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EPIDEMIOLOGICAL MODEL OF TYPHOID FEVER
AND ITS USE IN THE PLANNING AND EVALUATION OF ANTITYPHOID
IMMUNIZATION AND SANITATION PROGRAMMES¹

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SYNOPSIS

An epidemiological model for typhoid fever in a stable population has been constructed in order to study the transmission of infection at different levels of endemicity. It involves a number of parameters representing the proportions of epidemiological sub-groups in the population - such as the susceptible, the infected and the immune - and rates of transition between the groups. Numerical values based on available evidence were assigned to the parameters, to provide a realistic simulation of stable endemicity.

Changes were then introduced in the values of some of the parameters in order to study the consequences of mass vaccination and improvements in general health conditions and sanitation, in particular on the incidence of disease.

The model shows that a single mass vaccination reduces the incidence of disease considerably, but the gain is largely lost after a few years. Repeated vaccinations at five-year intervals will produce further decreases in incidence, though the additional gain becomes less at each consecutive vaccination.

The model was also used to estimate the possible effect of sanitation. The incidence descends to a new level of stability, when the transmission of the infection is reduced owing to improved sanitation. The effect of sanitation is long lasting and in this respect gives better results than vaccination.

The simultaneous application of mass vaccination and sanitation gives a cumulative effect which in some cases tends to be close to the effect of sanitation alone.

The model was used to forecast the probable effect of preventive measures against typhoid, such as mass immunization and sanitation programmes, on a selected population in terms of prevention of disease, as well as in terms of relative costs and benefits. It provides a useful guide for the rational use of funds and facilities set aside for typhoid fever control purposes.

Possible other uses of the model are briefly discussed.

The need for adjustment of the model to specific conditions in the community is stressed, as well as the necessity for readjustments to take into account changes in the pattern of life and the natural history of typhoid.

1. INTRODUCTION

Typhoid is a public health problem primarily in endemic areas, and, accordingly, we have studied mathematical models for typhoid fever in respect to endemic conditions.

The model has been constructed with a view to its possible use for forecasting trends of the natural course of infection and the effect of preventive measures - vaccination and sanitation - on such trends. For the sake of simplicity, stable endemic situations were taken as a basis for the model.

The epidemiological patterns of typhoid are sufficiently well known from numerous studies to permit the construction of a mathematical model.

The effectiveness of antityphoid vaccines has been evaluated¹ in controlled field trials in endemic areas. The degree of protection conferred by various vaccines, and the methods of production and testing have been established,² as well as immunization schemes and dosages.^{3,4,5,6}

The effect of sanitation⁷ has been demonstrated, although the available information does not give a clear idea of the exact quantitative effectiveness of each particular component of environmental sanitation.

We therefore believe that the essential information is available for construction of the model, in spite of certain inadequacies which make it difficult to determine with exactitude each specific factor and parameter in the model. For example, the effect of mass immunization cannot be expressed in simple equations taking into account only the protective effect of the vaccine and the number of people immunized and non-immunized. There are other factors which influence the outcome of vaccination programmes, for example, the sources of infection and routes of transmission, the size of the challenge dose and the degree of exposure of the population. Furthermore, transmission from the known sources of infection, sick persons or carriers, to other people depends on various characteristics of the population such as state of immunity, food habits, occupation, customs and personal hygiene, as well as on other factors and conditions.

Environmental sanitation, like immunization, has a considerable effect on the control of typhoid fever. However, many factors, such as level of education, economic status, etc., play a role, making the effect of specific sanitation measures much more difficult to determine than that of immunization programmes. All these and other factors and conditions should be taken into consideration in constructing and, in particular, in applying mathematical models to specific population groups.

It was hoped that the mathematical model could be used for determining the probable results and relative benefits and costs of mass immunization and sanitation programmes. An attempt was therefore made to construct a simple model which would enable health workers to plan and apply an effective typhoid control programme within the limits of their financial means and available facilities and resources.

2. BASIC EPIDEMIOLOGICAL FACTORS

For the construction of any mathematical model, it is necessary to establish some basic epidemiological factors and parameters as a point of departure.

2.1 Natural history of typhoid

The natural history of typhoid is known and will not be described here except in so far as it concerns the construction of the model.

Data on the natural history of typhoid fever used in the construction of the model, i.e. incubation period, duration of illness, relapse, morbidity, fatality, carrier and other rates, were compiled from numerous studies on typhoid in various countries. It was realized that, too often, the data obtained in one study differed from the results of other studies. This is due, in some cases, to different methods of investigation and field inquiry, laboratory techniques and procedures of data collection and analysis, as well as to different environmental and other conditions. For the construction of the model, it was necessary to take as a starting point some definite parameters.

In so doing, attention was paid to prevailing opinions,⁸ as well as to their critical appraisal. Many parameters varied considerably, and therefore it was necessary to come to some arbitrary compromises in order to arrive at definite numerical values to be used for the construction of the model.

Some basic values which were used are presented in schematic form below:

Incubation period: range 7-21 days; mean - 14 days
Duration of sickness: range 14-35 days; mean - 28 days
Duration of relapse: range 7-28 days; mean - 18 days
Frequency of relapses: 5% of cases
Proportion of cases: symptomatic (typical, febrile): 20%; asymptomatic (and mild): 80%
Case fatality rate: 1-10%; average 3%
Carrier rate: chronic, range 2-5%; average 3%
 temporary (mean duration, 90 days), range 7-20%; average 10%
Incidence in endemic areas per 10 000 population: 10-150

It is realized that some of the above ranges and averages vary greatly in different countries and under different circumstances.

Infection was considered in the light of the complex host-parasite-environment inter-relationship, and, as far as possible, from the quantitative point of view.

The host factor - number, immune status, resistance and susceptibility - has been taken duly into account in constructing the model as these aspects largely determine actual morbidity rates and levels of endemicity.

In some studies, a relationship has been demonstrated between age, sex and socio-economic status and the typhoid morbidity rate; young age-groups, females and the poor were the most affected, while women in particular tended to be carriers for a longer period and were more difficult to cure. These and possibly other factors might be important in specific population groups but we have, for simplicity's sake, omitted them in the construction of this model.

The parasite factor was also considered from the quantitative point of view and therefore the simple presence or absence of S. typhi was not the only criterion for determining the risks of infection. When proper techniques were used, some studies showed that carriers excrete regularly, rather than intermittently, large and fairly constant numbers of organisms.⁹ It seems that persons living under poor hygienic conditions in the vicinity of carriers are relatively heavily and constantly exposed to infection, and that infection and disease are the result of this exposure to considerable quantities of S. typhi.

Studies carried out on healthy volunteers¹⁰ have shown that ID_{50} is about 10^6 - 10^7 , and that ID_{25} is about 10^4 . However, people in natural conditions are usually infected with a lower dose.¹⁰ In most of the communities with endemic typhoid, the micro-organisms are spread widely by carriers, convalescents and sick persons. Accordingly, infection may be easily transmitted through contaminated food, water and hands under favourable conditions. Infected persons and carriers are often found accidentally and Salmonella detected in the blood stream of apparently healthy persons.¹² We have therefore considered that the parasite is more widely present than might be assumed from the incidence of clinical illness.

The morbidity rates in communities with different levels of endemicity of typhoid were determined from the available national statistical returns on morbidity, but these data were critically appraised in the light of the many studies on typhoid, which have always revealed much more infection than was indicated in health statistics reports on cases and carriers.

For example, among 40 students in an army school stricken by a typhoid epidemic, 15 had Salmonella typhi in their faeces and/or blood, but only two had a febrile illness while two more had been subfebrile and in routine clinical and public health practice would never have been diagnosed as typhoid cases.¹³ The typical clinical illness, we believe, occurs in only a small proportion of those infected, perhaps in 20%.

While many studies on carriers have revealed that the rate of temporary and chronic carriers after an illness varies, most often it is about 10% for the former, and about 3% for the latter.^{14,15} However, in old age-groups, the chronic carrier rate has been as high as 10%,¹⁴ or even higher among those having typhoid simultaneously with other conditions such as schistosomiasis¹⁶ and gall-bladder stones.¹⁷

There are other factors which must also be taken into account when constructing mathematical models. Specific conditions in population groups such as superimposed infections may change greatly the susceptibility and resistance of the host, and thus alter the natural history of the disease. For example, studies done in Egypt¹⁶ show that the carrier rate or urinary excretors of S. typhi among people infected with schistosomiasis is much higher and the carrier state lasts longer than among otherwise healthy people. Moreover, the presence of urinary carriers in rural areas with much stagnant water and poor sanitation leads to extensive environmental contamination and to high risk of infection. In areas where schistosomiasis is a common disease, this fact has to be taken into account when adapting our model.

Environment represents an important factor which, beyond any doubt, plays a role in the natural history of typhoid and should not be neglected, since the risk of transmission of infection depends greatly on environmental conditions.

There may be a greater risk of infection in certain specific population groups, such as nurses, schoolchildren, etc., due to the environmental conditions to which they are exposed.

The transmission of typhoid, which varies under different climatic, socio-economic and cultural conditions, determines, to a great extent, the level of endemicity and morbidity rates. The rapid decline of typhoid in the United States of America during the last few decades is primarily the result of rapid changes in environmental conditions and standards of personal hygiene.¹⁸ We have taken these environmental factors into account in the construction of our model, and have considered them to be the most important and decisive factors determining the actual level of endemicity in a community.

2.2 Effectiveness of vaccines and mass immunization

The effectiveness of vaccines was calculated from the data obtained in various controlled field trials of typhoid vaccines which were summarized by us earlier.¹ The degree of effective protection conferred by the vaccine was taken as being equal to that conferred by the most effective typhoid vaccines in the controlled trials. These were the acetone-dried and heat-phenol vaccines given in two doses; however, in endemic areas, similar results could be expected with only one dose.^{3,4}

In view of the field experience, it was considered that boosting with an effective vaccine should take place about every five years, and this was applied in the model. For reasons of simplicity, these factors were applied to a homogeneous population.

In constructing the model, we did not make adjustments for differences in the risk of infection and consequently in the expected morbidity rates between various population groups, including differences between those who did and those who did not volunteer to be immunized. It has been observed that, for various reasons, volunteers contract disease less readily and less often than those who do not accept vaccination. In one controlled field trial, the typhoid morbidity rate among volunteers belonging to the control group and receiving placebo

was 13 per 1000, while in non-volunteers in the same community it was 26 per 1000.⁶ The ratio was thus 1:2. In the same study, the difference in morbidity rates between volunteers and non-volunteers was especially great among populations exposed to a heavy challenge dose in a water-borne outbreak, the morbidity rates being in the ratio of 1:11. This important fact should not be neglected as the immunization of a volunteering population tends to give results far below those which would be expected from the application of simple arithmetic.

