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THE PRESENT EPIDEMIOLOGICAL SITUATION OF TUBERCULOSIS IN DEVELOPING COUNTRIES

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I. ESTIMATED WORLDWIDE INCIDENCE OF TUBERCULOSIS

1.1 Notification of tuberculosis

Bulla (1) has recently presented an overall picture of tuberculosis morbidity and tuberculosis mortality based on existing recording and reporting systems in the world. Consolidation of all the available information and extrapolation of figures to the total world population (3.4 billion in 1967 and 3.6 billion in 1971) gave an estimated worldwide incidence of tuberculosis (all forms) of over 3.8 million cases in 1967 and over 3.5 million in 1971 (111 cases per 100 000 in 1967 and 97 cases per 100 000 in 1971).

Bulla stressed that the risk of errors in these estimations is considerable and that direct comparisons are hazardous, because of the very diverse criteria used throughout the world for reporting tuberculosis and because little statistical importance is attached to bacteriologically confirmed cases and to the varying number of reporting countries. In our opinion, the major unreliability of these figures is mainly due to the fact that in many developing countries only as little as one-third of smear-positive cases - the transmitters of the disease - are diagnosed. In most developing countries the majority of cases positive by culture only cannot be diagnosed at all because of lack of culture laboratories and X-ray facilities. It is therefore not surprising that the statistics studied by Bulla (1) show that, for instance, the incidence rate in Europe in 1971 was 59 and in Africa 57 per 100 000 population, an obviously underestimated rate for the latter, since we know that the risk of tuberculous infection is 20 to 50 times higher in Africa than in Europe.

It is evident that one cannot expect a substantial improvement in case-finding even of smear-positive pulmonary tuberculosis in the near future in most of the developing countries, because there are still enormous obstacles in finding the majority of smear-positive cases, such as:

- A large proportion of the population lives in small villages and, because of lack of transport facilities, it is often difficult for a seriously ill patient to reach a health centre where diagnosis of tuberculosis can be made.
- In many developing countries there is a poor infrastructure of the general health services in which the tuberculosis work could be integrated.

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- There is a great shortage of medical doctors and qualified health workers, who have hardly any time for supervision and training of the auxiliary health personnel who are frequently entrusted with the (bacteriological) diagnosis of tuberculosis.
- X-ray facilities for examination of the chest are not, in most instances, available for screening for bacteriological examination of the sputum for tubercle bacilli in those persons who present themselves to a health service with symptoms suggestive of tuberculosis. Consequently sputa of all symptomatic patients must be examined, although some 90% of these could be excluded, if X-ray examination of the chest in such persons could be made.
- Poor socio-economic conditions and various cultural backgrounds often result in a high proportion of smear-positive cases of tuberculosis in developing countries remaining undiagnosed.

We conclude that the notification of new cases of tuberculosis in most developing countries is largely incomplete. It is unlikely that it will become sufficiently complete within the next 10 to 20 years to be used as an index of the magnitude of the tuberculosis situation and its changing pattern. But, hopefully, the diagnosis of smear-positive tuberculosis patients in developing countries will gradually be extended, and eventually most cases with symptoms will be diagnosed and treated. If there is a gradual extension of case-finding programmes for smear-positive cases, the number of notified cases will increase correspondingly. They will not, however, provide a reliable yardstick of the tuberculosis problem and its trend in developing countries for many years to come.

1.2 The annual tuberculosis infection rate (the risk of infection)

There is now general agreement that the annual tuberculosis infection rate is the best single indicator for evaluating the tuberculosis situation and its trend in developed and developing countries. It is an index which expresses the attacking force of tuberculosis within the community and, unlike mortality and notification rates, it is not linked directly with the intensity of the procedures of the tuberculosis programme (2).

The risk of tuberculous infection indicates the proportion of the population which will be primarily infected (or reinfected in those who have been previously infected) with tubercle bacilli in the course of one year, and is usually expressed as a percentage or as a rate.

