For a long time the epidemiological situation for tuberculosis in developed countries improved and there was a steady decline of the annual incidence of infectious cases. This decline continued until recently, helped by the use of antibiotics after World War II.1 At present, a reversal of the trend can be observed and the incidence of the disease has started to increase in some developed countries. This raises new issues for the public health authorities.2–3

As a first step towards addressing those issues, we have built a deterministic model of tuberculosis transmission, inspired by Waaler et al.4 but aiming at giving a more detailed description of the disease. Recent work by Blower et al.5 follows similar lines. The basic steps of the realization of the model are the definition of homogeneous groups based on the natural history of the disease, and the definition of rates of transfer between these groups, according to values quoted in the literature and stated efficiencies of public health policies. In our model, we will take only pulmonary disease into account, because other tuberculosis localizations are not contagious. Age has not been taken into account.

The annual risk of infection (ARI), defined as the probability for a susceptible to become infected in one year, will be used to characterize the tuberculosis situation in a country. Our primary aim is to show how the observed trend of the ARI can be broadly reproduced and the key parameters in the model which influence this trend.

The evolution of the ARI produced by our model is qualitatively compared to recorded evolutions in developed countries. We base this comparison on data describing the Netherlands epidemiological situation, since incidence data are available for this country. Subsequently the model is used to reproduce the French situation.

Finally, we try to assess the consequences of modifications, such as improvements or deterioration in detection rates and treatment efficiencies, or the ending of vaccination programmes.

Background. Tuberculosis has been declining in developed countries for a long time, as a result of the intrinsic epidemiological characteristics of this disease, combined with improvement in the standard of living and more recently the use of antibiotics. In these low prevalence countries, decisions concerning the objectives of tuberculosis programmes have to be taken and the consequences of short term changes in the sanitary situation have to be assessed.

Method. A deterministic model, without age structure, of the dynamics of pulmonary tuberculosis is proposed. The model extends that of Waaler and is intended to be more suitable for application to developed countries. The flows between seven subgroups of population, based on the natural history of the disease, are modelled and vaccination is taken into account. Values of model parameters and initial prevalences were deduced from published data.

Results. As a first step, qualitative comparisons are performed between the model-predicted decline in the annual risk of infection (ARI) and data from the Netherlands tuberculosis survey. Using parameter values suited to France, our model shows that the predicted decline is slower in France than in the Netherlands; a result which tallies with epidemiological observations. Uses of the model as a decision tool are illustrated in two cases, that of ending systematic BCG vaccination and that of a sudden increase in the number of infectious cases.

Keywords: tuberculosis, annual risk of infection, deterministic model, vaccination

* UR41, Institut Français de Recherche Scientifique pour le Développement en Coopération (ORSTOM), Paris, France and Unité 436, Institut National de la Santé et de la Recherche Médicale, (INSERM), Paris, France.
** Unité 169, Institut National de la Santé et de la Recherche Médicale, (INSERM), 16 Avenue Paul Vaillant-Couturier, 94807 Villejuif, France.
† Unité 170, Institut National de la Santé et de la Recherche Médicale, (INSERM), Villejuif, France.
Reprint requests to: Prof. J Maccario.
METHODS
The Model
The model may be described as a compartmental model with linear and non-linear transitions. The compartments (homogeneous subgroups of people classified with respect to their disease status) and their interconnections are given in Figure 1. The governing system of differential equations is presented in Appendix 1.

The rates of transfer between the groups of the model are supposed to be constant over time. We made the assumption that each subject in a group has the same status regarding the disease and thus has the same probability of transferring to another group. This is a usual hypothesis in compartmental models. Moreover the groups are supposedly large enough so that we need only consider the average number of transfers, leading to a deterministic model.

The Population Subgroups
Seven subgroups of people, based upon the natural history of the disease, are defined (Figure 1): the ‘susceptible’, S; the ‘protected’ by BCG vaccination (P); the ‘infected’ (I); the ‘open cases’ (O) (i.e. smear positive cases); the ‘non-open cases’ (NO) (i.e. smear negative cases); the ‘healed’ (H) and the ‘chronics’ (C).

