Epidemiological Research in Tuberculosis Control

Introduction

Growing concern is being expressed about the fact that the tuberculosis control programs introduced in developing countries, now some 20 years ago, apparently fail to produce a noteworthy reduction of the problem (1). Although it is generally recognized that these programs still have many shortcomings, there is a conviction that they will reduce transmission and thus cause a gradual decline.

The implied assumption that the trend of the tuberculosis problem is a suitable indicator of the achievements of a tuberculosis program perhaps should not be accepted uncritically. In Europe and North America a decline in tuberculosis set in long before the introduction of any specific antituberculosis measures. A pronounced change in the declining trend of the risk of infection was observed in the mid-1940s in many developed countries, with the discovery and widespread use of streptomycin for the treatment of tuberculosis. Whereas this no doubt caused a reduction in case-fatality, it should be noted that the ensuing reduction in the risk of infection also coincided with the upsurge in socioeconomic development after World War II. Then the rate of decline jumped suddenly from 3-5% to 10-14% a year, and this rate has been almost constant until now (2). Some discrepancies in this pattern have been observed. In the Netherlands, the sudden change took place a few years before the discovery of chemotherapy; one explanation advanced is that the decrease was caused by the compulsory pasteurization of milk enforced by law in 1940 (3). In Finland two abrupt changes were observed, one from 3.5% to 8.5% in the mid-1940s, and a second, doubling the rate of decline, to 16% in 1966 (4). No plausible explanation has yet been found for this observation.

Before chemotherapy, certain measures were applied which probably had some effect in limiting the spread of infection, such as the early diagnosis by radiography and the isolation of patients in hospitals. Artificial pneumothorax might have had bacteriological benefits too. It is impossible to separate by retrospective analysis the epidemiological impact of these measures from that of the continuous improvements in the standard of living for the period. No estimates of the risk of infection are available before 1910, but the steadily declining mortality curve does not show any change attributable to the introduction of a specific intervention. For instance, in England there was a gradual increase in the annual rate of decline in mortality from tuberculosis during the period 1851-1946 of almost 1% to 2% but no modification in this trend was seen when the tuberculosis services were established and developed (5).

In some developing countries, especially in Latin America, in the Western Pacific ridge, and the oil-producing Arab states, a modest annual decrease, in the rate of 2-5%, of the tuberculosis problem is probably occurring. These are countries with an intermediate level of socioeconomic development. Thus the attribution of all the credit for the decline to the tuberculosis programs, either in developed or in developing countries, is largely unwarranted.

A distinction must be made between epidemiological surveillance and program evaluation. Whereas
the trend of the problem will no doubt reflect any significant impact of the program, it certainly is unsuitable as a quantitative index of program performance, especially since problem reduction is not the only objective of tuberculosis control. The latter applies in particular to developing countries, where the basic programs are designed in the first place to prevent and relieve human suffering by providing BCG vaccination as well as diagnosis and treatment for patients demanding it. Although these programs may so far have had no measurable impact on the trend of the tuberculosis problem, they may to an appreciable extent have met their primary social objective.

Obtaining a reduction of the problem is essentially an associated objective of the current tuberculosis control programs, but an important one at that, and it is highly indicated that this question be studied amongst program conditions in developing countries. This means that adequate data must be gathered to reveal the dynamics and interactions of epidemiological events and the impact of control measures on the trend of the disease.

Measuring the Tuberculosis Problem

One of the first problems one encounters when examining the tuberculosis situation in developing countries is that there are only some rough indications of the magnitude of the problem, and that in actual fact little is known about the current trend and about the natural situation prior to the application of specific chemotherapy. The consensus that the problem is more or less stable in most developing countries is that there are only some rough indications of the magnitude of the problem, and that in actual fact little is known about the current trend and about the natural situation prior to the application of specific chemotherapy. The consensus that the problem is more or less stable in most developing countries is a general impression based on a few scattered observations.

