of reporting and registration is the major difficulty in compiling comparative morbidity statistics for European countries. As an example may be mentioned a comparative investigation in the Netherlands and Denmark made in 1955 on Dutch initiative in co-operation with WHO. Although through several decades (apart from the war years) the two countries have had the same tuberculosis mortality and comparable facilities for examination, diagnosis and treatment, the figures for the incidence of pulmonary tuberculosis in the Netherlands were nearly three times as high as in Denmark. Investigation revealed that differences in the notification systems, particularly the central registration of relapses, made the statistical unit " a new case " a very different concept in the two countries, and any comparison of incidence figures was consequently worthless.

The prevalence of tuberculous infection is more easily made a valuable comparative tuberculosis index than are morbidity statistics, and in those areas of the world where the eradication of tuberculosis is within sight this index can now undoubtedly be regarded as the most important guide in conducting the campaign. In former days, when nearly the entire population apparently acquired a tuberculous infection, tuberculin sensitivity was not considered an abnormality. Now, however, the positive tuberculin reaction must be considered an abnormality, and the prevalence of specific tuberculin sensitivity in children is a very important criterion in evaluating the amount of tuberculosis in the population. By specific tuberculin sensitivity is meant the sensitivity caused by natural infection with bovine or human tubercle bacilli. Tuberculous infection caused by avian tubercle bacilli is so rare that it need not be considered.

In determining the presence of tuberculous infection, the problem of non-specific tuberculin sensitivity of more or less unknown origin is encountered in various parts of the world (Edwards & Palmer, 1958; WHO Tuberculosis Research Office, 1955a). And in many places, particularly in Europe, difficulties are temporarily encountered because vaccination against tuberculosis has induced a tuberculin sensitivity which cannot be distinguished from the specific sensitivity caused by virulent tubercle bacilli. Thus, neither the prevalence nor the incidence of tuberculous infection can be determined in the vaccinated age-groups from the results of tuberculin testing surveys.

Research studies of the WHO Tuberculosis Research Office and the Danish Tuberculosis Index have shown that with the 5 TU or 10 TU dose of purified tuberculin the problem of non-specific tuberculin sensitivity from sources other than BCG is of little significance in Denmark (Danish Tuberculosis Index, 1955c; WHO Tuberculosis Research Office, 1955a, 1955b). And, as indicated in the following, the difficulties created by BCG vaccination in estimating the prevalence of tuberculous infection cannot have been substantial in Denmark until recent years.

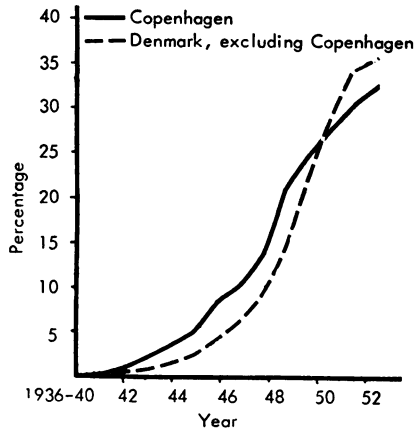
BCG VACCINATION IN DENMARK

It is generally believed by persons outside Denmark that BCG vaccination has been used extensively in the Danish population for many years, and that our low tuberculosis morbidity and mortality can be attributed to vaccination. This belief is not in accord with the facts. BCG vaccination was used on a large scale in Denmark for the first time in the years 1948-52, at which time mortality from pulmonary tuberculosis was already down to about 12 and morbidity to about 60 per 100 000 per year.

The reason for the misconception about the use of BCG in Denmark is probably that just after the war Denmark, together with Sweden and Norway, started the mass vaccination programmes (known as the International Tuberculosis Campaign) in the war-devastated countries of Europe. Curiously enough, it was just this international campaign which prepared the ground for mass vaccination in the homeland, even though BCG had been introduced into Denmark as early as 1927 by K. A. Jensen. In the mid-1930's Jensen's extensive experimental work had established the necessary confidence in the harmlessness of the latest batch of BCG received from the Institut Pasteur (Jensen, 1946); and at that time some chest clinics began to vaccinate a few persons, but only heavily exposed contacts. In 1942 somewhat more extensive use of BCG vaccination was proposed (Jensen, 1942) and in the following years several of the chest clinics started vaccinating all persons referred for examination who were found to be tuberculin negative (Slottved, 1947). But apart from mass vaccination programmes on the small island of Bornholm in 1941 (Olsen, 1953) and

FIG. 1

CUMULATED PERCENTAGES OF VACCINATED PERSONS IN THE POPULATION OF COPENHAGEN AND THE REST OF DENMARK, BY YEAR, 1936-52



in Copenhagen in 1946-48 (Winge, 1950), the general use of BCG was extended only gradually and slowly up to 1948, as shown in Fig. 1.

As late as the end of 1947, only 5%-10% of the population had been vaccinated (Groth-Petersen, 1949; Winge, 1949). For the country as a whole (exclusive of the city of Copenhagen and Copenhagen Country), the approximate proportions of vaccinated persons in the different age-groups were as follows:

0-5 years	2%
6-13 years	8%
14-24 years	13%
25 years and over	2%

Thus, even though vaccination had been carried out most extensively in the 14-24 year age-group, only about one-sixth of the tuberculin negatives of that age had been vaccinated. On 1 April 1949 a provision of the Danish School Health Act came into force, requiring that, through co-operation between the school health officers and the chest clinics, all schoolchildren should be examined annually for tuberculosis and all tuberculin-negative children should be offered BCG vaccination before they left school. In the years 1949-51 vaccination was actually given to somewhat more than 90% of tuberculin negative schoolchildren of all ages. Nation-wide vaccination of pre-school children and adults was not carried out until 1950-52.

Since then, mass vaccination of the succeeding generations has been mostly undertaken in schools. For some years the accepted practice in all counties but one (Groth-Petersen, 1955; Slottved, 1958) was to vaccinate all tuberculin-negative children as they entered school at the age of 7. However, as a consequence of the results of our studies of infection rate and morbidity, it has now been proposed to postpone mass vaccination to the age of 14-17 years (school-leaving age) in half of the counties outside the Copenhagen area.

PREVALENCE OF TUBERCULOUS INFECTION IN THE PAST

The only available figures on the prevalence of tuberculous infection in samples of the general adult population during the mid-1930's are from a small survey sponsored by the National Association for the Fight against Tuberculosis (Groth-Petersen, 1935). The survey included adults of all ages (printers, unskilled workers, office workers, journalists and employers) in 10 job-printing shops in Copenhagen and 93 job-printing shops and newspaper printing offices in several Jutland towns, who were tested uniformly with standardized old tuberculin up to 100 TU. From 90% to 95% of the reactors were found to be positive to the 10 TU test.

As shown in Fig. 2, the percentages of reactors were extremely high: after the age of about 35 years, it could truly be said that practically everyone had had a tuberculous infection.

Considerably more information is available on tuberculin sensitivity in schoolchildren and adolescents from the extensive epidemiological surveys carried out by the Statens Seruminstitut (Madsen,

FIG. 2

PERCENTAGE OF POSITIVE TUBERCULIN REACTORS, BY AGE, AMONG 1613 PRINTERS, JOURNALISTS AND OFFICE WORKERS IN COPENHAGEN AND SEVERAL PROVINCIAL TOWNS, 1934-35

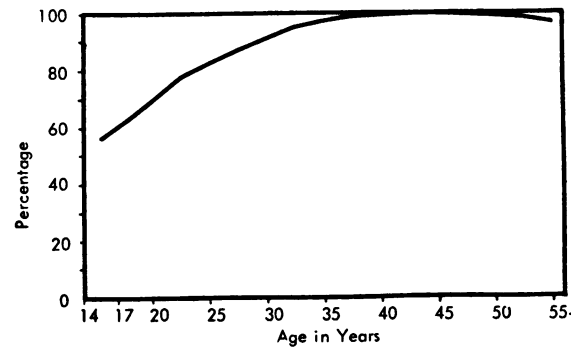
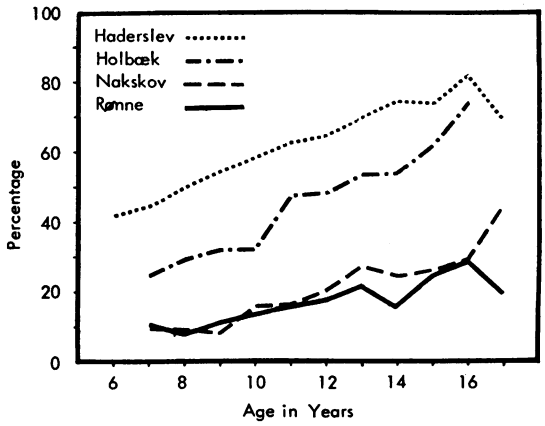


FIG. 3

PERCENTAGE OF POSITIVE TUBERCULIN REACTORS, BY AGE, AMONG CHILDREN IN FOUR DIFFERENT TOWNS IN DISTRICTS WITH DIFFERENT PREVALENCE OF TUBERCULOSIS IN CATTLE, DENMARK, 1937



Haderslev and Holbæk are in districts where tuberculosis in cattle is prevalent. Nakskov and Rønne are in districts free from tuberculosis in cattle.

Holm & Jensen, 1942). Fig. 3 gives examples of the large differences in the percentages of positive reactors found in different parts of the country. The frequency of reactors at the age of 7 years, for instance, is seen to vary geographically from about 10% to 45%. This variation was clearly correlated with the amount of tuberculosis in the cattle of the different areas (Madsen et al., 1942).

Tuberculosis in cattle was highly prevalent in Denmark in the 1880's (Plum, 1955). An early aim of the direct prophylactic work was the eradication of bovine tuberculosis, for which Bernhard Bang as early as 1892 presented his rational plan. But it was not until 1932 that the work assumed significant proportions, and, as shown in Fig. 4, it was not until 1952 that the goal of eradication was finally attained throughout the country. There is no doubt, however, that a substantial proportion of the tuberculin sensitivity still found in our older adult population is caused by infection years ago with bovine tubercle bacilli.

Results of the tuberculin testing done during the mass campaign in 1950-52 provided, for the first time, information on the nation-wide prevalence of tuberculous infection in the adult population outside Copenhagen. Fig. 5 gives a summary picture of the percentages of unvaccinated positive reactors, by age and sex, among the total examined population, amounting to nearly one million persons. Persons not previously vaccinated and with a reaction of 6 mm or more to the intradermal 10 TU test were classified as positive.

All previously vaccinated persons, regardless of their tuberculin reaction, are included in the total examined population on which the percentage figures for spontaneous positives are based. As more-detailed discussion of the tuberculin sensitivity of the population at the time of the mass campaign

FIG. 4

PERCENTAGE OF INFECTED HERDS IN THE DANISH ISLANDS, JUTLAND AND ALL DENMARK, BY YEAR, 1937-52

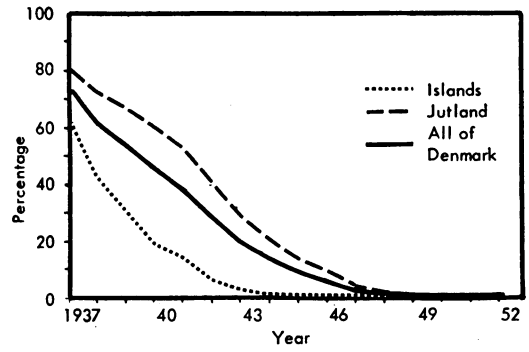
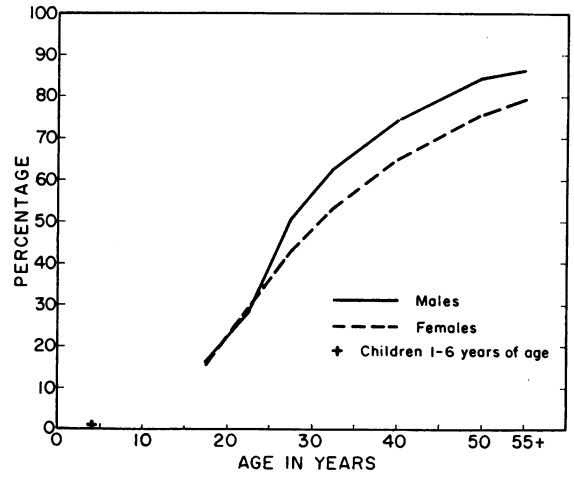


FIG. 5

PERCENTAGE OF UNVACCINATED POSITIVE TUBERCULIN REACTORS, BY AGE AND SEX, IN THE POPULATION EXAMINED IN THE DANISH MASS CAMPAIGN, 1950-52



is given in section 2 of this report (page 20), suffice it here to point out the pronounced reduction since the mid-1930's, particularly in young adults, in the percentages of positive reactors.

TUBERCULOSIS MORBIDITY AND MORTALITY

The diagnosis of pulmonary tuberculosis

The only specific criteria available for making a diagnosis of tuberculous infection are tuberculin sensitivity and the demonstration of tubercle bacilli. For many years the intradermal tuberculin test has been a routine part of each tuberculosis examination in Denmark, and since 1934 the test has been given with a standardized tuberculin (Madsen et al., 1942). Thanks to Otto Lassen, Johs. Holm, K. A. Jensen and Kjeld Tørning great importance has been attached to the bacteriological examination, both in diagnosis and in therapy; and standardized examination techniques have been established. The Tuberculosis Department of the Statens Seruminstitut serves as a central laboratory for the entire country. Since the early 1940's cultures of sputum have been made for tubercle bacilli as a matter of routine, regardless of whether the microscopic examination is reported as negative or positive. The culturing of gastric washings for diagnostic and continued follow-up work has also gained steadily in importance and since the 1930's has been a routine procedure for patients who cannot produce a relevant sputum specimen. All diagnostic examinations for tubercle bacilli are paid for by the chest clinics; and all positive findings on specimens sent in either from private physicians, from hospitals, or from the chest clinics are reported to the local chest clinic (Holm, 1946).

The average annual numbers of newly diagnosed cases of pulmonary tuberculosis since 1941 are given in Table 1, together with the percentages which had completed bacteriological examinations when reported for the first time. Of those for whom the results of the bacteriological examinations were obtained, nearly 90% have been positive on either sputum or gastric lavage cultures since 1944. It is evident that considerable progress has been made in increasing the percentage of completed bacteriological examinations.

Even though the definition of " a case of tuberculosis " involves certain medical difficulties, it has been generally agreed in Denmark that, aside from tuberculin sensitivity, the demonstration of tubercle bacilli is the one specific sign that can be proved in by far the greatest number of clinically and epidemiologically significant cases of pulmonary tuberculosis. In most cases—but not in all. An example of the exceptional case is the early stages of miliary tuberculosis of the lungs. We admit that subjective judgement in the diagnosis of activity cannot wholly be avoided; but it has been agreed among all the tuberculosis specialists and the Danish Tuberculosis Index that for the diagnosis of abacillary pulmonary tuberculosis the following criteria must generally be included: (1) other etiology improbable; (2) tuberculin reaction positive; (3) lung process chronic—and this presupposes at least two X-ray examinations with an interval of three months between examinations; and (4) roentgenological or clinical signs of activity.

TABLE 1

NUMBER AND BACILLARY STATUS AT THE TIME OF FIRST NOTIFICATION OF NEWLY DIAGNOSED CASES OF PULMONARY TUBERCULOSIS, DENMARK, 1941-56

Year	Total number (1)	Examined bacteriologically		With positive sputum or gastric lavage : % of (2) (4)
		number (2)	% of (1) (3)	
1941	3286	2345	71.4	81.7
1942	3248	2547	78.4	78.5
1943	3348	2658	79.4	85.2
1944	3343	2606	80.0	88.9
1945	3460	2670	77.2	85.5
1946	4122	3374	81.9	87.7
1947	3522	3021	85.8	88.0
1948	3351	2983	89.0	87.7
1949	2906	2576	88.7	89.6
1950	2514	2235	88.9	88.5
1951	2412	2178	90.3	87.9
1952	2060	1876	91.1	89.2
1953	1764	1626	92.2	88.2
1954	1547	1439	93.0	89.0
1955	1236	1121	90.7	87.4
1956	1127	1021	90.6	87.5

Registration

Since 1905 all Danish physicians have been required by law to report to the National Health Service every person needing treatment for tuberculosis of the lungs or larynx (Act of 14 April 1905). Notifications should be (and have been) made on official individual forms, and since 1920 the National Health Service has kept a central file of all cases notified from the whole country (Groth-Petersen & Wilbek, 1957; Lindhardt, 1939, 1950). The entire population has been covered since 1945 by twenty-three local chest clinics and their outlying branches. Private physicians and hospital staffs must notify or consult the local clinic with regard to all tuberculosis patients under their care; notification of patients to the National Health Service is made or checked by the chest clinics, and the central file is administered by the Danish Tuberculosis Index (Groth-Petersen, 1955; Groth-Petersen & Wilbek, 1957). Movement of patients from one area to another is reported through the Index, so the chest clinics are kept informed of all patients living in the district under their jurisdiction. Relapses have also to be reported, but they are reported as relapses and are not included in the annual count of new cases. In order to secure identification and to prevent a patient from being counted more than once in the statistics of new cases of pulmonary tuberculosis, the file in the National Health Service has two almost independent identification entries. As a check on the completeness of the file, records for all patients with positive bacteriological examinations at the Statens Seruminstitut are matched against the central file in the Danish Tuberculosis Index; 97% of all cases are notified within six months. Furthermore all death certificates on which tuberculosis is even mentioned are checked with the central file and reported to the local chest clinic; only about 2%-3% of the deaths in which active or inactive tuberculosis is mentioned have not previously been known and reported to the central file.

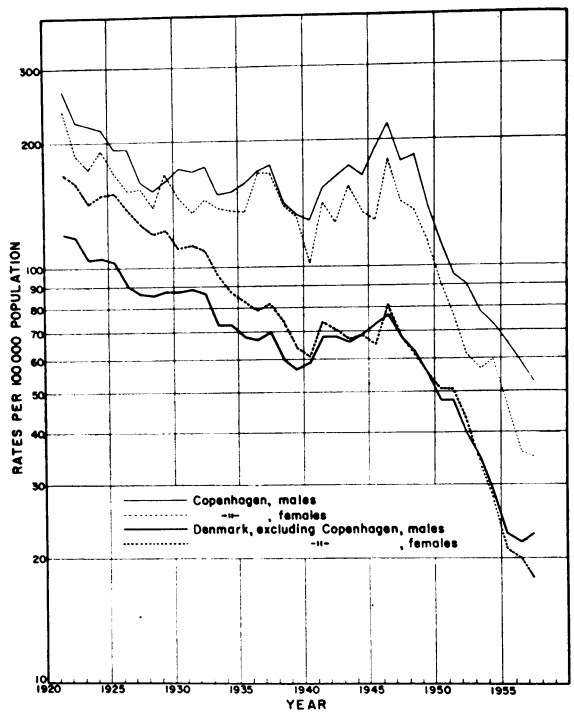
Compulsory notification for all other (extrapulmonary) forms of tuberculosis was not introduced until 1951.

