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The Use of an Epidemiological Model for Estimating the Effectiveness of Tuberculosis Control Measures

Sensitivity of the Effectiveness of Tuberculosis Control Measures to the Coverage of the Population *

H. T. WAALER [1] & M. A. PIOT [2]

Given an adequate definition of the disease problem in epidemiological terms, it is possible to measure the epidemiological effectiveness *of control measures in terms of problem reduction. This is to be distinguished from the* clinical efficacy *of the same measures. The practical difficulty in assessing the epidemiological effectiveness of control measures experimentally can be overcome by the construction of simulation models and the use of computers, whereby the problem reduction associated with various control strategies can be estimated numerically.*

By varying the levels of certain parameters of the model systematically, the sensitivity of the effectiveness of control measures to the epidemiological, operational, clinical and social parameters of a situation can be assessed. A series of articles analysing this relationship is under preparation. This first article analyses the sensitivity of the effectiveness of BCG vaccination and of the chemotherapy of tuberculosis to changes in the coverage of the eligible population groups. A previously formulated postulate stating that the marginal effectiveness of these measures decreases as their coverage increases is validated by this first series of simulations. The significance of this finding for planning national tuberculosis control strategies is discussed, as well as possible bias in the method applied.

INTRODUCTION

The concept of epidemiological effectiveness

The term " control measures " is often used in connexion with communicable diseases such as tuberculosis. It means the use of the available medical technology to interfere actively with the epidemiological dynamics of a disease, commonly by attempting to break the chain of transmission. Tuberculosis control measures are well known; they consist in case-finding and chemotherapy, BCG vaccination of non-infected persons, and chemoprophylaxis of certain categories of infected persons.

The epidemiological effectiveness of control measures must be judged by the changes in transmission that they bring about. Such a concept of epidemiological effectiveness rests on a definition of the disease problem, on the choice of a valid system to represent it, and on the feasibility of quantifying it in symbolic terms. It has been suggested by Waaler [3] that the tuberculosis problem in a community should be represented as the cumulated sum, over all future times, of the man-years of active, infectious disease that will ever be experienced by that community (cf., the definition given by the WHO Expert Committee on Tuberculosis (1964): " . . . the problem of tuberculosis can be conceived of as the sum total of the individual suffering caused by the disease, and the related social costs.").

On the basis of this definition of the disease problem, there is no conceptual difficulty in

* This investigation received financial support from the World Health Organization.

[1] Senior Statistician, National Tuberculosis Register, Oslo, Norway.

[2] Formerly Medical Officer, Tuberculosis, Division of Communicable Diseases, World Health Organization, Geneva, Switzerland. Present address: WHO Representative in Algiers, Algeria.

[3] Waaler, H. T. (1964) *A note on the formulation of anti-tuberculosis programmes* (unpublished working document WHO/TB/Techn. Information/29 Rev.1.65). A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Health Organization, 1211 Geneva, Switzerland.

measuring the effectiveness of control measures in terms of the "problem reduction" that their implementation would bring about. At this point, it may be useful to underline the difference between the concept of *epidemiological effectiveness* and the more customary notion of *clinical efficacy* since both terms are referred to in this article. The latter term relates to the recipients of the control measure themselves; thus, the clinical efficacy of chemotherapy is expressed in terms of the cure rate in treated subjects. Similarly, the protective efficacy of BCG vaccination is that observed, in a controlled clinical trial, among vaccinated individuals by contrast with the controls.

Epidemiological effectiveness, on the other hand, assesses the cumulative effect of these measures on the whole community over a period of time, in terms of man-years of prevented disease. A similar notion of "epidemiologic bonus" has been introduced (Ferebee, 1967), in respect of isoniazid prophylaxis, for expressing the effect of that control measure, over and above the direct benefit incurred by those individuals who take the prescribed course of self-medication.

With such an operational definition, epidemiological effectiveness does not lend itself to measurement through conventional experimental research, as clinical efficacy does. For one thing, many, if not most, of the variables involved in the longitudinal epidemiological research that would be required for this purpose are not independently controllable; this precludes a classical approach with experimental controls. Furthermore, the object of such research, if feasible, would be to provide estimates of effectiveness as elements of decision *before* the mass implementation of some or all of them, not as a mere *ex post facto* assessment of an experimentally convenient, but socially meaningless, pattern. Finally, the cost of the prolonged observation required to measure the cumulative effect would be prohibitive.

This practical difficulty in quantifying epidemiological effectiveness can be avoided by applying the model simulation techniques developed by operational research workers. Models are symbolic representations of real life, evidently simplified drastically so as to be logically or mathematically tractable. In recent years, the development of computers with a large core memory has obviated the need for explicit mathematical solutions, and thus has allowed for a much higher degree of complexity in the structure of models—thus making them more realistic. Epidemiological models depicting the dynamics of tuberculosis as a communicable disease have been suggested by various authors. Basically, all of them follow, over time, a population divided into relevant epidemiological classes. Demographic and epidemiological parameters govern the flows between classes in each discrete time interval, whereas operational and technical parameters allow control measures to be simulated. These models have been reviewed recently at a workshop on model methodology, held at Cornell University (Lynn & ReVelle, 1968) and at the Eighth International Congresses on Tropical Medicine and Malaria in Teheran in 1968 (Mahler, unpublished data).

The senior author developed one of these models under a grant from the World Health Organization, and operates it on a service basis (Waaler, 1968a). The epidemiological analyses are formulated and undertaken at the National Tuberculosis Register, Oslo, Norway, in co-operation with the World Health Organization. The computer treatment is done at the Norwegian Computing Centre, Oslo. Various problems pertaining to decision-making in tuberculosis control and, more precisely, to the allocation of resources, have been treated in this way (Waaler, 1968a; Piot & Sundaresan [1]).

The sensitivity of epidemiological effectiveness

It is a generally accepted view that control measures differ in their effectiveness in different situations. In other words, certain parameters (demographic, epidemiological, technical, social and economic) must exert an influence on the relative effectiveness of the measures. It is because of these influences that certain control measures are preferred to others in some countries and rejected outright in others; but in most instances an unfortunate inertia results from not knowing what factors influence, and to what extent, the effectiveness of control measures. If, instead of being purely intuitive, our assumptions in this field could be quantified, the choice of optimum strategies for tuberculosis control would be greatly facilitated.

It has been suggested that simulation models such as the one developed in Norway could be used as research tools to identify the relevant factors, to

[1] Piot, M. & Sundaresan, T. K. (1967) *A linear programme decision model for tuberculosis control* (unpublished working document WHO/TB/Techn. Information/67.55). A limited number of copies of this document is available to persons officially or professionally interested on request to Distribution and Sales, World Health Organization, 1211 Geneva, Switzerland.

analyse and quantify their influences on the relative epidemiological effectiveness of BCG vaccination, chemotherapy, and isoniazid prophylaxis. It is precisely the object of this series of articles to study, by means of a series of simulations in which these factors are kept variable, the sensitivity of the effectiveness of our tuberculosis control measures to a number of the factors. Ideally, it should be possible even to estimate the *elasticity*, i.e., the rate of change of the epidemiological effectiveness associated with a unit change in the level of these factors, or some of them at least.

Some of the factors under discussion are inherent in the initial situation; for instance, the initial age–sex structure of the population, distribution of the population into the relevant epidemiological classes, and the extent of pre-existing control measures, as indicated by the number of previously active cases on the case register, and the number of individuals previously vaccinated (with a scar or certificate to prove it), etc. As a matter of definition, these factors are not variable for a given community at a given time; therefore, whatever influence the initial situation exerts cannot be ascertained or ascribed to any one factor or combination of factors. Even the comparison of 2 different initial situations might not identify these influences, for the situations would differ in most respects since many factors are closely correlated.

Other factors relate to the dynamics of the situation. They are the forces at play in shaping the ever-changing situation, and they are explicit in the model in the form of the demographic, epidemiological, operational, technical, social and economic flow parameters mentioned earlier. For the purpose of a study of the present type, each parameter may be kept variable over a range of acceptable values.

Demographic parameters. Two parameters are relevant, namely, the birth rate and the (age-specific) death rate. Changes in one or both, by influencing the population dynamics, would affect the balance between the numerical strength of the various epidemiological classes and, through these changes, might increase, or reduce the epidemiological effectiveness of control measures. At a time when both death rates and birth rates are changing rapidly and spectacularly under the combined influences of public health and population-control measures, it might be worth while to study the influence of the resulting demographic changes over the next decades on the effectiveness of our technology of tuberculosis control.