For the above reasons, the "theoretical" effectiveness of typhoid vaccine, as determined in controlled field trials, differs from the "use" effectiveness in mass immunization campaigns. We have taken this into account and have made adjustments on the grounds of field experience^{6,11} to compensate for the differences in vaccine effectiveness in the volunteers and the non-volunteers.

Furthermore, there are other possible reasons why the impact of immunization on the natural course of infection in the community may not in fact follow the straightforward calculations based on effectiveness determined in controlled field trials and expressed as a percentage reduction of the incidence rates. The possibility that vaccine is less effective for the prevention of inapparent infection and its spread than for the prevention of clinical illness was not fully evaluated in any field trial and we still lack reliable information. We did not try to speculate or to make adjustments in our model in that respect, but this may become necessary if further research brings forth more clear-cut information on this question.

2.3 Effectiveness of sanitation

Environmental sanitation - primarily excreta disposal, but also water chlorination, food control, etc. - when introduced and practiced continuously considerably lowers the level of transmission of infection. The transmission rate or force of infection could easily be reduced to half its former level by the construction of privies and the provision of sufficient safe water.^{19,20} Environmental sanitation appears to be the determining factor in transmission of infection.

For the purpose of the model, the introduction of a specific sanitation programme could be considered simply as changing the force of infection. The construction of latrines would result in a diminished rate of transmission of infection from carriers, for example, to 50% of its original value. The data obtained from field observations support this connotation.

Sanitation campaigns which are not followed by sustained efforts to maintain adequate sanitary practices and hygiene may produce only temporary results. However, when sanitation is introduced together with health education and improvement of living standards, the effects tend to be cumulative resulting in a steady reduction of typhoid morbidity rates due to the decline in the force of transmission of infection.

3. CONSTRUCTION OF THE MODEL FOR TYPHOID FEVER ENDEMICITY

3.1 Structure of the model

The general population was divided into subgroups identifiable in the natural course of typhoid fever. The natural history and epidemiological evolution of the infection in the population depends essentially on chronological changes in the various classes of individuals. The structure and the class symbols adopted to simulate the dynamics of typhoid fever in the population^a are illustrated in the flow chart (Fig. 1).

^a The movement of births and deaths due to causes other than typhoid fever is not shown in the flow chart but was taken duly into consideration in the mathematical expression of the model.

It is not easy to estimate the numerous rates of transition directly from available quantitative evidence. It was found more convenient to consider the rate of transition as the product of the rate of change from one stage of the disease to the other stages (or rate of exit) by a coefficient of transfer, which would represent the relative size of the class going to any other subgroup.

3.2 Epidemiological parameters and daily rates of change

The epidemiological parameters involved in the present model are specified below. The numerical values of the corresponding daily rates of change are also indicated. They should, however, be considered as possible values only. Other simulations of typhoid fever dynamics could easily be worked out with different levels for these quantities.

An infected person may or may not become sick. In the present model it was assumed that the same dynamics of disease apply equally well to both types of infection with respect to the ability to transmit the infection to other persons and to maintain or lose resistance status. In the mathematical development, therefore, these two types of infection were treated, as far as possible, as one group, and, for convenience, the term "sickness" is used below also for asymptomatic infections.

(1) Period of incubation. The mean duration was fixed at 14 days. The daily rate of exit is therefore: $PI = 0.07143$ per person under incubation.

(2) Period of sickness. The mean duration was fixed at 28 days for both symptomatic and asymptomatic cases. In addition, it was assumed that 5% of affected persons would relapse for a mean period of 18 days. Hence the mean duration of the sickness period is:

$$.95 \times 28 + .05 (28 + 18) = 28.9 \text{ days per case.}$$

The daily rate of exit is therefore: $PS = 0.03460$ per case.

(3) Temporary carriers. The mean duration was fixed at 90 days. The daily rate of exit is therefore: $PC = 0.01111$ per temporary carrier. The permanent carrier can only exit by death.

(4) Resistants. The mean duration of short resistance was fixed at one year (365 days). The daily rate of exit is therefore: $PR_1 = 0.002740$ per short resistant. The mean duration of long resistance was fixed at 10 years. The daily rate of exit is therefore: $PR_2 = 0.0002740$ per long resistant.

(5) Clinical or symptomatic cases. It was assumed that 20% of the persons passing through the sickness period are detected as typical acute clinical cases (symptomatic). In this study, incidence rate refers to clinical cases only.

(6) Mortality from typhoid. It was assumed that 3% of the clinical cases would die from typhoid fever. Therefore 0.6% of the daily exit of persons in the sickness period was allocated to typhoid deaths.

(7) Natality and general mortality. For simplicity, a stable population was used in the model. The annual birth rate and crude death rate (all causes) were both fixed at the same level of 20 per thousand. The daily rates are therefore: $PE = PD = 0.0000548$ per person in the community.

(8) Force of infection. The risk of transfer of infection to a susceptible individual is proportional to the proportion of infectious persons in the population and to a factor (RI) which is an expression of the force of infection. This factor is the resultant of the mean values of several parameters: frequency of contact, effective challenge dose, degree of susceptibility, etc.

In the present study, the factor RI will be considered as the main variable determining the pattern of the epidemiological characteristics of the population. Four different values of RI were successively entered in the model: 0.0018, 0.0020, 0.0025 and 0.0040 per susceptible and per infectious person per day.

(9) Infectiousness. The infectious persons are: a small fraction of the incubating, the majority of the sick and all the carriers. The relative importance of the various classes was fixed as indicated in the matrix of coefficients of transfer (Table 1). The intensity of infectiousness was supposed to be constant for all persons in these classes.

3.3 Coefficients of transfer

All the transfers from one epidemiological subgroup to the other classes are represented in the flow chart (Fig. 1) by a set of coefficients $R_{i,j}$, which express at each stage of the disease the fraction of individuals transferred from class i to class j , out of all individuals leaving class i .

The numerical values of the coefficients of transfer $R_{i,j}$ were derived from available epidemiological evidence.

TABLE 1
MATRIX OF COEFFICIENTS OF TRANSFER $R_{i,j}$

Class of origin i	Class of destination j										Total
	1	2	3	4	5	6	7	8	9	10	
1	-	0.990	0.010	-	-	-	-	-	-	-	1.000
2	-	-	0.040	0.950	0.010	-	-	-	-	-	1.000
3	-	0.010	-	0.900	0.090	-	-	-	-	-	1.000
4	0.100	-	-	-	0.100	0.100	-	0.694	-	0.006*	1.000
5	0.100	-	-	0.200	-	-	-	0.694	-	0.006*	1.000
6	0.100	-	-	-	-	-	0.300	0.600	-	-	1.000
7	-	-	-	-	-	-	-	-	-	-	0.000
8	0.100	-	-	-	-	-	-	-	0.900	-	1.000
9	1.000	-	-	-	-	-	-	-	-	-	1.000
10	-	-	-	-	-	-	-	-	-	-	0.000

* Fatality rate is 0.03 of clinical cases. Assuming that 0.20 of classes x_4 and x_5 develop clinical symptoms, 0.006 of these classes are transferred to class x_{10} .

It is recognized that many of these coefficients can vary over a wide range and that for some of them the range of variation is not even known. It would, not however, be difficult to simulate typhoid fever dynamics with other values for the coefficients of transfer.

3.4 Mathematical model

The mathematical relationship between the 10 classes of individuals defined in Fig. 1 is expressed in the following system of 10 equations where the differentials dx_i are in fact finite daily increments, as all the rates were calculated on a daily basis:

$$dx_1 = - (x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + (x_4 R_{4.1} + x_5 R_{5.1})PS + x_6 R_{6.1} PC + x_8 R_{8.1} PR_1 + x_9 R_{9.1} PR_2 + x_t PB - x_1 (PD - dx_{10}/x_t)$$

$$dx_2 = R_{1.2}(x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + x_3 R_{3.2} PI - x_2 (PI + PD - dx_{10}/x_t)$$

$$dx_3 = R_{1.3}(x_3 + x_4 + x_6 + x_7)(x_1/x_t)RI + x_2 R_{2.3} PI - x_3 (PI + PD - dx_{10}/x_t)$$

$$dx_4 = (x_2 R_{2.4} + x_3 R_{3.4})PI + x_5 R_{5.4} PS - x_4 (PS + PD - dx_{10}/x_t)$$

$$dx_5 = (x_2 R_{2.5} + x_3 R_{3.5})PI + x_4 R_{4.5} PS - x_5 (PS + PD - dx_{10}/x_t)$$

$$dx_6 = x_4 R_{4.6} PS - x_6 (PC + PD - dx_{10}/x_t)$$

$$dx_7 = x_6 R_{6.7} PC - x_7 (PD - dx_{10}/x_t)$$

$$dx_8 = (x_4 R_{4.8} + x_5 R_{5.8}) PS + x_6 R_{6.8} PC - x_8 (PR_1 + PD - dx_{10}/x_t)$$

$$dx_9 = x_8 R_{8.9} PR_1 - x_9 (PR_2 + PD - dx_{10}/x_t)$$

$$dx_{10} = (x_4 R_{4.10} + x_5 R_{5.10})PS$$

$$\text{where } x_t = \sum_1^9 x_i$$

The annual number of cases is given by the formula:

$$\sum (x_2 (R_{2.4} + R_{2.5}) + x_3 (R_{3.4} + R_{3.5})) 0.2 PI$$

where the summation \sum is done over 365 days

The annual number of typhoid fever deaths is simply given by the sum of dx_{10} over 365 days.

The above set of equations would constitute a system of differential equations if the daily rates were replaced by instantaneous rates of change. However, it was suspected that such a system could not be solved analytically with all mathematical rigor. On the other hand, the daily changes of the classes x_i are extremely small and can be calculated at high speed on the electronic computer. It was therefore decided to apply this technique in the simulation of typhoid fever dynamics.

In order to facilitate their interpretation, the numerical results of computer simulations actually produced will mainly be presented here in graphical form.

4. APPLICATION OF THE MODEL IN EVALUATION OF THE EFFECT OF PREVENTIVE MEASURES

4.1 Stable endemicity

The first objective was to find out the set of x_i values which would correspond to a stable endemic situation for a given value of the force of infection RI ; it was then possible to study clearly the effect of specific preventive measures imposed upon the stable endemicity.

Several preliminary trials showed that situations corresponding to existing levels of endemicity were obtained with the following four values of the parameter RI : 0.0018, 0.0020, 0.0025 and 0.0040. The percentage distribution of the population in the various

epidemiological classes, when the stable situation is reached,^a are shown in Table 2 for the selected values of the force of infection.