Incidence

The incidence of new cases of pulmonary tuberculosis and deaths from all forms of tuberculosis for the years 1921 through 1957 are shown in Fig. 6 and 7 respectively, the data being given separately for Copenhagen and for the rest of the country; in Appendix Tables 1 and 2 the data are given for the country as a whole. Details for the years 1921-53 have been reported previously (Horwitz & Iversen, 1955; Iversen, 1957).

FIG. 6

INCIDENCE OF PULMONARY TUBERCULOSIS, PER 100 000, PER YEAR, BY SEX, FOR COPENHAGEN AND THE REST OF DENMARK, 1920-57

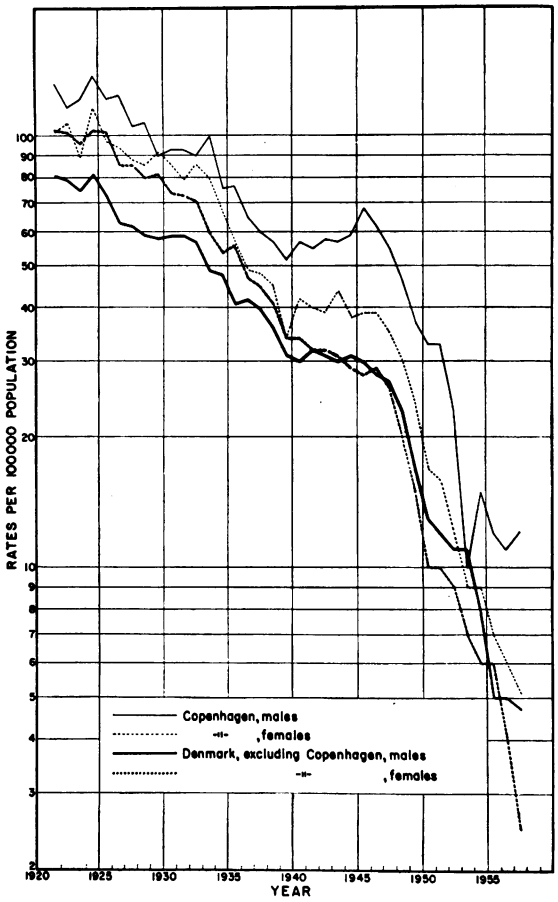


The morbidity data do not include extrapulmonary forms of tuberculosis because, as noted above, such forms of disease have been reported to the National Health Service only in recent years. In the registration and counting precedence is still given to pulmonary tuberculosis. Mortality data, on the other hand, include all forms of tuberculosis. They are derived from death certificates which state the cause of death and are issued by the physician who last attended the patient. Denmark has followed the International Lists of Diseases and Causes of Death since 1940 (Lindhardt, 1950) and adopted the Sixth Revision of the International Lists in 1951.

As may be seen in Fig. 6, the incidence of pulmonary tuberculosis is high in Copenhagen compared to the rest of the country, and its decline between 1921 and 1940 was rather irregular in Copenhagen, while in the rest of Denmark the decrease was more

FIG. 7

MORTALITY FROM ALL FORMS OF TUBERCULOSIS, PER 100 000, PER YEAR, BY SEX, FOR COPENHAGEN AND THE REST OF DENMARK, 1920-57



steady. There was a slight increase during the war years; but since 1946 the rate has been dropping rapidly, even though the number of routine examinations for tuberculosis has increased (Groth-Petersen, 1955). For the year 1957, the incidence was down to 25 per 100 000 in the country as a whole (Appendix Table 1).

In the 1930's bovine tuberculosis was responsible for a fair number of cases of pulmonary tuberculosis in the rural population (Madsen et al., 1942), Although cattle tuberculosis has now been eradicated, tubercle bacilli typed as bovine are still found in a small proportion of our new patients (Engbaek, personal communication, 1958).

Tuberculosis mortality including all forms of tuberculosis (Fig. 7 and Appendix Table 2) has fallen precipitously in the last ten years, dropping in the country as a whole from 25 per 100 000 in 1948 to 4 per 100 000 in 1957—a reduction of 84% in a single decade.

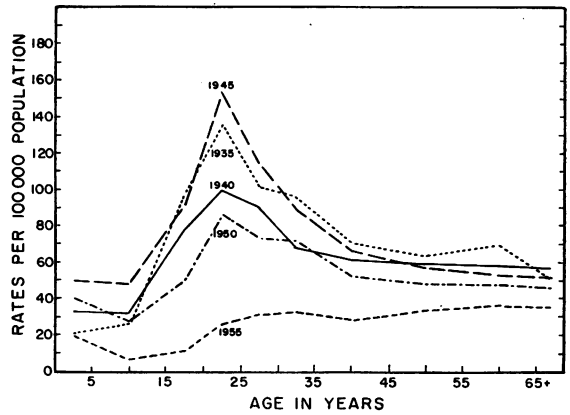
The proportion of tuberculosis deaths due to pulmonary tuberculosis has increased steadily from 75% in the 1920's to 90% in recent years.

A further breakdown of morbidity and mortality data of pulmonary tuberculosis in the country outside Copenhagen is presented in Fig. 8 and 9

FIG. 8

INCIDENCE OF PULMONARY TUBERCULOSIS, PER 100 000, BY AGE AND SEX, FOR SELECTED YEARS REPRESENTED BY THREE-YEAR AVERAGES, DENMARK (EXCLUDING COPENHAGEN), 1935-55

MALES



FEMALES

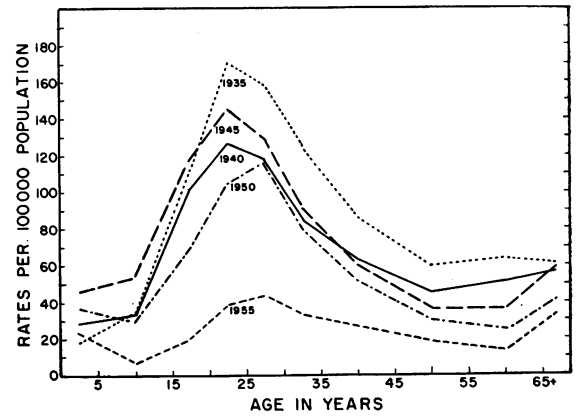
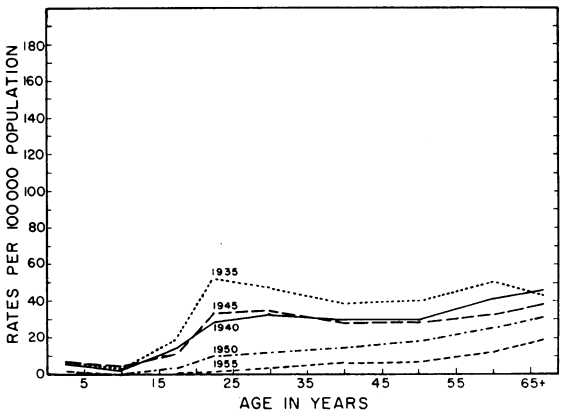


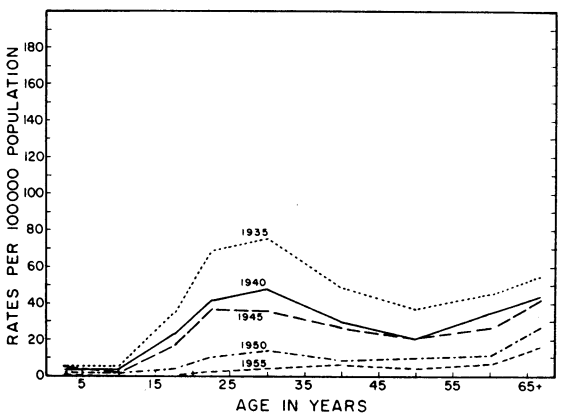
FIG. 9

MORTALITY FROM PULMONARY TUBERCULOSIS, PER 100 000, BY AGE AND SEX, FOR SELECTED YEARS REPRESENTED BY THREE-YEAR AVERAGES, DENMARK (EXCLUDING COPENHAGEN), 1935-55

MALES



FEMALES



and Appendix Tables 3 and 4, showing three-year averages by age and sex for five periods from 1935 to 1955. The outstanding feature of the time-trend of tuberculosis morbidity is that the decline has not been evenly distributed throughout the various age-groups in the population. The sharp peak of morbidity in young adults has nearly disappeared since 1950. And the peak of mortality in young adults which was so prominent two decades ago has now completely disappeared.

In Copenhagen (not shown) the morbidity and the mortality rates are in general higher than in the rest of the country; the sex-age pattern is largely similar, although the excess of the Copenhagen rates over the rates in the rest of the country is particularly striking for females below and for males above 35 years of age.

Prevalence

So far no definition has been adopted for international comparisons of the prevalence of tuberculous disease, prevalence including both newly diagnosed and previously diagnosed but still active cases. Prevalence figures usually are an inventory of the total number of cases on a register including various numbers of quiescent or even cured cases, and the figures from country to country are in no way comparable. In our opinion a very valuable measure of prevalence would be the total number of persons who during the year in question have had tubercle bacilli demonstrated in their sputum or gastric washings and are alive at the end of the year. This necessarily implies the carrying-out of adequate bacteriological examinations; and by adequate examinations we ordinarily mean at least two cultures for tubercle bacilli each year for the first three years after the last demonstration of tubercle bacilli and after completion of treatment.

Figures for the " prevalence ", as defined above, of tuberculosis in Denmark [1] for the years 1949-57 are given in Table 2 and Fig. 10. These figures cover a population of more than three million. There can be little doubt that there has been a remarkable drop in the total number of known bacillary patients. The prompt and favourable results obtained with chemotherapy and surgical intervention have meant that an increasing proportion of patients survive, although many feared that, as a result, the total number of either temporarily or permanently infectious patients in the population would also increase. This is not the case, however. The rate for " old " bacillary cases is decreasing just as fast as the rate for newly diagnosed cases. The important point is that the prevalence of both new and old cases of tuberculosis in Denmark is falling rapidly.

Volume of examination

The development and organization of tuberculosis control in Denmark have been described elsewhere,

[1] Excluding Copenhagen and two counties, for which figures are available from 1954 only

TABLE 2

NUMBER AND RATES OF CASES OF PULMONARY TUBERCULOSIS, NEWLY AND PREVIOUSLY DIAGNOSED, ALIVE AT THE END OF EACH YEAR AND REPORTED AS HAVING POSITIVE BACTERIOLOGICAL FINDINGS DURING EACH CALENDAR YEAR 1949-56 IN A 3 MILLION POPULATION IN THE MASS CAMPAIGN AREA

Year	Total, newly and previously diagnosed		Previously diagnosed		Newly diagnosed	
	number	per 100 000 population	number	per 100 000 population	number	per 100 000 population
1949	4112	134	2886	94	1226	40
1950	4210	136	3124	101	1086	35
1951	3797	122	2736	88	1061	34
1952	3520	112	2541	81	979	31
1953	3399	107	2531	80	868	27
1954	2636	82	1911	59	725	23
1955	2000	61	1482	45	518	16
1956	1618	51	1134	36	484	15

the latest account appearing in 1955 (Groth-Petersen, 1955). As mentioned earlier, morbidity statistics are influenced by the proportion of the population examined. In the 1950's more than a quarter of the total adult population of Denmark has been examined each year, with only small variations.

FIG. 10

CASES OF PULMONARY TUBERCULOSIS REPORTED AS HAVING POSITIVE BACTERIOLOGICAL FINDINGS, PER 100 000, PREVIOUSLY DIAGNOSED AND NEWLY DIAGNOSED, 1949-56, AMONG A 3 MILLION POPULATION IN THE DANISH MASS CAMPAIGN AREA

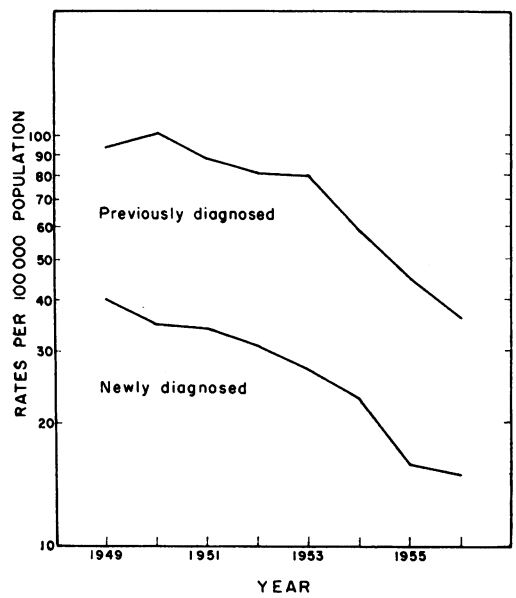


Table 3 shows the annual average of adulte examined at chest clinics in the years 1954-56, as well as the reasons for examination, which are classified into three groups. The annual averags of 824 000 represents 25% of the total adult population. As seen in the table, the examinations were in most cases (88%) simple routine checks; only 8% were examined on account of symptoms.

TABLE 3

ADULTS EXAMINED AT THE CHEST CLINICS (AVERAGE FOR 1954, 1955 AND 1956)

Reason for examination	Number of examined persons	% of population
Symptoms	68 000	2
Contact with tuberculosis .	35 000	1
Routine examinations and other reasons	721 000	22
Total	824 000	25

THE DANISH MASS CAMPAIGN 1950-52 AS A BASIS OF THE EPIDEMIOLOGICAL FOLLOW-UP STUDY

MOTIVATION FOR THE MASS CAMPAIGN AND CREATION OF THE DANISH TUBERCULOSIS INDEX

As late as 1950 the incidence of tuberculosis in Denmark still showed a peak in young adults (Fig. 8). Most of these cases, and also many of the cases in older adults, were generally believed to arise in recent tuberculin converters. A number of small follow-up studies conducted during the 1930's and 1940's had indicated that in Denmark —as in Norway and Sweden—the risk of developing tuberculous disease was higher for tuberculin non-reactors than for reactors during the first few years after the initial examination (J. Holm, 1941; J. Holm & Helweg-Larsen, 1938; S. Holm, 1947; Hyge, 1947; Olsen, 1953). Moreover, the proportion of non-reactors in the adult population was thought to be sufficient to allow a large proportion of the new cases to appear among recent converters. A thorough discussion of the problem in question and a review of the Scandinavian studies has been given by Nissen Meyer (1949).

Even though adequate control studies of BCG were not available, common experience, derived primarily from vaccination of contacts, mass vaccination on the small island of Bornholm (Olsen, 1953), and especially the well-known study of a unique school epidemic (Hyge, 1947) had created the impression in Denmark that BCG could protect, to a considerable extent, against the development of disease within the first years after tuberculous infection. The hope was that BCG would also give some protection against the late endogenous breakdown of infections acquired after the vaccination. Finally, the international mass vaccination campaigns, started soon after the war in many parts of Europe, had stimulated considerable public interest in BCG. Thus the stage was set for mass BCG vaccination in Denmark a few years after the Second World War.

In the years 1946-48 the population of Copenhagen was offered tuberculin tests, chest X-rays and vaccination of non-reactors (Winge, 1950). In 1949 mass vaccination was begun in the schools throughout Denmark. Furthermore, a committee was appointed by the National Health Service to develop a nation-wide programme (exclusive of Copenhagen) for tuberculosis examinations of pre-school children and young adults, with special emphasis on vaccinating tuberculin non-reactors. It was realized that the programme could be designed not only for case-finding and vaccination, as is usually done, but also to provide material for long-range epidemiological research on tuberculosis. Such studies, it was foreseen, could provide basic data for determining the risk of developing tuberculosis for different groups in the population. More precise knowledge of the potential sources of future cases would undoubtedly permit more efficient and effective tuberculosis control work and hasten the achievement of our avowed (though still perhaps remote) goal—the eradication of tuberculosis in Denmark.

As it was considered that results of the research aspects of the campaign would be useful to other countries where the situation with regard to tuberculosis was approaching, or might be expected to approach, the conditions which already existed in Denmark, technical and financial assistance was requested from the WHO Tuberculosis Research Office in Copenhagen. Among other requirements introduced to ensure the collection of accurate and unbiased data suitable for research purposes, the Tuberculosis Research Office insisted on the creation of a special office to implement and direct both the mass campaign and the follow-up studies. Agreement on these matters resulted in the establishment in 1950 of the Danish Tuberculosis Index as a co-operative undertaking of the National Health Service of Denmark and the WHO Tuberculosis Research Office.

THE MASS CAMPAIGN

The mass campaign was financed by the State, administered by the National Association for the Fight against Tuberculosis, and technically directed by the Danish Tuberculosis Index in co-operation with the local chest clinics. The entire country was covered by the campaign with the exception of Copenhagen County (including the City of Copenhagen), the island of Bornholm and a few small communities where campaigns had previously been carried out. The population of the area covered by

the campaign is close to three and a half million, but, as mentioned below, the campaign concentrated on selected age-groups. The tuberculin testing, X-raying and vaccinating were done by four specially trained teams, each with a mobile 35-mm photofluorographic unit. The campaign took almost three years to complete—from February 1950 to December 1952.

The first task was to secure the co-operation of the twenty-two county chest clinics and to draw up detailed instructions for uniform and exact procedures for the examinations and for writing and handling the records. Pre-school children, age 1-6 years, and the adult population, age 15-34 years, were individually invited to come for a tuberculin test, a photofluorogram of the chest and BCG vaccination if indicated. Persons over 35 years of age did not receive a personal invitation but were informed by way of the radio and press that they were welcome to attend the examination. Children of school age (7-14 years) were not invited because since 1949 they were being tuberculin tested and vaccinated in the schools.