Epidemiological parameters. Most prominent among the relevant rates are: the effective contact rate (i.e., the number of new infections resulting from 1 infectious source over 1 unit of time, e.g., 1 year), the "breakdown" rate (the risk of a person's developing an infectious form of the disease, once infected—perhaps as a function of the time that has elapsed since infection), the spontaneous healing rate among infectious cases and the excess death rate associated with the infectious form of the disease. Changes in the levels of these rates, singly or combined, together with implicit or explicit assumptions regarding the exo-endogenicity of the disease, would influence the effectiveness of our control measures, probably in a different way for each of them. It is often assumed that the effective contact rate is sensitive to socio-economic changes, especially housing and general hygiene; similarly, the breakdown rate is presumed to be correlated with nutrition, and so on. Whatever the causative mechanism, these rates are observed to vary, and such variations can be simulated in order to study their influence.

Operational parameters. By operational parameters is meant those required to express the implementation of control measures adequately. Practically any strategy can be simulated by specifying the number and characteristics of persons eligible for, and subjected to, some control measure, and the period during which this is implemented. Thus *eligibility*, *coverage* and *intensity of implementation* are the relevant operational parameters.

Coverage. It has been postulated (Waaler, *op. cit.*) that the marginal effectiveness, that is, the effectiveness of the next unit of any control measure, decreases as the coverage of the eligible population by this particular measure increases, and, furthermore, it decreases also as the coverage of the eligible populations by other specific control measures increases. This postulate, which reflects the general law of diminishing returns, seems to be correct, judging by preliminary investigations with the model. The relationship between coverage and effectiveness should be further elucidated and quantified.

Intensity of implementation. Health strategies are classically divided into mass campaigns and integrated programmes. The former may be defined as the intensive application of the available technology at a point in time or, more correctly, over a short period. The latter, on the contrary,

spreads thinly but extensively the application of a control measure over a long period—presumably permanently. It is easily conceivable that the same number of units of a given control measure may affect the transmission of the disease quite differently depending on the period during which they are distributed, although it is not altogether clear in what way that effect would be felt namely, in reducing or enhancing epidemiological effectiveness.

Eligibility. The age at which a susceptible individual is vaccinated, or at which a patient with active disease is treated, can easily be construed as having an influence on the aggregate effectiveness of these measures. The correctness of this assumption has been verified in respect of the effect of vaccination (Bjartveit & Waaler, 1965). This should be further studied.

Technical parameters. The state of development of the medical technology is the most easily recognized among the factors capable of exerting an influence on the effectiveness of control measures.

The clinical efficacy of BCG vaccination, of chemotherapy and of chemoprophylaxis has been established in well-known clinical trials. It is expressed in terms of cure rates and prevention rates, as observed during the experiments from which these are determined. A certain amount of controversy has arisen in respect of the universality of these findings, more as regards BCG and chemoprophylaxis than as regards chemotherapy. Clearly, differences in clinical efficacy may be expected to be reflected in changes of the epidemiological effectiveness of these measures as well; presumably, these changes would be associated positively, but their exact relationship is difficult to ascertain.

Survival and relapse rates have been published after the long-term follow-up of patients in controlled clinical trials of chemotherapy regimens (Dawson et al., 1966) and, though these findings would not seem to modify grossly the conclusions of the trials in respect of the clinical efficacy of treatment, they might well exert some influence on its epidemiological effectiveness. In the successive follow-ups of the subjects in the British BCG trial (Great Britain, Medical Research Council, Tuberculosis Vaccines Clinical Trials Committee, 1963) no statistically significant trend could be demonstrated in the protective effect of vaccination but, from the published results, a waning of immunity cannot be excluded. The possible epidemiological consequences of a waning of immunity should be borne in mind. In the clinical trial of chemoprophylaxis (Ferebee, 1968), the findings suggest a rather rapid loss of the clinical efficacy of this measure in treated individuals; the epidemiological implications of such a possible waning cannot be disregarded.

The simulation of control measures with various degrees of initial clinical efficacy and tendencies to wane—if relapse is assimilated to a waning—would enable the epidemiologist to study the sensitivity of these control measures to such parameters.

The release of a drug or product of which the clinical efficacy is judged to be superior to that of drugs already available is generally accepted as a sufficient justification for reviewing tuberculosis control policies. By implication, it is expected that the epidemiological effectiveness of medical technology also would be enhanced; to what extent, if at all, is not a trivial question. The question may be reversed, and one may test, by simulation, how great a technical advance would be required to justify changes in existing policies—thus throwing light on the significance of basic research in given circumstances.

Social parameters. Epidemiological effectiveness has been based on a measurement of the disease problem which, it is recalled, embodies a time dimension. However objective such a measurement may appear to be, paradoxically it may not necessarily be of value. Let us consider 2 control measures that would, say, halve the disease problem in exactly 100 years, measure A starting to do this immediately and proceeding gradually and measure B achieving the same result drastically but much later, say after 40 years. Our criterion of effectiveness does not distinguish between A and B, because it is indifferent to the time pattern of the epidemiological benefit. In real life, both the medical man and the public will tend to attach more value to an otherwise equally effective measure if it shows its effect immediately, as measure A does. On the other hand, anyone choosing measure B prefers a spectacular improvement tomorrow to a gradual one starting today. To introduce in the assessment of the epidemiological effectiveness of control measures such a value judgement in the form of a social time preference amounts to applying a kind of discount rate, the changing value of which simulates all possible time preferences including indifference. The sensitivity of the effectiveness of a measure to wide changes in time preference is an important social policy parameter (Piot, 1968) which needs further study in the present context.

Economic parameters. The relevant factor here is the cost of the control measure, more precisely the marginal unit cost reflecting the economies and "diseconomies" of scale involved in operating at different levels of coverage. Where efficiency is defined in terms of marginal output per unit of input (in our case, marginal problem reduction per monetary unit), such consideration of cost would be essential. This point is made here, however, to stress that the present analyses are not concerned with output–input efficiency but exclusively with epidemiological effectiveness as defined at the beginning of this article. Economic parameters will not, therefore, be studied in the present series of papers.

In order to study the interrelationship between the various factors listed above, and their ultimate influence on the effectiveness of tuberculosis control measures, it has been found necessary to proceed step by step, by introducing more variables into the model of the situation in successive simulations, and ultimately varying the initial situation itself. The material thus available for analysis is enormous, and it has been found convenient to present it in a number of short, self-contained articles, each dealing with 1 variable or group of variables. The order in which it is proposed to present this material is shown in the following list.

1. The sensitivity of the effectiveness of tuberculosis control measures to operational parameters: (a) coverage of the population; (b) intensity of implementation; (c) criteria of eligibility.

2. The sensitivity of the effectiveness of tuberculosis control measures to social parameters: time preference.

3. The sensitivity of the effectiveness of tuberculosis control measures to demographic parameters: population growth.

4. The sensitivity of the effectiveness of tuberculosis control measures to epidemiological parameters: (a) levels of prevalence in the initial situation; (b) effective contact rate; (c) exo-endogenicity of disease.

5. The sensitivity of the effectiveness of tuberculosis control measures to technical parameters: (a) clinical efficacy; (b) waning of efficacy.

OBJECTIVE

This article describes the study, in a given situation, of the sensitivity of the epidemiological effectiveness of tuberculosis control measures, especially BCG and chemotherapy, to coverage levels feasible in vaccination and treatment programmes.

MATERIAL

The epidemiological effectiveness of these control measures has been applied to a hypothetical, but realistic, model of a demographic and epidemiological *situation.*

A population of 10 million inhabitants has been considered; the age distribution reflects birth and death conditions close to those observed in the population of Norway and similar western European countries. The age distribution of the total population and the subgroup of infected persons is shown graphically in Fig. 1.

The subdivision of the total population by age and epidemiological groups is given in Appendix Table 1. Epidemiologically, this situation is characterized by low prevalence rates. Thus, the age-specific initial prevalence of infection, shown in Fig. 2, corresponds to a total prevalence of 39%. Whereas this is probably higher than the observed values in some western countries, it corresponds well to many others. Only human sources of infection are considered here. No previous BCG vaccination has been applied.