TABLE 2
STABLE PERCENTAGE DISTRIBUTION IN POPULATION
CLASSES FOR DIFFERENT LEVELS OF FORCE OF INFECTION (RI)

Population class	Daily force of infection (RI)			
	0.0018	0.0020	0.0025	0.0040
Susceptible	94.5	84.9	67.3	41.7
Incubating non-infectious	0.0244	0.0661	0.143	0.254
Incubating infectious	0.00122	0.00331	0.00716	0.0127
Sick infectious	0.0511	0.139	0.300	0.534
Sick non-infectious	0.00583	0.0158	0.0342	0.0609
Temporary carriers	0.0158	0.0430	0.0930	0.166
Permanent carriers	0.966	2.62	5.73	10.3
Short resistant	0.527	1.43	3.09	5.51
Long resistant	3.96	10.7	23.3	41.5
TOTAL	100	100	100	100
Annual typhoid incidence rate ¹	12.8	34.8	75.2	133.9
Annual typhoid death rate ²	4.3	11.7	25.3	45.1

¹ Per 10 000 population.

² Per 100 000 population.

NB Birth rate and crude death rate are both equal to 20 per thousand population

It was found that the size of the epidemiological classes is almost linearly related to the reciprocal of the force of infection RI. This fact facilitated the derivation of a stable situation from another already known stable situation. It is thought that a stable level of endemicity can only establish itself if the rate RI remains above a certain critical value and that this value is a function of the birth and death rates. Further study in this direction might be fruitful.

^a The mathematical problem consists in finding the set of values of the x_i which render simultaneously null all the dx_i . Asymptotic solutions were obtained with the computer by successive trials on long periods.

4.2 Immunization

The mathematical model was then used to simulate the dynamic changes which would occur in the various epidemiological categories of the population under conditions of stable endemicity when mass immunization is carried out.

It was assumed that, by vaccination, a certain proportion of the susceptibles were directly transferred to the short resistant class. This proportion is measured by the efficacy of the immunization, which is itself the product of the immunization coverage by the effectiveness of the vaccine used. Ranges covering the more common values for these factors, as used for the computation of the resulting efficacy of the mass vaccination, are shown in Table 3.

TABLE 3
EFFICACY OF VACCINATION AGAINST TYPHOID
FEVER FOR VARIOUS COMBINATIONS OF POPULATION COVERAGE
AND VACCINE EFFECTIVENESS

Population coverage	Effectiveness of vaccine		
	.60	.75	.90
.60	.36	.45	.54
.80	.48	.60	.72
1.00	.60	.75	.90

The effects of different typical levels of mass vaccination efficacy are analysed in the present study:

(1) Single mass immunization

The effects of a single mass immunization on the annual incidence rate of typhoid fever as well as on the various epidemiological categories are shown in Fig. 2 for the two extreme levels of vaccination efficacy (36% and 90%). Separate graphs were drawn for each of the four levels of endemicity stability (see Table 2).

It is clearly seen that the sudden transfer of a certain proportion of susceptible to resistant has an immediate effect on the incidence rate (per 10 000 population), the importance of the decrease being, of course, directly related to the efficacy of the mass immunization. It is, however, observed that after this spectacular drop the incidence rapidly rises and, depending on the initial level of endemicity, between 50% and 90% of the gain is lost 10 years later. The speed of the loss is then considerably reduced and the curve tends slowly to the initial stability level. This fact is believed to be a consequence of the delayed repercussion of the mass vaccination on the carriers (see Fig. 2).

(2) Periodic mass immunization

The results of seven successive mass immunizations carried out at a periodicity of five years are illustrated in Fig. 3 for the situation characterized by a low endemicity level (RI = 0.0018) and a medium level of vaccination efficacy (60%). ^a

^a Computer runs were also produced for other levels of these parameters but are not reported here.

Repeated vaccinations compensate largely the rapid loss in the benefit observed on the incidence curve after each immunization, but it is noted that the additional gain decreases at each subsequent inoculation. Nevertheless, the long-term level, which establishes itself when the vaccination programme is interrupted, is considerably affected by the number of successive vaccinations carried out. In the example illustrated in Fig. 3, the long-term gain on the incidence is, after seven inoculations, at least four times as large as after one immunization only.

It is also interesting to observe the effect of periodical vaccinations on the carriers. Slight decreases occur by successive vaccination, but the movement is less and less accentuated and, sometimes, after the last immunization, the curve shows a definite tendency to the re-establishment of the original level.

4.3 Improvements in sanitation

Any improvement in sanitation - primarily excreta disposal but possibly also the provision of safe water, the adoption of hygienic habits, etc. - would result in a decrease in the risk of infection, as measured in this model by the force of infection RI and presented in Fig. 4.

The shift in time of the size of each epidemiological subgroup x_1 from one stability level to another was simulated with the model.

The thick lines of Fig. 4 show the pattern of change of the annual incidence rate (per 10 000 population) and of the percentages of carriers, susceptibles and resistants on the assumption that a high force of infection ($RI = 0.0040$) is suddenly reduced, at the fifth year, to a lower level ($RI = 0.0020$) as a consequence of the reduction in the risk of transmission.

As seen in Fig. 4 the size of the various epidemiological classes will ultimately pass from the initial stability level to the new, more favourable level of endemicity.

The 50% reduction in the force of infection causes an immediate decrease in the annual incidence rate to about 50% of its original level, followed by a temporary increase due most probably to the slower decrease in the reservoir of infection (see the trend of the percentage of carriers in Fig. 4). A long-term decrease is then observed, bringing asymptotically the incidence rate to its new stability level.

4.4 Combined effect of immunization and sanitation

Fig. 4 shows also the additional gain on the incidence of the disease which can be expected from combined mass immunization and sanitation programmes with either single immunization or periodical vaccinations at five-year intervals. For the present illustration, the degree of immunization efficacy was fixed at the medium value of 60%, and the degree of efficacy of sanitation at a value of force of infection 50% lower than before the application of sanitary measures. Broadly speaking, the results of combined measures are quite comparable in the long run to those obtained with sanitation alone. The main feature of interest is perhaps that the long-term benefit of immunization is largely ruled by the permanent gain resulting from the favourable change in the force of infection due to the improvement of sanitation. This finding is of great importance for the long-term planning of control and, possibly, eradication of typhoid fever.

5. APPLICATION OF THE MODEL IN COST-BENEFIT EVALUATION

While the relative effectiveness of various preventive measures is of great practical interest to public health workers for both the planning and application of such measures, the costs and benefits must be taken into consideration in order to make the best use of available resources. We have therefore tried to apply our model in evaluation of the relative merits of immunization and sanitation in the control of typhoid fever from the point of view of costs and benefits.

5.1 Determination of costs and benefits

Determination of the costs of vaccination and sanitation is not difficult. To the cost of material (vaccines, syringes, needles; or latrines, water mains, etc.) was added, the cost of transportation and manpower (professional and auxiliary). The benefits were calculated from saved funds which would otherwise be spent on the treatment of typhoid cases, hospital and other expenses, as well as lost wages. We did not attempt to cost human lives in terms of money as some authors have done.²¹ In view of this the actual benefits are always higher than can be presented by simple financial gains.

There were two main difficulties in the evaluation of costs and benefits, namely:

(1) The costs of immunization and treatment of cases, like other costs, differed greatly from country to country in view of the different stages of development of the medical services and the economy and the different socio-economic systems. In some countries, most of the costs of treatment were borne by individuals, in others, by the state (social or health insurance, for example). Costs and benefits were therefore distributed in various ways to individuals and to state services. It was thus impossible to find a common international denominator and to express, in terms of one currency, for example United States' dollars, the costs and benefits which would be applicable generally.

(2) So far as sanitation is concerned, the benefits cannot be limited to its effect on typhoid alone. Sanitation affects other illnesses - enteric, parasitic or skin infections - and leads to a rise in the standards of hygiene in general, bringing also (as in the case of water supplies) economic benefits.

We were therefore obliged to study each country or area separately, applying the same principles but taking into account specific conditions. The differences between the countries were so great that generalization was impossible. Each individual country has to be studied for itself.

We collected data on costs from several countries at various levels of development and with various socio-economic systems, and found that one can roughly divide them into several categories; for example:

- (a) countries with a subsistence economy, the state being responsible for the provision of modest health services;
- (b) countries with intermediate economic development in the sense of free enterprise with limited financial responsibility of the state for health matters and services;
- (c) countries such as (b) but with a greater financial responsibility of the state for social and health matters and services;
- (d) countries with a high degree of economic development, but limited responsibility of the state for financing immunization and treatment of typhoid; and finally

(e) countries with a high degree of economic development where the state is largely (if not totally) responsible for providing free immunization, treatment and wage compensations in case of illness.

Since typhoid is endemic and represents a problem in those countries with a lower level of development (a, b, c), we have limited our study to those categories.

5.2 Use of the model for long-term cost-benefit evaluation

Immunization and sanitation, even if envisaged as short-term programmes, have a long-lasting effect. The costs of initial investment are compensated over a long period of time. For practical reasons, a cost-benefit analysis should be considered on a long-term basis if one wishes to obtain meaningful information.

In view of the fact that conditions change during the lapse of time, the cost-benefit analysis must be re-examined from time to time in the light of these changes and should become a continuous process in the planning and evaluation of public health programmes.

5.3 Use of the model for the planning of preventive measures

The model can be used for the planning of preventive measures in various countries and areas only if the necessary parameters, as described above, are known and relevant information collected. Some of the parameters and information may be available from existing statistical returns and others may have to be collected in special surveys or studies designed for this purpose.

Once the data are available, they can be fed into the model and computer to predict the trend of typhoid for years to come, assuming that no special preventive measures will be taken. The model can also be used to simulate the possible effect of the application of various immunization and/or sanitation programmes. On the grounds of costs and benefits, one can compare the merits of relevant preventive measures and select those most suited to the goals envisaged and the resources available.

In order to illustrate these uses of the model with an example, we shall take actual data on the epidemiological situation in a small, typical Pacific island with an initial population of about 150 000. The annual birth rate was taken as 35 per 1000 inhabitants, and the annual death rate as 8 per 1000 population. The annual natural incidence of typhoid fever cases was taken at the level of 7.2 per 10 000 inhabitants. These data correspond closely to the actual situation in Western Samoa and resemble that in some other islands.

The effect of one type of vaccine in two different immunization campaigns with vaccination repeated at five-year intervals (A = 75% coverage, B = 50% coverage) on the population of this island is presented in Fig. 5. This shows how the incidence of typhoid would decline after immunization and indicates that higher coverage of the population with the same type of vaccine would give better results. The data thus obtained could be used for cost-benefit analysis. The cost of immunization could be compared with the benefit derived from savings on the cost of treatment or typhoid cases which have been prevented by immunization.