The examination

The examination consisted of a single intradermal test with 10 TU of PPD tuberculin, lot RT XXII mg 0.00013, from the Statens Seruminstitut.[1] At the time the test was given, a 35-mm photofluorogram was taken of all persons of 15 years of age and over. The tuberculin reactions were read by specially trained nurses on the fourth day after the injection. The reaction was inspected and the diameter of induration was carefully measured and recorded on an individual record card. All persons with a reaction measuring less than 6 mm were offered BCG vaccination (except for a small group with suspicious findings on the microfilm). In the first five counties covered by the campaign the films were read only by the local tuberculosis specialist (who is head of the chest clinic and the county tuberculosis hospital), but 75% of the films were read independently by one of two specialists serving as central readers as well as by the local specialist. The results of both X-ray readings were sent to the field teams so that when the people returned for the reading of the tuberculin tests, each person with either definite or questionable signs of disease, according to one or both readers, could be referred to the local chest clinic for further examination. The readings of the X-rays necessarily could not be biased by results of the tuberculin tests, and precautions were taken in the field so that the readings of the tuberculin tests would not be biased by the X-ray readings or by whether or not the person had been vaccinated.

If the microfilm taken in the campaign was found to be " technically insufficient," a repeat microfilm was taken by the field team, if possible when the person returned for the reading of the tuberculin test. Persons with either technically insufficient films or suspicious lung findings who did not return to the field team were recalled by the local chest clinic for further examination—fluoroscopy, a 70-mm photofluorograph or, generally, a large roentgenogram. If fluoroscopy or repeated photofluorography revealed suspicious findings, a large roentgenogram was taken as a matter of routine. If the roentgenogram also showed suspicious findings a sputum specimen or a gastric lavage was obtained for bacteriological examination.

Records

A public registration office in each community *(kommune)* of Denmark keeps a current census of all persons living in that community. All births, deaths, marriages and changes of address should, by law, be notified within five days of the event. The registration offices were therefore asked to prepare, from their files, an individual record card containing identification data for each person in the age-groups 1-6 years and 15-34 years. This was done during the month before the mass campaign was scheduled to begin in the community; at the same time, an individual invitation to attend the campaign was sent by mail from the registration office to all persons 1-6 and 15-34 years of age. The record cards and detailed instructions for entering the required data on the cards were provided by the Danish Tuberculosis Index, and the work was supervised by a statistician from the field staff of the Index.

As persons arrived for examination at the campaign premises, their record cards were located in the file and a check was made of the completeness and accuracy of the name, date of birth, occupation and address previously entered on the cards. For those outside of the invited age-groups, for whom no record card had been prepared, the required identification data were obtained by direct questioning and entered on a record card. All the cards were

[1] A dose of 5 TU was used in two counties for approximately 35 000 persons, or 4% of the total number tested in the campaign.

FIG. 11

THE FIELD RECORD CARD FOR THE DANISH MASS CAMPAIGN, 1950-52

1 Surname:			3 F	4 Date of birth day / month / year			13
2 Christian name:				7a Place of birth:			15 Name of local chest clinic
5 Marital status:	Maiden name:						Mass Campaign 1950-52
6 Occupation:				7 County & kommune no.			Record no.
8 Address:							Physician
							Diagnosis
9 Previous BCG Number		☐ Yes	☐ No	☐ Don't know			9a Number of previous BCG vacc.:
10 Date of examination	Test	Induration	Type	Remarks	Reader		Place of vaccination (Institution or physician)
							Approx. date:
	Mx 10 TU						11 Mass Campaign BCG number
12 Photofluorogram					(Local reader's description of photofluorographic findings)		14 (Central reading)

NON OBSERVANDUM:

1 ☐ Nihil
2 ☐ Variatio extrapulm.
3 ☐ Pl. seq
4 ☐ Var. pulm excl. calcif.
5 ☐ Calcif. hil.
6 ☐ Calcif. pulm.

OBSERVANDUM:

7 ☐ Var. extrapulm.
8 ☐ Var. pulm.
9 ☐ Techn. insuff.

checked for completeness and accuracy four days later, when the persons returned for the reading of the tuberculin reactions and the report of the X-ray examination.

In addition to the checking of identification data, a systematic inquiry was made of each person about previous BCG vaccination. The questions, prepared in advance by the Danish Tuberculosis Index, were carefully phrased to avoid suggesting any "expected" type of answer and creating any confusion with other types of vaccination or previous tuberculin tests (Groth-Petersen, 1953). The responses were entered on the record cards; and, for persons who had brought a vaccination certificate with them, the data on the certificate were copied on to the record card. By far the greatest number of vaccinations before the mass campaign were given by the chest clinics, which issued a vaccination certificate as evidence that the person had been vaccinated.

The field record card is reproduced in Fig. 11.

Before as well as during the campaign every effort was made to find and, if possible, rectify sources of error in each link in the procedure of the mass tuberculosis examination; to avoid systematic errors; and to evaluate the magnitude of inevitable random errors, particularly in the identification data, which are obviously critical for follow-up studies.

In spite of detailed written as well as oral instructions pertaining to the primary identification data entered on the record card (name; day, month and year of birth), discrepancies between the data given by the registration offices and the data given by the examined persons themselves amounted to 7% early in the campaign, afterwards a little less. Checking of the record cards corrected during the campaign with subsequent tuberculosis case reports and death certificates indicates that the certainty of later identification may be estimated to be about 99% for persons who attended the campaign and about 94% for those who did not attend. A certain proportion

of the errors were simply mistakes in copying. As the copying of records can be expected to introduce a source of error meriting particular attention, we took the precaution of always having the records proof-read by two persons.

Special precautions are also necessary when material entered on field record cards is later to be transferred to punch cards. For example, when the campaign started the field cards were filled out in accordance with the ordinary instructions previously used for service campaigns; the punching of these cards—done in the State Department of Statistics—provided a good measure of their legibility and completeness. About 30%-35% of these cards were rejected in the routine control punching. However, in the case of records from the first counties where the special instructions prepared by the Danish Tuberculosis Index were introduced, the proportion of rejections dropped to 3%-4%, and this proportion was further reduced as the campaign progressed.

Some of our special investigations on the reliability of the information obtained about previous BCG vaccination (Groth-Petersen, 1953), the results of the tuberculin tests (Danish Tuberculosis Index, 1955c; Guld, 1954; Wilbek, 1954; WHO Tuberculosis Research Office, 1955b), and the X-ray examinations (Danish Tuberculosis Index, 1955b; Groth-Petersen, Løvgreen & Thillemann, 1952), have already been reported.

As a result of these special investigations we believe that our material is sufficiently accurate and reliable for research purposes. But our experience has shown that continuous close supervision and frequent repetition of instructions were very necessary for both the field and the central office personnel.

Card files

The record cards from the mass campaign as well as supplementary information needed for the follow-up studies were assembled into three main card files in the office of the Danish Tuberculosis Index.

(1) *The Mass Campaign Roster* consists of nearly 1.5 million punch cards, prepared from the field record cards for all persons in the age-groups 1-6 and 15-34 years, whether or not they attended the mass campaign, and for all persons of other ages who attended the campaign. All of the punch cards carry identification data and information about vaccination; for those who attended the campaign, the cards also contain the result of the tuberculin test and the reading of the photofluorogram. The punch cards are filed by sex, date of birth, and name, to facilitate identification. With the use of only these data about 90% of the cases of tuberculosis reported during the follow-up period could be quickly and accurately determined as either matching or not matching a roster card; but for the remaining 10% the result was doubtful on the first attempt at matching. For these doubtful cases a decision was made according to certain rules for the use of supplementary data, such as birth-place and occupation. Inquiries addressed to the Public Registration Offices have shown that the decision based on the information on the roster card was practically always correct.

After removal of duplicate cards, which amounted to about 4% of the total number, the entire roster was reproduced to provide a complete working set for tabulations and analysis of the material. The original field record cards were sent to the local chest clinics after the punch cards for the roster had been prepared.

(2) *The Vaccination File* consists of handwritten cards for about 500 000 persons of 15 years of age or more at the time of the campaign who had a record of having been vaccinated before the campaign, regardless of whether or not they attended the campaign. To prepare this file, copies were made of all available records of vaccinations given by the chest clinics, hospitals, the military and so on. About 10% of the cards were found to be duplicates and were removed from the file after the data on revaccinations had been transferred to our primary vaccination card.

(3) *The Tuberculosis Case Register* consists of nearly 50 000 punch cards for all cases of pulmonary tuberculosis reported in 1937 or later, all cases of extrapulmonary tuberculosis reported since 1951, and cases of pulmonary tuberculosis from 1920 to 1936 for whom a card could be found in the Mass Campaign Roster. The source of this file was the records of the National Health Service, to which all cases of tuberculosis are reported. The tuberculosis register is kept up to date by the addition of newly reported cases of both pulmonary and extrapulmonary tuberculosis. The availability of this register makes it possible to check whether or not cases of tuberculosis diagnosed in the campaign, and during the follow-up period after the campaign, are new cases or have been previously reported.

THE STUDY POPULATION

The base population for the follow-up studies of the Danish Tuberculosis Index comprises the 1 468 000 persons represented in the Mass Campaign Roster, as shown in Fig. 12. (Numbers are given only to the nearest thousand.) All persons in the age-groups 1-6 years and 15-34 years are included in the study population—the 65% who attended the mass campaign as well as the 35% who did not attend. In addition, 284 000 older persons who attended the campaign are also included in the study population. Thus, the total study population contains over one million persons who were examined in the campaign.

For the present report, details will be given only for the adults—i.e., the 795 000 persons of 15 years of age and over—who were examined in the campaign. No account will be taken here of geographic differences.

Table 4 gives the census population of persons of 15 years and over for the part of the country covered by the mass campaign. The table also shows the proportion of various age-sex groups examined in the mass campaign; and the proportion included in the study population. From 15 to 45 years of age the census population is fairly well represented numerically by the examined population, with women somewhat better represented than men. Above the age of 45 years, however, only about 12% of the census population was examined (22.5% for persons of 45-54 years of age and 5.5% for persons of 55 years or more).

Apart from purely numerical representation, the more critical question for our purposes is how well the examined population represents the general population with respect to various pertinent factors. Comparisons of age, sex, residence, occupation, and the proportion vaccinated before the campaign indicate that persons up to 55 years of age who were examined in the mass campaign are fairly representative of the corresponding general population. In addition, the results of follow-up studies for the first three years after the campaign show that the examined group is also representative of the general population with respect to the prevalence of tuberculosis (Groth-Petersen, Knudsen & Wilbek, 1957).

FIG. 12

COMPOSITION OF THE STUDY POPULATION, SHOWING NUMBERS OF PERSONS IN THE INVITED AGE-GROUPS, AND TOTAL NUMBERS OF PERSONS ATTENDING THE DANISH MASS CAMPAIGN, 1950-52

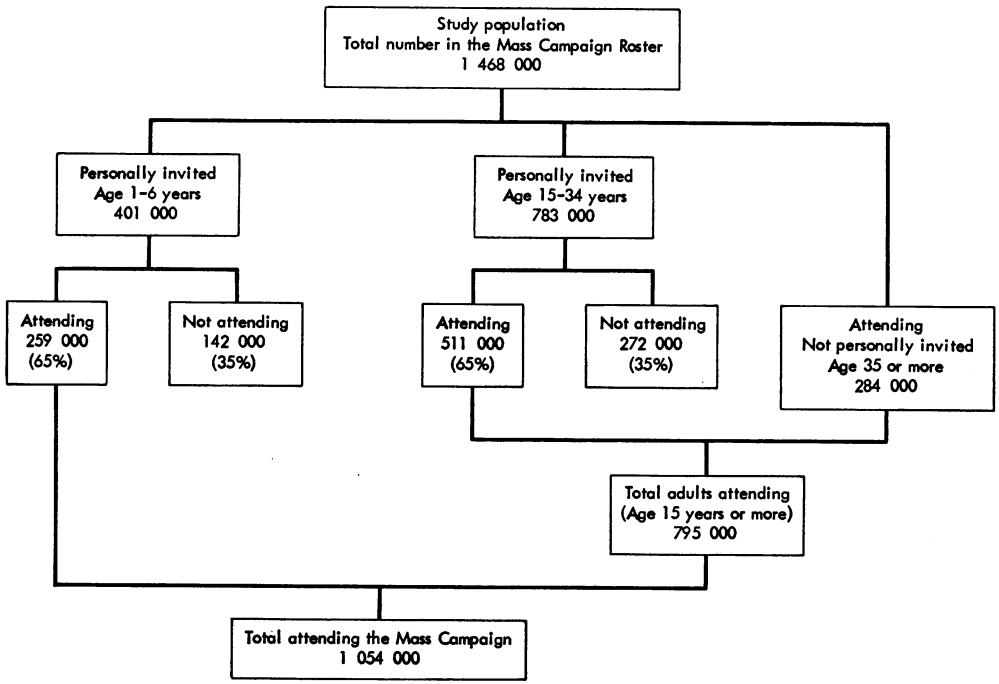


TABLE 4

CENSUS POPULATION, EXAMINED POPULATION AND STUDY POPULATION, BY SEX AND AGE, FOR PERSONS OF 15 YEARS OR MORE

		Age in years	Census population *	Examined population		Study population	
				number	% of (2)	number	% of (2)
		(1)	(2)	(3)	(4)	(5)	(6)
Men	Personally invited	15-24	193 000	116 000	60.1	193 000	100.0
		25-34	200 000	126 000	63.0	200 000	100.0
	Not personally invited	35-44	209 000	84 000	40.2	84 000	40.2
		45 or more	440 000	56 000	12.7	56 000	12.7
	Total	15 or more	1 042 000	382 000	36.6	533 000	51.2
Women	Personally invited	15-24	191 000	129 000	67.5	191 000	100.0
		25-34	199 000	140 000	70.3	199 000	100.0
	Not personally invited	35-44	202 000	92 000	45.5	92 000	45.5
		45 or more	446 000	52 000	11.7	52 000	11.7
	Total	15 or more	1 038 000	413 000	39.8	534 000	51.4
Grand total		15 or more	2 080 000	795 000	38.2	1 067 000	51.3

* Census figures for ages 15-34 years were obtained from the community registration offices ; figures for ages 35 years or more were estimated from the national census of 1950.

THE EXAMINED ADULT POPULATION

Vaccination status and tuberculin reaction

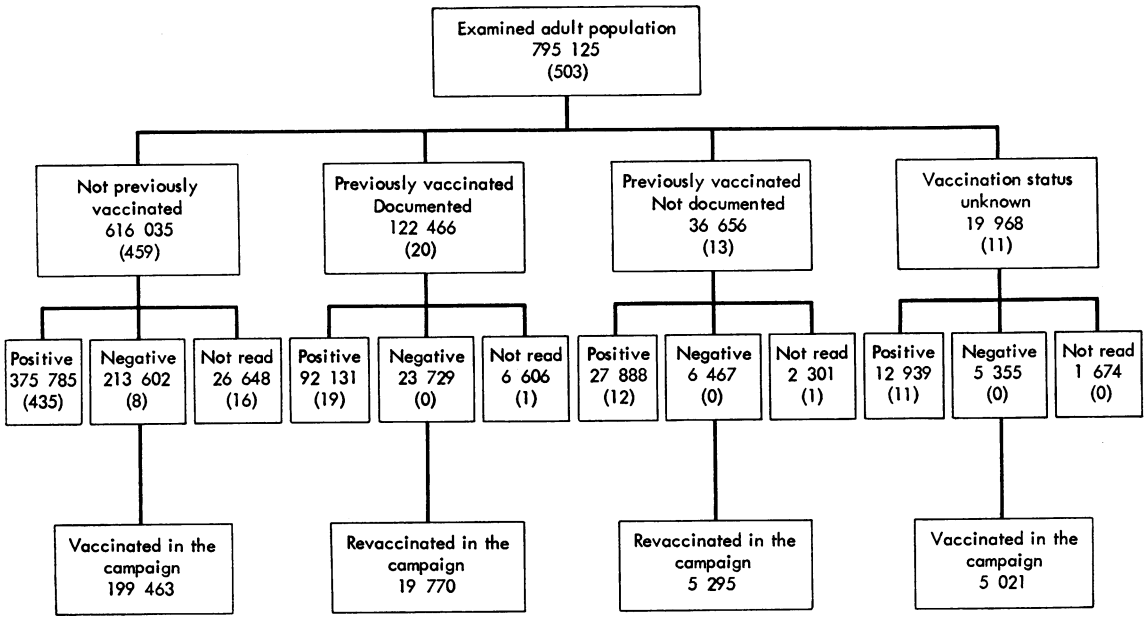
In Fig. 13 a survey picture is given of the total examined adult population, divided into four main groups according to vaccination status before the campaign. A further subdivision has been made according to the results of the tuberculin test given during the campaign. For each category the chart shows the number of persons and, in parentheses, the number of cases of active pulmonary tuberculosis diagnosed either immediately or within the first six months after the campaign among persons with suspicious findings on the photofluorogram.

Classification according to vaccination status before the campaign was based on direct questioning of each person, a vaccination certificate brought by the person to the campaign, and the matching of the Vaccination File to the roster of the study population. A total of 616 000, or about 77% of the 795 000 adults, had not been previously vaccinated. Among the remaining 179 000 the fact of previous vaccination was verified (either by a vaccination certificate or the Vaccination File) for 122 000 persons. This group is classified as " documented vaccinated ". Nearly 37 000 persons who claimed they had been vaccinated, but for whom no record could be found to verify their claim, were classified as " undocumented vaccinated ". Finally, a group of about 20 000 had to be classified as " vaccination status unknown ".

Results of the intradermal 10 TU tuberculin test given in the campaign served as the basis for classifying the examined population into tuberculin positives and negatives. Persons who did not return for their reactions to be read comprise a third subgroup. The technique of the testing procedure as well as results for sample groups have been published in a previous paper, which gives an analysis of frequency distributions of the sizes of the reactions for different age-groups in relation to evidence of pulmonary calcification and active tuberculous disease (Danish Tuberculosis Index, 1955c). The findings indicated that an induration of 6 mm or more for a positive reaction

FIG. 13

ADULT POPULATION EXAMINED AND THE NUMBER OF NEW CASES OF TUBERCULOSIS (IN PARENTHESIS) DIAGNOSED IN THE MASS CAMPAIGN, GROUPED ACCORDING TO PREVIOUS BCG VACCINATION AND TUBERCULIN REACTION



and less than 6 mm for a negative reaction is a fairly good criterion for distinguishing the infected from the uninfected members of the unvaccinated population below 55 years of age.[1]

This criterion of 6 mm or more for a positive reaction was used for all persons, although before the campaign we had no way of knowing how well it would apply to the previously vaccinated. However, in order to determine who should be revaccinated, we arbitrarily decided to classify as negative, and revaccinate, all previously vaccinated persons with a reaction of less than 6 mm.