Non-infected people are free from tuberculosis bacillus (TB). In countries where BCG vaccination is systematic, the non-infected are separated in two groups: the protected, whose vaccination is successful and hence are not susceptible to contamination by TB, and the others, who escaped the vaccination programme or were unsuccessfully vaccinated, referred to as the susceptible. We shall not assume that protection conferred by vaccination is permanent, and thus include a flow P to S. A non-infected person (S) becomes infected (1) by contact (if intense enough6) with an open case (O), giving a flow S to I. Once infected, the person stays infected for the rest of his life. A large proportion of the infected escape any disease development but a fraction of them, assumed to be 10%, convert and become cases7 (flows I to O and I to NO). It is necessary to distinguish two groups of cases according to their infectiousness. Cases where the TB is revealed at direct examination of the sputum are called smear-positive or open cases (O). They are the only infectious cases. The other cases, smear-negative or non-open (NO), are unable to transmit TB. When a case is detected, he or she is treated. If cases are open cases, the treatment will rapidly sterilize their sputum and suppress their infectiousness and they become non-open (flow O to NO). In Western Europe, it can be safely assumed that the case is healed and will never relapse or be re-infected if treatment is correctly applied and followed.

FIGURE 1 Diagram of the model representing the seven subgroups and their inter-relationships

b: birth rate.
S: susceptible to infection (not vaccinated or unsuccessfully vaccinated).
P: protected by BCG.
I: infected by TB.
O: open case.
NO: non-open case.
C: chronic (uncompletely healed, submitted to relapse or endogeneous reactivation).
H: completely healed.
d1: death rate.
d2: tuberculosis induced mortality.
k1, ..., k6: transition rate from one subgroup to another. The values used for these rates are presented in Table 1.
This group corresponds to the ‘healed’ H and to the flow NO to H. On the other hand, a case inadequately treated is incompletely healed and becomes a chronic (C) (flow NO to C). By defining such groups and flows, our aim was first to allow for endogenous reactivation from distant infection and the higher mortality rate of chronic cases (10% higher than the overall mortality rate); and secondly to study the efficiency of chemotherapy (flow O to NO) and the compliance to treatment (flows NO to H or NO to C) in contrast to the model considered by Blower et al.5

Demographic Parameters
Demographic parameters were chosen in line with the French situation. An annual death rate of 8 per 1000 was adopted, and in order to control the increase in the total population during the simulations, we translated the annual birth rate of 11 per 1000 to a constant inflow of births. Obviously the results concerning the decline in the rate of ARI are not affected by these choices.

Epidemiological Flow Parameters
We shall first present the flow parameters linked to the linear part of the model. In general these parameters are strongly dependent on population characteristics (genetic make-up, health status ...), as well as environmental ones (mycobacterial environment, access to health services ...) with highly variable reported values from one survey to another.8–10 Therefore, for some parameters we have used average values. For others, mainly those related to the efficiency of public health policy, we performed several simulations with sets of values given in Table 1. Moreover the values usually reported in the literature had to be translated into first order flow rates for the governing differential system. If during a period of time \( t \), a proportion \( \pi \) of people experiences a transition, the rate \( k \) is given by

\[
k = - \frac{1}{t} \ln(1 - \pi)
\]

The selected values of \( t \), \( \pi \) and the corresponding \( k \) are presented in Table 1.

Flow \( P \) to \( S \). It is admitted that protection conferred by the BCG11 wanes in 15 years. We translated this into a loss of immunity of 50% of the still protected every 3 years, so that after 15 years around 93% of the vaccinated will have lost their immunity.

Flow \( I \) to \( O \) and \( NO \). The transfer from infected to cases depends on the intensity of infection, on age, and health status of the infected.6,12 Time is also an important parameter, and the risk of developing the disease is greater during the first years following infection.13–16 Sutherland7 found 8.1% of those infected developing clinical tuberculosis within 15 years, whereas Comstock14 estimated this breakdown at 5% in the year following infection. A Tuberculosis Surveillance Research Unit (TSRU) study of European data found 6% of converters in 5 years.16 In order to take this variability into account we have used different values for this parameter in the simulations (Table 1). Whatever the value used, the ratio between smear-positive and smear-negative is around 0.5.