The model used for this purpose contains a series of variables and parameters defining the population *dynamics* and the epidemiology of tuberculosis.

The number of births during any period is calculated as a constant fraction of the population during the child-bearing period (20–34 years of age); this is a simple but satisfactory assumption for the present purpose.

The survival rates from which the probability of surviving from one age-group into the next has been calculated are given in Fig. 3.

There are various kinds of epidemiological transfer rates, e.g., infection, breakdown, healing and relapse, depending on the susceptibility of non-infected subjects, the force of infection produced by the infectious cases, the protective efficacy of vaccination, the curative efficacy of treatment, etc. Details on this point have been reported elsewhere (Waaler, 1968b).

The parameter estimates have been extracted from various European sources. Their exact values are subject to discussion but are not crucial in the present context; the effect of varying the values of these important epidemiological and demographic parameters arbitrarily will be studied in a later paper.

FIG. 1

AGE DISTRIBUTION OF THE TOTAL POPULATION AND OF THE SUBGROUP OF INFECTED PERSONS

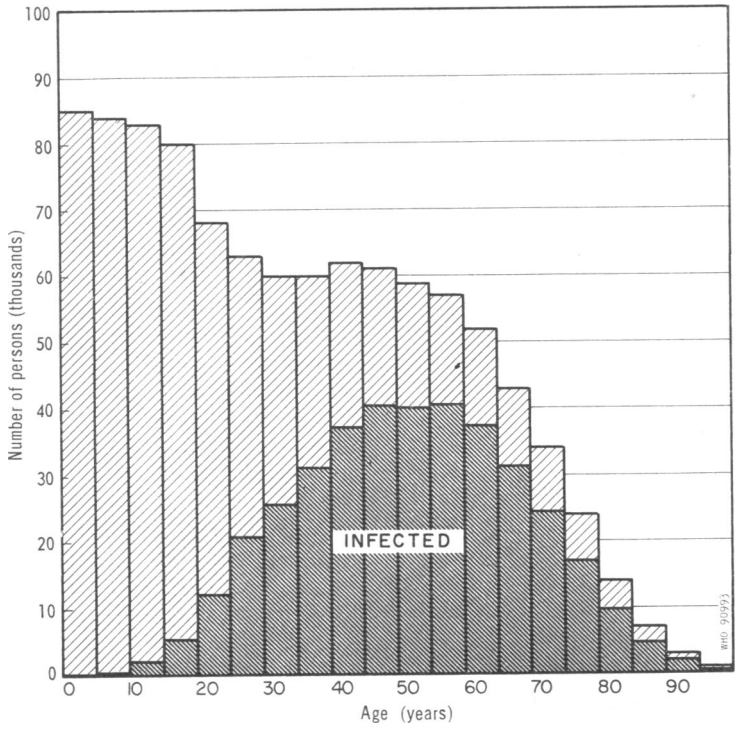


TABLE 1

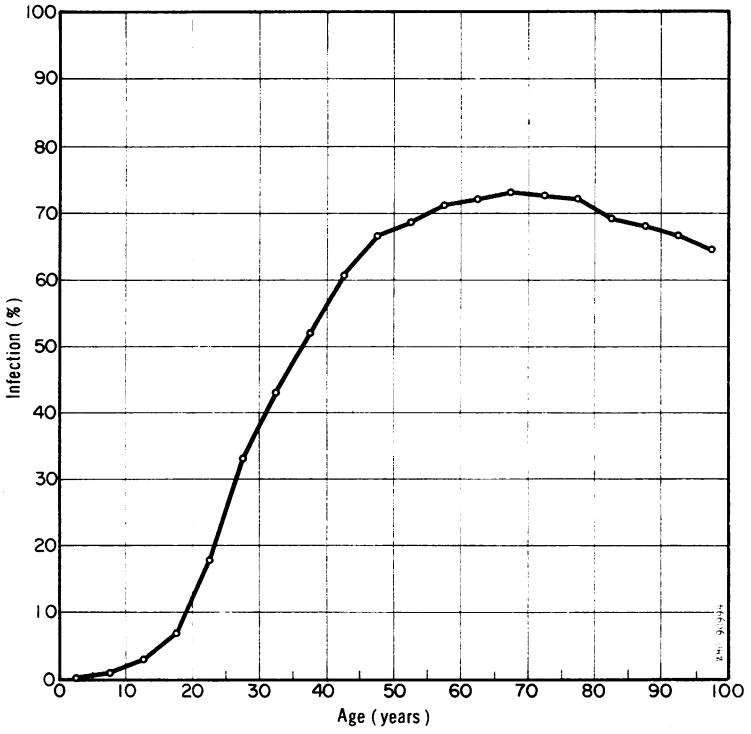
ESTIMATES OF 5-YEAR TRANSFER RATES

From \ To		Non-infected 1.	Infected ≤ 5 years 2.	Infected > 5 years 3.	BCG-protected 4.	Active cases: Non-infectious 5.	Active cases: Infectious 6.	Previous cases: Non-infectious 7.	Previous cases: Infectious 8.
Non-infected	1.		Infection parameter [a]		Operational parameter				
Infected ≤ 5 years	2.			Age-progression		32 %	32 % [b]		
Infected > 5 years	3.					0.3 %	0.6 %		
BCG-protected	4.	5 %							
Active cases: non-infectious	5.						5 %	100 %	
Active cases: infectious	6.								50 %
Previous cases: non-infectious	7.					4 %	0 %		
Previous cases: infectious	8.					0 %	4 %		

[a] This transfer (tuberculin converters) depends upon the current prevalence of infectious cases. The number of infectious cases at time t : C_t; the number of non-vaccinated, non-infected at time t : N_t; the total population at time t : P_t; the force of infection at time t : $\frac{C_t}{P_t}$; and the general susceptibility, 1.5. The value 1.5 is estimated so that $N_t \times \frac{C_t}{P_t} \times 1.5$ gives the number of converters as estimated from other sources.

[b] Partly age-specific: 0–4, 1 %; 5–9, 2 %; 10–14, 10 %; 15–19, 20 %; >20, 32 %.

FIG. 2
PREVALENCE OF INFECTION BY AGE



The basic transfer rates are given in Table 1. For a detailed discussion of the actual relationships underlying the dynamics of the model, the reader is referred to Waaler (1968b).

METHOD

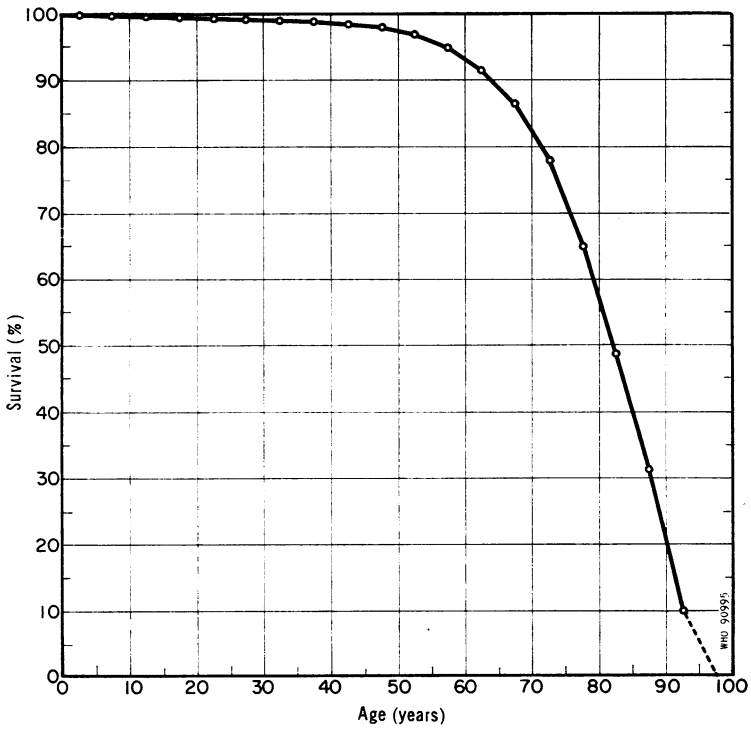
The changes in a dependent variable (effectiveness) associated with arbitrary changes in 1 or more independent variables (coverages) are estimated by computer simulation.