In technically advanced countries the annual incidence, which usually is known from notifications, is an excellent indicator of both the case-load and the trend of the problem, but obviously this does not apply to situations in which the program is still expanding and the diagnostic services are still deficient both in quantity and quality.

The prevalence of the disease, measured in occasional surveys, provides an estimate of the potential case-load and therefore is obviously highly relevant to program planning, but it is not a suitable indicator for determining the trend in epidemiological terms. Prevalence surveys are technically difficult and costly.\(^1\) A large number of prevalence surveys were carried out under WHO auspices in the 1950s in all regions but in particular in Africa (7). In most individual countries the sample size was rather small, consisting of 2,000-3,000 persons living in about five or six clusters, and precise estimates therefore were obtained for the regions rather than for the individual countries. The practice of conducting periodical prevalence surveys has been maintained for a long time in the South East Asia and Western Pacific Regions (Korea, Japan, Philippines, Malaysia, Singapore, India, Burma, and Thailand) in spite of the technical difficulties and the high cost involved.

Longitudinal studies in large population groups to measure the incidence and its trend have scarcely been undertaken. The best known examples are those conducted in India, in Bangalore (8) and in the Chingleput area (9) in connection with the BCG trial. Such studies are extremely costly, technically difficult, require a long period of time, and have the inherent flaw of themselves influencing the problem.

Repeated surveys carried out in random population samples would not themselves influence the problem, but they would show merely the trend in prevalence, not in incidence, and thus rather reflect the program’s performance than its epidemiological impact. Occasional limited prevalence surveys have been recommended to provide data for program planning and evaluation, but very often data collected in supervision and through the normal reporting system are ample to provide a sufficiently instructive picture of the state of the program.

As to surveillance of the tuberculosis problem in epidemiological terms, attempts could be made to measure the prevalence of infection at regular intervals in a specified (low) age group, which would make it possible to determine the annual risk of infection and its trend. The annual risk of infection, as revealed by tuberculin testing, was shown—in technically advanced countries—to roughly reflect the incidence (10), but in developing countries this is not necessarily so, and its determination proves technically very difficult owing to the usually high prevalence of nonspecific tuberculin sensitivity caused by atypical mycobacteria and a high coverage of BCG vaccination in children.

This means that there is at present no reliable and easily applicable methodology for epidemiological surveillance and program evaluation in developing countries. This problem deserves a high priority in

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\(^1\) The cost of the 1980 Tuberculosis Prevalence Survey (Republic of Korea) was estimated to be US$147,000, i.e. 5.65 per head of the population sample (26,000) (6).
WHO's tuberculosis research program. The most promising approach is to devise a more precise technique to measure the prevalence of infection in children in developing countries. A method has been proposed to determine the prevalence of infection in areas with a high prevalence of environmental mycobacteria (11). The method also seems to be applicable to population groups given BCG vaccination at birth. This method could be tested and applied forthwith. In the long term, research on the isolation of specific antigens for skin tests will be promoted through the application of modern immunological methods, notably the use of monoclonal antibodies.

The Amenability of Tuberculosis to Control

The question of no decline being observed in many developing countries has had the attention of various expert groups. A variety of reasons have been advanced, all related to deficiencies in the application of the available technology. As regards the case-finding and treatment program, which is assumed to be potentially the most powerful tool since chemoprophylaxis is generally impractical, it should be noted that this is a concatenation of interventions. A maximum impact can only be achieved if every single element is fulfilled for 100%. As in practice there are often shortcomings all along the line, the final impact may be quite low indeed: if there are 10 elements, all fulfilled for 50%, the impact will be 0.5\(^{10}\), or less than 1 pro mille, of what could be achieved.