Flow \( O \) to \( NO \). If an open case is detected and treated early, he will become uninfectious in a few weeks.6,17–18

The parameter governing this transition represents the ability of the health system to detect and treat a tuberculosis case in the community. The values used for this parameter in our simulations are shown in Table 1.

Flow \( NO \) to \( H \). If a smear-negative case complies with the prescribed treatment, his cure probability is greater than 90%. We have used for this parameter three possible values (90%, 95% and 97% per year) as shown in Table 1 (cure rate).

Flow \( NO \) to \( C \). The cases who are not completely healed enter the ‘chronic’ population subgroup with
complementary probabilities (10%, 5% and 3% per year) from which $k_4$ is deduced.

Flows C to O and NO. Chronics are liable to relapse, which accounts for endogenous reactivation from distant infection. A great variability of the relapse rate has been found, and we have used two plausible values as shown in Table 1.

Flow S to I. The probability for a susceptible to become infected is related to the number of open cases. It depends on several factors like intensity, length and frequency of contact with TB but probably also on individual characteristics of the susceptible like age, nutritional and immunological status.

In developed countries, where the proportion of susceptibles is very high compared to the proportion of open cases, it is not reasonable to suppose that all those uninfected have the same probability of meeting all the open cases. Other factors come into play, like the hygiene level in the community and the time interval during which an open case remains uncured. Furthermore, the degree of crowding between the group of open cases and the group of susceptibles is probably low as open cases are mostly adults or older subjects with easy access to health services.

Instead of using in all cases a simple mass action law term $O \times S$ to model the non-linear flow S to I, we have introduced a constraint to control and limit the contagion of the disease. We defined a threshold of 1000 people, representing the maximum number of susceptible (uninfected) with whom an open case can interact in one year. In particular, when the number of susceptibles is less than the threshold, the influx of the newly infected is directly proportional to the product of the sizes of the susceptible and the open cases subgroups; whereas when the number of uninfected people is greater than this threshold, the influx becomes solely related to the number of open cases. This behaviour is represented by $\phi[S]$ in the model equations given in Appendix 1.

Although it is admitted that in some developed countries one infectious case may cause around three new infections in one year,21 we assumed that this number presents an important variability. This variability is partly due to uncertainty in some parameters such as the degree of crowding between communities, and it is also strongly linked to the efficiency of health services. In some countries with an efficient TB programme and a very high proportion of susceptibles compared to the proportion of infectious cases, we assumed that the number of new infections caused in the general population by one open case in one year may be on average lower than one (Appendix 2). However, in order to take into account this variability, we have used in our model different values for this parameter. Other ways of modelling this variability have been proposed.5 To reproduce the Netherlands’ situation2 we assumed that one open case may infect at most 0.25 susceptibles. In the French situation we have increased this fraction to 0.5. We thus model $\phi[S]$ as follows:

- When the number of susceptibles ($S$) is less than the threshold (1000)
  - $\phi[S] = 0.25 \times S/1000$ (Netherlands’ situation)
  - $\phi[S] = 0.5 \times S/1000$ (French situation).

- When this number ($S$) is greater than the threshold (1000)
  - $\phi[S] = 0.25$ (Netherlands’ situation)
  - $\phi[S] = 0.5$ (French situation).

The appearance of ‘high risk communities’ for TB, e.g. those infected with HIV, refugees or homeless people, could modify the value of this parameter. However, mixing between such communities and the general population of susceptible individuals is certainly low, and parameters accounting for these specific levels of transmission are currently unknown. In order to assess the influence of such ‘high risk communities’ we performed simulations with higher values of $\phi[S]$.

The Annual Risk of Infection

The ARI indicates the proportion of the population that will be infected or re-infected with TB during one year. The ARI links the uninfected and the smear-positive cases, hence it depends on the number of open cases present at any time.