The effect of privy construction is anticipated to produce a 50% drop in incidence due to prevention of the spread of disease by means of the excreta of carriers. Even if the effect of privy construction were less, e.g. 30%, it would still be considerable, as shown in Fig. 6 which presents the effect of a sanitation programme comprising construction of privies for the whole population in a 10-year period. The effect is long lasting, and produces a continuous decline in the trend of typhoid due to the gradual elimination of carrier-transmitted infection.

Fig. 7 shows the effect of sanitation, namely privy construction, on the incidence of typhoid when construction is accomplished in a period of five years and covers the whole population (case A). This is compared with privy construction spaced over a 10-year period (case B). It is obvious that only a small additional long-term gain is achieved by early construction of all privies. This simulation (Fig. 7) shows, as does Fig. 6, that the endemicity level of typhoid in this community would, as a result of sanitation, begin to decline steadily and continuously. The same data can also be used for cost-benefit analysis.

Figs 8a and b compare the effect of privy construction alone with the cumulative effect of vaccination and privy construction combined, taking into account possible different levels of effectiveness of vaccination and sanitation. The effect of sanitation and vaccination is obviously greater, but a tendency to return to an earlier level of endemicity is obvious after immunization, whereas sanitation produces a definite and constant downward trend in the endemicity level. It is therefore clear that sanitation would give a more permanent effect than immunization, although vaccination alone, or combined with sanitation, might, in the short run, be more effective for the control of typhoid.

In the present study, the numerical application of the cost-benefit calculation will be limited to three examples of single or combined activities drawn from the above-described situations.

The cost factors have been determined from actual records available for the community and fixed as follows:

The estimated average cost of immunizing one person was taken as US\$ 0.20, while the treatment of a typhoid case including the cost of medical and paramedical personnel (but not lost wages) was estimated at US\$ 100.00.

The cost to the government of constructing a new, satisfactory privy or making sanitary an existing privy serving an average of six persons was estimated to be US\$ 8.40 or US\$ 4.20 respectively. This represents the cost of the services of a sanitary inspector to aid and supervise construction or reconstruction of the privy. The expenses of construction (material, etc.) are readily borne by the population. The total cost of construction of a new, sanitary privy was estimated to be US\$ 38.00. Thus the government's contribution represents about one quarter of the total cost of a new privy.

The costs and benefits are presented from the government's point of view, the government being fully responsible for the cost of immunization and treatment of cases, while contributing only partly to the cost of privies; the population would provide, free of charge, the necessary material and manpower for construction of the privies.

The actual computer runs are presented graphically (Figs 9a, b and c), and only final values for a 30-year period are given in table form (Table 4).

Example of costs and benefits of vaccination campaigns

The cost of vaccination and the saving on case treatment are cumulated over time in Fig. 9a for an immunization programme corresponding to the situation illustrated in Fig. 5 (line A).^a The cost of the first mass immunizations of 75% of the population would already be offset by savings on treatment in a five-year period. After the third vaccination, due to the decrease in case incidence, the difference between the cost of vaccination and the benefit on treatment is definitely positive and the balance is progressively augmented by the subsequent mass immunizations. One should not forget, however, that the incidence will slowly return to its initial level if vaccination activities are stopped.

^a That is, vaccination at five-year intervals with 80% effective vaccine of 75% of a community affected by a typhoid endemicity level of 7.2 per 10 000, the initial size of the population being about 150 000 and the natural annual growth 2.7%.

TABLE 4

SUMMARY OF THE COSTS AND BENEFITS EXPRESSED IN US\$ OF VARIOUS DIFFERENT TYPHOID CONTROL PROGRAMMES IN A 30-YEAR PERIOD

Activity	Cumulated cost			Cumulated cost of treatment of typhoid cases			Balance between cost and benefit
	Vaccination	Privy construction	Total cost	Without activity	With activity	Benefit on treatment cost	
1. Vaccination, single	21 924	-	21 924	477 913	367 332	110 581	+ 88 657
2. Vaccination, repeated*	188 305	-	188 305	477 913	161 137	316 776	+ 128 471
3. Privy construction	-	166 149	166 149	477 913	219 001	258 912	+ 92 763
4. Vaccination** and privy construction	145 632	166 149	311 781	477 913	93 525	384 388	+ 72 607

* Six successive mass campaigns at five-yearly intervals

** Five successive mass campaigns at five-yearly intervals

Example of costs and benefits of privy construction

This example shows the cost of a programme for sanitation through the construction or amelioration of privies. The parametric values and epidemiological effects of this programme were taken as described in Fig. 6 (line A). Furthermore, it was assumed that there was a necessity to rebuild one-half and make sanitary the second half of the privies required by the population, the cost of material and manpower being borne by the population and the services of a sanitary inspector being provided by the government. The programme would be covered in 10 years and would then continue at a reduced rate only to satisfy the needs of the annual population increase.

Fig. 9b shows that the savings due to the reduction in the number of typhoid cases grow slowly during the early years of the programme, and that the balance between the cost of privy construction and the benefit on case treatment starts to be positive only after 20 years. It should be observed that such a programme would ultimately lead to the eradication of the disease and thus provide an important and definite benefit (see Fig. 6). One should also take into account the beneficial effect of privies on other intestinal infections and the saving in lives and wages.

Example of costs and benefits of immunization and sanitation combined

The last example illustrates the impact of the combined strategy described in Fig. 8a (situation B). The cumulated cost of the five successive mass immunizations and the construction and improvement of privies (government contributions only) is presented in Fig. 9c, which also shows the corresponding benefits on case treatment expected from this programme of activities. With the numerical values given to the parameters in this example, it is only after 25 years that the balance between cost and benefit begins to be positive, but in the meantime the disease would have been reduced to a considerably lower level than by any of the other control programmes.

The costs of vaccination and/or sanitation and the benefits obtained from savings on the treatment of prevented cases corresponding to the above three examples have been consolidated for a 30-year period in Table 4. In addition, the first line of the table shows the cost and benefit estimates corresponding to a single mass vaccination campaign with the same parametric values as in Example 1. The last two columns of this table show that the most favourable balance does not necessarily correspond to the greatest benefit as expressed in terms of saving on case treatment. In fact, as expected, the most substantial benefit results from combined immunization and sanitation, although the balance appears less satisfactory because the cost of this policy includes an expensive initial investment in privy construction.

One must insist on the fact that these examples considerably over-simplify the economic and financial treatment of the actual health problem and the strategy of control envisaged; for example, no allowance was made for interest on investments, changes in absolute and relative costs of immunization, privy construction and treatment which would occur in the lapse of time, and numerous other factors.

Our examples are limited by necessity to a single community in a developing country.

Numerous other possibilities arise in different communities and conditions which could be analysed in the same way. If, for example, the construction of privies proves unprofitable from a cost point of view for the government, when the government is responsible for the total cost of construction, it may prove profitable if the population contributes 1/2 or 3/4 of the cost. In cases such as this when the proposed programmes, because of relatively high costs and low benefits, prove unacceptable to the health authorities, simulation will indicate the need to explore alternative approaches. In addition, there are a number of economic and other factors not applied in these examples which could be taken into account.

6. OTHER USES OF THE MODEL

So far, the examples have shown how the model can be used to simulate the effects of preventive measures and to analyse their costs and benefits, and how it can assist in the planning and evaluation of typhoid control programmes.

The model has various other uses such as the prediction of future trends of typhoid, and, accordingly, the requirements in material and manpower for specific typhoid control projects.

We used the model by applying recent typhoid morbidity data from certain countries and simulating present typhoid trends. Comparing data obtained through the model with actual incidence in the countries studied, we observed a regularity and parallelism in the declining trend of typhoid. However, in Great Britain, the natural decline was recently much slower than the model had predicted. On checking this discrepancy it was found that the majority of current cases of typhoid in Great Britain are imported or occurring among immigrants. The trend towards eradication of typhoid shown by the model was therefore not borne out by fact. However, eradication would still be possible if cases and carriers were no longer imported into the country.

This theoretical exercise demonstrates how the model could be used to explore the possibilities of eradicating typhoid in a country and to determine the factors to be taken into account should eradication be the aim of the health authorities.

7. DISCUSSION

The typhoid fever model which has been developed represents a simplified natural epidemiological process. However, it could be used in its present form for drawing up long-term public health programmes, in particular with respect to the use of both vaccines and sanitation in the control of typhoid. Whenever this model is applied to an actual population, it is necessary to keep in mind some factors which have been mentioned in the Introduction and in the chapter on epidemiological factors, but which have not been included in the model. These factors differ from population to population. They should first be evaluated and then, if necessary, introduced according to their relative merits and importance.

The number of carriers in a population, which is very helpful for determining the dynamics of typhoid, will differ by age-groups according to the past incidence of typhoid in these population groups. When most carriers are aged, one should expect, if other factors do not change, that they will be eliminated by death, and that a somewhat more favourable level of endemicity will be established. However, it should be mentioned that many old-age carriers represent a particular risk for the population since their standard of personal hygiene tends to deteriorate and thus they become a dangerous source of infection.

The increase of population under favourable environmental conditions should also lead to an amelioration, particularly if new generations are immunized. Where unfavourable conditions exist, the increase of population may lead to a deterioration due to overcrowding and general lowering of standards of living, sanitation and personal hygiene. The growth of population should therefore be considered in the light of other pertinent epidemiological factors.

There are numerous other factors which may also play a role, for example, natural calamities, superimposed infections such as schistosomiasis, change of food and hygienic habits, etc., which can hardly be enumerated but which could have an important impact on the trend of incidence of typhoid in the community. It is the task of the epidemiologists and public health workers to evaluate them critically and to use the mathematical model creatively in practice.

A few other factors have also to be kept in mind, such as timing of the immunization campaign and selective protection of groups at high risk. The effect of mass immunization, as shown by the model, is of only a temporary nature. However, if repeated at proper intervals and on sufficiently large portions of the population, immunization will lead to a definite decline in the endemic level of the disease. There are a few important facts that should not be overlooked. While more potent vaccine and a greater number of immunized persons signify a lower incidence of disease, they also mean an increased number of susceptibles and a decreased number of resistant persons in the population. In practice, this means that once an immunization campaign has started it should continue in order to retain the gains, since the carriers not eliminated by immunization represent a constant danger of further spread of infection. The effect of mass immunization campaigns should not be overestimated as is often the case. Immunization campaigns have only temporary effects and, in addition, have other limitations as mentioned above.