Whereas a lack of decline is readily explained and advice on how to improve the performance of the programs is not difficult to find, explicit statements about the reduction of the problem that can be obtained with adequately implemented programs in third world countries have been either unsupported or vague. Surely, in developed countries, and actually also in some developing countries, a distinct decline is being observed which offers a promising outlook, but it is impossible to extrapolate these findings quantitatively. It had been observed that the tuberculosis situation in developing countries is different from that in technically advanced countries; for instance, in some developing countries tuberculosis is not mainly an urban problem but is also rife in rural areas. Still, it was generally taken that time-honored concepts about the transmission and pathogenesis of tuberculosis, and on the effectiveness of the various control measures, would equally apply in developing countries.

A generally accepted concept was that tuberculosis is refractory to control. The explanation was that disease, although more frequent shortly after infection, could occur at any time in later life and therefore would continue to occur in the large infected reservoir even if transmission of infection were interrupted. Observations in European countries appeared to confirm this viewpoint, and lent support to the underlying idea that disease was largely the consequence of endogenous reactivation of existing foci. A related technical observation was that the infectious forms of tuberculosis did not necessarily develop gradually, from milder forms. This suggested that in practice transmission could not be prevented by early detection and treatment of patients, but merely could be reduced by timely and adequate treatment of the detected infectious cases. Some support for this idea was derived from observations—in developed countries—that mass X-ray screening every 2–3 years only contributed a minor part of the detected case-load (12).

These ideas led to the concept that a massive attack, limited in time, could scarcely have a lasting effect on the tuberculosis problem. More recent observations indicate that this may not be so. Some crash programs in eskimo societies produced a remarkable decrease in the incidence of tuberculosis, and this decrease was observed both in the noninfected population and in those already infected (13). Also in developed countries a decrease in incidence has been observed in the infected populations when the risk of infection declined. Notably in England the risk of tuberculosis in infected adolescents is nowadays less than 10% of what it was in the late 1950s (14). Clearly, these observations are incompatible with the view that endogenous reactivation is the only pathogenetic mechanism of post-primary pulmonary tuberculosis.

Observations made in the Prevention Trial, in India, confirm that in developing countries the tuberculosis problem may present itself in quite a different way than had been assumed. A surprising finding was that the large majority of new cases occurred not in newly infected persons but in persons who probably had been infected for the first time many years ago, in particular elderly men. This, and also the absence of protection from BCG vaccination, is compatible with most tuberculosis being caused by exogenous reinfection and not endogenous reactivation (15). An incidental observation, which is of interest as regards the prospects of tuberculosis control, was that over a 5-year period the incidence de-
increased by about 25% in spite of the fact that case-finding improved consistently during the period (16). The project provided extensive case-finding facilities, but no other treatment was made available than the standard regimens of one year’s duration recommended by the national tuberculosis program.

Several of the more affluent developing countries have witnessed a decline in the tuberculosis problem, but invariably the coverage and quality of the health system has been quite high and extensive use has been made of X-ray and cultures for the diagnosis of tuberculosis, at least in the urban areas. And even then, the question of how much the decline is actually produced by the program and how much occurs as a result of general socioeconomic development is difficult to answer.

All developing countries, for social reasons, must give priority to affording immediate relief from suffering. Still, in formulating programs to attain the latter objective they would wish to select techniques and strategies that are also propitious to achieving a gradual reduction of the program and thus a durable social benefit. Any reduction in the risk of infection would have a relatively rapid effect on the incidence of childhood tuberculosis, a problem given little attention so far, which is not directly alleviated by the basic case-finding and treatment programs. Current programs notably appear not to eliminate intrafamilial transmission of infection. Quantitative information on the magnitude of the problem in children, and on the epidemiological significance of infection in childhood, is badly needed.