Data reported by Sutherland et al.3 suggest that the ARI and the prevalence of open cases have empirically a nearly constant ratio and hence their logarithms would follow approximately the relationship:

$$\ln \text{ARI} = a + \ln(O)$$

The linear decline of In ARI with calendar time thus implies a linear relation with the same slope, i.e. rate of decline, for log prevalence. As the computations of Sutherland et al.3 concerned new cases and not re-infections or relapses, we studied the decrease in the prevalence of open cases given by the model by way of qualitative comparison.

Initial Prevalences

As our model is mostly linear, it reaches a state of stable evolution, i.e. stable flows, stable groups proportions and especially a stable rate of decline in ARI.
Although the time taken to reach this stable evolution is indeed dependent on the choice of initial values, the stable state itself depends only on the values of flow parameters. Consequently, with initial values inspired loosely from a pre-war situation without vaccination,1 we ran the model with vaccination until it reached the stable evolution state. The prevalence of TB infection was then found to be around 5%. This point became our initial state for studying the effects of changes of flow parameters.

There is no available data in France for prevalence of the disease. We have had to estimate it from incidence data taking into account natural history of the disease and public health efficiency.1,23 It is postulated10 that without treatment the ratio between incidence: prevalence is 1:2. It is not unreasonable to assume that, on average, the effect of treatment has halved the duration of the disease, leading to similar values for prevalence and incidence rates. The French incidence of pulmonary TB observed in the 1980s was 25 per 100 000.24 The steady evolution phase of our model was able to reproduce this value of prevalence/incidence. We labelled our time axis so that the value was reached at t = 1980.

The distribution of the non-infected according to their vaccinated status depends on the vaccination programme. As, in France, vaccination is carried out during the first months of life,25 we assumed that 60% of newborns are protected. This is consistent with a coverage of 90% and an efficiency of 70%26 for BCG vaccination.

**RESULTS**

Computer programs have been written using Turbo PASCAL®. The resolution of the differential equations was performed by Runge-Kutta method27 with Gill’s modification.

Results from three sets of simulations are presented. The first two attempt to reproduce situations in developed countries, namely the Netherlands and France, comparing our results with real data. As a validation criterion, we focus on the annual decline in the ARI or rather the annual decline of the number of open cases. The last set of simulations illustrates a practical use of the model in a public health setting. It describes the epidemiological consequences of changes such as a sudden increase in the number of infected and consequently of open cases, with or without loss of efficiency of the TB programme.

**Model Validation Based on the Netherlands Situation**

The Netherlands tuberculosis programme is based solely on the detection and treatment of cases, without any BCG vaccination programme. It is thought that in the Netherlands, at least 90% of open cases are detected and rapidly sterilized. Good compliance with treatment and careful follow-up of treated cases, lead to proportions of healed cases as high as 95% of 97%. Other parameters (transfer from infected to case and relapse rate) present an important variability and we have used different values in the simulations (Table 2). The evolution of the annual decline in ARI for each simulation is illustrated in Figure 2. The annual decline in ARI in the

**Table 2 Values of the parameters used to reproduce the Netherlands’ situation**

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Figure</th>
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<tbody>
<tr>
<td>Transfer from infected to case</td>
<td>Detection rate</td>
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<tr>
<td>proportion</td>
<td>time (years)</td>
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<tr>
<td>8</td>
<td>3</td>
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*Including sterilization of their sputum.

*Once detected and sterilized.

(%) proportion experiencing a transition (Figure 2).
2.1: transfer from infected to case = 8% in 3 years.
   detection rate = 90% in 1 year.
   cure rate  A = 95% in 1 year.
   B = 97% in 1 year.
   relapse rate = 1% in 1 year.
2.2: transfer from infected to case = 8% in 3 years.
   detection rate = 90% in 1 year.
   cure rate  A = 95% in 1 year.
   B = 97% in 1 year.
   relapse rate = 0.1% in 1 year.
2.3: transfer from infected to case = 5% in 1 year.
   detection rate = 90% in 1 year.
   cure rate  A = 95% in 1 year.
   B = 97% in 1 year.
   relapse rate = 1% in 1 year.
2.4: transfer from infected to case = 5% in 1 year.
   detection rate = 90% in 1 year.
   cure rate  A = 95% in 1 year.
   B = 97% in 1 year.
   relapse rate = 0.1% in 1 year.