The effect of sanitation is more spectacular and permanent. However, it is difficult to determine with certainty the degree of effectiveness in practice of any one of numerous sanitary measures or of their combinations, supported or not by health education and a rise in the standard of living.

A combined immunization and sanitation programme, while not much more effective than sanitation alone, is indicated in particular in cases of disaster when disruption of usual sanitary installations and measures often occurs and maximum protection is required.

We have limited ourselves, in this instance, primarily to evaluation of the effect of immunization and/or sanitation programmes on the natural course of typhoid in an endemic community, but other preventive measures could also be evaluated by use of the same model.

There are other uses to which this model could be put, such as evaluation of relative costs and benefits of immunization and/or other measures such as sanitation, treatment and isolation of cases, treatment of carriers, etc., in various economic and epidemiological circumstances and at different levels of endemicity.

The model could also be used for evaluation of the effect of application of vaccines with increased potency, or the effect of immunization of increased numbers of people in the campaigns. The relative costs and benefits of such measures could also be evaluated. Finally, the model could be used for operational research in the evaluation of various public health programmes, their benefits and costs, thus enabling programmes to be set up which will give the best results with the financial means available.

No attempt was made at this stage to determine optimal use of funds for typhoid control in a wider public health programme since it is difficult to evaluate all the economic and other consequences of an effective typhoid control or eradication programme. This would involve a complex study of balanced economic and health development and detailed cost-benefit analysis of numerous interrelated activities in the field of health and other spheres.

8. CONCLUSIONS

Using available basic epidemiological data on the natural history of typhoid, a mathematical model has been constructed for stable populations in endemic areas at different levels of endemicity. It has proved useful for evaluation of the relative effectiveness, costs and benefits of antityphoid immunization and sanitation programmes.

This model makes it possible to predict the trends of incidence of the disease when vaccines of various potencies are used and different proportions of the population immunized. Thus the model renders feasible the long-term planning of public health activities. It indicates that initial gains following a single immunization campaign are lost after a few years unless immunization is repeated. Repeated immunization campaigns produce a further

decrease in incidence but there is a smaller gain with each subsequent vaccination. Conversely, sanitation gives more pronounced and long-lasting effects; when combined with immunization, the results are even more favourable, producing a continuous decline in the trend of the disease.

When dealing with specific population groups and in specific circumstances, some adjustments will need to be introduced in the model in view of the many factors which play a role in the epidemiological patterns of typhoid.

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Figure 1
FLOW CHART FOR EPIDEMIOLOGICAL MODEL OF NATURAL COURSE OF TYPHOID FEVER

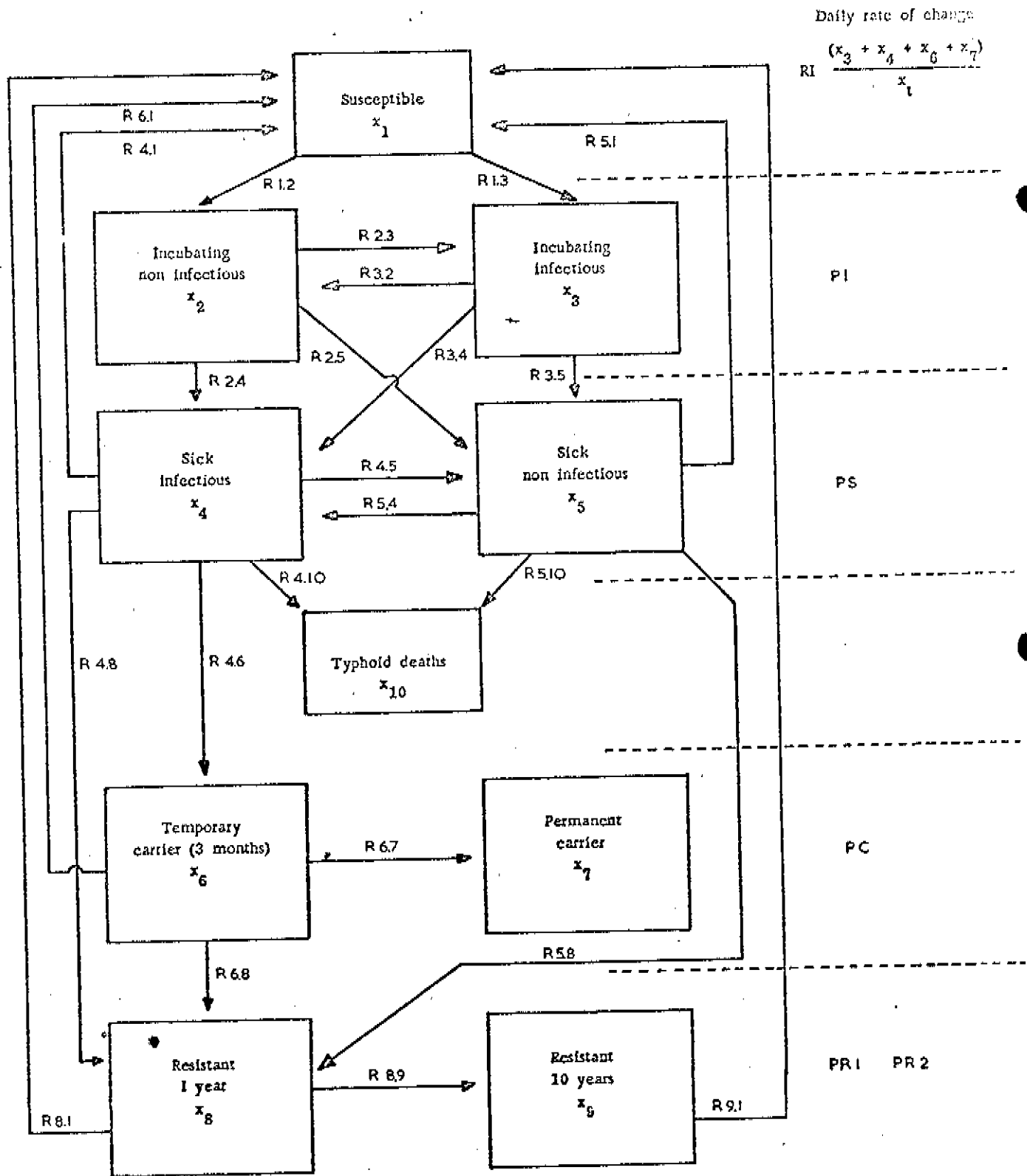


Figure 2 EFFECT OF A SINGLE MASS VACCINATION ON THE DYNAMICS OF TYPHOID FEVER
AT DIFFERENT LEVELS OF ENDEMICITY AND EFFICACY OF VACCINATION

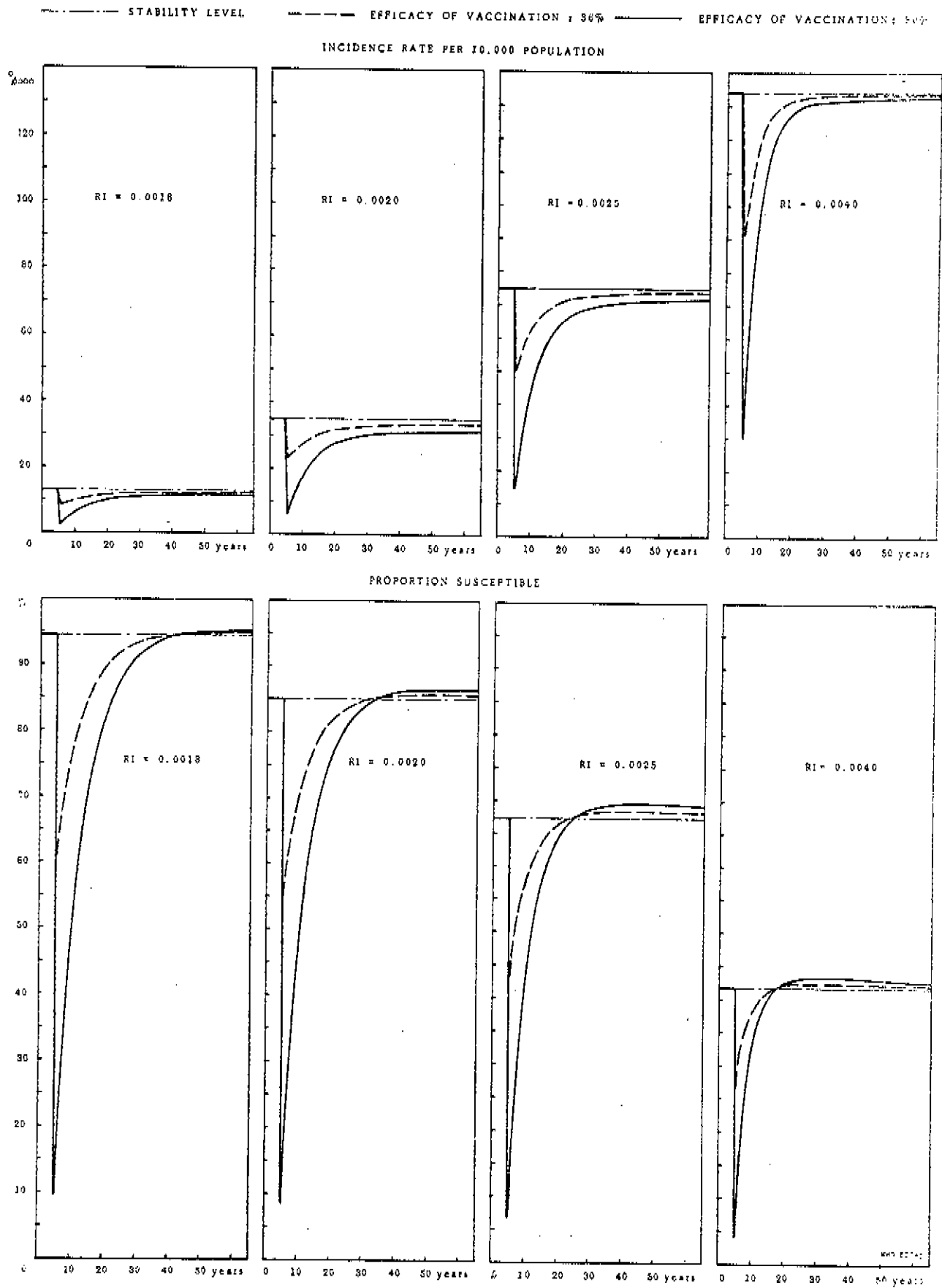


Figure 2 (continued)