The Impact of Various Control Measures

**BCG Vaccination**

It seems scarcely worth discussing this subject at a moment when serious doubts have been raised about the efficacy of BCG, but its potential epidemiological impact retains its interest. Extrapolating from findings in Europe, in particular from a large trial in England, it seemed that BCG vaccination not only could reduce considerably the incidence of tuberculosis in adolescents and young adults but also prevent an appreciable proportion of new sources of infection. Observations in other areas, however, did not substantiate this point of view. In the BCG trials in the United States, and very much so in the trial in India, new infectious cases of tuberculosis almost entirely occurred in the already infected population; during the first two and one-half years of the follow-up of the trial in India only some 4% of the cases of infectious tuberculosis had been potentially preventable. Thus, even mass vaccination with an effective vaccine could not possibly produce a significant immediate impact. A sustained vaccination program could produce an impact in the long run if the protection from BCG were appreciable and long lasting. This matter still needs to be studied, but it should be clear already that especially vaccination of the newborn will not prevent many sources of infection in situations where infectious tuberculosis is mainly a disease of late adulthood. The current priority is to investigate the protective effect of BCG vaccination against childhood tuberculosis in tropical and subtropical areas. Especially since young children do not benefit directly from efforts to detect and treat infectious pulmonary tuberculosis, BCG vaccination retains its potentially important role in the control of tuberculosis in children. A comprehensive program has been started by WHO to evaluate the effectiveness of BCG vaccination programs in young children and to identify and quantify factors and determinants that may influence the efficiency of BCG, including the characteristics of various strains of *Mycobacterium tuberculosis*, the role of exogenous reinfection, the host response, and environmental mycobacteria.

**Passive Case-finding by Microscopy, Followed by Treatment**

Currently this is the main control measure applied in developing countries. Microscopy fairly reliably gives a positive result if there are large amounts of bacilli in the sputum. Therefore it is considered that microscopy can discover, and subsequent chemotherapy will remove, the most important sources of infection. This in turn should reduce the risk of infection and thus the number of new cases arising among the noninfected. The question is—how much? The matter appears to be an intricate one. In developed countries, with extensive case-finding activities and almost maximum treatment results, there has been a decline in the risk of infection in the order of 12-14% per year, of which some 7-9% have been attributed to the control program. The part played in this rather modest reduction in the transmission of infection by the diagnosis of self-

2The reduction is considered very modest when compared with the effectiveness of other public health programs such as smallpox and measles immunization and chlorination of municipal water supplies, by which the transmission of infection is reduced by almost 100% in one year.
reporting smear-positive patients and their treatment is unknown. In developed countries many persons were treated on radiological evidence or when their sputum was positive on culture only. A significant proportion of these cases would have become smear-positive if left untreated, within a relatively short period of time. The removal of these potential sources of infection may have had a far larger epidemiological impact than that of the self-reporting established sources.

In the European countries disease used to occur relatively shortly after infection, so that a reduction in the risk of infection was soon to be followed by a reduction in incidence. Thus, the removal of sources of infection had a noticeable indirect effect. However, if a small reduction in the risk of infection is obtained in a situation where both the prevalence of infection is high and the interval between infection and disease is long, there may not be any measurable impact on the incidence for several decades.

Thus the effect on the epidemiological situation of passive case-finding by microscopy and treatment may be very small. It therefore appears of great interest to conduct prospective studies of the relative epidemiological merits of diagnosing and treating different categories of pulmonary tuberculosis, and to study the effect of introducing different case-finding strategies and diagnostic techniques.

Once an infectious case of tuberculosis has been detected it remains to be treated effectively if a source of infection is to be removed. In developing countries treatment often remains deficient, and this obviously further reduces the epidemiological impact of the program. In actual fact, the impact may be less than suggested by the proportion of patients cured; defective treatment may prolong the infectiousness together with the life of the patient. It would appear difficult to study this matter in isolation, but one attempt in Madanapalle, India, tended to show that an extended inefficient treatment program in fact produces an increase, both in the prevalence of tuberculosis and the risk of infection (17), which seemed, in epidemiological terms, worse than not to treat at all. Surveillance of tuberculosis infection among contacts of patients may provide information on this matter.