Frequency distributions of the sizes of reactions to the 10 TU test are given in Fig. 14 and 15. All four main groups have bimodal distributions. The distributions of reactions for the documented and undocumented vaccinated are very similar to one another, while the distribution for persons of unknown vaccination status are more like those for the unvaccinated. The 6 mm criterion for separating positives and negatives appears to be satisfactory for the unvaccinated, and more satisfactory than expected for the previously vaccinated. (Exceptions for groups vaccinated with especially weak batches of vaccine are shown in a previous paper (Viskum & Munch-Jensen, 1955).) It is also evident from these distributions that the tuberculin test cannot be used to separate naturally acquired tuberculin sensitivity from BCG-induced sensitivity in the Danish population.

In accordance with the 6 mm criterion, the percentages of tuberculin positives and negatives in each of the four main groups, subdivided according to age and sex, are shown in Table 5. Persons whose tuberculin reactions were not read are excluded. The documented and undocumented vaccinated appear to be very similar, although there are differences indicating that the undocumented vaccinated include some unvaccinated persons. However, with respect both to tuberculin reactions and to X-ray findings, the documented and undocumented vaccinated appear to be so much alike that it seems justifiable in the following pages to deal with them as a single group. With respect to tuberculin reaction, those with vaccination status unknown fall between the vaccinated and the unvaccinated, which suggests that the group includes relatively many unvaccinated persons.

[1] Although the 5 TU test — used in two counties — gave slightly smaller reactions than 10 TU, the 6 mm criterion is equally satisfactory for either test in the Danish population (WHO Tuberculosis Research Office, 1955b).

FIG. 14

FREQUENCY CURVES OF SIZES OF REACTIONS TO THE INTRADERMAL 10 TU TUBERCULIN TEST FOR MEN, AGED 15-24 AND 25-34, ACCORDING TO VACCINATION STATUS

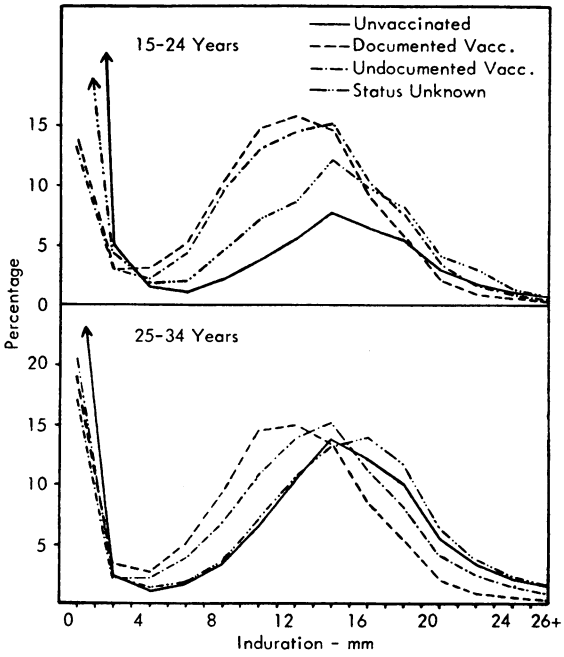


FIG. 15

FREQUENCY CURVES OF SIZES OF REACTIONS TO THE INTRADERMAL 10 TU TUBERCULIN TEST FOR WOMEN, AGED 15-24 AND 25-34, ACCORDING TO VACCINATION STATUS

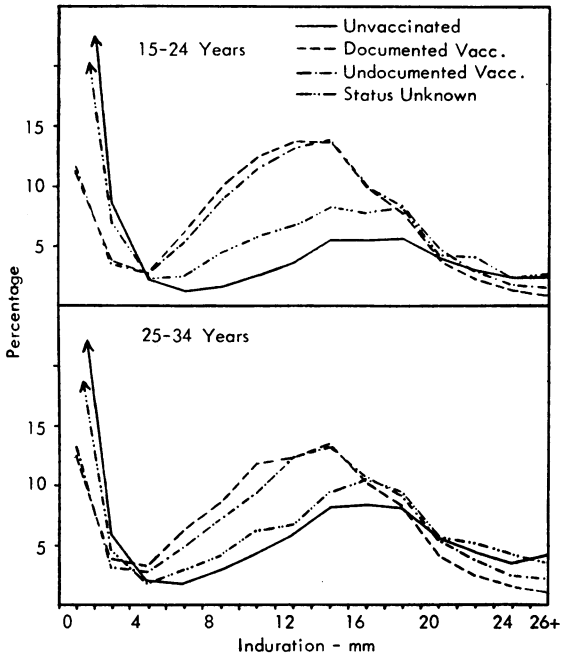
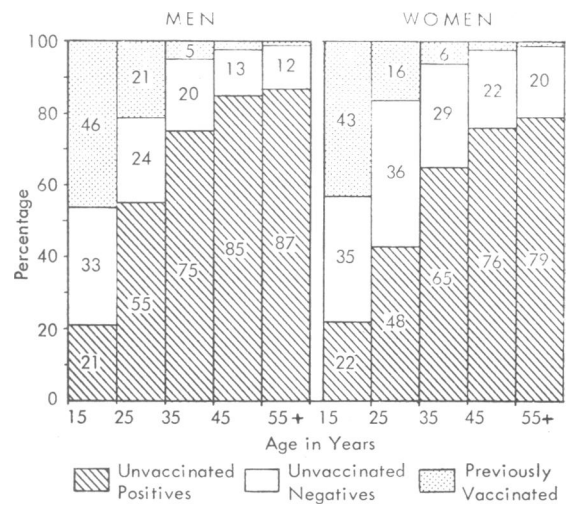


Fig. 16 shows the relative proportions of unvaccinated tuberculin positives, unvaccinated negatives and all previously vaccinated, by sex and age. The nearly 27 000 unvaccinated persons who did not return for their tuberculin reaction to be read, as well as the 20 000 classified as " vaccination status unknown ", have been excluded. It is immediately evident that the percentage of unvaccinated positive reactors, as expected, increases sharply with age for men and somewhat less sharply for women. The proportion of previously vaccinated, for both sexes, is about 45% in the 15-24 years age-group but decrease rapidly to a negligible percentage after the age of 45 years.

FIG. 16

PERCENTAGES OF UNVACCINATED TUBERCULIN POSITIVES, UNVACCINATED TUBERCULIN NEGATIVES, AND ALL PREVIOUSLY VACCINATED PERSONS, BY AGE AND SEX



The prevalence of tuberculous infection, calculated from the number of unvaccinated positive reactors, is undoubtedly under-estimated for the younger age-groups because among the previously vaccinated it is impossible to identify those who have had a natural infection. However, it is not likely that we have greatly under-estimated the prevalence of infection. The large majority of vaccinations in young adults were given during the years 1948-52—that is, shortly before the mass campaign; and evidence from our examinations of pre-school children (see Fig. 5, page 9) and from other sources indicates that the infection rate in the Danish population in recent years has been very low.

TABLE 5

PERCENTAGES OF POSITIVE AND NEGATIVE REACTORS TO THE INTRADERMAL 10 TU TUBERCULIN TEST, BY SEX, AGE AND VACCINATION STATUS, AMONG ADULTS EXAMINED IN THE MASS CAMPAIGN

Age in years	Unvaccinated			Vaccinated before mass campaign						Unknown vaccination status		
				documented			undocumented					
	number	positive	negative	number	positive	negative	number	positive	negative	number	positive	negative
MEN												
15-24	58 285	39	61	36 079	80	20	11 005	81	19	4 629	62	38
25-34	90 950	70	30	18 035	75	25	5 214	79	21	5 502	76	24
35-44	75 522	78	22	2 670	71	29	754	80	20	1 498	84	16
45-54	37 191	86	14	496	70	30	144	84	16	638	90	10
55+	14 953	87	13	92	72	28	50	88	12	299	89	11
Total	276 901	69	31	57 372	78	22	17 167	80	20	12 566	73	27
WOMEN												
15-24	70 344	38	62	37 730	82	18	12 087	82	18	2 312	57	43
25-34	111 456	57	43	16 112	80	20	3 995	81	19	1 913	68	32
35-44	82 544	69	31	3 914	77	23	927	83	17	964	74	26
45-54	36 223	77	23	644	75	25	153	86	14	356	83	17
55+	11 919	80	20	88	83	17	26	85	15	183	86	14
Total	312 486	59	41	58 488	81	19	17 188	82	18	5 728	66	34

Results of X-ray examination

Abnormalities of the heart and great vessels as well as other extrapulmonary pathology were recorded in the X-ray readings, but this paper will deal only with abnormalities of the respiratory tract, most of which were pulmonary. Abnormalities of hilar and mediastinal glands and of the pleura will, for present purposes, be included with pulmonary lesions.

The photofluorographic examination in the mass campaign was regarded only as a preliminary screening. We wanted to be reasonably sure that all persons with definite or suspicious signs of pulmonary disease were identified for further examination. The microfilms were therefore deliberately over-read: the slightest suspicion of an active lesion was recorded, even if the suspicious shadow might well have been due to some non-pathological anomaly —muscles, confluent vessel shadows, etc. It must be emphasized that the term " active lesion " as used above does not necessarily mean active tuberculosis. In our opinion the diagnosis of active tuberculosis rarely can be made only on the X-ray findings; suspicion of activity therefore denotes any kind of pathological lesion which cannot be interpreted as definitely healed.

Signs of healed lesions were also recorded, but few pathological findings were allowed to be interpreted as healed if there was anything more than calcification or a costophrenic adhesion. In the classification of findings both for further examination and for analysis of results, precedence was given to the most serious finding recorded by either of the two readers.

Strict criteria were used for the diagnosis of intrathoracic calcification: in the hilar areas, shadows had to be definitely " hard ", gritty or irregular in

outline, not rounded; and in the pulmonary parenchyma, shadows had to be dense, sharply defined and larger than any normal blood-vessel could be in that part of the lung. Calcifications, so defined, were recorded as present or not present for all films, regardless of other findings.

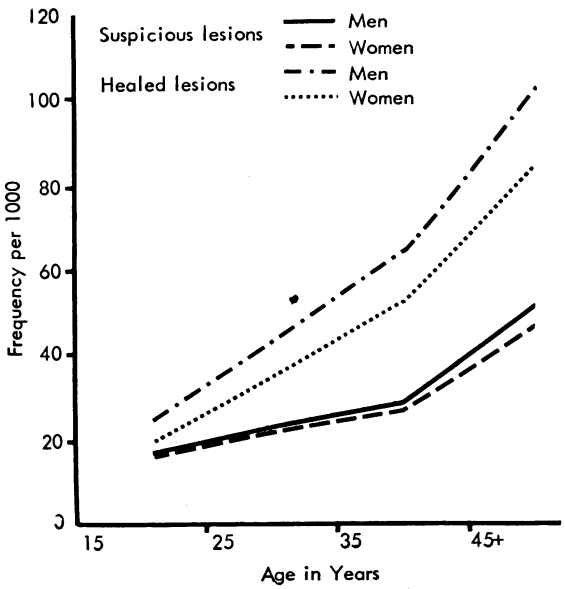
Results of the photofluorographic examination for the total adult population may be grouped into the following three broad categories:

	Number	*Percentage*
No pathological pulmonary findings	738 487	92.8
Pathological pulmonary findings interpreted as definitely healed	36 218	4.6
Suspicious shadows representing possibility of pulmonary disease	20 420	2.6
Total number of persons	795 125	100.0

The frequencies of pathological findings by sex and age are shown in Fig. 17.

FIG. 17

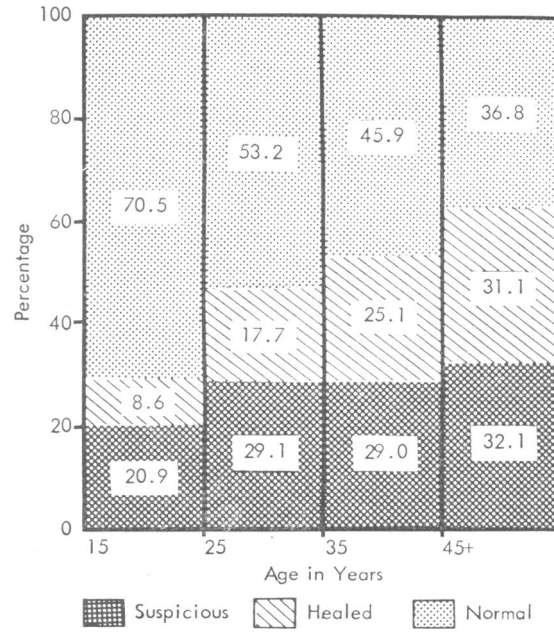
FREQUENCY OF SUSPICIOUS AND HEALED LESIONS PER 1000 PHOTOFLUOROGRAMS, ACCORDING TO SEX AND AGE



The 20 420 persons with suspicious shadows were referred to the local chest clinics for further examination. Of these, 1051 did not appear for examination during the first six months—that is, 5.1% of the persons with suspicious shadows or 0.13% of the total examined population. The defaulters will be excluded in the following material on results of the roentgenographic examination, unless specifically mentioned. The chest clinics reported half of the examined referrals as having completely normal roentgenograms; slightly less than a quarter with pulmonary lesions interpreted as definitely healed; and just over a quarter with definite or suspicious lesions requiring clinical observation or treatment. As shown in Fig. 18, the proportion of persons with suspicious lesions was relatively uniform in the different age-groups, while the proportion with healed lesions—in accordance with the cautiousness in interpreting lesions as healed on microfilms alone —increased substantially with age.

FIG. 18

PERCENTAGES OF ROENTGENOGRAPHIC SUSPICIOUS AND HEALED LESIONS, ACCORDING TO AGE, FOR THE ADULT POPULATION WITH SUSPICIOUS PHOTOFLUOROGRAPHIC FINDINGS



The results of our later follow-up studies show that persons with suspicious photofluorographic shadows are especially liable to develop active tuberculosis, even if the shadows are not reported from the supplementary roentgenographic examination. Nevertheless it must be assumed that the combined results of photofluorographic and supplementary roentgenographic examination, shown below, give

the best expression of the X-ray status of the population:

	Number	*Percentage*
No pathological pulmonary findings	748 241	94.2
Pathological pulmonary findings interpreted as definitely healed	40 354	5.1
Suspicious shadows representing possibility of pulmonary disease	5 479	0.7
Total number of persons	794 074	100.0
Defaulters (no roentgenogram) . .	1 051	
Grand total	795 125	

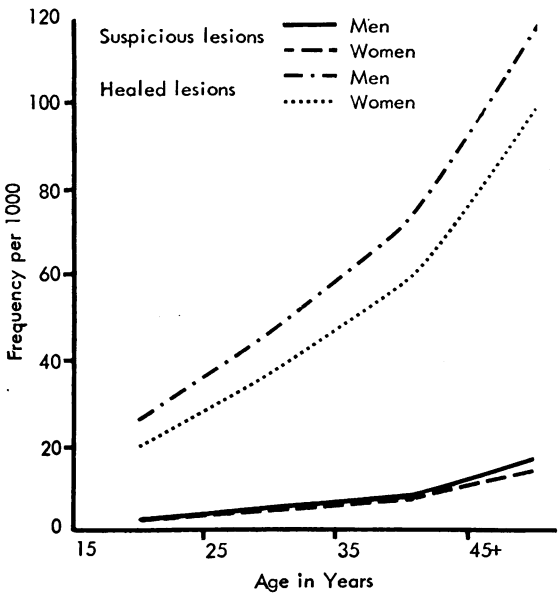
The frequency of suspicious shadows, as well as that of healed lesions, increases with age, as seen in Fig. 19; the rates of increase are almost the same for the two types of finding. Only the frequency of healed lesions shows differences by sex, the men having slightly higher frequencies than the women.

X-ray findings related to tuberculin reaction

In general, tuberculin sensitivity is the only practical indicator of tuberculous infection, and therefore the relation between X-ray findings and the tuberculin reaction is of interest, when these two factors are judged independently. Of particular interest is the question of the prognostic significance of different combinations of X-ray findings and tuberculin sensitivity.

FIG. 19

FREQUENCY OF SUSPICIOUS AND HEALED LESIONS PER 1000 PHOTOFLUOROGRAMS OR ROENTGENOGRAMS, ACCORDING TO SEX AND AGE



In regard to prognosis, previously known cases of tuberculosis are a special group and will be discussed elsewhere. Here we can briefly mention that the matching of our Tuberculosis Case Register with the Mass Campaign Roster revealed that 4539 persons, or 0.57% of the examined population, had been reported at some time during the past 30 years as having had active pulmonary tuberculosis. In the different groups with pulmonary lesions, previously reported cases constituted only 4%-5% of the total numbers, and variations by sex and age were so small that the trends by age, shown in Fig. 18 and 19, remain the same whether or not previously known patients are included. This also holds true when the population is divided according to the tuberculin reaction and vaccination status, but, as we want as " clean " a picture as possible (with a view to the follow-up studies), all previously known cases of tuberculosis have been excluded in the following material dealing with the relation between the tuberculin reaction and X-ray findings.

Healed lesions

Table 6 and Fig. 20 give a survey of the frequency of healed lesions, according to either the photofluorogram or the roentgenogram, in the examined population. The material is broken down by age and by tuberculin reaction for two groups: persons who were unvaccinated before the campaign and the documented and undocumented vaccinated combined as a single group. Although the data are not given, healed lesions were found more frequently in men than in women at all ages and in all other subdivisions, but the differences are small enough to justify combining results for the two sexes. More important is the comparison of tuberculin positives with tuberculin negatives. In the unvaccinated population the frequency of healed lesions is nearly three times higher for the positives than for the negatives. Rates for the vaccinated population differ but little from those for the unvaccinated negatives, although the vaccinated positives show slightly (but significantly) higher rates than the vaccinated negatives. In all four groups the frequency of healed lesions increases with age.