Figure 2: Decline in annual risk of infection in Netherlands
Netherlands was until recently about 10%. Nowadays, it is thought to be between 3% and 5% (UICT, personal communication). This range is in agreement with the range of values that we found for the annual decline in ARI (Figure 2).

Figures 2.1 and 2.2 represent an epidemiological situation in which the transfer flow from infected to case (k2) is 8% in 3 years (5% in 1 year for Figures 2.3 and 2.4). The transfer flow from infected to case seems to be a very influential parameter, with higher rate of transfer corresponding, as expected, to slower decline (Figures 2.3 and 2.4 versus Figures 2.1 and 2.2). The effect of an improvement in the cure rate is also notable when the relapse rate is higher (Figures 2.1 and 2.3, comparisons of B versus A). On the other hand, with a low relapse rate (Figures 2.2 and 2.4), improvement in health services efficiency has no clear influence on the overall evolution.

Simulation of the French Situation
The French situation with regard to tuberculosis is somewhat different from the Netherlands. There is a systematic vaccination programme by BCG, which prevents a direct estimation of the ARI by means of epidemiological surveys. As stated previously, we consider that 60% of newborns are protected by vaccination. The detection rate and the cure rate are lower than in the Netherlands; the latter is believed to be due to a weaker compliance with treatment. It is difficult to quantify these differences partly because there is an underdeclaration of cases by practitioners. However, it seems reasonable to consider that detection rates should lie between 75% and 90%. The set of values of flow parameters are given in Table 3 and results shown in Figure 3.

As for the Netherlands, it appears that the most important parameter is the transfer from infected cases (Figures 3.1 and 3.2 versus Figures 3.3 and 3.4). Here the increase in the detection rate improves decline in ARI, as shown by comparisons between A, B and C curves. Note also that changes in relapse rate (Figure 3.2 versus 3.1; and Figure 3.4 versus 3.3) modulate mildly the decline in ARI in all circumstances. This sensitivity reflects the poorer underlying public health situation in France compared to the Netherlands.

As expected, our results give an average value of the annual decline in the ARI in France which is lower than in the Netherlands; varying between 2.9 and 5.4.

Use of the Model as a Public Health Tool
Effect of stopping systematic BCG vaccination. According to our model results, the ending of systematic vaccination against TB has no effect on the annual decline in the ARI, whatever the values of the other parameters

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### Table 3 Values of the parameters used to reproduce the French situation

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<tr>
<td>Detection rate&lt;sup&gt;a&lt;/sup&gt;</td>
<td>Cure rate&lt;sup&gt;b&lt;/sup&gt;</td>
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<sup>a</sup> Including sterilization of their sputum.
<sup>b</sup> Once detected and sterilized.
<sup>c</sup> (% ) proportion experiencing a transition (Figure 3).
Figure 3: Decline in annual risk of infection in France

3.1: transfer from infected to case = 8% in 3 years. 3.3: transfer from infected to case = 5% in 1 year.

detection rate
A = 75% in 1 year.
B = 80% in 1 year.
C = 90% in 1 year.
cure rate
= 90% in 1 year.
relapse rate
= 1% in 1 year.
detection rate
A = 75% in 1 year.
B = 80% in 1 year.
C = 90% in 1 year.
cure rate
= 90% in 1 year.
relapse rate
= 1% in 1 year.

3.2: transfer from infected to case = 8% in 3 years. 3.4: transfer from infected to case = 5% in 1 year.

detection rate
A = 75% in 1 year.
B = 80% in 1 year.
C = 90% in 1 year.
cure rate
= 90% in 1 year.
relapse rate
= 0.1% in 1 year.
detection rate
A = 75% in 1 year.
B = 80% in 1 year.
C = 90% in 1 year.
cure rate
= 90% in 1 year.
relapse rate
= 0.1% in 1 year.
may be. We have checked this finding by repeating the same simulations for the French situation, but suppressing the vaccination programme. In all these cases the model reproduced the same values of ARI decline as previously shown in Figure 3.