The model contains variables, some of which are uncontrollable from the point of view of a tuberculosis programme; for instance, the birth rate or the infectivity of a case. Others are affected by the control measures themselves; e.g., relapse and breakdown rates. Finally, there are operational variables, such as coverages, which affect the control programmes themselves. In this first article, the coverage of a vaccination programme and the coverage of a case-finding and treatment programme are simulated as independent variables.

When simulating various coverages of control measures for the present purpose, the following clinical assumptions are made. The development of tuberculosis in the infected individual is a purely endogenous process. BCG vaccination is assumed to give 80% protection to vaccinated individuals; this means that a vaccination coverage of 100% amounts to transferring 80% of non-infected individuals into the BCG-protected group. Furthermore, the protective efficacy is assumed to wane constantly at a rate of 1% per annum. The curative efficacy of treatment also reaches a high value: 95% of those treated who are still alive after 5 years are considered to be cured, i.e., non-infectious. Out of 100 cases not receiving treatment, 50 are cured spontaneously, 25 are dead and in 25 the disease remains active after 5 years.

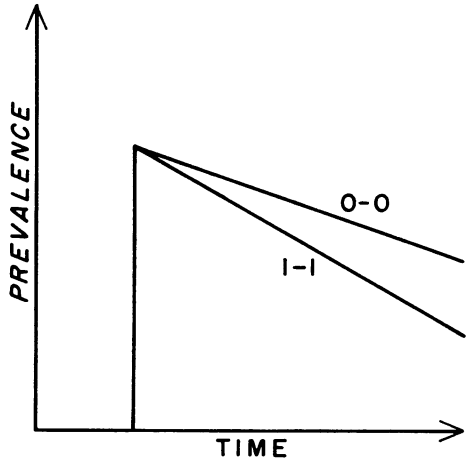
If, in a given situation, no control measures at all are applied (which can be simulated by giving zero values to the vaccination and case-finding or treatment coverages or both) the epidemiological

FIG. 3
SURVIVAL RATES



course of tuberculosis in the future can be represented by the projected curve of prevalence as a function of time, 0–0 in Fig. 4.

FIG. 4
FUTURE TRENDS OF TUBERCULOSIS UNDER EXTREME ASSUMPTIONS



The tuberculosis problem, defined there as the cumulated sum of man-years of tuberculosis during the next 100 years, is then measured directly by the area under this prevalence curve. The size of the problem in a situation of non-interference is taken as the baseline for comparison with other situations.

On the other hand, the maximum possible achievement of a control programme, in any situation, is 100% coverage with these measures; this might yield a hypothetical future trend such as that represented by the curve 1–1 in Fig. 4. With such a programme, the problem is measured by the area under the curve, and the area between curves 0–0 and 1–1 represents the problem reduction. Similarly, one can simulate all possible combinations of coverages between 0–0 and 1–1 in a given epidemiological situation. Each combination will result in an estimated problem reduction, by comparison with the 0–0 (non-interference) level.

Of course, the epidemiological situation that is used as the basis for such simulations in this article may itself be a result of previously applied control

measures, for instance, a highly efficient treatment programme. In such a situation, the simulation of 0% treatment coverage is artificial; it does not imply that the authors suggest the withdrawal of treatment as an applicable policy. The intention in carrying out simulations of this kind is to learn how the measures operate, both independently and in interplay with each other.

A computer programme allowing a rather large series of simulations to run rapidly was specially written for this paper in ALGOL-60. The print-out format is designed in the present runs to provide what is considered to be the minimum amount of information required for our purpose: the *number of new cases* (incidence), by age and by period of time—both in 5-year steps from 0 years to 100 years, and the *problem* (cumulative sum of man-years of infectious tuberculosis over 100 years), are printed for each simulation. The value of the problem is discounted at rates varying from 0.00 to 0.16. The cumulative input of control measures is also computed and printed, i.e., the number of vaccinations and of courses of treatment given in accordance with the pre-established " policy " of each simulation.

FINDINGS

Effectiveness of BCG vaccination

In order to test the sensitivity of the effectiveness of BCG to vaccination coverage, it is assumed in the first series of simulations that, given the initial situation already defined, a single policy variable is allowed to change, namely, the vaccination coverage. All other parameters are kept at a constant level. Appendix Table 2 shows the number of new infectious cases of tuberculosis during 20 5-year periods, corresponding to vaccination coverage levels of 0.00, 0.10, 0.33, 0.66 and 1.00, reproduced from the computer print-out.

Fig. 5 shows the projected time trend of incidence of infectious tuberculosis associated with 4 of these vaccination coverages, namely, 0.00, 0.33, 0.66 and 1.00.

The top curve in Fig. 5 represents the projected incidence if case-finding and treatment and vaccination were both maintained at 0 coverage level, i.e., without interference. This trend, which represents a baseline, corresponds to halving the problem over a period of 46 years. The second, third and fourth curves represent the projected incidence if, in addition to maintaining treatment coverage at zero level, 0.33, 0.66 and 1.00, respectively, of the uninfected children aged 14 years were vaccinated in any year; a moderate gain is shown by the slightly steeper slope of the curve. Each successive curve thus indicates a further reduction in the incidence. The trend shown in the lowest curve corresponds to halving the problem over 34 years. The graph suggests that the gain gradually diminishes from step to step.

Appendix Table 3 gives the estimated problem levels corresponding to various BCG coverage levels on the vertical scale, and treatment coverage levels on the horizontal scale. The BCG coverage levels 0.00, 0.33, 0.66, 1.00 and the treatment coverage level 0 are relevant here.

Table 2 shows the levels of the problem (in terms of the undiscounted cumulated sum of man-years of infectious tuberculosis over 100 years) that may be expected with each of the 4 vaccination coverages and the zero level of treatment coverage; the difference between these levels, and the problem reduction associated with these coverages. Problem reduction is shown as both absolute values and as a percentage of the baseline problem level.

TABLE 2

PROBLEM LEVELS AND PROBLEM REDUCTIONS ASSOCIATED WITH VARIOUS VACCINATION COVERAGES

Vaccination coverage	Problem		Problem reduction	
	Level (P) (man-years)	Difference (man-years)	Man-years	As % of P
0.00	492 677			
		68 457		
0.33	424 220		68 457	13.9
		49 712		
0.66	374 508		118 169	24.0
		37 711		
1.00	336 797		155 880	31.6

The *level* of the problem is seen to decrease with each step increase in vaccination coverage. The maximum problem reduction is observed with the first 0.33 rate of coverage, where it represents 13.9% (68 457 : 492 677); it is less substantial when the coverage is raised from 0.33 to 0.66, namely, 10.1% of the problem level at 0.00 coverage. The problem reduction is least when the coverage is further raised from 0.66 to 1.00, it represents 7.6% of the problem level at the 0.00 rate of coverage. The problem reduction values in Table 2 can be presented graphically as in Fig. 6.

FIG. 5
INCIDENCE OF INFECTIOUS TUBERCULOSIS OVER TIME, ASSOCIATED WITH DIFFERENT BCG VACCINATION COVERAGES OF THE UNINFECTED AT 14 YEARS OF AGE