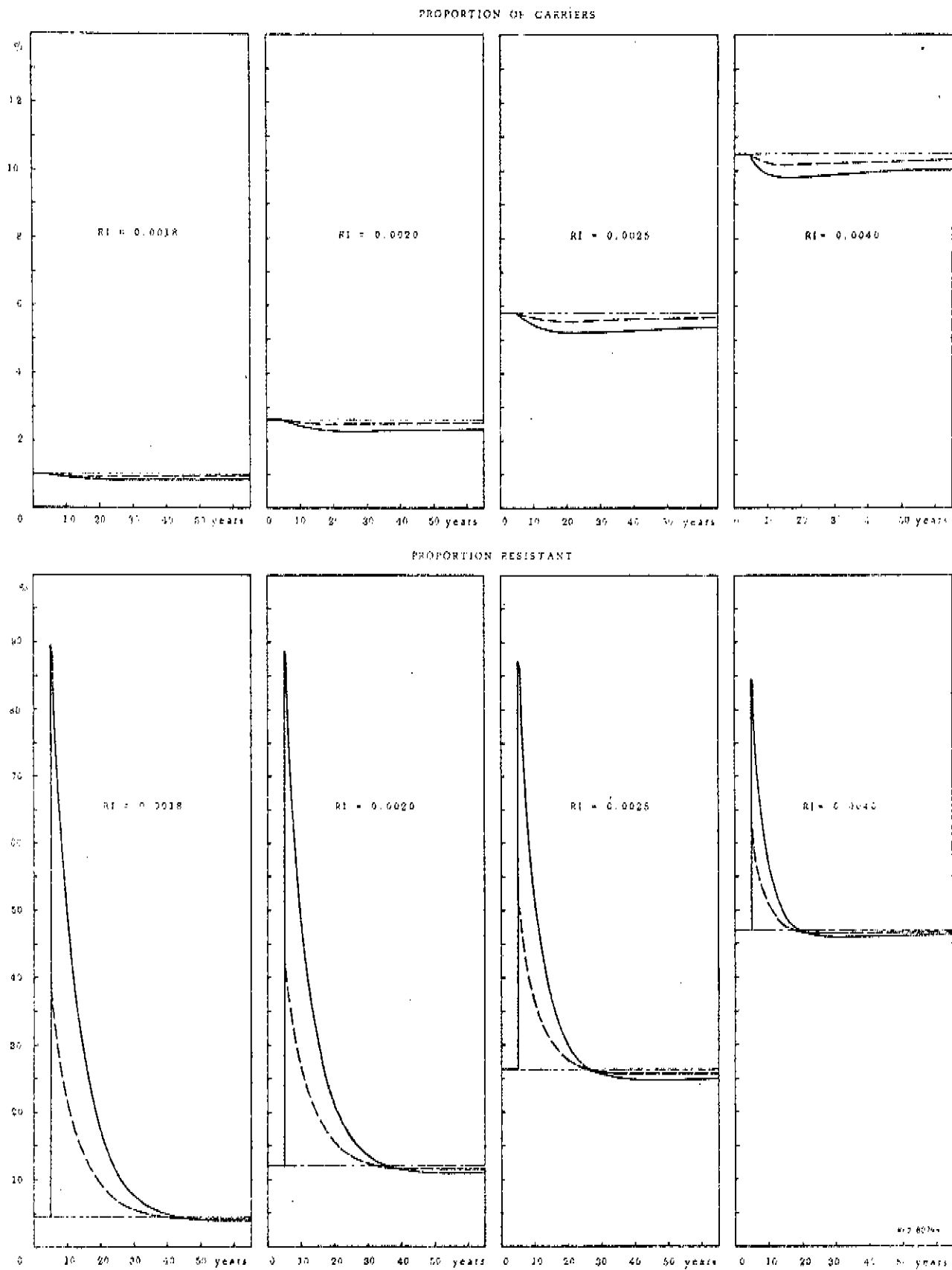


Figure 3 COMPARISON OF THE EFFECTS OF SINGLE AND PERIODIC MASS VACCINATION ON DYNAMICS OF TYPHOID FEVER (Efficacy of vaccination : 60%)

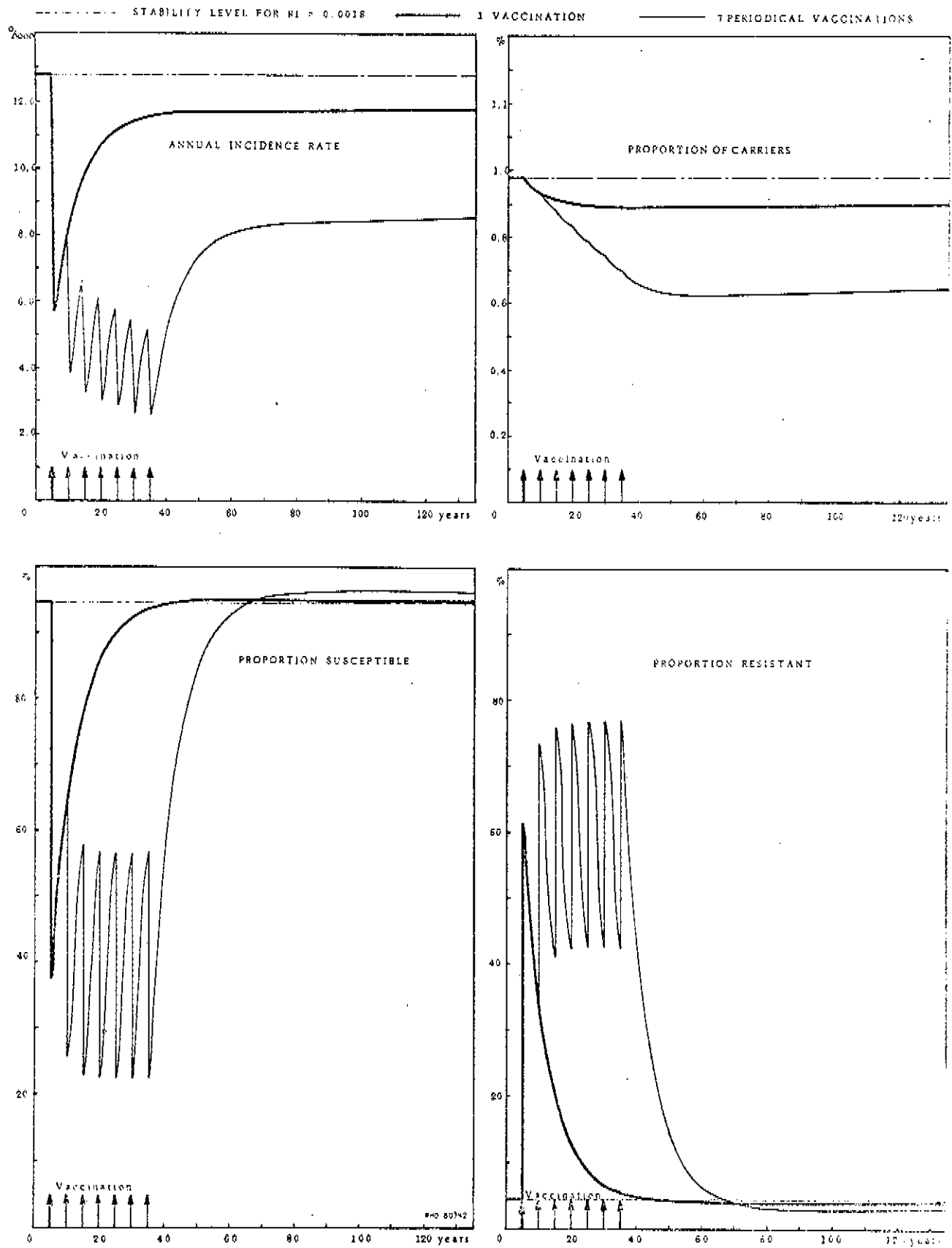


Figure 4 EFFECT OF A CHANGE IN THE FORCE OF INFECTION ON DYNAMICS OF TYPHOID FEVER, WITH OR WITHOUT MASS VACCINATION

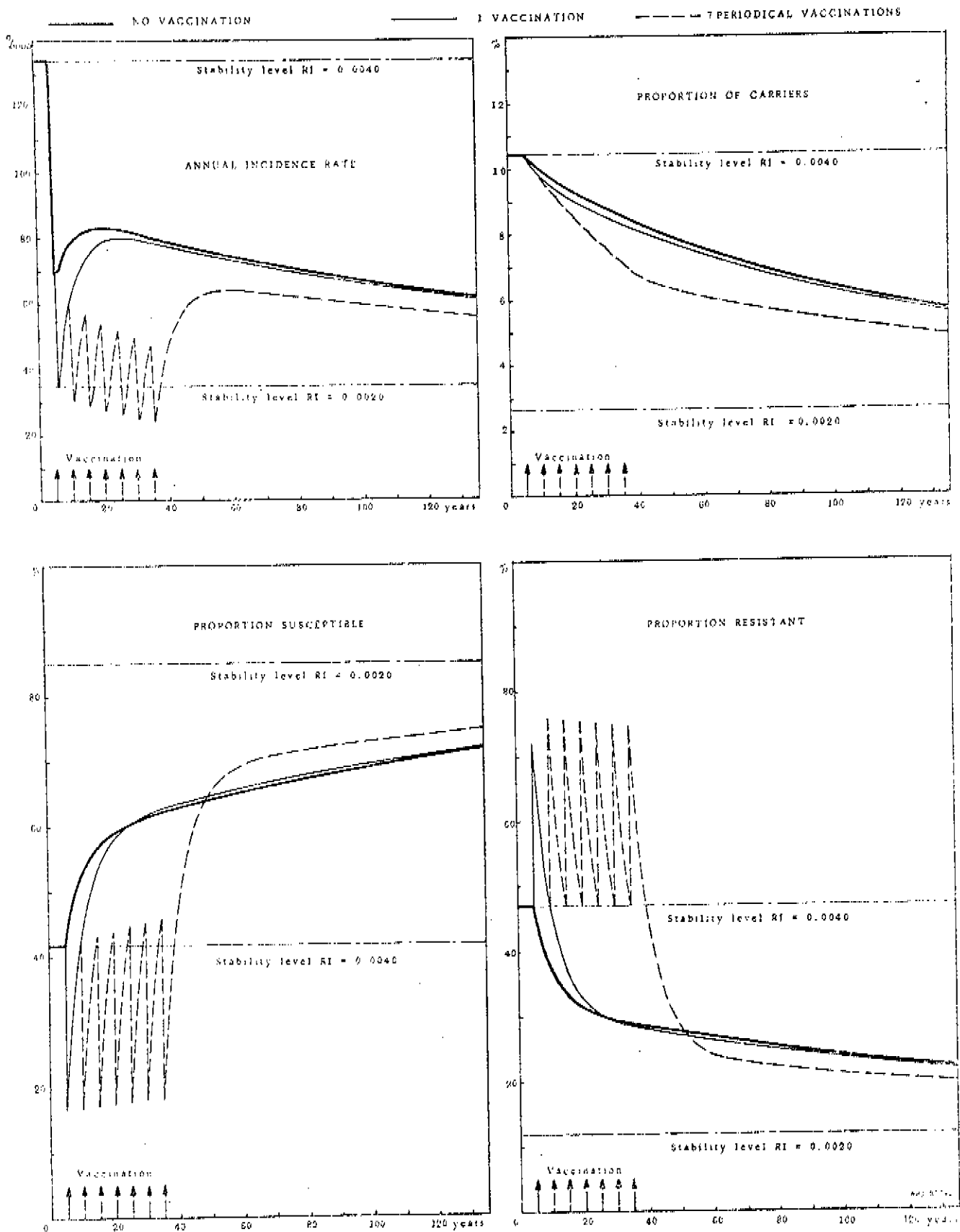


FIG. 5 ANNUAL INCIDENCE RATE OF TYPHOID CASES (PER 10 000 POPULATION)
EIGHT SUCCESSIVE MASS VACCINATIONS AT 5-YEAR INTERVALS