The fact that the frequency of healed lesions among the previously vaccinated is close to the

TABLE 6

FREQUENCY OF HEALED LESIONS PER 1000 PHOTOFLUOROGRAMS OR ROENTGENOGRAMS ACCORDING TO AGE AND TUBERCULIN REACTION OF UNVACCINATED AND VACCINATED (DOCUMENTED AND UNDOCUMENTED) ADULTS EXAMINED IN THE MASS CAMPAIGN *

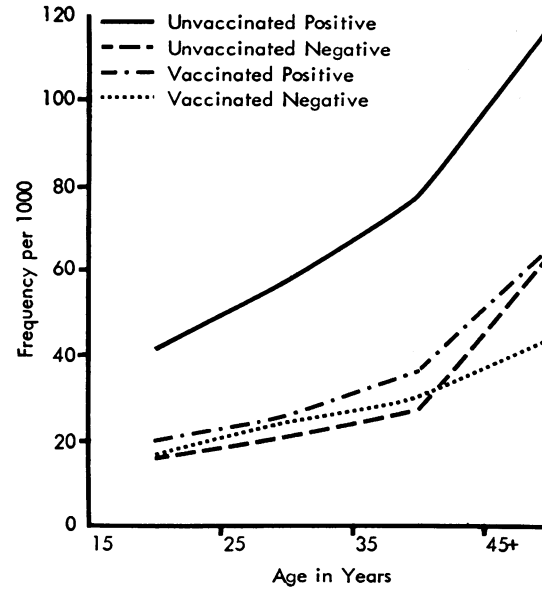
	Unvaccinated		Vaccinated	
age	positive	negative	positive	negative
	Population			
15—	48 911	79 126	78 586	18 251
25—	126 508	74 730	33 719	9 572
35—	114 852	42 014	6 297	1 953
45+	82 072	17 583	1 282	402
Total	372 343	213 453	119 884	30 178
	Number of lesions			
15—	2 050	1 246	1 578	286
25—	7 298	1 545	889	235
35—	8 957	1 184	232	60
45+	9 691	1 139	84	18
Total	27 996	5 114	2 783	599
	Lesions per 1000			
15—	41.9	15.7	20.1	15.7
25—	57.7	20.7	26.4	24.6
35—	78.0	28.2	36.8	30.7
45+	118.1	64.8	65.5	44.8
Total	75.2	24.0	23.2	19.8

* Previously notified tuberculosis patients are excluded.

frequency among unvaccinated negatives is not surprising. The vaccinated were all tuberculin tested before vaccination and were judged at that time to be tuberculin negative. In the interval between vaccination and the mass campaign — an average of three years — some of them of course, but only a small proportion, must have had a tuberculous infection which, in some cases, would leave evidence of a healed lesion. As these persons would also have a positive tuberculin reaction, this would account for the difference between the vaccinated positives and the negatives in the frequency of healed lesions.

FIG. 20

FREQUENCY OF HEALED LESIONS PER 1000 PHOTOFLUOROGRAMS, OR ROENTGENOGRAMS, ACCORDING TO AGE, TUBERCULIN REACTION AND VACCINATION STATUS

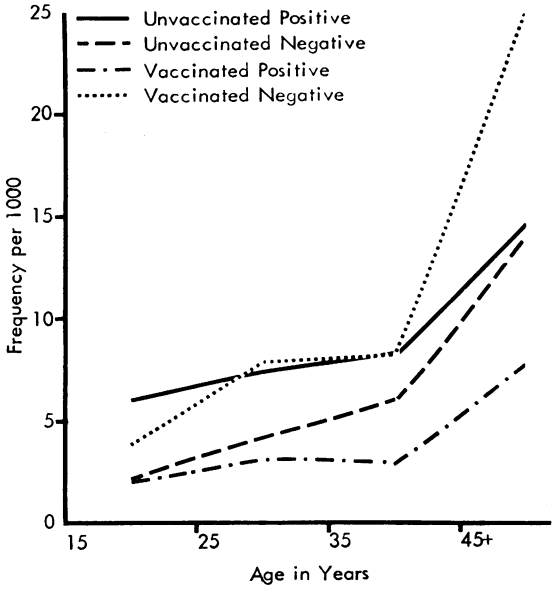


Previously notified tuberculosis patients are excluded.

Suspicious lesions

The frequencies of suspicious lesions " verified " by the roentgenographic examination are given in Table 7 and Fig. 21. The trend by age is much the same as shown previously (see Fig. 19) for the total population, but a remarkable difference is found between the unvaccinated and the vaccinated in the relation of suspicious lesions to the tuberculin reaction. The unvaccinated positives show a substantially higher frequency of suspicious lesions than the unvaccinated negatives and, even though the difference diminishes with increasing age, it is highly significant ($P<0.001$). The vaccinated population shows the opposite picture. The frequency of suspicious lesions is two to three times higher among the negatives than the positives; the difference increases with age but is highly significant for all ages ($P<0.001$). This higher frequency of suspicious lesions in vaccinated negatives than in vaccinated positives is found for men as well as for women, for documented vaccinated as well as for undocumented vaccinated (though not for the group called " vaccination status unknown "), and for the roentgenographic as well as the photofluorographic findings.

FIG. 21
FREQUENCY OF ROENTGENOGRAPHIC SUSPICIOUS LESIONS PER 1000 PERSONS, ACCORDING TO AGE TUBERCULIN REACTION AND VACCINATION STATUS



Previously notified tuberculosis patients are excluded.

That the vaccinated negatives contain an extraordinarily large number of persons with suspicious pulmonary lesions is supported by the fact that the frequency is significantly higher than the frequency for unvaccinated negatives ($P<0.01$).

If these suspicious lesions represented tuberculous infection in persons whose vaccination was " unsuccessful ", one would not expect the tuberculin reaction to remain negative. Obviously some other interpretation must be sought.

A simple and reasonable hypothesis would be that a large proportion of the vaccinated tuberculin negatives with suspicious lesions had pulmonary sarcoidosis before they had been vaccinated. If that were the case, however, the lesions should have been detected before the campaign, because only infants were vaccinated without first having a roentgen examination.

We do not know the causes of the syndrome called sarcoidosis; most of our cases of pulmonary sarcoidosis are diagnosed only on the combination of the roentgenological findings, a low degree of tuberculin sensitivity and negative results of bacteriological examination. The custom has been to vaccinate these patients, but many of them remain tuberculin negative in spite of vaccination and this might be a possible explanation of our findings—although not, however, the correct one. Only 4%-5% of the persons with suspicious lesions have been reported as known before the campaign and these persons are equally frequent among the vaccinated positives and vaccinated negatives. There is, however, a difference in the kind of suspicious lesions: about 25% of the lesions among the vaccinated positives and about 50% among the vaccinated negatives were reported as only enlarged hilar glands; and for both groups these percentages are more than twice the percentages in the corresponding unvaccinated groups.

TABLE 7
FREQUENCY OF ROENTGENOGRAPHIC SUSPICIOUS LESIONS PER 1000 PERSONS ACCORDING TO AGE AND TUBERCULIN REACTION OF UNVACCINATED AND VACCINATED (DOCUMENTED AND UNDOCUMENTED) ADULTS EXAMINED IN THE MASS CAMPAIGN *

	Unvaccinated		Vaccinated	
age	positive	negative	positive	negative
	Population			
15—	48 911	79 126	78 586	18 251
25—	126 508	74 730	33 719	9 572
35—	114 852	42 014	6 297	1 953
45+	82 072	17 583	1 282	402
Total	372 343	213 453	119 884	30 178
	Number of lesions			
15—	299	164	156	71
25—	936	317	104	76
35—	958	255	19	16
45+	1 208	247	10	10
Total	3 401	983	289	173
	Lesions per 1000			
15—	6.1	2.1	2.0	3.9
25—	7.4	4.2	3.1	7.9
35—	8.3	6.1	3.0	8.2
45+	14.7	14.0	7.8	24.9
Total	9.1	4.6	2.4	5.7

* Previously notified tuberculosis patients are excluded.

TABLE 8

PATIENTS FOUND IN MASS CAMPAIGN ACCORDING TO VACCINATION AND TUBERCULIN STATUS, BY SEX AND AGE

MALE

age	Non-vaccinated									Documented vaccinated			Undocumented vaccinated			Vaccination status unknown			Total		
	positives			negatives			non-read														
	population	cases		population	cases		population	cases		population	cases		population	cases		population	cases		population	cases	
		No.	rate*		No.	rate		No.	rate		No.	rate		No.	rate		No.	rate		No.	rate
15-24	22 847	34	149	35 438	0	—	2 991	1	—	38 232	3	—	11 724	2	—	5 040	2	—	116 272	42	36
25-34	63 839	61	96	27 111	3	—	4 634	1	—	19 085	3	—	5 581	4	—	5 940	5	—	126 190	77	61
35-44	59 083	42	71	16 439	3	—	3 192	0	—	2 813	1	—	813	1	—	1 642	1	—	83 982	48	57
45 or more	45 087	37	82	7 057	0	—	2 237	0	—	619	0	—	218	1	—	1 057	0	—	56 275	38	68
Total	190 856	174	91	86 045	6	7	13 054	2	15	60 749	7	12	18 336	8	44	13 679	8	58	382 719	205	54

FEMALE

15-24	26 638	47	176	43 706	0	—	3 321	3	—	39 816	6	—	12 871	4	—	2 524	1	—	128 876	61	47
25-34	63 796	115	180	47 660	1	—	4 998	8	—	17 040	7	—	4 270	1	—	2 092	0	—	139 856	132	94
35-44	56 911	71	125	25 633	0	—	3 174	2	—	4 098	0	—	994	0	—	1 076	1	—	91 886	74	81
45 or more	37 584	28	74	10 558	1	—	2 101	1	—	763	0	—	185	0	—	597	1	—	51 788	31	60
Total	184 929	261	141	127 557	2	2	13 594	14	103	61 717	13	21	18 320	5	27	6 289	3	48	412 406	298	72
Grand total (males + females)	375 785	435	116	213 602	8	4	26 648	16	60	122 466	20	16	36 656	13	35	19 968	11	55	795 125	503	63

* Per 100 000 population

BCG vaccination itself must have something to do with these remarkable findings, but further information is clearly needed before making any inferences. The preliminary diagnosis reported by the chest clinics for persons with previously unknown roentgen findings and negative tuberculin reaction was relatively often sarcoidosis; but that does not add new facts to the solution of our problem as the diagnosis was rarely supported by biopsy. Clinical cases of a similar kind have been discussed in the literature, only a few examples of which can be cited here (Birkhauser, 1957; Larsen, 1950; Pfisterer, Wespi & Herzog, 1954).

Although the data are not given, the frequency of photofluorographic healed as well as suspicious lesions among persons whose tuberculin reaction was not read did not appear to differ from the frequency found in persons of corresponding vaccination status whose tuberculin reaction was read.

PREVIOUSLY UNKNOWN CASES OF PULMONARY TUBERCULOSIS FOUND IN THE MASS CAMPAIGN

A few words should be said about these patients. The term " tuberculosis patients found in the mass campaign " is used here to mean new cases of tuberculosis diagnosed either immediately or during the first six months of observation among the 20 420 persons having photofluorographic suspicious shadows representing possibility of pulmonary disease (cf. page 24). As the diagnosis of active pulmonary tuberculosis is rarely made by X-ray findings alone, an interval of six months was chosen as a reasonable period in which to make clinical observations and to complete at least two successive bacteriological examinations (in case the first specimen was contaminated or reported as negative).

In all, 503 previously unknown cases of active pulmonary tuberculosis were found among 795 000 adults examined in the mass campaign—a rate of one case per 1500 examined.

The patients are distributed in Table 8 by sex, age, and vaccination status and, for the unvaccinated, also by tuberculin reaction. The unvaccinated, tuberculin-positive population comprises less than half of the total population examined in the campaign, but contributed nearly 90% of the tuberculosis patients found in the campaign; and it may be noted that the rate is considerably higher in women than in men. Eight patients were found among the 213 602 unvaccinated tuberculin negatives but only 5 of them were bacteriologically confirmed. It would be surprising if a few patients were not found in this group in view of unavoidable observational errors and the fact that some persons with small tuberculin reactions, classified as negative, actually have had a tuberculous infection. Their small reactions comprise the left tail of the frequency distribution of reactions of infected persons (cf. Fig. 14 and 15). Previously vaccinated persons and those of unknown vaccination status are not broken down in the table according to the tuberculin reaction because so few—only 44 patients—were found in these groups; and of these 42 were tuberculin positive and two were not read.

According to the notifications of the 503 cases found in the mass campaign, 461 had tubercle bacilli proved on cultures from sputum or gastric washings and 28 were negative;[1] and for 14 the culture was contaminated or was not reported. Thus the diag-

TABLE 9

NUMBER OF PATIENTS EXAMINED BACTERIOLOGICALLY AND PERCENTAGE WITH POSITIVE CULTURE OF SPUTUM OR GASTRIC WASHINGS AMONG 503 NEW CASES OF TUBERCULOSIS FOUND IN THE MASS CAMPAIGN, ACCORDING TO SEX AND AGE

Sex	Age in years	Patients examined	Sputum positive	Gastric washings positive	Total positive
		number	%	%	%
Men	15-24	40	50.0	42.5	92.5
	25-34	74	54.1	39.2	93.3
	35-44	48	66.7	27.1	93.8
	45 or more	38	60.5	34.2	94.7
	Total	200	57.5	36.0	93.5
Women	15-24	60	41.7	53.3	95.0
	25-34	131	40.5	52.7	93.2
	35-44	70	42.9	55.7	98.6
	54 or more	28	28.6	64.3	92.9
	Total	289	40.1	54.7	94.8
Both sexes	Total number completed	489	47.2	47.0	94.2
	Number not completed	14	—	—	—

[1] Two of these 28 had positive cultures of pleural fluid.

nosis of tuberculosis was confirmed in 94% of the 491 cases for whom bacteriological examinations were completed.

Table 9 shows that the sputum was positive in relatively more men than women, as is usually the case—58% compared with 40%. In contrast, the gastric lavage was positive more frequently in women than in men (55% and 36%). Taken together, however, the percentage positive on either sputum or gastric lavage was about the same—close to 94% for both sexes.

Even though the mass campaign revealed a substantial number of unknown cases with tubercle bacilli, the prevalence of bacillary patients as defined in section 1 (page 13) was increased by only 15%. No doubt the increase would have been greater if the older population had been better represented in the campaign.

In Table 10 the rates for new patients found in the mass campaign are compared with the incidence of newly diagnosed cases in the same geographic area for the year 1949, the year before the campaign started. Relatively few cases were found in the campaign among young persons, and relatively many among the older persons. In the age-group 15-24 years the rate was less than half the incidence in 1949. But among men over 35 years of age, the rate for just one point in time—the mass campaign—was higher than the rate during an entire year of case-finding which utilized every possible approach:

TABLE 10

INCIDENCE OF PULMONARY TUBERCULOSIS REPORTED IN THE MASS CAMPAIGN AREA IN 1949 (THE YEAR BEFORE THE MASS CAMPAIGN) AND NEW CASES FOUND IN THE MASS CAMPAIGN, PER 100 000, ACCORDING TO SEX AND AGE

Age in years	Men		Women	
	in 1949	in the mass campaign	in 1949	in the mass campaign
15-24	78	36	102	47
25-34	71	61	97	94
35-44	50	57	52	81
45 or more	45	68	36	60

examinations because of symptoms, because of contact, routine examinations of healthy persons, group examinations and voluntary periodic check-ups. Among women over 35 years the rate was more than one and a half times higher.

A comparison of the follow-up morbidity among the attendants and the non-attendants (to be published later) indicates that a great part of these 503 patients probably would have been found in the following years even if there had been no mass examination.

SOURCES OF NEW CASES OF PULMONARY TUBERCULOSIS IN DENMARK: RESULTS OF THE FIRST FOUR YEARS OF FOLLOW-UP

In the fight against tuberculosis early diagnosis and case-finding are of well established value, and with the availability of the antituberculous drugs their value is of even more importance now than formerly. The number of chest X-ray examinations, as an integral part of early diagnosis and case-finding, has increased greatly in many countries—and this is certainly true in Denmark (Groth-Petersen, 1955). In many instances, however, the same persons are examined year after year, the majority of them being healthy young adults. We must therefore ask the following questions: Are the large numbers of X-ray examinations necessary and appropriate, particularly in view of their questionable safety? Are they being used to the best advantage of the community and of the individual?

With reference to the future, the campaign described in the preceding section was planned not only as a community health service, but also to provide information for dividing the population into groups with significantly different chances or risks of developing tuberculosis. If such groups could be identified, then repetitive X-ray examinations could be reduced for low-risk groups and the resources of local, county, and national health units could be concentrated on preventive and follow-up measures for the high-risk population.

MATERIALS

As has been described earlier, the 795 000 adults who participated in the campaign were given an intradermal tuberculin test and a 35-mm photofluorogram, which was read by a pair of tuberculosis specialists. All persons whose films were interpreted by both readers as " normal " or " definitely healed lesions " were immediately classified as healthy with respect to tuberculosis. Individuals whose films were read by one or both readers as showing the possible presence of an active pathological process were referred to the local chest clinics for roentgenographic and clinical examinations. Approximately 20 000 persons were thus referred; and of these, 503 were diagnosed within the following six months as having active tuberculosis. These 503 are not included in the healthy adult follow-up population. Approximately 4500 persons who had been reported as tuberculous patients before the mass campaign were also excluded, as were about 46 000 persons whose tuberculin test was not read or whose status with respect to vaccination with BCG before the campaign was unknown. Thus, after eliminating persons with active tuberculosis, persons previously reported as having tuberculosis, and those for whom no tuberculin or previous vaccination information was available, there remain 744 261 individuals who were judged, so far as tuberculosis is concerned, as healthy at the time of the mass examination.