The annual tuberculosis infection rate can be established in developing countries much more easily than the incidence of smear-positive cases of pulmonary tuberculosis. It is derived from the results of tuberculin testing in a representative sample of unvaccinated children. Techniques for converting information on prevalence of infection into a smooth series of annual rates of tuberculous infection has been developed by the Tuberculosis Surveillance Research Unit (TSRU) and published in comprehensive reports (2, 3, 4). To obtain reliable estimates of the annual tuberculosis infection rates and changes in a particular period, several tuberculin surveys are required at intervals, each in a representative sample of non-BCG vaccinated subjects of the same age, tested by the same technique. For routine tuberculosis control, a simple method of estimating the annual tuberculosis rate is described in the short section VIII of TSRU Report N°1 (2) and by Bleiker (5).

The Tuberculosis and Respiratory Infections Unit of the WHO recently proposed to the TSRU to pursue research on tuberculosis epidemiology by specifying indices for the measurement of the magnitude of the trend of the tuberculosis problem in terms of infection risk, and to determine parameters which express the relationship in a community between the risk of infection and the risk of developing infectious tuberculosis.

Analyses of the mortality data from the Netherlands (1921-1938), as well as of the incidence of smear-positive pulmonary tuberculosis (1951-1968), the prevalence of smear-positive cases in developing countries (WHO surveys between 1956 and 1961), mortality data on Eskimos (1948-1951) and prevalence of smear-positive pulmonary tuberculosis in India (1961-1968) suggest that there is a relatively constant ratio (lower for developed and higher for developing countries)

between the annual tuberculosis infection rate and the incidence of smear-positive tuberculosis, irrespective of the level of the annual tuberculosis infection rate (except if the rate is extremely low) (6).

It seems that in developing countries 1% of the risk of tuberculous infection corresponds to about 50 smear-positive cases of pulmonary tuberculosis per 100 000 general population.

The main sources of information for studying the annual tuberculosis infection rate in developing countries are the results of tuberculosis surveys which were carried out by WHO teams in the 1950's and 1960's. For Africa, the results of the WHO surveys were analysed by Roelsgaard et al (7). It was shown that weak degrees of tuberculin sensitivity, attributable to infection by non-specific mycobacteria, were much more common in some of the countries than in others, so that no single criterion could be used in all of them. Each of the original reports included a discussion of the findings on this point, and an appropriate criterion was put forward for each country or district.

From the estimated prevalence of tuberculous infection in subjects aged 5-9, 10-14 and 15-19 years, Bleiker and Styblo (8) have calculated the annual tuberculosis infection rates for 18 African countries and summarized the findings in Table 1.

Table 1. Annual risk of tuberculous infection in 18 African countries - 1950 - 1974

| Estimated annual risk of tuberculous infection (per cent)* | | | |
|--|-------------------|------------------|---------------------|
| 2.0 - 2.9 | 3.0 - 3.9 | 4.0 - 4.9 | > 5.0 |
| Kenya (1959) | Egypt (1951) | Algeria (1951) | Bechuanaland (1956) |
| Lesotho (1957) | Ghana (1957) | Morocco (1950) | Somalilands (1956) |
| Uganda (1958) | Libya (1959) | Nigeria (1958) | Transkei (1974) |
| Tanzania (1957) | Mozambique (1961) | Swaziland (1957) | |
| Zaire (1971) | | | |
| Zanzibar (1960) | | | |

* The year of the survey is indicated in parenthesis.

It is seen that the annual tuberculosis infection rate in many countries is 3% or more (corresponding to an incidence of 150 or more smear-positive cases of pulmonary tuberculosis per 100 000 population), in some of them 5% or more (corresponding to an incidence of 250 or more smear-positive cases per 100 000).