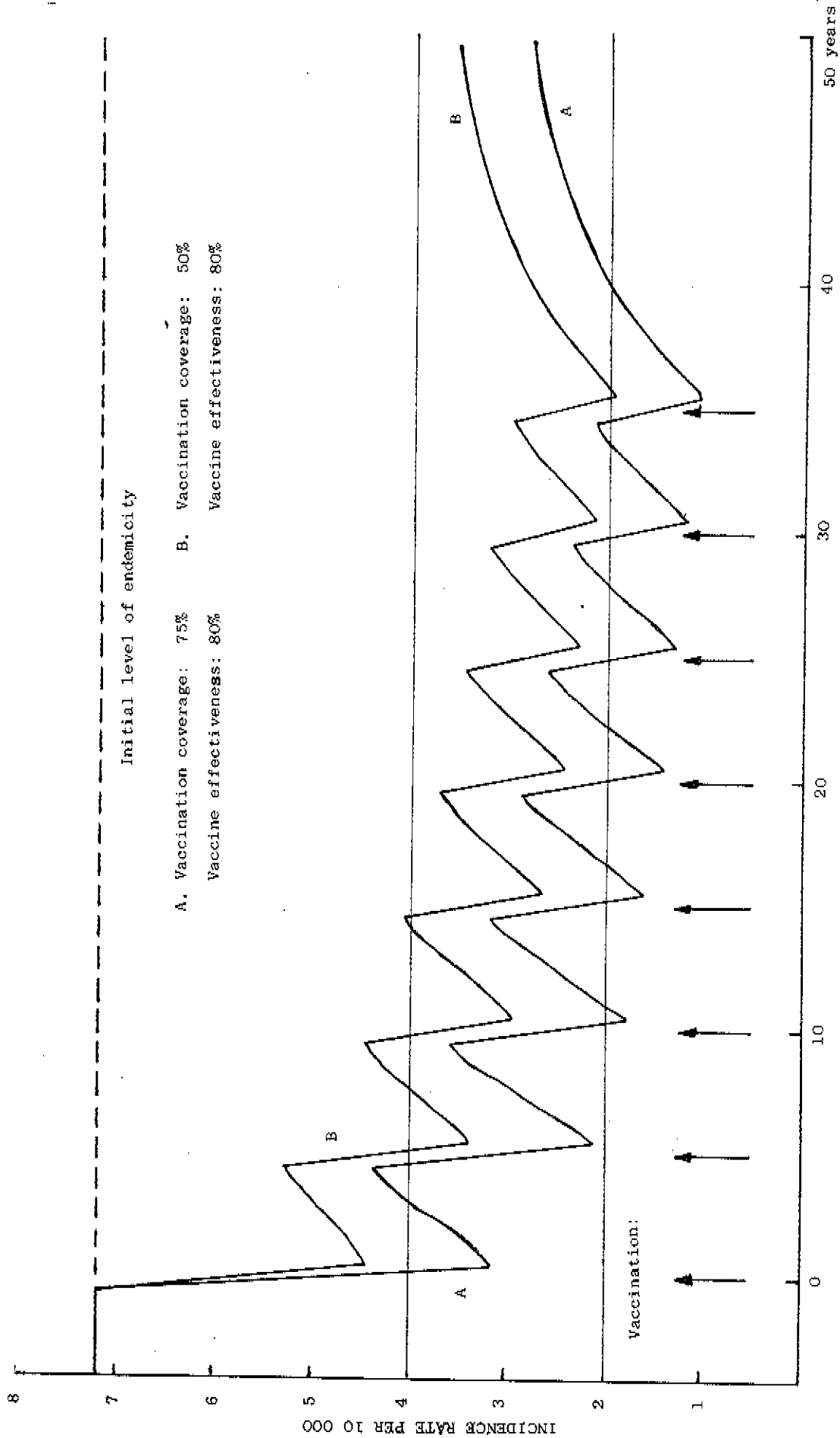


FIG. 6 ANNUAL INCIDENCE RATE OF TYPHOID CASES
(per 10 000 population)

Incidence rate
per 10 000

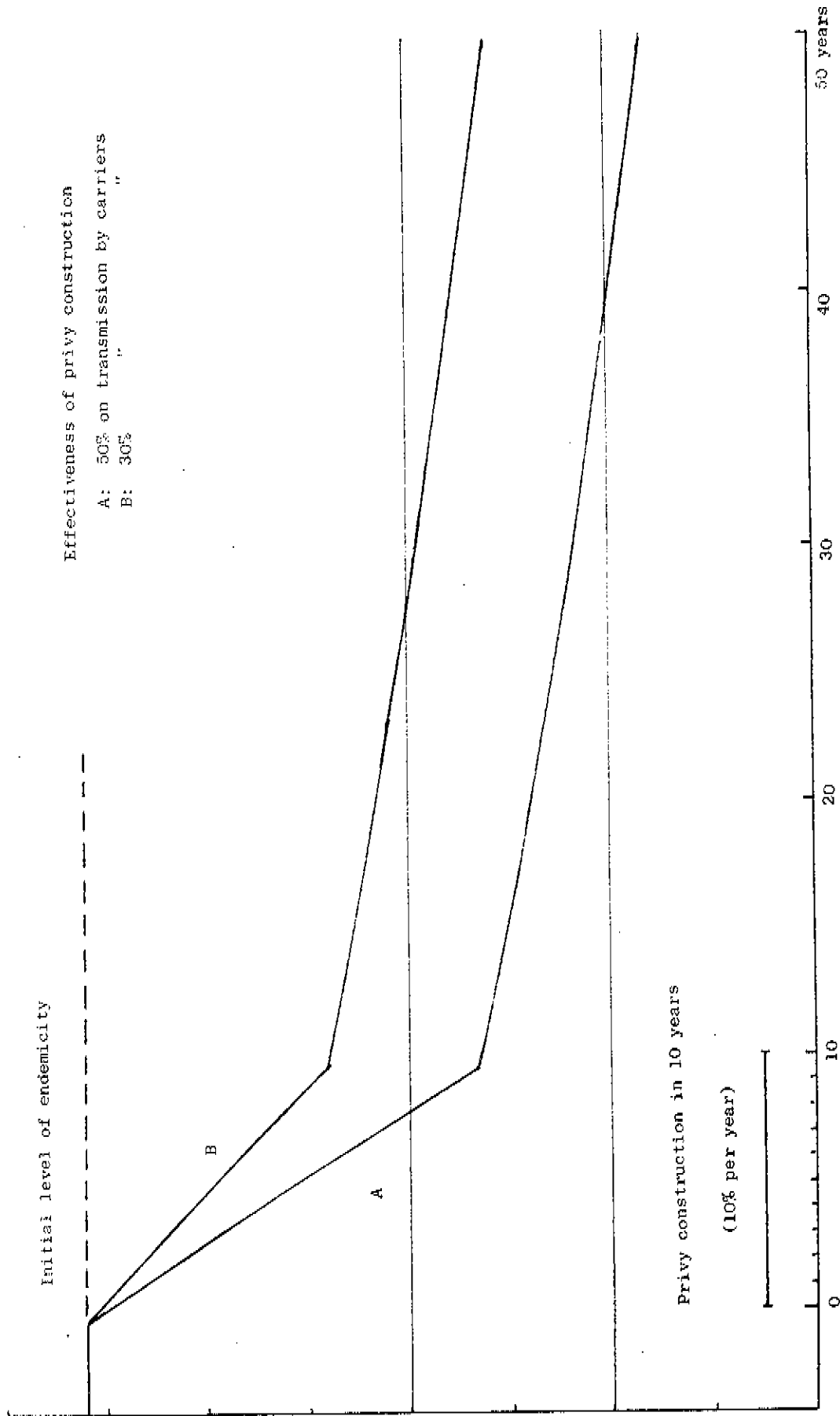


FIG. 7 ANNUAL INCIDENCE RATE OF TYPHOID CASES (PER 10 000 POPULATION)