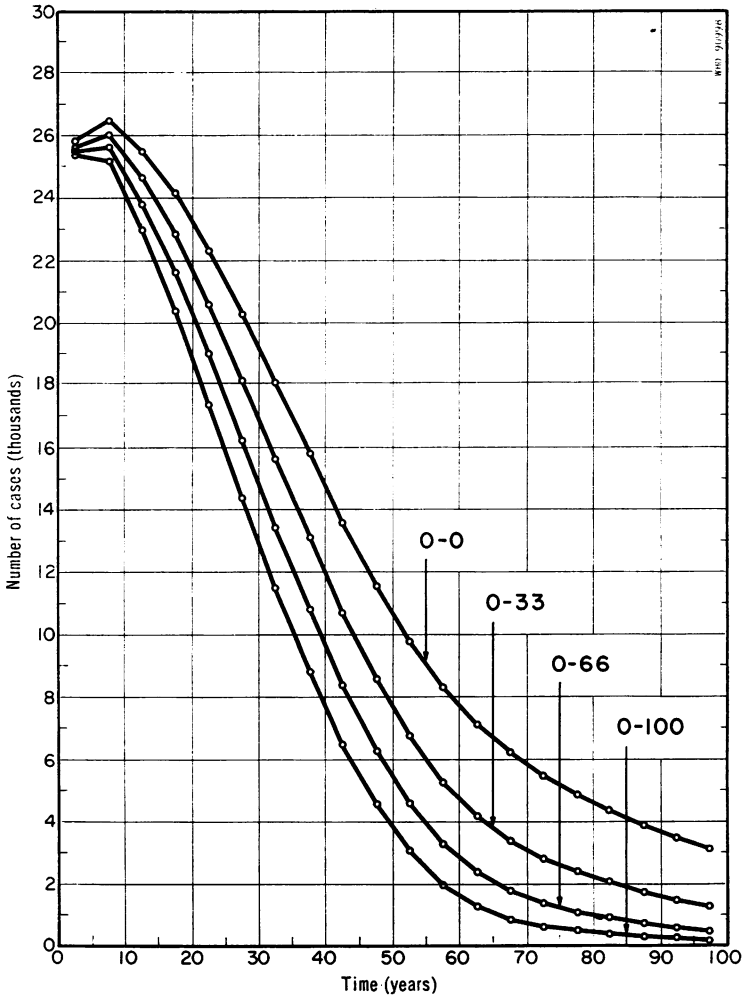
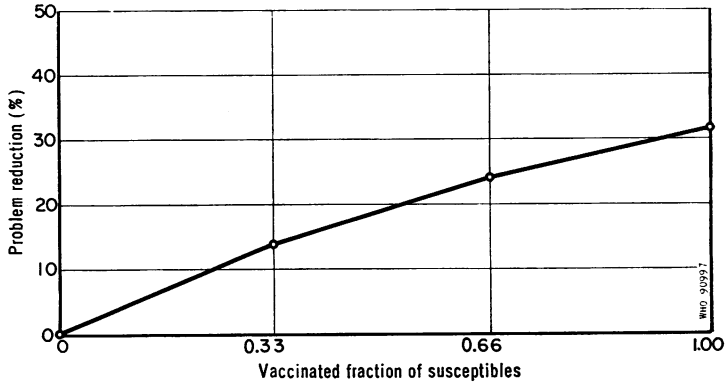


FIG. 6
EFFECTIVENESS OF BCG AT VARIOUS VACCINATION COVERAGE LEVELS



In order to concentrate more closely on the sensitivity of effectiveness to coverage, one may attempt to study the effect of a few vaccinations given at various levels of coverage, thus obtaining a truly marginal value corresponding to the slope of the effectiveness curve at discrete coverage points. This is easily achieved by further simulations.

By differentiating between problem levels corresponding to coverages 0.00 and 0.01, 0.09 and 0.10, 0.32 and 0.33, 0.65 and 0.66, and 0.99 and 1.00, respectively, the resulting values will be truly comparable measures of marginal effectiveness of vaccinations as a function of coverage.

Table 3 (extracted from Appendix Table 3) presents the levels of the problem and the differences between levels, i.e., problem reduction, as well as the differences between problem reduction corresponding to the changes of vaccination coverage mentioned above.

TABLE 3

PROBLEM LEVELS, MARGINAL PROBLEM REDUCTION AND RATE OF CHANGE OF MARGINAL PROBLEM REDUCTION, ASSOCIATED WITH VARIOUS VACCINATION COVERAGES

Vaccination coverage	Problem level (P) (man-years)	Marginal problem reduction	
		Difference (man-years)	Rate of change (% of P)
0.00	492 677	2 421	4.91
0.01	490 256		
0.09	471 734	2 213	4.69
0.10	469 521		
0.32	425 985	1 765	4.14
0.33	424 220		
0.65	375 399	1 291	3.44
0.66	374 508		
0.99	337 755	968	2.87
1.00	336 797		

Table 3 thus provides us with evidence of the marginal decrease of effectiveness of BCG with increasing vaccination coverage.

Effectiveness of chemotherapy

In order to test the sensitivity of the effectiveness of chemotherapy to treatment coverage, this series of simulations is based on the assumption that, in an initial situation such as that already described, only the treatment coverage is variable, all other parameters being kept at a constant level. Appendix Table 4 presents the estimated numbers of new cases of tuberculosis, during 20 5-year periods, corresponding to various treatment coverage levels (0.00, 0.10, 0.33, 0.66 and 1.00).

Fig. 7 shows some of the projected time trends of incidence, namely, those associated with treatment coverages of 0.00, 0.33, 0.66 and 1.00.

The top curve in Fig. 7 represents the projected trend if case-finding treatment and vaccination were both kept on the zero level of coverage. This is the same no-interference curve, taken as a baseline, as in Fig. 5.

The second, third and fourth curves represent the projected incidence if 0.33, 0.66 and 1.00, respectively, of all new cases were treated at any time, while keeping vaccination coverage at the zero level throughout. Each successive curve shows a substantial reduction of incidence, and there is some suggestion that at each successive step the additional gain gradually decreases. The lowest curve represents a trend corresponding to a halving of the incidence over 32 years, whereas the baseline corresponds to halving over 46 years.

Appendix Table 3 provides the data for estimating the problem levels corresponding to the various treatment coverages (on the horizontal scale) at different levels of vaccination coverage (vertical scale). Treatment coverage levels 0.00, 0.33, 0.66, 1.00 and vaccination coverage level zero are relevant here. Values from Appendix Table 3 are summarized in Table 4.

The level of the problem decreases with each step increase in treatment coverage. The maximum difference is observed with the first 0.33 coverage, where it represents 24.9% of the baseline value. Raising the coverage from 0.33 to 0.66 reduces the problem by a further 14.6%, whereas the last 0.33 of coverage increases the problem reduction by only 9.7%. The problem reduction values can be presented graphically as in Fig. 8. Both Table 4 and Fig. 8 suggest that the marginal effectiveness of chemotherapy is gradually reduced as the coverage of cases by treatment increases.

For a closer study of this phenomenon, one may simulate treatment programmes with coverage levels such as 0.00–0.01, 0.09–0.10, 0.32–0.33, 0.65–0.66 and 0.99–1.0. Thus the effect of presumably equal numbers of chemotherapeutic courses between these

FIG. 7
INCIDENCE OF INFECTIOUS TUBERCULOSIS OVER TIME, ASSOCIATED WITH DIFFERENT TREATMENT COVERAGES OF CASES

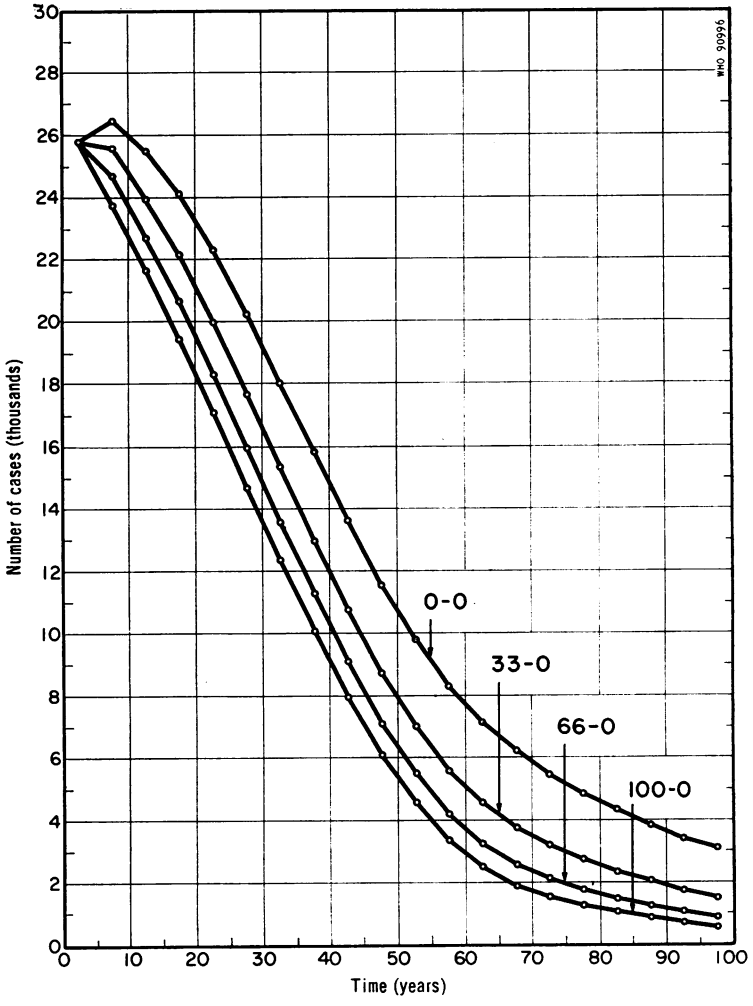


TABLE 4
PROBLEM LEVELS AND PROBLEM REDUCTIONS ASSOCIATED WITH VARIOUS TREATMENT COVERAGES

Treatment coverage	Problem		Problem reduction	
	Level (P) (man-years)	Difference (man-years)	Man-years	As % of P
0.00	492 677			
		122 915	122 915	24.9
0.33	369 762			
		71 889	194 804	39.5
0.66	297 873			
		47 694	242 498	49.2
1.00	250 179			

levels can be differentiated. The resulting values presented in Table 5, extracted from Appendix Table 3, are comparable measures of marginal effectiveness.