Thus if we consider for Africa the average annual risk of tuberculous infection of 3%, the incidence of smear-positive pulmonary tuberculosis in 1971 in this continent was in the order of 540 000 smear-positive pulmonary cases of tuberculosis (population 360 million, see Bulla (1)), and more than 1 million cases if cases positive by culture only, culture-negative cases (in children, etc.) and extra-pulmonary cases are considered. However, the estimated number based on the reported cases in 19 countries (1) was 204 000 (all forms), a grossly underestimated figure.

The epidemiological situation of tuberculosis in the Far East has been evaluated by Tao (9). In some of the developing countries of this region, the annual rate of tuberculous infection in the first half of the 1950's was very high indeed: more than 10% in Hong Kong, and between 5-10% in Brunei, Cambodia, Taiwan, Philippines, Sarawak, Singapore, Malaysia and

Vietnam (2). On the other hand, the rates of the risk of infection in Laos, New Hebrides, Tonga and Western Samoa were relatively low, between 1.5 and 2%.

The annual rate of tuberculous infection in a rural population of South India was found to be about 1.3% (10). This broadly corresponds to the estimate of the annual rate of 1-2% reported by Frimodt-Møller (11). The estimates of the risk of tuberculous infection were higher in the Tuberculosis Prevention Trial, Madras, namely more than 4% by the direct method and nearly 3% by Raj Narain's method (12). The annual tuberculosis infection rate in Indonesia might be about 3% (13).

In the majority of South and Middle American countries, the present annual risks of tuberculous infection are between 1 and 2%, and in some of them even less than 1%.

THE ABOVE MENTIONED DATA ON THE RISK OF TUBERCULOUS INFECTION IN DEVELOPING COUNTRIES OF AFRICA, ASIA AND LATIN AMERICA INDICATE THAT THE RATES WERE HIGH IN THE GREAT MAJORITY OF THE DEVELOPING COUNTRIES DURING THE LAST 25 YEARS, RANGING BETWEEN 2 AND 5% IN MOST OF THEM. FOR THE 3 BILLION PEOPLE LIVING AT PRESENT (1981) IN DEVELOPING COUNTRIES, A CONSERVATIVE ESTIMATE IS 4 TO 5 MILLION HIGHLY INFECTIOUS CASES OF TUBERCULOSIS DEVELOPING EACH YEAR, WITH 2 TO 2 ½ MILLION DEATHS FROM TUBERCULOSIS EACH YEAR.

2. TREND IN THE TUBERCULOSIS SITUATION

Information on the level of the annual risk of tuberculous infection is insufficient for a full evaluation of the epidemiological situation of tuberculosis in a country under study. It is essential to know, in addition, the trend in the risk of infection in that country, that is to say, whether the annual rate has been decreasing or not, and if so, what is the annual decrease in the risk of infection.

As already mentioned, to obtain reliable estimates of the annual tuberculosis infection rates and their changes in a particular period, several tuberculin surveys, each in a representative sample of non-BCG vaccinated subjects of the same age and tested by the same technique, are required at intervals. For a continuous evaluation of the tuberculosis problem in a particular population, tuberculin testing of a representative sample of children must be repeated every, say, 5 years.

It must be stressed that there is a major difference in the trend of the tuberculosis situation in developed and developing countries.

2.1 Developed countries

We now have information on the trends in the risk of infection in six countries or areas, as shown in Figure 1 (8). Two main conclusions can be drawn:

- In most developed countries the tuberculosis infection rate is at present of the order of 1 to 3 per thousand, and in a few of them even less than 1 per thousand per year.
- The tuberculosis infection rate continues to decrease, in these countries, by about 11 to 13%, halving itself every 5 to 7 years.

The data from the Netherlands suggest that there was no interruption in the steady decrease of the infection rate in that country, at least since 1910 (2). It is obvious that this decrease profoundly changed the prevalence of infection in the population. It is estimated that in some developed countries as many as 75-80% of the population are uninfected with tubercle bacillus. Recent studies show that a substantial decrease in the tuberculosis problem is observed in all developed countries.