EFFECTIVENESS OF PRIVY CONSTRUCTION: 50% ON CARRIERS

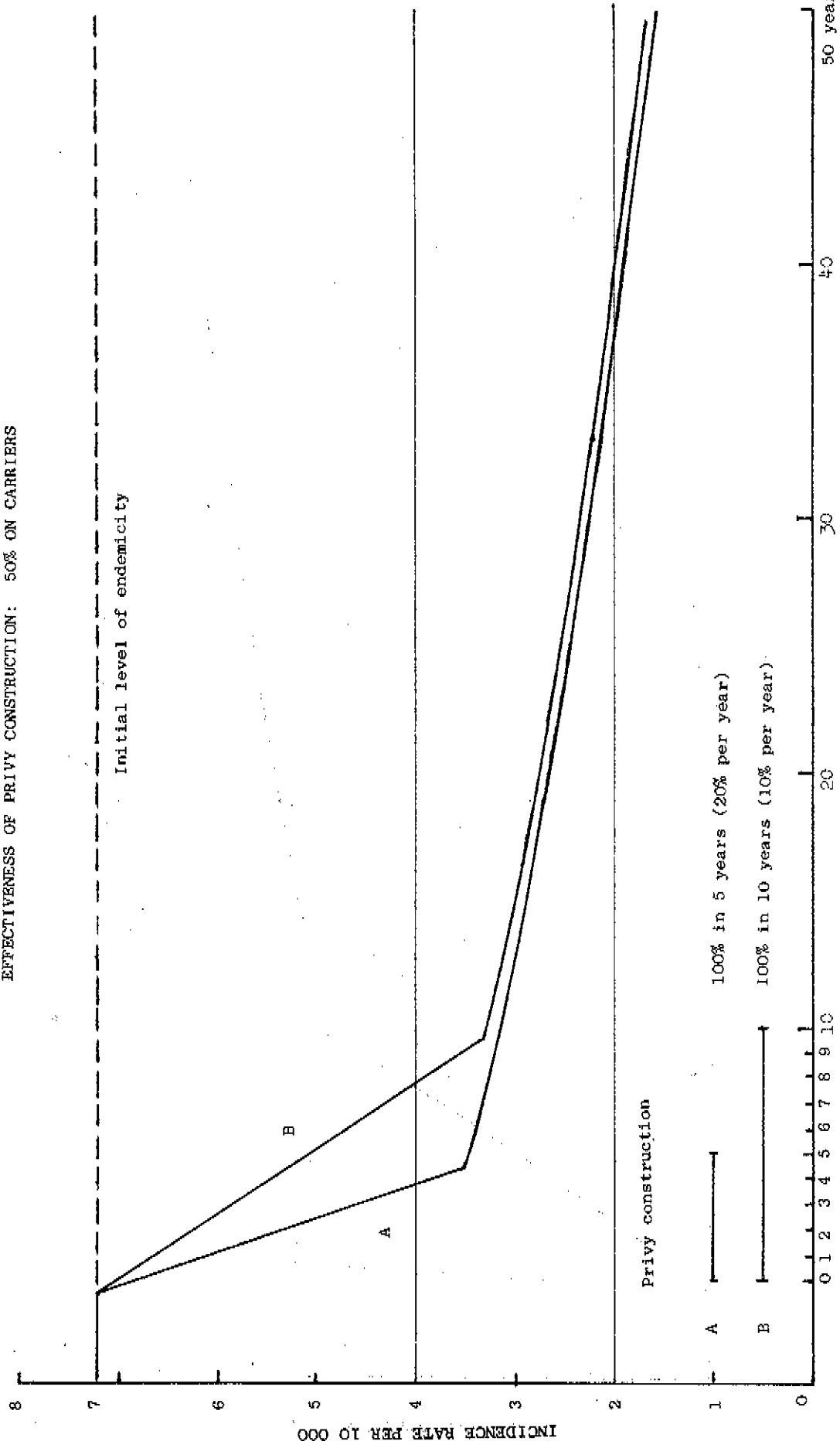
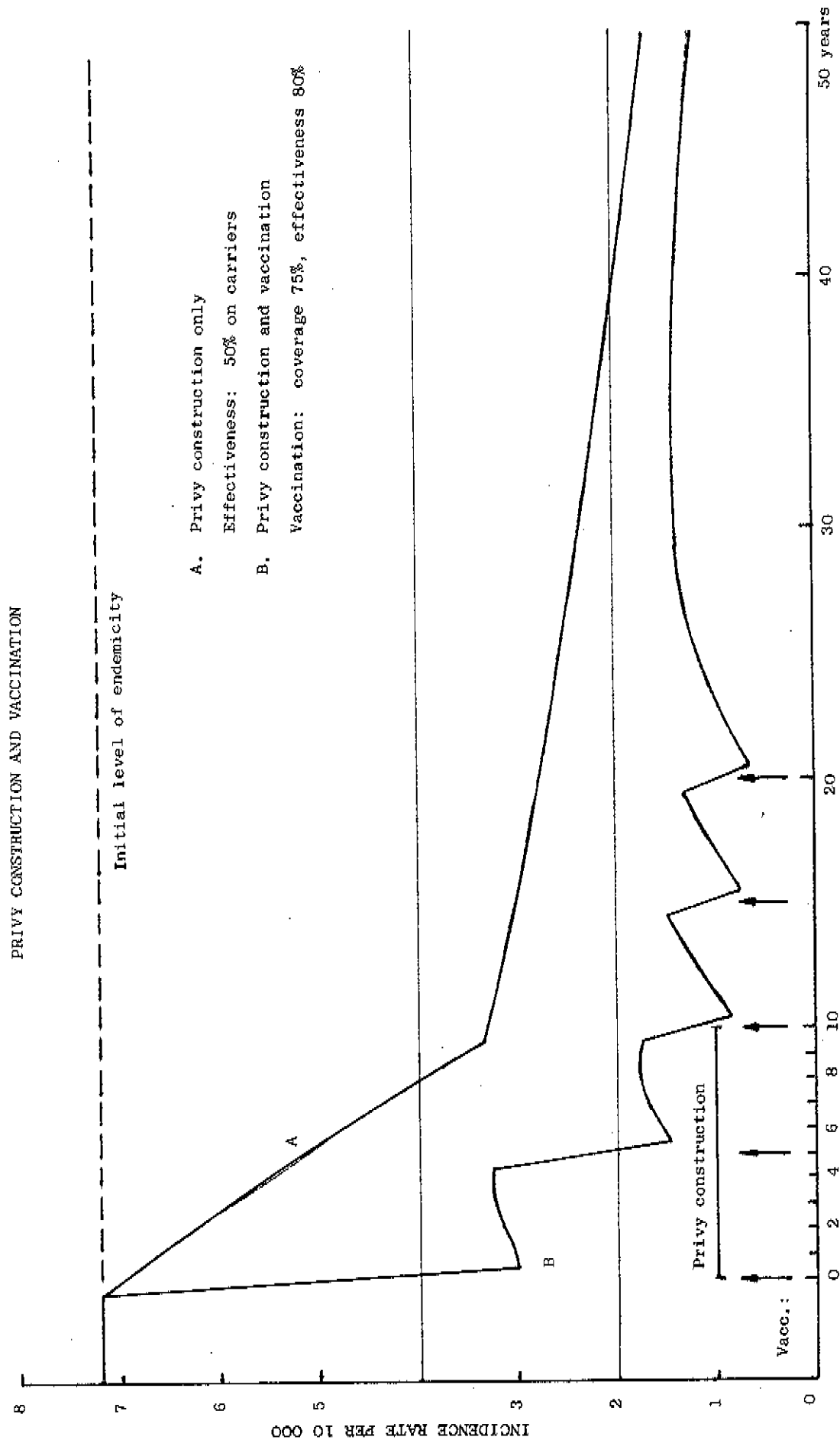


FIG. 8a ANNUAL INCIDENCE RATE OF TYPHOID CASES (PER 10 000 POPULATION)



Incidence rate
per 10 000

FIG. 8b ANNUAL INCIDENCE RATE OF TYPHOID CASES (PER 10 000 POPULATION)

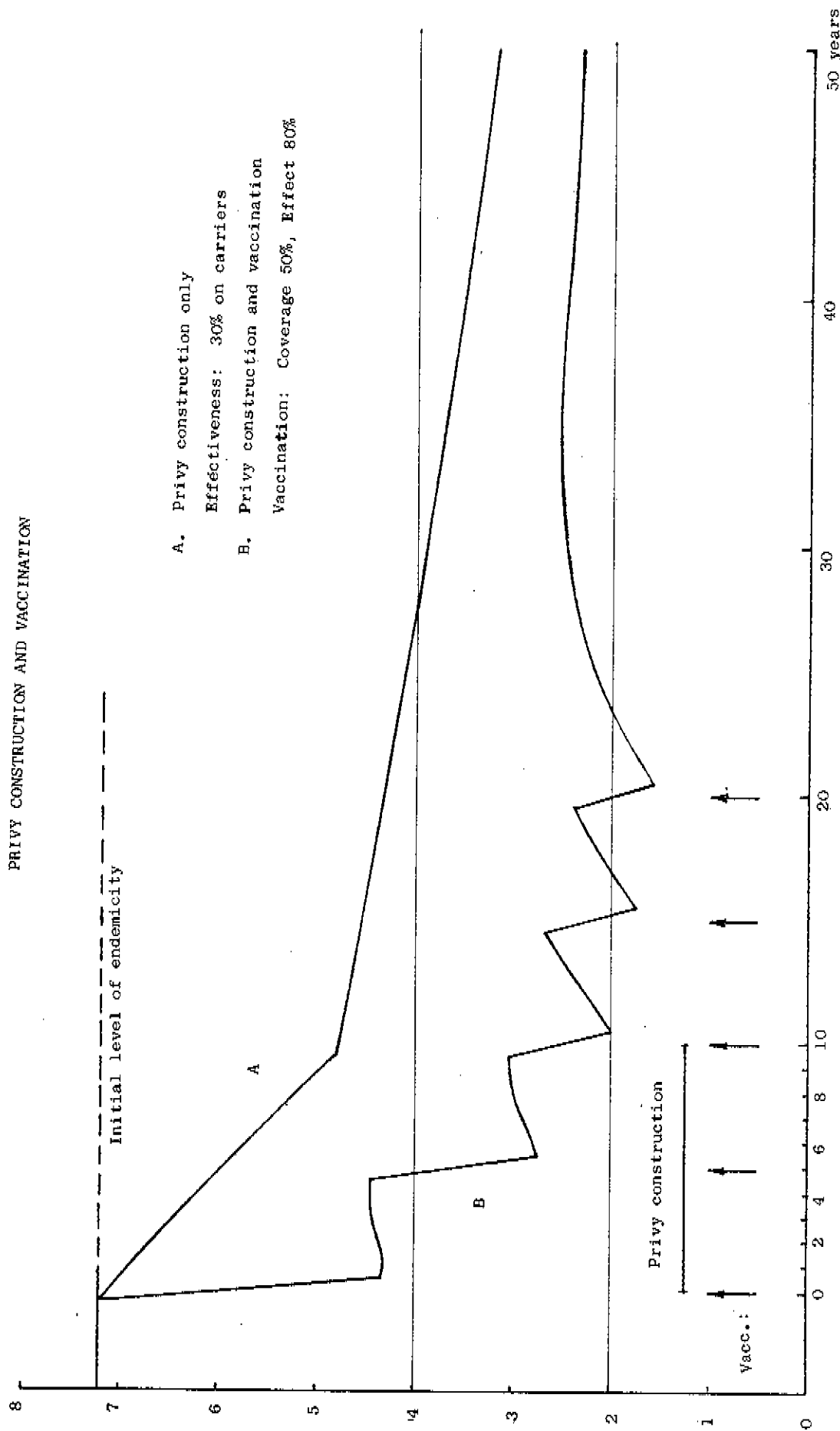


FIGURE 9. VARIOUS TYPHOID CONTROL PROGRAMMES

Their impact on incidence of the disease and cumulative costs and benefits

Incidence of typhoid cases
(per 10 000 population) ———
Cumulative costs ———
Cumulative benefits ———