For purposes of analysis this healthy population is divided into four groups: " unvaccinated tuberculin positives ", " unvaccinated tuberculin negatives ", " vaccinated in the campaign ", and " vaccinated before the campaign " (Fig. 22 and Table 11). The unvaccinated tuberculin positives, who presumably have had a natural tuberculous infection, make up half of the healthy examined population, with by far the greatest concentration of numbers in the age-group 25-44 years. The second, or unvaccinated tuberculin-negative, group, totalling 14 000, or only 2% of the examined population, is made up of persons who refused vaccination at the time of the campaign or who were not offered vaccination because of suspicious pulmonary findings on the photofluorograms. The group vaccinated in the mass campaign is the second largest of the four groups. It includes 30% of the population discussed in this paper, with the largest concentration of numbers (41%) in the youngest age-class (15-24 years) and steadily decreasing numbers among older

FIG. 22

THE HEALTHY ADULT POPULATION EXAMINED IN THE MASS CAMPAIGN SUBDIVIDED INTO FOUR MAIN GROUPS ACCORDING TO TUBERCULIN AND VACCINATION STATUS

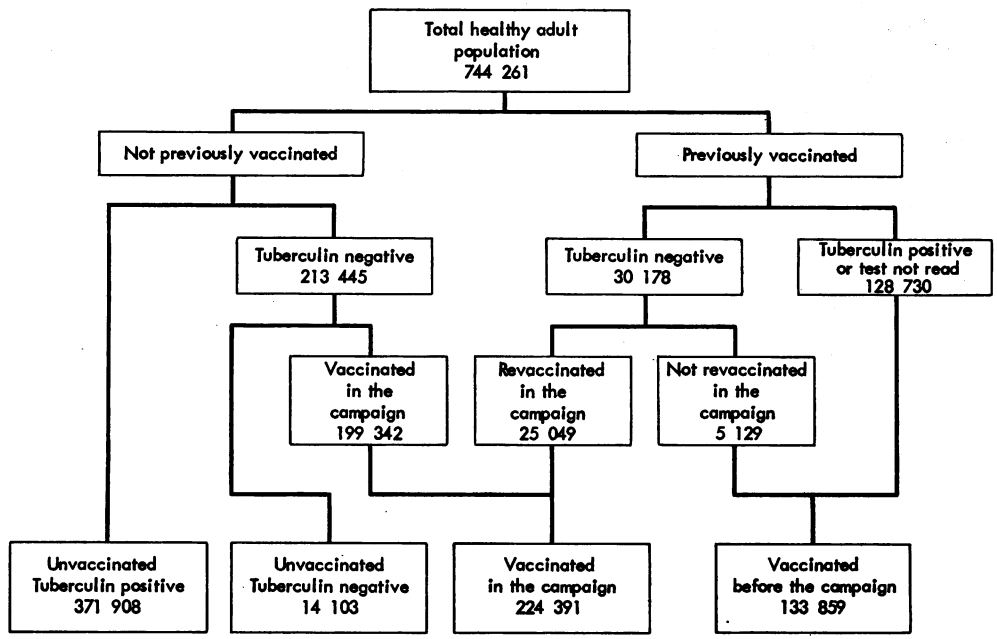


TABLE 11

THE HEALTHY ADULT POPULATION EXAMINED IN THE MASS CAMPAIGN SUBDIVIDED INTO FOUR MAIN GROUPS BY AGE

Age in years	Unvaccinated		Vaccinated		Total
	tuber-culin positive	tuber-culin negative	in the campaign	before the campaign	
15-24	48 830	3 174	91 012	87 496	230 512
25-34	126 332	4 474	78 301	37 831	246 938
35-44	114 739	3 554	40 083	7 071	165 447
45+	82 007	2 901	14 995	1 461	101 364
Total	371 908	14 103	224 391	133 859	744 261

persons. This group includes not only those who had never been vaccinated before but also those who were revaccinated at the time of the campaign because of a negative tuberculin reaction. The fourth group is composed of those who had been vaccinated before the mass campaign and were not revaccinated in the campaign: 90% had a positive tuberculin reaction; 6% did not return to have the tuberculin test read; and 4%, although they had negative tuberculin reactions, refused revaccination. This group which was vaccinated before the campaign represents 18% of the healthy population and, as with the other vaccinated group, there is a high concentration of numbers in the youngest age-class (65%) and a rapid drop in numbers with increasing age.

Fig. 23 shows the percentage distribution of these four main groups in each age classification.

FOLLOW-UP PROCEDURES

The organizational structure of the total tuberculosis control programme in Denmark permitted the healthy population discussed in this paper to be followed through the normal procedures used in our routine tuberculosis work (Groth-Petersen, 1955).

All reports of cases of tuberculosis, as well as all deaths due to tuberculosis, in the entire country are matched against three basic card files in the office of the Danish Tuberculosis Index: the Mass Campaign Roster, the Vaccination File, and the Tuberculosis Case Register, which are described in the preceding section. Only 2% of all tuberculosis cases are first known through death certificates, and these are included in morbidity statistics as new cases. Thus, routine reporting procedures of the National Health Service permit the identification of new cases of tuberculosis appearing in the study population. The follow-up period considered in the present section is four years, except in the case of a small proportion (3%) of the study population who had suspicious findings on the photofluorograms taken in the mass campaign. For that small group the follow-up period is three and a half years because six months were considered necessary to complete the clinical and bacteriological examinations of persons referred to the local chest clinics.

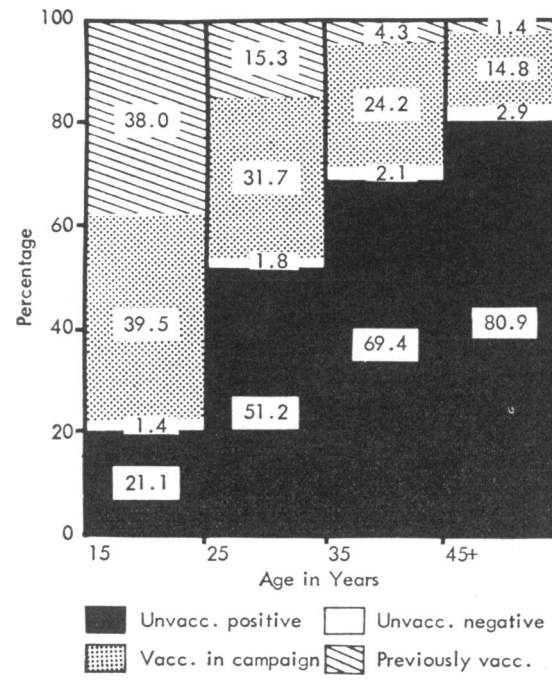
Preliminary follow-up results have previously been published (Groth-Petersen, 1958a, 1958b, 1958c; Groth-Petersen, Knudsen & Wilbek, 1957).

FOLLOW-UP RESULTS

During the follow-up period 878 new cases of tuberculosis, of which 742 (84.5%) had pulmonary disease,[1] were diagnosed in the population classified as healthy at the time of the mass campaign. Seven-

FIG. 23

PERCENTAGE DISTRIBUTION OF THE HEALTHY ADULT POPULATION IN FOUR MAIN GROUPS, BY AGE



[1] Classification of the 136 new cases of extrapulmonary tuberculosis is shown in Appendix Table 5.

teen of these patients have died, 12 of them of tuberculosis and 5 of other causes; and it may be noted that all of the deaths occurred in unvaccinated tuberculin positives. As the pulmonary form of the disease is of greatest epidemiological interest and has public health significance as a source of infection, the present paper will deal only with this type of tuberculosis. Of the 742 cases of pulmonary disease, results of the bacteriological examination for 691 were available when the case was first reported: 564 (82%) of the 691 had a positive culture.

Table 12 shows that the average annual incidence of tuberculosis per 100 000 of the healthy population during the follow-up period has been 25, which is about one-third of the incidence found in the adult population of the same areas during the year before the mass campaign. The incidence for women is greater than for men up to the age of 35; for both sexes the rates drop in the 35-44 year age-class; and after 45 the rate is higher for men than for women. The differences, however, are relatively small, and would seem to indicate that the combination of age and sex alone can no longer be used as a criterion for determining tuberculosis risk in the adult Danish population. However, as may be seen in Table 13, case rates differ greatly for the four main groups of the healthy population.

In the unvaccinated tuberculin positives, who form the largest of the four groups, the case rates for the four age-classes are 5-8 times higher than those for comparable ages in the group vaccinated in the campaign. The morbidity for the unvaccinated tuberculin positives shows a pronounced peak in the youngest age-class, which has a case rate more than three times higher than that for persons over 35 years. The decreasing trend in incidence with increase in age is also seen in both vaccinated groups, only a small fraction of whom can have been infected during the follow-up period.

The group which was vaccinated before the campaign and is represented primarily by the two youngest age-classifications has a case rate more than twice that of the group vaccinated in the campaign. It should be noted that the former group was vaccinated three years, on an average, before the latter.

The unvaccinated tuberculin negative group is so small—less than 2% of the healthy population—that the numbers in the different age-classes are too few for the rates to be meaningful. Only 12 known cases of tuberculosis appeared in the entire group during the four years of the follow-up period.

This finding supports the evidence from our examinations of pre-school children in 1950-52 that the infection rate in Denmark has been very low in recent years: less than 1% of 260 000 children of 1-6 years of age were positive to the 10 TU tuberculin test, and some of the " positives " had been previously vaccinated.

As was stated in the introduction, one of our major purposes is to define, if possible, those groups within the healthy adult population who have the greatest risk of developing tuberculosis. From the data just presented it is possible to arrive at rough ratios which represent the tuberculosis risk for the divisions of the healthy population examined in the

TABLE 12

COMPOSITION OF THE HEALTHY ADULT POPULATION BY AGE AND SEX, AND NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½-4 YEARS AFTER THE MASS CAMPAIGN

Age in years	Population		New cases of pulmonary tuberculosis				
			number		annual rate per 100 000		
	men	women	men	women	men	women	men and women
15-24	107 902	122 610	106	151	25	31	28
25-34	114 983	131 955	107	166	23	32	28
35-44	78 556	86 891	61	68	19	20	20
45+	52 658	48 706	54	29	26	15	21
Total	354 099	390 162	328	414	23	27	25

TABLE 13

NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½-4 YEARS AFTER THE MASS CAMPAIGN AMONG THE HEALTHY ADULT POPULATION, SUBDIVIDED INTO FOUR MAIN GROUPS, BY AGE

Age in years	Unvaccinated		Vaccinated		Total
	tuber-culin positive	tuber-culin negative	in the campaign	before the campaign	
	Number of new cases				
15-24	154	3	36	64	257
25-34	211	4	24	34	273
35-44	116	3	7	3	129
45+	80	2	1	—	83
Total	561	12	68	101	742
	*Annual rate * per 100 000*				
15-24	79.0	24.1	10.0	18.3	27.9
25-34	41.9	22.8	7.7	22.5	27.7
35-44	25.4	21.5	4.4	10.6	19.6
45+	24.5	17.5	1.8	—	20.6
Total	37.8	21.7	7.6	18.9	25.0

* Based on population figures given in Table 11

mass campaign. On the whole, the youngest age-class throughout the four major groups shows the highest incidence of tuberculosis during the follow-up period; and they account for 35% of all the new cases. If the risk of tuberculosis for the 15-24 year age-class of the group vaccinated in the mass campaign is scored as 1, it may then be said that the risk for the same age-class of the unvaccinated tuberculin positive reactors is eight times as great; and of the group vaccinated before the campaign approximately twice as great. The precise ratios are slightly higher for women than for men.

No attempt was made to set up a randomly selected unvaccinated control group. It follows then, that these ratios of tuberculosis risk cannot be interpreted as indicative of the protective value of vaccination. It can be stated here, however, that despite the fact that the case rates of tuberculosis in the groups vaccinated before and during the campaign are low, a substantial number of cases did occur in these groups: 23% of the new cases in the total follow-up population arose among persons who were vaccinated. And in the youngest age-class—15-24 years—almost 40% of the new cases arose in the vaccinated groups, as shown in Fig. 24. Since the frequency and types of cases of tuberculosis that appear in the vaccinated groups are of great epidemiological and diagnostic interest, they will be considered in another report.

UNVACCINATED TUBERCULIN-POSITIVE REACTORS

An important and immediate problem to be faced in the eradication of tuberculosis is the elimination of sources of infection. A study of the data just presented indicates that the unvaccinated tuberculin-positive reactors must be the major source of infection in the entire Danish population. They have had a natural tuberculous infection and, during the follow-up period, they have shown a far greater case rate than any of the other three groups of healthy adults examined during the campaign. In fact, 76% of all new cases have occurred in this group; and this is of particular interest because a similar percentage has been reported from other countries not using mass vaccination (Palmer, Shaw & Comstock, 1958).

FIG. 24

PERCENTAGE DISTRIBUTION OF NEW CASES OF PULMONARY TUBERCULOSIS IN FOUR MAIN GROUPS, BY AGE

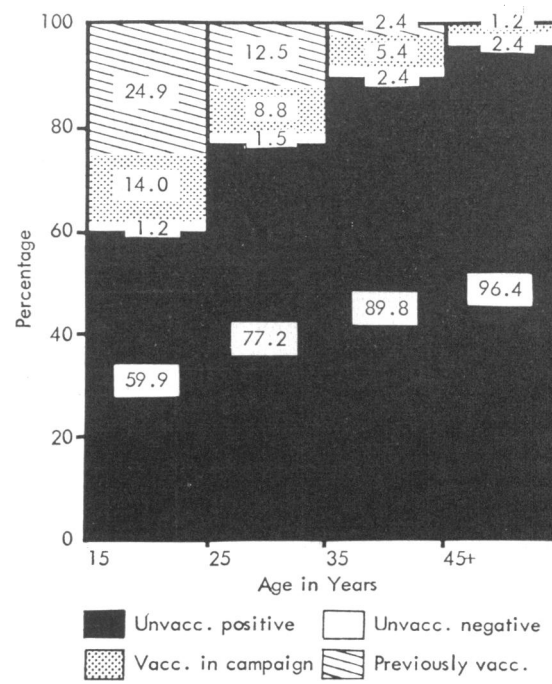


TABLE 14

NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½-4 YEARS AFTER THE MASS CAMPAIGN AMONG THE UNVACCINATED TUBERCULIN-POSITIVE GROUP, BY SEX AND AGE

Age in years	Men			Women		
	population	new cases		population	new cases	
		No.	annual rate per 100 000		No.	annual rate per 100 000
15-24	22 558	64	71	26 272	90	86
25-34	63 268	78	31	63 064	133	53
35-44	58 523	53	23	56 216	63	28
45+	44 776	53	30	37 231	27	18
Total	189 125	248	33	182 783	313	44

The differences in tuberculosis case rates for men and women with a naturally positive tuberculin reaction are shown in Table 14. The two younger age-classes of both sexes have substantially higher rates than the older classes. The difference in risk between the two sexes, however, is not large enough to justify considering them separately in the various subdivisions which will now be discussed.

The large unvaccinated group with a natural tuberculous infection can be subdivided into three categories with widely different case rates for tuberculosis. Table 15 and Fig. 25 show that both photofluorogram readers diagnosed as normal a very large portion of the group in question (90%), and that for these persons with normal lungs, the average annual case rate of tuberculosis for all ages is only 27 per 100 000. In contrast to this, the smallest of the three categories, made up of persons whose photofluorograms one or both readers described as suspicious, has a case rate of 370, which is almost 14 times greater than the category of those with normal lungs. For persons described by both readers as having healed lesions (7% of the unvaccinated tuberculin positives) the annual case rate for all ages is 51, approximately twice that for those diagnosed as normal.

In the second part of this report, it was mentioned that the photofluorograms were deliberately overread to give reasonable assurance that all persons with definite or suspicious lesions would be identified for further examination. Because of this overreading, it was anticipated that many persons referred for roentgenographic examination on the basis of suspicious findings on the photofluorograms would eventually be classified as having normal lungs. Actually 43% of those so referred were finally diagnosed as normal by the local tuberculosis specialist. (Results of the independent readings of the roentgenograms made at a later date by a central reader are not considered in the present report.)

Undoubtedly, the results of the roentgen examination for those referred to the clinics for further examination come closer to the truth than do the findings of the single photofluorogram. On the other hand, it does not necessarily follow that when a reading of the roentgenogram differs from that of

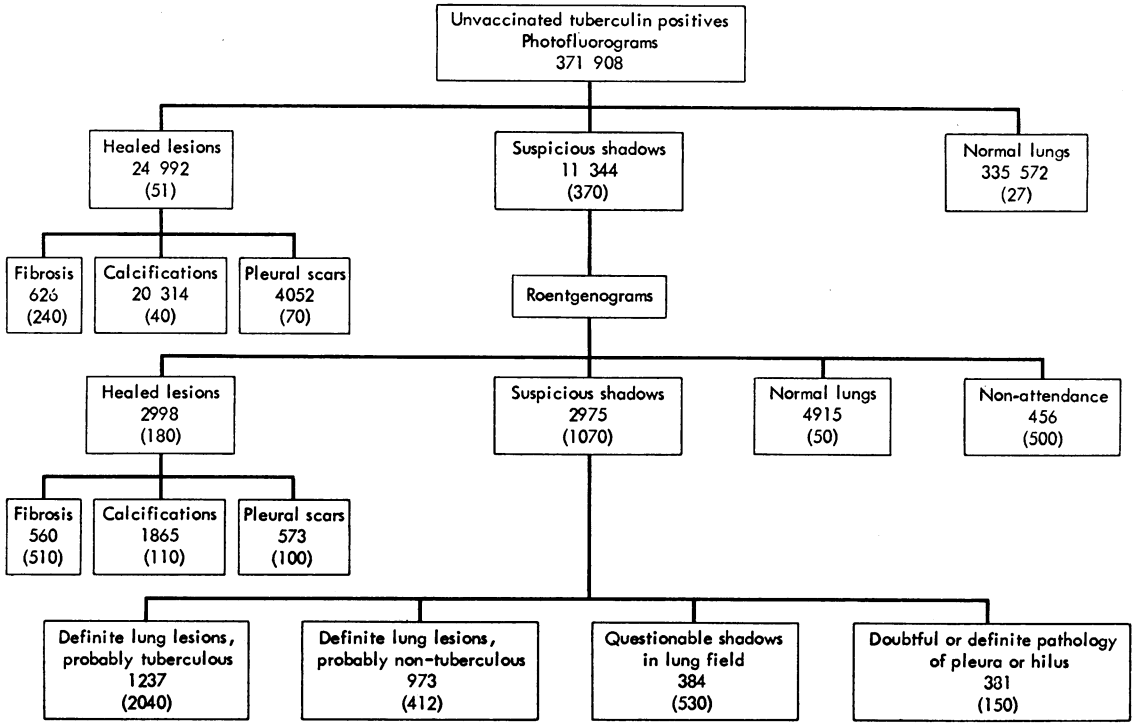
TABLE 15

PHOTOFLUOROGRAPHIC FINDINGS AMONG THE UNVACCINATED TUBERCULIN-POSITIVE GROUP AND NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½-4 YEARS AFTER THE MASS CAMPAIGN

Age in years	Suspicious shadows	Healed lesions	Normal lungs	Total
	Population			
15-24	979	1 898	45 953	48 830
25-34	3 043	6 650	116 639	126 332
35-44	3 313	8 053	103 373	114 739
45+	4 009	8 391	69 607	82 007
Total	11 344	24 992	335 572	371 908
	Number of new cases			
15-24	35	11	108	154
25-34	48	16	147	211
35-44	33	10	73	116
45+	31	14	35	80
Total	147	51	363	561
	Annual rate per 100 000			
15-24	1 022	147	59	79
25-34	451	60	32	42
35-44	285	30	18	25
45+	220	40	13	25
Total	370	51	27	38

FIG. 25

POPULATION AND CASE RATES (IN PARENTHESIS) FOR THE UNVACCINATED TUBERCULIN POSITIVE GROUP SUBDIVIDED ACCORDING TO PHOTOFLUOROGRAPHIC FINDINGS AND, FOR THOSE WITH SUSPICIOUS SHADOW ACCORDING TO ROENTGENOGRAPHIC FINDINGS



the photofluorogram the interpretation of the latter is in error. Substantiation of this statement can be seen if certain data in Table 16 are compared with like data in Table 15. Table 16 represents the breakdown of the results of the roentgen examination of the unvaccinated tuberculin-positive reactors whose photofluorograms were read as suspicious. During the follow-up years, the case rate for the two categories described as " healed lesions " and " normal lungs " on the basis of the single reading of the roentgenogram is greater than the rates for the categories defined in a like manner from the dual readings of the photofluorograms.