2.2 Developing countries

Reliable repeated tuberculin testing of representative samples of unvaccinated children or young adolescents in developing countries is very rare. Figure 2 shows the trend in the

tuberculosis infection rate in a few countries where repeated tuberculin testing was carried out several years after the first tuberculin survey (8).

In Lesotho (Basutoland), the first tuberculin survey was carried out in 1957, and the second one in 1965. It was concluded in the WHO report that children living in the rural lowlands were exposed to the same risk of infection in 1965 as in 1957, namely about 3%.

In Uganda, the first tuberculin survey was carried out in 1958 and the second in 1970-1971. The annual tuberculosis infection rate for children aged 10 years was nearly constant throughout the period 1950 (2.6%) to 1970 (2.3%).

In Morocco, the first survey was carried out in 1949-1951 and the second in 1971. The diagram shows that in the rural area of the district of Kenitra the risk of infection decreased from 3.1% in 1950 to 2.3% in 1971, i.e. by 1.5% annually. On the other hand, in Kenitra City the risk of infection decreased from 4.8% in 1950 to 1.6% in 1971, i.e. by more than 5% annually.

Finally, in the district of Tangarang (Indonesia) there was about 17% decrease in the annual tuberculosis infection rate between 1972 and 1978, from 3.9% to 2.6%.

The authors (8) concluded that:

- *IN MOST DEVELOPING COUNTRIES THE PRESENT RISK OF TUBERCULOUS INFECTION IS 20 TO 50 TIMES HIGHER THAN IN DEVELOPED COUNTRIES,*
- *THE TREND IN THE RISK OF INFECTION IN DEVELOPING COUNTRIES VARIES CONSIDERABLY. IN A FEW, THERE IS MODERATE DECREASE IN THE RISK OF INFECTION, BUT IN MANY DEVELOPING COUNTRIES THE RISK HAS REMAINED NEARLY CONSTANT FOR YEARS OR HAS BEEN DECREASING ONLY VERY SLOWLY.*

3. IMPACT OF THE PRESENT CONTROL MEASURES ON THE TUBERCULOSIS SITUATION

The impact of the present control measures on the tuberculosis situation can only be measured in developed countries because data in developing countries are inadequate for this purpose.

The two basic tools used for tuberculosis control are BCG vaccination and case-finding/treatment.

3.1 Impact of BCG vaccination

There is general agreement that BCG vaccination has a high "direct" effect by preventing the development of tuberculosis. This "direct" effect may be measured in terms of the proportion of cases prevented in the vaccinated age-groups.

Bjartveit and Waaler (14) made a comparative analysis of age-specific trends in the incidence of active tuberculosis in three Scandinavian countries (Denmark, Norway and Sweden), where mass BCG vaccination of specific age groups has been carried out, and two states of the USA (upstate New York and Ohio), where mass BCG has never been used. The study covers the period 1948 to 1961. The authors demonstrated the direct effects of various BCG programmes, both by comparing the incidence trends in different age groups (directly affected and not affected by BCG) in the same country, and by comparing the incidence trends in age groups directly affected, and not affected, by BCG in different countries.

Styblo and Meijer (15) confirmed the substantial direct effect of BCG vaccination on the total tuberculosis incidence of infectious tuberculosis.

It is also claimed that mass BCG vaccination - especially at school-leaving age - will influence the chain of transmission and so prevent the development of tuberculosis in unvaccinated subjects. This is what one may call the "indirect" effect of BCG vaccination.

The latter study (15) shows that BCG vaccination, even if used in a mass-campaign throughout the age-range 15 to 30 years, will not substantially influence the chain of transmission, especially if the risk of tuberculous infection is high and has not been decreasing.