Table 5 strongly suggests that the marginal effectiveness of chemotherapy decreases as a function of increasing treatment coverage. The sensitivity of effectiveness to coverage is evident.

Combined influence of vaccination and treatment coverages

In the simulations so far presented, it is recalled that one of the coverages was kept at a constant level

FIG. 8
EFFECTIVENESS OF CHEMOTHERAPY AT VARIOUS TREATMENT COVERAGES

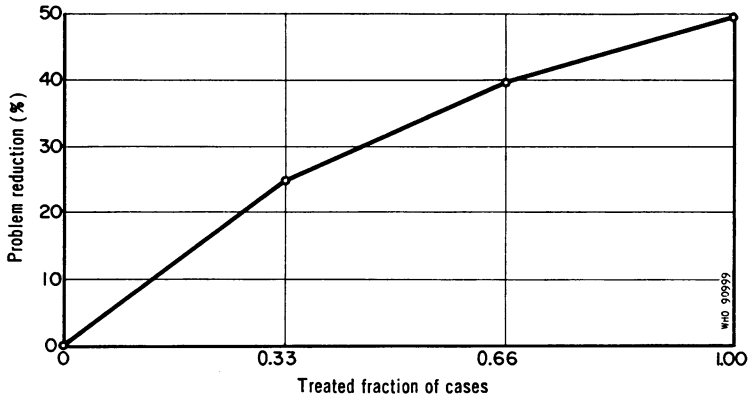


TABLE 5
PROBLEM LEVELS, MARGINAL PROBLEM REDUCTION AND RATE OF CHANGE OF MARGINAL PROBLEM REDUCTION ASSOCIATED WITH VARIOUS TREATMENT COVERAGES

Treatment coverage	Problem level (P) (man-years)	Marginal problem reduction	
		Difference (man-years)	Rate of change (% of P)
0.00	492 677	4 839	9.82
0.01	487 738		
0.09	451 515	4 151	9.19
0.10	447 364		
0.32	372 545	2 783	7.47
0.33	369 762		
0.65	299 599	1 726	5.76
0.66	297 873		
0.99	251 331	1 152	4.58
1.00	250 179		

while the other was kept variable. In order to test the sensitivity of the effectiveness of BCG to the combined influences of vaccination and treatment coverages, both these policy parameters are made to vary concurrently in a third series of simulations. This is done systematically over the same range as previously, and with the same increment steps. All other parameters are kept constant.

The marginal effectiveness of BCG in terms of *problem reduction*, as a function of vaccination and treatment coverages, is presented in Table 6, which is based on Appendix Table 3. The value of the marginal effectiveness in each cell has been estimated as in the previous sections; indeed, the values in the first row and column are those presented there.

This table bears out the postulate that the marginal effectiveness of BCG is sensitive to both vaccination and treatment coverages; it decreases consistently at each successive step increase of vaccination coverage at any level of treatment coverage, and it takes decreasing sets of values with each successive step increase in treatment coverage.

Following a symmetrical analysis, the effectiveness of chemotherapy can be studied successively as a function of treatment and vaccination coverage (Table 7).

The pattern of interactions observed in Tables 6 and 7 is one and the same phenomenon, but seen from 2 different angles. It can be visualized graphically in the following way (Fig. 9).

The effectiveness of control measures is shown on the vertical axis in terms of problem reduction (man-years), the vaccination coverage on the left horizontal axis, and the treatment on the right horizontal axis. The curve C_1 corresponds to the effectiveness of BCG at a zero treatment coverage level, as seen in Table 2 and corresponding to Fig. 6. Similarly, curve C_2 corresponds to the effectiveness of chemotherapy at zero vaccination coverage level, presented in Table 4 and Fig. 8. The curves have been smoothed for graphical convenience.

TABLE 6

MARGINAL EFFECTIVENESS OF BCG AS A FUNCTION OF VACCINATION AND TREATMENT COVERAGES IN MAN-YEARS AND AS A PERCENTAGE OF THE PROBLEM

Marginal vaccination coverage	Treatment coverage [a]				
	0.00	0.10	0.33	0.66	1.00
0.00-0.01	2 421 (4.91)	1 989 (4.45)	1 326 (3.59)	816 (2.74)	544 (2.17)
0.09-0.10	2 213 (4.71)	1 826 (4.26)	1 228 (3.44)	765 (2.64)	515 (2.10)
0.32-0.33	1 765 (4.16)	1 472 (3.77)	1 015 (3.06)	651 (2.38)	448 (1.92)
0.65-0.66	1 291 (3.45)	1 097 (3.14)	783 (2.59)	523 (2.05)	373 (1.69)
0.99-1.00	958 (2.84)	828 (2.62)	612 (2.20)	425 (1.78)	312 (1.49)

[a] Percentages in parentheses.

At each coverage level of one control measure, a curve has been fitted to the problem reduction achieved by the other with values derived from Appendix Table 3. These curves together form the surface in Fig. 9.

One point on this surface represents the combined effectiveness of BCG *and* chemotherapy, at the stated vaccination and treatment coverages. At the point defined by a treatment coverage of 66% and by a vaccination coverage of 10%, for instance, the corresponding marginal effectiveness of BCG and chemotherapy are 2.64% and 5.59% of P, respectively, yielding a combined reduction of the problem equal to 102 706 man-years (492 677–289 971); 2.64 and 5.59 represent the slope of the surface on the 2 axes at that point.

A family of points achieving the same problem reduction through different combinations of treatment and vaccination coverages may be visualized as a line of iso-effectiveness on the surface. One such

TABLE 7

MARGINAL EFFECTIVENESS OF CHEMOTHERAPY AS A FUNCTION OF TREATMENT AND VACCINATION COVERAGES, IN MAN-YEARS AND AS A PERCENTAGE OF THE PROBLEM

Marginal treatment coverage	Vaccination coverage [a]				
	0.0	0.10	0.33	0.66	1.00
0.00-0.01	4 939 (10.02)	4 482 (9.55)	3 619 (8.53)	2 742 (7.32)	2 144 (6.37)
0.09-0.10	4 151 (9.28)	3 787 (8.84)	3 100 (7.93)	2 396 (6.87)	1 906 (6.02)
0.32-0.33	2 783 (7.53)	2 574 (7.21)	2 175 (6.56)	1 752 (5.80)	1 447 (5.19)
0.65-0.66	1 726 (5.79)	1 622 (5.59)	1 418 (5.18)	1 194 (4.69)	1 025 (4.30)
0.99-1.00	1 152 (4.60)	1 095 (4.47)	982 (4.20)	854 (3.87)	753 (3.61)

[a] Percentages in parentheses.