Films read as showing healed lesions (Table 17 and Fig. 25) have been subdivided into three types. The first one, defined as " fibrosis ", includes not only well defined fibrotic scars but also incompletely calcified parenchymatous lesions as well as combinations of these conditions with pleural scars and/or completely calcified lesions. The second subdivision is made up of clear-cut calcifications and nothing more; and the third comprises only pleural scars. In the Danish population almost all intrathoracic calcifications are of tuberculous origin; whereas some pleural scars, which most often are obliterated costophrenic sinuses, are due to non-specific pneumonias.

As a rule it is easier to distinguish between normal lungs and so-called healed lesions than between normal lungs and suspicious shadows which might represent active lesions. Therefore, a certain amount of over-reading occurred on the roentgenograms interpreted as suspicious shadows. Exclusive of lesions interpreted as definitely healed, this category includes all persons whose roentgen films were read as showing evidence, or even the slightest suspicion, of pathology in the lung, hilus and/or pleura. The reader indicated whether he interpreted the lesion as definite or questionable and also indicated whether he considered it to be probably of tuberculous, of questionable, or of non-tuberculous etiology. In spite of this gross classification the total category described as suspicious on the roentgenogram has a

TABLE 16

ROENTGENOGRAPHIC FINDINGS AMONG UNVACCINATED TUBERCULIN-POSITIVE ADULTS WITH SUSPICIOUS PHOTOFLUOROGRAMS AND NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½ YEARS AFTER THE MASS CAMPAIGN

Age in years	Suspicious shadows	Healed lesions	Normal lungs	Non-attendance	Total
	Population				
15-24	219	152	557	51	979
25-34	761	645	1 503	134	3 043
35-44	847	903	1 445	118	3 313
45+	1 148	1 298	1 410	153	4 009
Total	2 975	2 998	4 915	456	11 344
	Number of new cases				
15-24	23	7	3	2	35
25-34	39	4	2	3	48
35-44	26	4	2	1	33
45+	23	4	2	2	31
Total	111	19	9	8	147
	Annual rate per 100 000				
15-24	3 000	1 320	150	1 120	1 022
25-34	1 460	180	40	640	451
35-44	880	130	40	240	285
45+	570	90	40	370	220
Total	1 070	180	50	500	370

tuberculosis risk 40 times greater than the group read as normal on the photofluorograms (Tables 15 and 16, and Fig. 25).

For further analysis of this category, made up of persons whose roentgenograms were described as suspicious, the films have been grouped into four types: definite lung lesions, probably of tuberculous etiology; definite lung lesions, probably of non-tuberculous etiology; questionable shadows in the lung field; and definite or questionable pathology in the pleura or hilus. It is among these four types of suspicious roentgenogram findings that we discover a very small segment of our total healthy population—less than one-half of one per cent—with an extremely high risk of tuberculosis. As is seen in Table 18 and Fig. 25, 1237 persons whose

TABLE 17

NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½-4 YEARS AFTER THE MASS CAMPAIGN AMONG UNVACCINATED TUBERCULIN-POSITIVE ADULTS ACCORDING TO TYPE OF HEALED LESION SEEN ON THE PHOTOFLUOROGRAM OR THE ROENTGENOGRAM

Type of healed lesion	Photofluorogram			Roentgenogram		
	population	new cases	rate *	population	new cases	rate *
Fibrosis	626	6	240	560	10	510
Calcification	20 314	33	40	1 865	7	110
Pleural scar	4 052	12	70	573	2	100
Total	24 992	51	49	2 998	19	180

* Annual rate per 100 000

roentgenograms showed definite lung lesions of probable tuberculous origin had, in the follow-up period, a case rate 76 times greater than that of the 335 572 persons whose photofluorograms were read as normal (Table 15).

Having identified as an extremely high-risk group a very small segment of the healthy adult population examined in the mass campaign, let us take a comprehensive look at the chances of developing active

TABLE 18

NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 3½ YEARS AFTER THE MASS CAMPAIGN AMONG UNVACCINATED TUBERCULIN-POSITIVE ADULTS ACCORDING TO TYPE OF SUSPICIOUS SHADOW SEEN ON THE ROENTGENOGRAM

Type of suspicious shadow	Population	New cases	Annual rate per 100 000
Definite lung lesion, probably tuberculous	1 237	88	2 033
Definite lung lesion, probably non-tuberculous . .	973	14	412
Questionable shadow in lung field	384	7	530
Questionable or definite pathology in the pleura or hilus	381	2	150
Total . . .	2 975	111	1 070

TABLE 19

RELATIVE RISK OF DEVELOPING TUBERCULOSIS FOR UNVACCINATED TUBERCULIN-POSITIVE ADULTS, ACCORDING TO PHOTOFLUOROGRAPHIC OR ROENTGENOGRAPHIC FINDINGS

Risk group	Composition of risk group *	Number in group	Annual rate per 100 000
Major	R : definite lung lesion, probably tuberculous (8)	1 237	2 033
Moderate	R : questionable shadows in lung field (8)	384	530
	R : healed lesions (fibrosis) (7)	560	510
	P : suspicious shadows, but did not appear for roentgenographic examination (6)	456	500
	R : definite lung lesion, probably non-tuberculous (8)	973	412
	Total . . .	2 373	470
Minor	R : questionable or definite pathology of pleura or hilus (8)	381	150
	R : healed lesions (calcification) (7)	1 865	110
	R : healed lesions (pleural scars) (7)	573	100
	P : healed lesions (5) . .	24 992	51
	R : normal lungs (6) . . .	4 915	50
	Total . . .	32 726	56
Minimal	P : normal lungs (5) . . .	335 572	27

* Based on reading of roentgenogram (R) or photofluorogram (P). Figures in parenthesis refer to source tables.

tuberculosis for other subdivisions of the healthy unvaccinated tuberculin-positive persons. Table 19 shows each of the various subdivisions arrayed according to the magnitude of their average annual tuberculosis case rate during the follow-up period. It is immediately obvious that persons with a naturally positive tuberculin reaction can be readily divided into four main groups with widely different risks of developing active tuberculosis. These groups are identified in the table as major, moderate, minor and minimal risk groups.

Table 20 presents for each age-class within these groups the number of new cases of tuberculosis and the case rates during the follow-up period. The differences between the case rates of the minimal risk group and those of the minor, moderate, and major risk groups are substantial. The major risk group—persons with definite lung lesions of probable tuberculous origin—had a tuberculosis case rate 76 times greater than that of the minimal risk group—persons with normal findings on the photofluorogram; while the case rates of the moderate and minor risk groups were, respectively, 17 and 2 times greater than that of the minimal risk group. It is also to be noted that the case rates for the age-class 15-24 years of all four risk groups were

TABLE 20

EFFECT OF AGE ON RISK OF DEVELOPING TUBERCULOSIS FOR UNVACCINATED TUBERCULIN-POSITIVE ADULTS, SUBDIVIDED INTO FOUR DIFFERENT RISK GROUPS BASED ON PHOTOFLUOROGRAPHIC OR ROENTGENOGRAPHIC FINDINGS

Age in years	Risk group				Total
	major	moderate	minor	minimal	
	Population				
15-24	84	171	2 622	45 953	48 830
25-34	277	580	8 836	116 639	126 332
35-44	339	687	10 340	103 373	114 739
45+	537	935	10 928	69 607	82 007
Total	1 237	2 373	32 726	335 572	371 908
	Number of new cases				
15-24	21	6	19	108	154
25-34	27	17	20	147	211
35-44	20	8	15	73	116
45+	20	8	17	35	80
Total	88	39	71	363	561
	Annual rate per 100 000				
15-24	7 143	1 003	188	59	79
25-34	2 785	837	58	32	42
35-44	1 686	333	37	18	25
45+	1 064	245	40	13	24
Total	2 033	470	56	27	38

considerably higher than those of the older age-classifications (cf. Cochrane, Cox & Jarman, 1955; Cochrane et al., 1956; Springett, 1951).

In the introduction we posed the question: Can individuals or groups with a high risk of developing tuberculosis be identified? The answer is " yes ". Such groups can be identified through the routine tuberculosis examination. All persons in the major risk group and the two youngest age-classes in the moderate risk group have average annual case rates for the follow up years ranging from approximately 7000 to 837 per 100 000 and make up a population of less than 2000 persons, which is not even one-half of one per cent of nearly three-quarters of a million healthy persons examined. The fact that persons with an extremely high risk of developing active tuberculosis make up such a very small portion of the general population, and can be identified through the routine tuberculosis examination, means that it is both feasible and practicable to consider seriously for this group early medical attention such as prophylactic chemotherapy or, at least, frequent follow-up examinations.

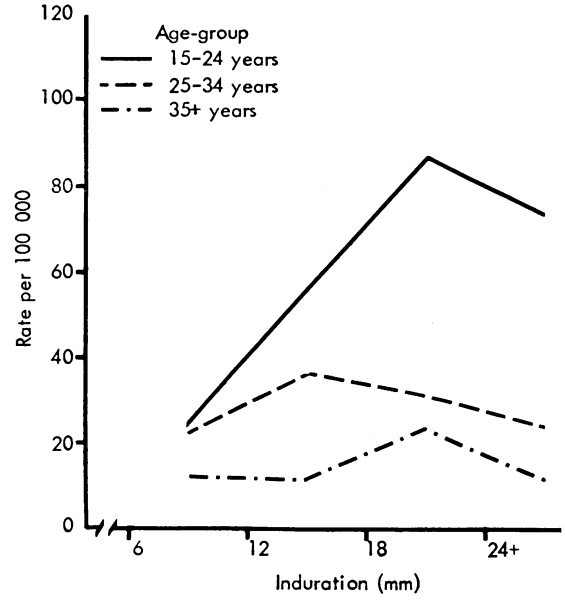
DEGREE OF TUBERCULIN SENSITIVITY AND SUBSEQUENT MORBIDITY

As described in the preceding section, in the mass campaign tuberculin tests were given and the indurations were carefully measured by a few selected and highly skilled nurses. The results are, we believe, adequate for research purposes (Danish Tuberculosis Index, 1955c), and make it possible to study in detail the complex question of the relation between the degree of tuberculin sensitivity and the risk of developing tuberculous disease. Considerable information on the question is now at hand; but at this time we shall consider only briefly the size of the tuberculin reaction as a prognostic index of later disease for the large group of 336 000 unvaccinated tuberculin positive reactors whose photofluorograms were read as normal by both readers. Of this population, 320 000 were tested with 10 TU, and 16 000 with 5 TU. The latter dose was used on a trial basis in two counties and, although the follow-up results were essentially the same for the groups tested with the two doses, data presented here will include only the population tested with 10 TU. Although women show a slightly larger induration than men in the same age-group (Danish Tuberculosis Index, 1955c), the difference does not affect the relation between the degree of sensitivity and the magnitude of risk for the two sexes. Results for men and women will therefore be combined.

Table 21 and Fig. 26 give the average annual case rates during the four-year follow-up period according to the measured size of the 10 TU tuberculin reaction for three age-classes. For young persons, a strong reaction is a danger signal: the risk is almost proportional to the degree of sensitivity. Among persons of 15-24 years of age a reaction of 6-11 mm is associated with a low morbidity rate. For those with a reaction measuring 12-17 mm the rate is more than twice as high, and for those with reactions of 18-23 mm it is more than three times higher. For persons with the largest reactions—indurations of 24 mm or more—the risk seems to be diminished.

FIG. 26

INCIDENCE OF NEW CASES OF PULMONARY TUBERCULOSIS IN UNVACCINATED TUBERCULIN POSITIVE ADULTS, ACCORDING TO SIZE OF REACTION TO THE 10 TU TEST, BY AGE



The incidence of tuberculosis in the follow-up period is much lower in the older than in the younger population and the association between the size of the tuberculin reaction and morbidity is much less pronounced.

The observation that the incidence of tuberculosis is lower for persons with small reactions than for

those with large reactions—particularly young adults—has been reported from other studies (Comstock & Porter, 1959; Palmer, Jablon & Edwards, 1957; Palmer et al., 1958; South African Medical Research Committee, 1932; Great Britain, Medical Research Council, Tuberculosis Vaccines Clinical Trials Committee, 1956). In the USA, the lower rate in persons with small reactions has been attributed to a " dilution " of the group with small reactions by persons with non-specific tuberculin sensitivity. In Denmark, there must be in the group with the smallest reactions some who have not had a tuberculous infection; but these are probably too small in number to account for the increased risk that is found with an increasing degree of sensitivity.

The possibility that people with a high degree of sensitivity had acquired their infection within a short time before the mass campaign cannot be excluded, but our material does not support that hypothesis. As shown in Table 21, there is little difference between the number of cases arising in the first two years and the number occurring in the next two years of the four-year follow-up period. There is the possibility, of course, that the population who initially had a strong tuberculin reaction is most exposed to reinfection and might, therefore, have a higher rate. This interpretation does not, however, take into account that in all age-classes the groups with reactions of 12-23 mm tend to have higher morbidity rates than those with very large reactions. The possibility also cannot be excluded that our findings may in some way reflect the fact that a considerable proportion of the tuberculin sensitivity in Denmark may be a result of infection a few decades ago with bovine tubercle bacilli (Danish Tuberculosis Index, 1955a).

From the material presented here, it is apparent that the relation between the size of the tuberculin

TABLE 21
NEW CASES OF PULMONARY TUBERCULOSIS APPEARING IN THE FIRST 4 YEARS AFTER THE MASS CAMPAIGN ACCORDING TO SIZE OF REACTION TO THE 10 TU TEST AMONG UNVACCINATED TUBERCULIN-POSITIVE ADULTS WITH PHOTOFLUOROGRAMS READ AS SHOWING NORMAL LUNGS

Age in years	Size of tuberculin reactions (in millimeters)	Population	Number of new cases			Annual rate per 100 000
			1st and 2nd years	3rd and 4th years	Total years	
15-24	6-11	7 146	3	4	7	24.5
	12-17	19 063	21	22	43	56.4
	18-23	13 097	28	18	46	87.8
	24+	4 134	7	5	12	72.6
	Total	43 440	59	49	108	62.2
25-34	6-11	18 330	7	10	17	23.2
	12-17	50 405	34	40	74	36.7
	18-23	32 643	20	21	41	31.4
	24+	10 436	3	7	10	24.0
	Total	111 814	64	78	142	31.7
35+	6-11	34 204	10	7	17	12.4
	12-17	73 962	16	20	36	12.2
	18-23	42 058	19	22	41	24.4
	24+	14 233	4	3	7	12.3
	Total	164 457	49	52	101	15.4

reaction and subsequent morbidity is a complex problem; but taken together with material presented in other recent papers it seems to support the evidence that the greater part of the new cases appearing in the unvaccinated tuberculin positive population is due to endogenous reinfection.

DISCUSSION AND CONCLUSIONS

We can estimate, from the material presented in this paper and from information available on the adult population who did not participate in the campaign, that approximately 60% of the entire adult Danish population has had a natural tuberculous infection and that 85%-90% of our new cases of pulmonary tuberculosis are coming from that portion of the population. The importance of this group as the major source of infection for the Danish population is obvious.

On the basis of a single photofluorographic examination, apparently healthy tuberculin-positive adults can be divided according to their risk of developing active tuberculosis into three broad categories: those with suspicious findings (3%); those with healed lesions (7%); and those with normal lungs (90%). The average annual case rate for the small percentage with suspicious findings is seven times greater than for those with healed lesions, and 14 times greater than for those with normal lungs.

The findings of the supplementary roentgen examination of the 3% whose photofluorograms were read as showing suspicious lesions permits an even sharper pinpointing of small groups with significantly high degrees of risk. The highest case rate—roughly 2000 per 100 000 persons per year—is associated with roentgenographic findings interpreted as definite lesions, probably of tuberculous origin. This major risk group of about 1200 persons comprised less than half of one per cent of the three-quarters of a million healthy adults examined in the mass campaign. Lesser, though still high, degrees of risk are found for persons with questionable parenchymal shadows, fibrosis or definite lesions thought to be of non-tuberculous origin. Case rates for those groups range from 412 to 530—one-quarter as high as for the major risk group but many times higher than the rate of 27 for the large group of 336 000 persons with normal photofluorographic findings.

Age (but not sex) has an important effect on the chances of tuberculin-positive persons to develop tuberculosis. Within each of the various risk groups, young adults have substantially higher case rates than older persons, the rates showing a steady downward trend with increasing age.

Thus, with the tuberculin test to identify the naturally infected members of the population and the photofluorogram to identify those with suspicious lesions for further roentgenographic examination, we are able to isolate the extremely small percentage of the healthy adult population who have a very great chance of developing tuberculosis. On the other hand, we must not overlook the fact that in terms of numbers rather than rates nearly two-thirds of all the new cases in the tuberculin positives arose in the 336 000 with normal findings on the photofluorogram. Here the size of the tuberculin reaction together with age helps to focus attention on those with the highest risk. For young persons, a large tuberculin reaction is a danger signal. All but a handful of the 108 cases in the 15-24 year age-class arose in persons with a reaction of 12 mm or more to the 10 TU test. For all ages, young as well as old, a reaction of less than 12 mm is associated with a low risk.

It might be thought that the validity of our results is weakened because of the subjective descriptions of suspicious X-rays. Admittedly, our studies of multiple readings of films have shown inconsistencies between readers (Danish Tuberculosis Index, 1955b; Groth-Petersen et al., 1952; Groth-Petersen & Møller, 1954, 1955). Yet highly qualified American roentgenologists and tuberculosis specialists, despite extensive work, have not so far been able to arrive at uniform, objective, morphological descriptions of chest films or to obtain consistent results in dual readings of X-rays (Yerushalmy, personal communication, 1958). For practical purposes, however, the single interpretations of the roentgenograms made by nineteen different chest physicians and the dual readings of the photofluorograms by different pairs of readers evidently have striking prognostic value. The very small group of naturally infected healthy adults whose roentgenograms were described as showing suspicious or definite lung lesions, but who did not show signs of active tuberculosis during the first six months of close observation, had during the following years a morbidity 76 times greater than persons with photofluorograms interpreted as normal.