The main error in the postulate that BCG vaccination would have a considerable impact on the transmission of infection is due to the incorrect assumption that a case of tuberculosis prevented by BCG vaccination is identical with a prevented source of infection. Actually, more than 95% of tuberculosis cases in children, and 75% of cases in subjects aged 15-29 years which should have been prevented by BCG vaccination, are smear-negative. As the high protection induced by BCG vaccination is limited in time, the vast majority of newly developed smear-positive cases of pulmonary tuberculosis among the general population cannot be prevented by mass BCG vaccination.

3.2 Impact of case-finding/treatment

The most powerful weapon in tuberculosis control is case-finding plus chemotherapy. This is considered as an entity, as case-finding is a preliminary to treatment and cure.

It is easy to measure the effect of chemotherapy in a group of bacillary patients. But what is its effect on the overall tuberculosis situation? In other words: to what extent do case-finding and chemotherapy influence the infection rate?

This is more difficult to answer, as the trend in the tuberculosis infection rate (risk of infection) mirrors several factors:

- the "natural" trend (see 3.1)
- some effect of BCG vaccination (see 3.2)
- the effects of case-finding and chemotherapy.

Even if we can reliably assess the tuberculosis situation and its trend (given reasonable knowledge of its "natural" trend) and observe those developed countries where no mass BCG vaccination was carried out, two conditions are necessary to estimate the impact of case-finding/treatment:

- the presence of intensive case-finding for many years, and
- the presence of treatment, near-100% successful in the whole population studied.

For the Netherlands population, data are available for these conditions (21).

3.2.1 Presence of an intensive case-finding programme

In the Netherlands, tuberculosis is diagnosed by specialized and non-specialized out-patient and in-patient nation-wide health services. Distances to health centres are short and transport facilities very good. Mass miniature radiography (MMR) was started in 1949.

MMR is used for indiscriminate surveys of the entire population over 14 years (since the mid-1970's over 40 years), and group surveys in factories, offices, etc. The yield of MMR for the period 1951 to 1967 has been reported by TSRU (22). From 1954 to 1966, about 2 1/2 million persons over 14 years of age were submitted to MMR per year; this corresponded approximately to examining one-quarter to one-third of the adult population per year. During these 18 years, more than 50 000 non-primary tuberculosis cases were reported in the Netherlands (relapse excluded). The yield of MMR surveys (population and group) never exceeded 15% in the smear-positive group, 25% in the culture-positive group and 30% in the group of culture-negative cases. From 1968 to 1978, the MMR programme was continued at the same intensity.

The data on bacillary tuberculosis from 1973-1975 have recently been analysed. During that period a total of 724 smear-positive and 795 culture-positive new cases of post-primary pulmonary tuberculosis (relapse excluded) were reported in the Netherlands (23). 104 (14%) and

203 (26%) respectively were discovered by MMR. This shows that the proportion of MMR cases during 1973 to 1975 is closely in line with the 1951-1967 period.

Within these limitations, the case-finding programme during the last three decades in the Netherlands can be considered "intensive".

3.2.2 Treatment near-100% successful countrywide

There is evidence that in some developed countries chemotherapy results under routine conditions are nearly as good as those in controlled clinical trials. Results for 1973-1975 in the Netherlands (23) and in 1975 in Bavaria (West Germany) (24) show that 99% and 97 1/2% respectively of those with bacillary pulmonary tuberculosis were culture-negative 2 years after treatment was initiated. Hefferman et al (25) also reported extremely good routine treatment results in a 2 year follow-up of a 50% random sample of newly-notified cases of pulmonary tuberculosis in Scotland in 1968 (26).

3.2.3 Quantified estimate of case-finding/treatment on the tuberculosis situation in a community

- The decrease in the tuberculosis infection rate during the last 3 decades in developed countries is approximately 12-13% annually (see 2.1).
- The "natural" downward trend of tuberculosis in developed countries prior to chemotherapy was about 4-5% annually (see 3.1).
- In the absence of BCG-vaccination, the 8% (12-13% minus 4-5%) decrease in the infection rate is mainly due to intensive case-finding and adequate treatment of all diagnosed bacillary cases.