### Awareness and Motivation

An inherent weakness of the passive “case-finding” method is that it relies entirely on patients having to be aware of the fact that they are ill and being sufficiently motivated to seek relief at the right address. In these respects the situation in developing countries is on the whole much less favorable than it used to be in technically advanced countries. Only a fraction of the patients come to the attention of the competent health services. Moreover those who are positive only on culture remain undiagnosed until they possibly become smear-positive. Follow-up is therefore essential.

Increasing the awareness and motivation through health education, but also by providing adequate relief for respiratory complaints other than tuberculosis, may bring about significant improvements in the effectiveness of case-finding, especially if the quality of microscopy is high and can be complemented with culture examination. The development of primary health care, and in particular of active community participation, offers new prospects for achieving adequate levels of awareness and motivation. The returns of efforts in this field may be studied in comparison with those of further improvements in the specific control measures.

### Smear and Culture Examination

Any diagnostic test discovers severe cases of disease more readily than mild cases. For this reason microscopy appears an acceptable technique in programs relying on passive case-finding, and probably also if a hard screening test is applied. Still, when the prevalence of tuberculosis among symptomatics is low, the method not only becomes impractical, but would also produce false results, as was demonstrated in Papua New Guinea, where among highlanders 1,400 smears would have to be examined to find one positive result, and the chance of this one being tuberculosis would be as little as 1.1% (18). With increased awareness and motivation the effectiveness of microscopy as a diagnostic test will diminish as the prevalence of disease among those examined reduces, and the yield of case-finding actually may not noticeably increase unless a more sensitive diagnostic measure is introduced. It has been demonstrated that if health education shortens “patient’s delay” in diagnosis, “doctor’s delay” increases to the extent that the overall effect is negligible (19). Studies on the sensitivity and specificity of smear microscopy as compared with culture examination need to be carried out under different program situations, preferably in connection with studies on the epidemiological significance of the various categories of patients.
X-ray Examination

In developed countries X-ray examination has been used for two distinct purposes: diagnosis and mass screening. Although not strictly pathognomonic, X-ray examination proved a suitable test in serious cases of disease, but in mild and early cases both sensitivity and specificity are much reduced. The latter results in a low effectiveness in populations where the prevalence is low, as was confirmed in mass screening in developed countries.

Diagnostic use of X-ray examination was not recommended as a priority for developing countries, since in passive case-finding approximately similar results can be obtained with sputum microscopy, which is much cheaper. Also mass X-ray screening was considered incompatible with a situation in which the first felt need of the population, i.e., diagnosis for persons with symptoms, and adequate treatment for patients, is not yet satisfied.

As a diagnostic facility at the referral level of the general health service, X-ray examination makes it possible to examine patients whose sputum is negative on smear examination, and thus to obtain further information in cases with unexplained chest symptoms. If adequate treatment facilities have been established at the community level, X-ray examination of high-risk groups would make it possible to discover at least a large proportion of the prevalence cases. Obviously the relative inefficiency of mass X-ray observed in developed countries should not be extrapolated to developing countries, but the matter should be examined under local circumstances.

Conclusion

Reviewing the epidemiological basis for tuberculosis control in the light of more recent observations, a number of approximations and plain gaps in knowledge appear to call for prospective quantitative epidemiological research into several issues. In particular the concept that control measures aimed at attaining the primary social target of control will also bring about a reduction of the problem, seems worth investigating. The relative importance of alternative measures will become relevant when developing countries will have the opportunity of extending control beyond the first priority stage, which is likely to occur with the widespread effective coverage of primary health care. Practical methods for program evaluation and surveillance need to be described if the situation in developing countries is to be duly appreciated in the future.

References

(16) Tripathy, S. P. Personal communication.

(Source: H. G. ten Dam, Scientist, and A. Pfo, Chief, Tuberculosis and Respiratory Infections Unit, WHO, Geneva.)