FIG. 9. INTERACTION OF VACCINATION AND TREATMENT COVERAGE

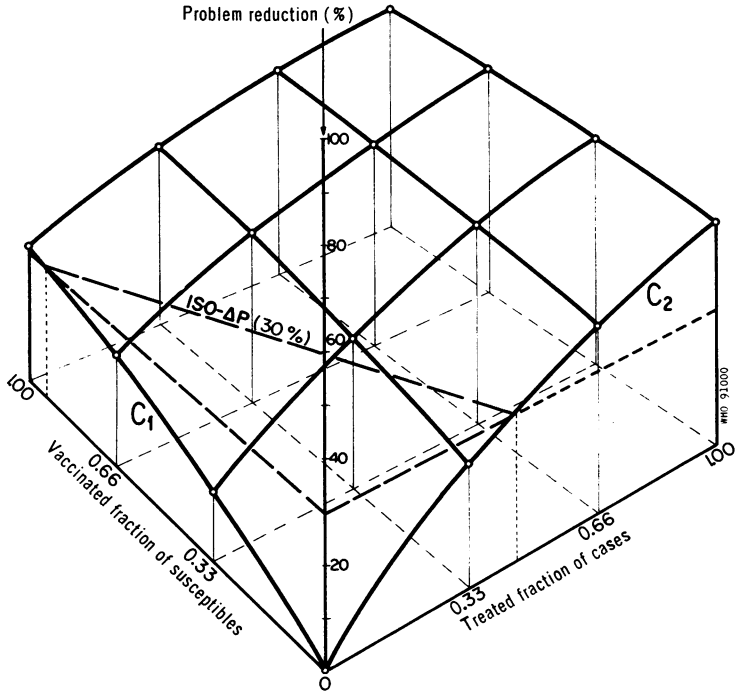
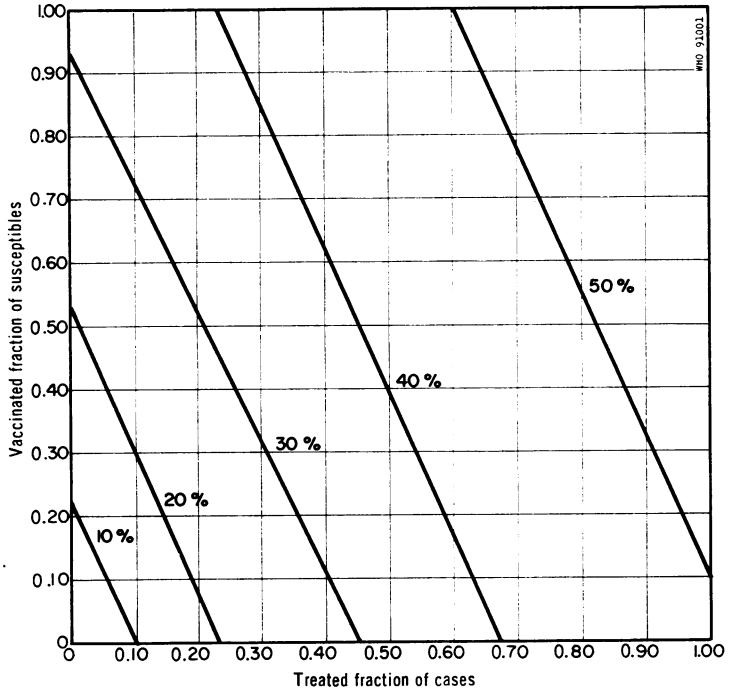


FIG. 10. ISO-EFFECTIVENESS[a] AS A FUNCTION OF COMBINATION OF TREATMENT AND VACCINATION



[a] As percentage of problem reduction.

line represents the intersection with the surface of a horizontal plane situated at a given problem reduction level. Fig. 9 presents 1 such iso-effectiveness line, precisely that corresponding to a 0.30 problem reduction. To arrive at a series of iso-problem reduction lines corresponding to 0.10, 0.20, 0.30, 0.40 and 0.50 problem reduction levels, a series of additional computer runs were undertaken which resulted in the nomogram presented in Fig. 10. For instance, a 0.93 vaccination coverage without any treatment achieves 155 880 man-years of problem reduction, and it can be calculated that a 0.30 coverage with treatment combined with a 0.33 vaccination coverage achieves very nearly the same problem reduction. From an *epidemiological* standpoint, these 2 programme combinations are equivalent or iso-effective.

An analysis of this type supplies a catalogue of the possible alternatives that achieve similar problem reductions and this provides the desired epidemiological basis for decision-making.

DISCUSSION

The results of the model simulations reported here throw light on the consequences of varying operational coverages on the effectiveness of control measures. For instance, it is shown in Fig. 10 that a 0.30 problem reduction can be achieved by a 0.45 rate of treatment coverage, or by a 0.93 vaccination coverage, or by a combination of a 0.32 treatment coverage and a 0.31 vaccination coverage, etc. (The occurrence of 0.30 problem reduction with coverages very near 0.30 for both measures is purely coincidental.)

The meaning of these findings is that the same epidemiological result can be achieved in many different ways, and their implication is that the sole epidemiological criterion is insufficient to guide the public health administrator towards optimal decisions. For instance, the nomogram in Fig. 10 shows that, under the particular set of assumptions retained for the purpose of this study, the 2 major control measures, if applied with a maximum coverage, are capable of reducing the tuberculosis problem by 58%. Thus, even a 1.00 rate of coverage with both measures cannot prevent new cases from occurring nor interrupt the transmission of bacilli completely. Here lies the rationale invoked by the defenders of chemoprophylaxis. When BCG vaccination is excluded, the problem reduction under the sole influence of a 1.00 treatment coverage falls from 0.58 to 0.49. The relatively modest effect of BCG vaccination at a 1.00 rate of treatment coverage level has sometimes been used as an argument against its application under epidemiological conditions close to those simulated here.

The fallacy of such arguments without reference to the cost factor has been pointed out elsewhere (Waaler, 1968a). The further relationship between the economic and epidemiological aspects of the problem is omitted from the present discussion.

The main finding of this study is that there is interdependence of coverage and effectiveness, both within a single control measure and between 2 measures. This finding, which is in agreement with *a priori* postulates that the law of diminishing returns applies in the purely epidemiological field independently of any cost consideration, poses a problem of interpretation. Is the agreement between postulate and simulation findings to be taken as a validation of the postulate of the model used for the simulation, or should one suspect that the agreement merely indicates that the model builders have been able to feed their prejudices into the model? To anyone concerned with simulation models of the type used for the present study, it would seem highly improbable that the concept of marginally decreasing effectiveness could be consistently translated into terms of the parameters affecting the 6000 or so flows that occur within 1 simulation run, so as to obtain the intended result. Another possibility would be that the law of diminishing returns and the other postulates that have been confirmed with the present model should be programmed into the initial conditions of the simulations, i.e., initial demographic and epidemiological characteristics of the population, while the flow parameters are more indifferent. Again, this is a very unlikely hypothesis, as the initial conditions were not arbitrarily created by the authors, but specified from observed sets of real-life situations.

Finally, assuming that the postulate could not be, and was not, fed into the simulations, one is inclined to accept it as valid, and with it the model that produces the evidence, though perhaps some will reject both concept and model as one and the same fabrication. The authors conclude that the model is a fairly realistic representation of tuberculosis epidemiology, the major evidence being that it is able to reproduce and confirm a set of previously formulated *a pr ori* postulates that are both epidemiologically appealing and, more generally, consistent with a number of natural laws.

The analyses reported here are limited to BCG vaccination of susceptibles and to chemotherapy of infectious cases. Similar analyses could be made of BCG vaccination and chemoprophylaxis, of chemotherapy and chemoprophylaxis, and of all 3 measures in competition. While the simulations reported here do not warrant any conclusion regarding the interdependence of chemoprophylaxis, with the other 2 control measures, they do not suggest independence either. By analogy, interdependence is more likely than not. To assert this point, and also to give the order of magnitude of such an interdependence, if any, further sets of simulations involving chemoprophylaxis are necessary. The model used in this study can be used for this purpose.