3.3 Case-finding/Treatment in developing countries

At present, the situation regarding case-finding of persons with smear-positive pulmonary tuberculosis is very unsatisfactory, as discussed under 1.1 of this report. However, even an improvement in identification of smear-positive cases, for instance from 30 to 50%, will considerably increase the impact of the control measures on the overall tuberculosis situation.

As to chemotherapy programmes, Table 2 shows that in some developing countries quiescence of the disease was achieved in only 60-65% of all patients (16). The fatality rate was about 10-16%, and the proportion of chronic bacillary excretors remained high (about 25%). In many developing countries, the success rates may be even worse. Fox estimates that they can fall to levels of the order of 50%, if the relapse rate is taken into account (17).

Evidently, long-term chemotherapy of tuberculosis is beyond the resources of nearly all developing countries. We would plead for reduction of the cost of rifampicin so that short-course chemotherapy might be widely applied in most countries.

The results of recent studies show that an 80% cure can be achieved in 3 months (Fox (18) personal communication).

Table 2. Fate of bacillary cases of tuberculosis when treated under mass chemotherapy programmes in certain developing countries.

| Country | No. of cases | Year | Duration of follow-up | Percent died | Bacteriology | |
|---------|--------------|------|-----------------------|--------------|--------------|--------|
| | | | | | % Pos. | % Neg. |
| Taiwan | 237 | 1968 | 2 years | 10.5 | 24.1 | 65.4 |
| Korea | 288 | 1968 | 1.5-2 years | 11.1 | 26.0 | 62.9 |
| Kenya | 739 | 1968 | > 1 year | 15.6 | 21.5 | 62.9 |
| India | 292 | 1974 | 1 year | 9.6 | 27.0 | 63.4 |

Source of information: Grzybowski, S. et al.