Undoubtedly the time has come for the traditional methods of tuberculosis control in Denmark, so effective in the past, to be readjusted and brought into line with our present knowledge of the foci of infection in our population and recent developments

in the chemotherapeutic field. During 1958-59 many aspects of the material presented here have been studied and discussed by our tuberculosis specialists; changes in the service programme have been proposed (Groth-Petersen, 1958c; Hagn-Meincke, 1958; Slottved, 1958) and will soon be introduced in selected counties.

Routine X-raying of children has already been abolished, and in some counties routine BCG vaccination of infants and children will be abolished until the last year of school. The tuberculin test could then be used clinically and as a matter of routine each year among all children to find the few who have already had a natural infection and the even smaller number who will become infected during the coming years. We should also be able to measure the infection rate prevailing in the community, to facilitate the detection of new sources of infection, and to treat newly infected children.

Certainly the enormous numbers of routine repetitive X-ray examinations of adults can be drastically reduced and the case-finding nevertheless intensified. Persons in the older age-groups with normal findings on a single photofluorogram, even though they have positive tuberculin reactions, need not be called back for examination year after year. They can be left in peace. But persons of any age with suspicious X-ray lesions and young people with large tuberculin reactions should be followed systematically. These high-risk groups comprise such a small percentage of the total population that continuous and close supervision is both practicable and profitable. The very least we can do is to watch them carefully for early signs of disease and, possibly, with the use of a chemoprophylactic agent (Groth-Petersen, 1956, 1957; US Public Health Service, 1957) we may take another forward step towards our ultimate goal—the eradication of tuberculosis.

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RÉSUMÉ

La découverte de médicaments efficaces contre le bacille tuberculeux a changé l'orientation de la prophylaxie antituberculeuse, fondée essentiellement, il y a quelque dix ans encore, sur l'amélioration des conditions de vie. Dans les pays où la morbidité par tuberculose et le taux d'infection sont faibles et où l'on dispose des facilités nécessaires, on peut raisonnablement songer à l'éradication de la maladie. La réalisation d'un tel programme exige comme point de départ un tableau épidémiologique précis de la maladie, qui, lui-même, ne peut être tracé qu'en collationnant des données réunies systématiquement durant plusieurs années. Le Danemark, avec sa population de 4,5 millions environ, a fait dans ce domaine œuvre de pionnier. Ce pays est en effet à l'avant-garde de la lutte antituberculeuse. Il possède depuis longtemps des services de lutte antituberculeuse bien organisés, une grande expérience du travail pratique, et des services centralisés d'enregistrement des cas et de diagnostic de laboratoire.

Le « Dansk Tuberkulose Index » (DTI) — bureau d'étude de la tuberculose au Danemark — est le centre d'intérêt de l'article ici résumé. Il est l'une des pièces maîtresses de l'œuvre entreprise en vue de supprimer la tuberculose en territoire danois. Il est conçu de façon telle qu'il pourra servir de guide aux services nationaux d'autres pays qui se fixeront les mêmes buts. Le DTI a été institué en 1950 par le Bureau de Recherches sur la Tuberculose, de l'OMS, et le Service national de Santé du Danemark, en relation avec la campagne nationale de vaccination par le BCG.

Cet article condense les expériences faites depuis une dizaine d'années. Les principaux indicateurs de la tuberculose et leur valeur pour des comparaisons internationales sont présentés. La situation concernant la tuberculose au Danemark au cours des trente dernières années est décrite, afin de situer l'activité du DTI. La campagne de masse contre la tuberculose, comportant à la fois un programme de lutte et un programme de recherches, ainsi que les résultats de cette campagne présentant un intérêt pour la surveillance de la population examinée sont également considérés. L'analyse des résultats, sur la base des nouveaux cas enregistrés depuis la campagne, indique l'existence de groupes fortement exposés à la maladie qui doivent être spécialement surveillés et protégés, et celle de groupes moins exposés qui ne requièrent pas un contrôle aussi soutenu.

Dans l'introduction aux études sur la tuberculose, les auteurs présentent sous forme de diagrammes la fréquence globale de l'infection tuberculeuse humaine et bovine. Ils rappellent que la sensibilité non spécifique à la tuberculine due à d'autres causes que la vaccination au BCG n'a qu'une importance minime au Danemark. Il semble que la fréquence globale de l'infection tuberculeuse soit destinée à devenir un indice de la tuberculose plus important que les statistiques de morbidité, dans les pays qui envisagent l'éradication de la maladie.

La mortalité due à toutes les formes de la tuberculose, au Danemark, a été parmi les plus faibles enregistrées dans le monde depuis plus de trente ans. Il en est de même pour la fréquence des nouveaux cas de tuberculose pulmonaire qui, au cours des dix dernières années, a baissé de 80 à 25 pour 100 000, la mortalité tombant de 25 à 4 pour 100 000.

Le diagnostic de tuberculose pulmonaire se fonde principalement sur la culture des bacilles tuberculeux présents dans les crachats ou les lavages gastriques. Tous les examens bactériologiques sont exécutés au Statens Seruminstitut et toutes les cultures positives sont signalées aux dispensaires antituberculeux qui, à leur tour, notifient les cas de tuberculose au Service national de Santé.

Il y a lieu de penser que, pour mesurer la fréquence globale des cas de tuberculose pulmonaire, le meilleur indice comparable est le nombre total, pendant l'année civile, des cas nouveaux et anciens présentant encore des cultures positives de bacilles tuberculeux. D'après ce critère, la fréquence globale, au Danemark, à l'exclusion de Copenhague, a été de 134 pour 100 000 habitants en 1949 et a diminué progressivement depuis lors, atteignant 51 pour 100 000 en 1956.

La campagne de masse qui s'est déroulée de 1950 à 1952 sur l'ensemble du territoire danois, sauf Copenhague et l'île de Bornholm, était placée sous la direction technique du DTI. Un de ses principaux objectifs était de généraliser la vaccination par le BCG. On s'est attaché également à réunir des renseignements uniformes, non faussés par un biais systématique, sur l'épreuve tuberculinique et l'examen radiologique de sections importantes de la population. Les fichiers du DTI se composent de quelque 1,5 million de fiches individuelles de la campagne, d'un registre des vaccinations avant la campagne et d'un registre des cas de tuberculose depuis 1921.

Toutes les personnes âgées de 1 à 6 ans et de 15 à 34 ans ont été personnellement invitées à se prêter à la campagne. Les autres ont été admises à participer à titre volontaire. Chaque sujet a reçu une injection intradermique de 10 UT de tuberculine PPD; une radiographie sur 35 mm a été faite pour toutes les personnes âgées de 15 ans et plus.

La lecture des films a été effectuée indépendamment par des équipes de deux spécialistes de la tuberculose. Les sujets présentant des signes précis ou suspects ont été dirigés vers les dispensaires antituberculeux locaux pour des examens cliniques et radiographiques plus complets.

L'article donne les résultats détaillés des épreuves tuberculiniques et des examens radiologiques effectués sur les sujets non vaccinés, sur les sujets vaccinés possédant un dossier médical et ceux qui n'en possédaient pas. Les observations suspectes qui appelaient des examens plus approfondis ont été, comme on s'y attendait, plus fréquentes chez les sujets non vaccinés positifs à la tuberculine que chez les sujets négatifs. En revanche, on fut surpris de constater que les lésions suspectes, chez les sujets vaccinés antérieurement, étaient beaucoup plus fréquentes chez les sujets qui avaient réagi négativement que chez ceux qui étaient positifs à la tuberculine.

Le nombre des cas nouveaux de tuberculose pulmonaire évolutive a été de 503 parmi les 795 000 personnes examinées, soit un taux global de 63 pour 100 000. Ce taux variait considérablement selon les sections de la population: 116 pour 100 000 chez les sujets positifs à la tuberculine, qui n'avaient jamais été vaccinés, contre 21 chez ceux qui avaient été vaccinés avant la campagne, et 4 chez les sujets négatifs à la tuberculine qui n'avaient jamais été vaccinés. La confirmation bactériologique du diagnostic de tuberculose évolutive a été obtenue dans 94% des cas nouveaux découverts au cours de la campagne.

Les auteurs analysent les cas nouveaux de tuberculose pulmonaire évolutive qui sont apparus 3½ à 4 ans plus tard dans une population générale de 750 000 habitants examinés pendant la campagne de masse 1950-52. Cette population ne comprend que les personnes trouvées sans signes de tuberculose active et qui n'avaient pas été déclarés comme cas de tuberculose précédemment. Les trois quarts des 878 cas nouveaux de tuberculose ont été diagnostiqués dans le groupe de population composé des sujets non vaccinés avec réaction tuberculinique positive au cours de la campagne.

Sur la base des examens radiologiques et de la réaction au test tuberculinique intradermique à 10 UT, on a constaté que les risques de contracter la tuberculose sont extrêmement variables parmi les sujets positifs qui n'avaient jamais été vaccinés et que l'on considérait comme indemnes de tuberculose au moment de la campagne. Parmi le groupe le moins exposé, qui comprenait environ 336 000 sujets présentant des clichés normaux,

on a enregistré un taux annuel moyen de 27 cas pour 100000. A l'autre extrême, pour le groupe le plus exposé, qui comprenait environ 1200 sujets présentant des lésions certaines, probablement d'origine tuberculeuses, mais sans signe d'activité à l'examen radiographique (et qui ont été soumis à un examen radiologique plus poussé en raison des ombres suspectes révélées par le microfilm), le taux des cas nouveaux a dépassé 2000 pour 100 000. Quant aux sujets présentant des ombres douteuses ou des lésions guéries, leurs taux se sont situés entre ces deux extrêmes. Dans chacun des groupes considérés, les taux ont été plus élevés parmi les classes jeunes que chez les plus âgées. Ils ont aussi été plus élevés chez les personnes ayant réagi fortement à la tuberculine que chez celles qui avaient présenté une réaction modérée (6-11 mm).

On a proposé de réduire le nombre des examens périodiques de contrôle pour les adultes et de concentrer les efforts sur les mesures préventives en faveur des groupes très exposés. Les examens radiologiques réguliers des enfants ont déjà été supprimés, et dans quelques comtés, la vaccination ne sera pratiquée que pendant la dernière année scolaire; quant à l'épreuve à la tuberculine, elle sera pratiquée systématiquement, et sera suivie d'une surveillance attentive avec une chimiothérapie préventive chez les sujets qui virent de la négativité à la positivité.

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APPENDIX TABLE 1
INCIDENCE OF PULMONARY TUBERCULOSIS IN DENMARK, 1921-57

Calendar year	Number					Per 100 000 population				
	Copenhagen		Denmark excl. Copenhagen		total Denmark	Copenhagen		Denmark excl. Copenhagen		total Denmark
	males	females	males	females		males	females	males	females	
1921	690	721	1626	2323	5360	266	238	121	168	163
22	589	570	1614	2227	5000	224	186	119	160	150
23	584	541	1447	2018	4590	220	173	105	143	137
24	581	611	1467	2131	4790	216	192	105	150	142
25	518	542	1455	2170	4685	193	170	104	151	137
1926	524	490	1282	2000	4296	193	153	91	138	124
27	442	500	1241	1866	4049	161	156	87	128	116
28	422	451	1227	1778	3878	153	140	86	121	111
29	449	547	1262	1805	4063	162	168	88	123	115
30	490	490	1273	1636	3889	173	143	88	111	110
1931	489	458	1302	1677	3926	170	136	89	113	110
32	514	495	1286	1639	3934	175	146	87	110	110
33	443	477	1087	1448	3455	150	139	73	96	95
34	465	478	1088	1319	3350	152	137	73	87	92
35	487	483	1033	1269	3272	158	136	68	83	89
1936	532	602	1026	1210	3370	170	168	67	79	91
37	559	611	1078	1252	3500	176	168	70	82	93
38	460	522	920	1136	3040	143	141	60	74	80
39	437	492	879	998	2806	134	132	57	64	74
40	421	381	927	958	2687	130	102	59	61	70
1941	507	536	1071	1173	3286	155	143	68	74	85
42	541	484	1094	1129	3248	164	128	68	71	83
43	589	600	1073	1086	3348	175	156	66	67	85
44	559	522	1141	1121	3343	166	136	69	69	84
45	659	510	1216	1075	3460	193	130	73	65	86
1946	762	719	1289	1352	4122	219	181	77	81	101
47	635	582	1157	1148	3522	179	144	68	68	85
48	661	555	1081	1054	3351	185	137	63	62	80
49	500	466	976	964	2906	140	115	56	56	69
50	416	375	839	884	2514	116	93	48	51	59
1951	347	313	856	896	2412	96	77	48	51	56
52	324	252	723	761	2060	91	62	40	43	48
53	281	231	641	611	1764	78	57	35	34	40
54	261	241	533	512	1547	73	60	29	28	35
55	233	186	429	394	1236	66	47	23	21	28
1956	207	143	402	375	1127	59	36	22	20	25
57	186	136	439	344	1105	53	35	23	18	25

APPENDIX TABLE 2

MORTALITY FROM ALL FORMS OF TUBERCULOSIS IN DENMARK, 1921-57

Calendar year	Number					Per 100 000 population				
	Copenhagen		Denmark excl. Copenhagen		total Denmark	Copenhagen		Denmark excl. Copenhagen		total Denmark
	males	females	males	females		males	females	males	females	
1921	343	309	1091	1420	3153	132	102	81	103	96
22	308	329	1073	1429	3139	117	107	79	102	94
23	321	279	1029	1350	2979	121	89	75	96	89
24	371	369	1132	1463	3245	138	116	82	103	96
25	327	307	1020	1460	3114	122	97	73	102	91
1926	336	301	895	1248	2780	124	94	63	86	80
27	289	284	880	1255	2708	105	88	62	86	78
28	295	278	846	1175	2594	107	86	59	80	74
29	249	299	833	1210	2591	90	92	58	82	74
30	262	286	861	1093	2502	93	86	59	74	71
1931	268	264	857	1083	2472	93	79	59	73	69
32	265	291	847	1059	2462	90	86	57	71	69
33	295	273	733	897	2118	100	80	49	60	58
34	233	233	720	818	2004	76	67	48	54	55
35	238	204	613	844	1899	77	57	41	56	52
1936	202	176	640	718	1736	65	49	42	47	47
37	190	175	605	694	1664	60	48	40	45	44
38	182	167	559	631	1539	57	45	36	41	41
39	170	125	479	533	1307	52	34	31	34	34
40	184	157	477	539	1357	57	42	30	34	35
1941	179	151	503	512	1345	55	40	32	32	35
42	193	148	500	509	1350	58	39	31	32	35
43	192	169	482	500	1343	57	44	30	31	34
44	197	146	510	476	1329	59	38	31	29	33
45	233	151	495	458	1337	68	39	30	28	33
1946	216	156	469	488	1329	62	39	28	29	32
47	194	143	466	442	1245	55	35	27	26	30
48	163	123	403	345	1034	46	30	23	20	25
49	132	96	303	252	783	37	24	17	15	19
50	118	67	223	180	588	33	17	13	10	14
1951	119	66	217	171	573	33	16	12	10	13
52	81	50	189	152	472	23	12	11	9	11
53	37	36	191	119	384	10	9	11	7	9
54	54	35	144	108	341	15	9	8	6	8
55	42	27	99	110	278	12	7	5	6	6
1956	39	23	87	78	205	11	6	5	4	5
57	43	20	88	48	199	12	5	5	3	4

APPENDIX TABLE 3

INCIDENCE OF PULMONARY TUBERCULOSIS IN DENMARK (EXCLUDING COPENHAGEN) PER 100 000 POPULATION BY AGE AND SEX IN SELECTED YEARS 1935-55 *

Age	Males					Females				
	1935	1940	1945	1950	1955	1935	1940	1945	1950	1955
0- 4	22	33	50	40	20	19	28	46	36	23
5-14	26	32	48	27	7	34	33	53	30	7
15-19	98	78	92	50	11	113	102	117	70	20
20-24	136	100	153	86	26	170	127	145	105	39
25-29	102	91	115	74	31	158	118	129	116	44
30-34	97	68	89	70	33	125	85	91	80	33
35-44	72	62	67	53	28	87	63	60	51	27
45-54	64	59	57	49	34	60	45	37	30	19
55-64	70	58	53	48	37	64	51	37	25	14
⩾ 65	52	57	52	47	36	61	56	58	42	33
Total	69	61	72	50	25	83	66	71	52	23

* To avoid excessive random variations the figures for 1935, 1940... 1955 have been computed as average rates for the three-year periods 1934-36, 1939-41... 1954-56, respectively.

APPENDIX TABLE 4

MORTALITY FROM PULMONARY TUBERCULOSIS IN DENMARK (EXCLUDING COPENHAGEN) PER 100 000 POPULATION BY AGE AND SEX IN SELECTED YEARS 1935-55 *

Age	Males					Females				
	1935	1940	1945	1950	1955	1935	1940	1945	1950	1955
0- 4	6	5	6	1	1	5	3	5	2	1
5-14	2	2	3	0	0	5	3	1	1	0
15-19	19	14	11	3	0	34	23	17	4	0
20-24	52	28	34	10	1	69	42	37	10	2
25-34	47	33	35	12	3	75	48	36	14	4
35-44	38	30	28	14	6	49	30	27	9	6
45-54	40	30	28	18	6	37	21	21	10	4
55-64	50	42	33	25	12	45	35	27	11	6
⩾ 65	43	46	38	31	19	55	44	43	27	19
Total	31	24	23	12	5	40	27	23	9	4

* To avoid excessive random variations the figures for 1935, 1940... 1955 have been computed as average rates for the three-year periods 1934-36, 1939-41... 1954-56, respectively.

APPENDIX TABLE 5

NEW CASES OF EXTRAPULMONARY TUBERCULOSIS APPEARING IN THE HEALTHY ADULT POPULATION IN THE FIRST FOUR YEARS AFTER THE MASS CAMPAIGN

Classification	Number	%
Genito-urinary system	52	39.3
Lymphatic system *	29	21.9
Skeletal system	24	18.2
Tuberculous meningitis	1	0.8
Miliary tuberculosis	1	0.8
Intestines, peritoneum, abdominal nodes	6	4.6
Skin and subcutaneous tissue .	11	8.3
Other organs	8	6.1
Site unknown	4	—
Total . . .	136	100.0

* Excluding tracheo-bronchial and abdominal nodes