RÉSUMÉ

EMPLOI D'UN MODÈLE ÉPIDÉMIOMÉTRIQUE POUR ÉVALUER L'EFFICACITÉ DES MESURES DE LUTTE ANTITUBERCULEUSE:

VARIATION DE L'EFFICACITÉ EN FONCTION DU TAUX DE COUVERTURE DE LA POPULATION

Le contrôle d'une maladie transmissible comme la tuberculose repose sur l'application de mesures visant à interrompre le cycle de transmission. L'efficacité épidémiologique de la vaccination par le BCG ou de la chimiothérapie ne peut être établie expérimentalement. Mais pour autant que soit défini, en termes épidémiologiques, le problème de la tuberculose, on peut évaluer l'efficacité épidémiologique de ces mesures en fonction de la réduction du problème qu'elles déterminent. Une définition du problème de la tuberculose est donnée dans le huitième rapport du Comité OMS d'experts de la Tuberculose. Elle a trouvé sa formulation mathématique dans un article de l'auteur principal, où il propose qu'on évalue le problème en années-hommes de maladie, cumulées sur tous les temps à venir. Grâce aux modèles épidémiométriques, et en particulier à leur traitement par l'ordinateur, il est possible de simuler l'application des mesures de lutte antituberculeuse sur des populations hypothétiques et dans des conditions diverses. Le modèle qui a été développé à Oslo en collaboration avec l'OMS comprend un certain nombre de paramètres démographiques, épidémiologiques, opérationnels, techniques et sociaux, que l'on peut faire varier dans certaines limites, de façon à simuler diverses situations. Ces propriétés du modèle permettent d'étudier les relations existant entre l'efficacité épidémiologique des mesures de lutte d'une part, et les changements apportés aux divers paramètres d'autre part. En d'autres termes, il est possible d'étudier la sensibilité de l'efficacité épidémiologique aux diverses valeurs que peuvent prendre ces paramètres. Cela forme le sujet d'une série d'études, dont la première est exposée dans le présent article. Elle a trait à la vérification du bien-fondé d'un postulat, énoncé il y a quelques années par l'auteur principal, et selon lequel l'efficacité marginale de la vaccination, comme celle de la chimiothérapie, tendrait à décroître au fur et à mesure que le taux de couverture des groupes de population qui en sont justiciables augmente. Selon le même postulat, cette dépendance devrait se vérifier aussi bien avec une seule des deux mesures envisagées qu'avec les deux associées. Une série de simulations, où seuls les taux de couverture ont été pris comme variables indépendantes, a permis de vérifier la validité du postulat énoncé plus haut. Que l'on considère les courbes d'incidence, ou le problème de la tuberculose, l'efficacité épidémiologique du BCG et de la chimiothérapie se confirme comme étant sensible aux taux de couverture mis en œuvre. Les incidences de cette sensibilité sur la planification de la lutte antituberculeuse sont exposées dans le présent article. Les auteurs y examinent la validité de la méthode employée.

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APPENDIX TABLE 1

SUBDIVISION OF THE POPULATION BY AGE AND EPIDEMIOLOGICAL GROUP

Age-groups (years)	Non-infected	Infected		BCG-protected	Active cases		Previous cases		Totals
		≤ 5 years	> 5 years		Non-infectious	Infectious	Non-infectious	Infectious	
	1	2	3	4	5	6	7	8	
0–3	848 800	1 000	0	0	200	0	0	0	850 000
5–9	833 400	4 200	946	0	320	44	1 070	20	840 000
10–14	805 872	4 150	14 096	0	1 388	174	4 040	280	830 000
15–19	744 693	4 000	41 320	0	1 527	470	6 780	1 210	800 000
20–24	558 282	3 700	102 187	0	1 668	1 163	9 130	3 870	680 000
25–29	422 495	2 750	184 080	0	1 845	2 080	9 290	7 460	630 000
30–34	342 342	2 100	227 528	0	1 788	2 632	11 590	12 020	600 000
35–39	288 364	1 700	270 070	0	1 796	3 120	15 750	19 200	600 000
40–44	248 316	1 400	329 942	0	1 954	3 608	14 770	20 010	620 000
45–49	207 717	1 200	369 566	0	1 983	3 704	10 930	14 900	610 000
50–54	189 118	1 000	374 690	0	1 872	3 450	8 420	11 450	590 000
55–59	165 759	900	383 456	0	1 701	3 234	6 560	8 390	570 000
60–64	146 007	800	355 518	0	1 573	3 182	5 460	7 460	520 000
65–69	116 431	700	298 298	0	1 344	2 197	5 250	5 780	430 000
70–74	95 420	500	232 428	0	1 060	1 542	4 480	4 570	340 000
75–79	69 866	475	160 887	0	694	988	3 830	3 260	240 000
80–84	43 596	325	90 133	0	374	512	2 730	2 330	140 000
85–89	22 596	215	43 257	0	114	228	2 190	1 400	70 000
90–94	10 040	110	17 192	0	0	88	1 690	880	30 000
95–99	3 550	50	4 823	0	0	27	1 040	510	10 000
Totals	6 162 664	31 275	3 500 417	0	23 201	32 443	125 000	125 000	10 000 000

APPENDIX TABLE 2
NEW CASES OF INFECTIOUS TUBERCULOSIS UNDER VARIOUS BCG-VACCINATION COVERAGE LEVELS

Vaccination coverage level	Time intervals (years)																		
	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76–80	81–85	86–90	91–95	96–100
0.00	25 722	26 405	25 430	24 083	22 234	20 184	17 998	15 757	13 552	11 501	9 713	8 234	7 071	6 170	5 449	4 845	4 319	3 852	3 432	3 051
0.10	25 689	26 284	25 181	23 699	21 716	19 538	17 235	14 896	12 618	10 519	8 703	7 215	6 059	5 180	4 494	3 936	3 460	3 042	2 672	2 339
0.33	25 615	26 007	24 609	22 824	20 551	18 103	15 572	13 060	10 673	8 524	6 708	5 259	4 172	3 386	2 813	2 377	2 024	1 724	1 464	1 239
0.66	25 508	25 610	23 791	21 588	18 940	16 170	13 404	10 757	8 337	6 243	4 543	3 251	2 338	1 734	1 342	1 078	881	721	587	474
1.00	25 397	25 200	22 952	20 341	17 354	14 332	11 428	8 765	6 435	4 509	3 016	1 942	1 237	815	578	443	355	285	227	177

APPENDIX TABLE 3
ESTIMATED PROBLEM LEVELS CORRESPONDING TO VARIOUS TREATMENT COVERAGE LEVELS AND BCG-VACCINATION COVERAGE LEVELS

BCG-vaccination coverage levels	Treatment coverage levels									
	0.00	0.01	0.09	0.10	0.32	0.33	0.65	0.66	0.99	1.00
0.00	492 677	487 738	451 515	447 364	372 545	369 762	299 599	297 873	251 331	250 179
0.01	490 256	485 365		445 375		368 436		297 057		249 635
0.09	471 734			430 122		358 224		290 736		245 401
0.10	469 521	465 039	432 083	428 296	359 570	356 996	291 593	289 971	245 981	244 886
0.32	425 985			392 178		332 416		274 444		234 312
0.33	424 220	420 601	393 806	390 706	333 576	331 401	275 211	273 793	234 846	233 864
0.65	375 799			349 970		302 846		255 110		220 781
0.66	374 508	371 766	351 269	348 873	303 815	302 063	255 781	254 587	221 262	220 408
0.99	337 755			317 406		279 204		239 015		209 161
1.00	336 797	334 653	318 484	316 578	280 039	278 592	239 615	238 590	209 602	208 849

APPENDIX TABLE 4
NEW CASES OF INFECTIOUS TUBERCULOSIS UNDER VARIOUS TREATMENT COVERAGE LEVELS

Treatment coverage levels	Time intervals (years)																		
	1–5	6–10	11–15	16–20	21–25	26–30	31–35	36–40	41–45	46–50	51–55	56–60	61–65	66–70	71–75	76–80	81–85	86–90	91–95	96–100
0.00	25 722	26 405	25 430	24 083	22 234	20 184	17 998	15 757	13 552	11 501	9 713	8 234	7 071	6 170	5 449	4 845	4 319	3 852	3 432	3 051
0.10	25 722	26 136	24 951	23 446	21 470	19 324	17 063	14 772	12 538	10 477	8 694	7 234	6 099	5 236	4 560	4 004	3 527	3 109	2 737	2 403
0.33	25 722	25 517	23 933	22 147	19 961	17 673	15 317	12 980	10 739	8 704	6 971	5 579	4 525	3 755	3 178	2 723	2 346	2 023	1 741	1 492
0.66	25 722	24 630	22 683	20 632	18 296	15 928	13 544	11 228	9 043	7 092	5 457	4 171	3 227	2 567	2 101	1 754	1 476	1 245	1 047	876
1.00	25 722	23 716	21 651	19 410	17 051	14 665	12 315	10 052	7 947	6 083	4 540	3 346	2 487	1 908	1 518	1 242	1 029	855	708	582