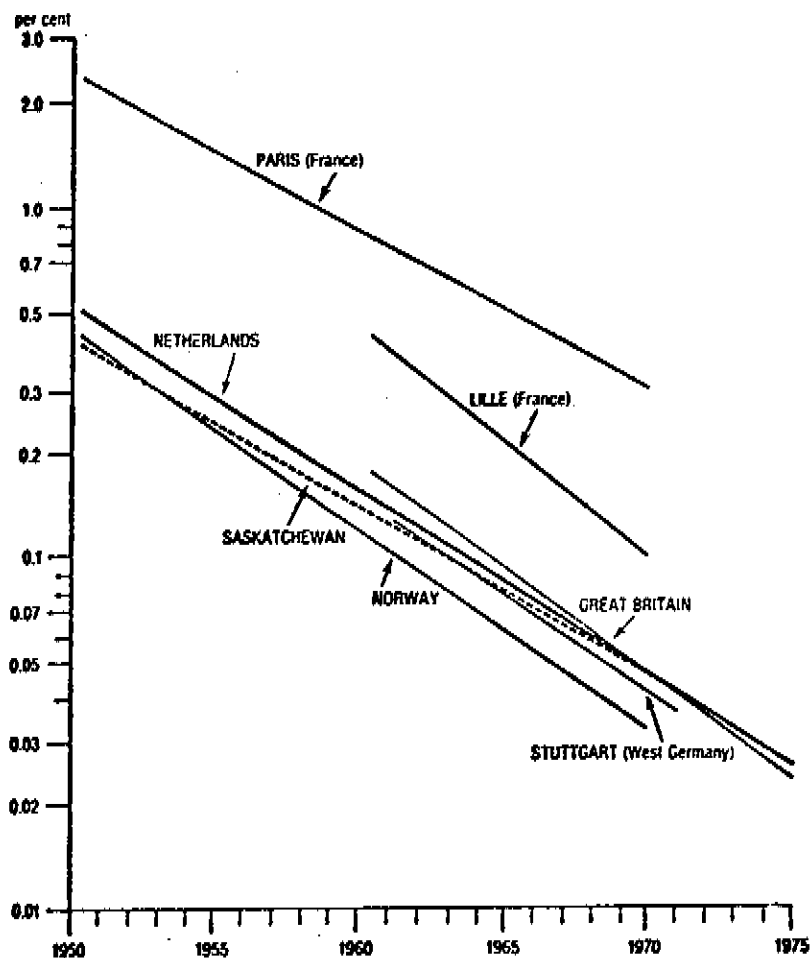


Figure 1. Estimated annual risks of tuberculous infection in low-prevalence countries, 1950-1975.

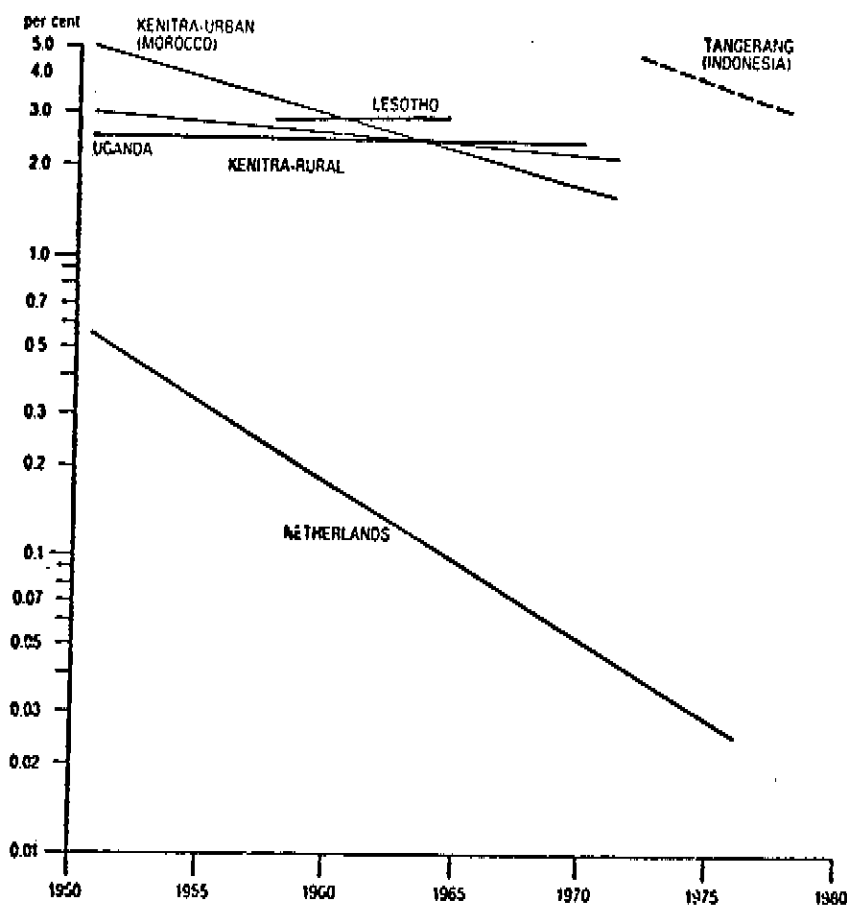


Figure 2. Annual risks of tuberculous infection and their trend in high prevalence countries, 1950-1978.

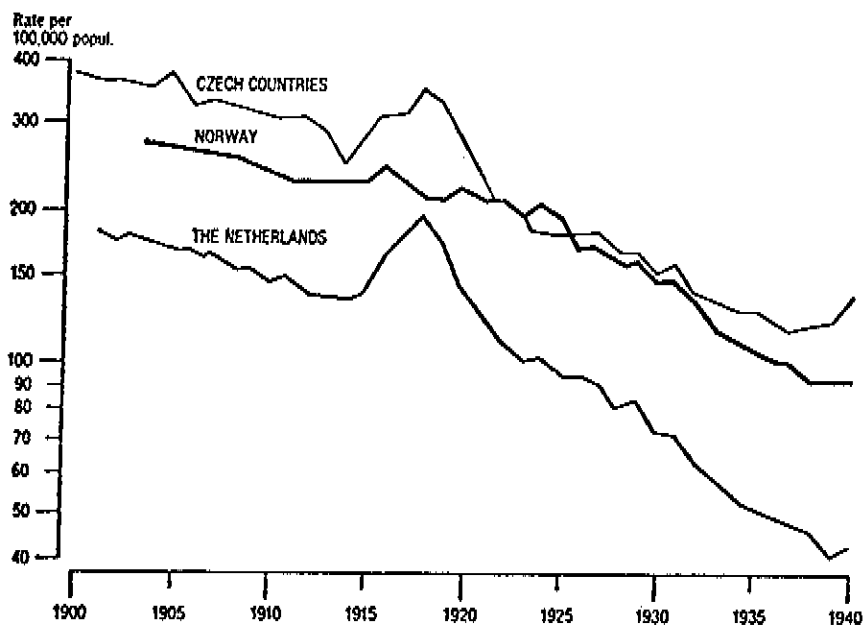


Figure 3. Tuberculosis death rates from all forms of tuberculosis in Czech countries, the Netherlands and Norway, 1900-1940.

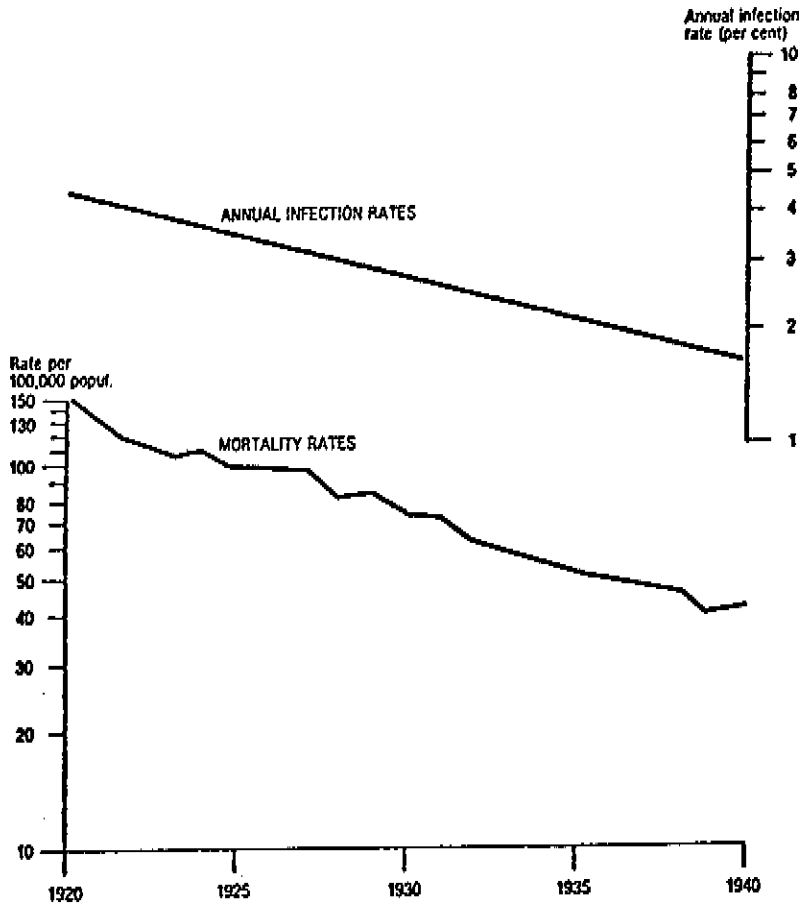


Figure 4. Annual tuberculosis infection rates and tuberculosis death rates in the Netherlands, 1920-1940.

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