Effects of modifications in the underlying sanitary situation. Figure 4 represents the effects of a tenfold increase in the infectious population in the case where the TB programme is able to maintain its efficiency (i.e. to detect and treat rapidly these cases). Curves A represent the basic situation and Curves B those corresponding to the tenfold increase. Simulation results show that the values and rate of decline in ARI are not substantially modified.

The conclusions are different when the TB programme is unable to maintain its efficiency (Figure 5). Our simulations have shown that the key factor is the number of susceptibles infected by an open case. Increasing this number from 0.5 to 0.6 leads to a weaker decline in ARI as shown in Figure 5, by comparing curves A to curves B. Such a situation could result from various circumstances, e.g. appearance of antibiotic resistant strains or influx of populations (refugees, the homeless, etc) with poor access to health care.

DISCUSSION
The quantitative comparison of our results with the literature relies on the value that we have assumed for the ratio between the annual rate of decline in the number of open cases and the annual rate of decline in the ARI. This ratio is known to increase with time, due to a general improvement in the TB situation and a gradual ageing of the population in developed countries. For the period 1973–1984, this ratio has been evaluated at around two in France. With this value as reference, the different declines in the number of open cases simulated by our model led to realistic values for the decline in ARI. In the pre-chemotherapeutic era the annual decline in ARI was around 5%. Using tuberculin surveys in army recruits and schoolchildren from 1910 to 1966, the TSRU has estimated that the annual decline in ARI was 13.7% after 1940. Other tuberculin surveys in army recruits and primary or secondary schoolchildren between 1966 and 1979, have shown that this decline was around 10% from 1969 to 1979. The difference between the decline before and after World War II is, to a large extent, due to diagnosis and treatment programmes combined with an improvement in the standard of living, hygiene and health education. In the Netherlands, results of tuberculin surveys since 1980 are available and show that the annual decline in ARI has recently fallen: from 1980 to 1984 the average annual decline was 7.4% but became less than 5% between 1984 and 1987. The results of our model are consistent with such values.

The French epidemiological situation is not as well known as the one in the Netherlands. However, it is generally admitted that the French tuberculosis programme is less efficient than that in the Netherlands, partly because of a poorer follow-up during treatment. Our results confirm that the decline in ARI is influenced by the cure rate and that, even if the detection rate of open cases increases to 90% as in the Netherlands, the difference in the annual decline in ARI between the two countries would be maintained for years. The respective influences of detection rate and cure rate on the decline in ARI also depends on the epidemiological context. In the Netherlands where the detection rate is high, the consequences of an increase in the cure rate from 95% to 97% seem more important when the relapse rate is 1% than when it is 0.1%. In France where the cure rate is probably below 90%, the detection rate is still a key parameter. Tuberculosis ought to be presented as a potential public health problem during medical training, and practitioners have to be aware of the weaknesses of the French programme. Our model has shown that an improvement in the detection rate would lead to a faster decline in ARI, and thus a change to a better TB situation; confirming the previous results of the model of Hock and Loy in Singapore. Our results are consistent with Joesoef et al. who confirmed the importance of the detection and cure rates for the control of TB in the population and pointed out the cost-effectiveness aspect for the choice of treatment strategy.

These results, combined with those obtained under the hypothesis of an increased population of infected, raise the important question of the efficiency of the vaccination compared to improvements in the health care system. According to our results, BCG vaccination is no longer influential on the decline in ARI. Indeed, we have shown that if the cure rate and the relapse rate influence crucially the decline in ARI in developed countries, these rates are not influenced by vaccination. Moreover, nowadays in developed countries, cases are mainly the elderly who relapse rather than new young patients; these elderly cases have fewer contacts with children and thus are out of reach of vaccination effects. A current opinion on BCG vaccination policy in developed countries is that its main benefit lies in the prevention of complications such as meningitis but this aspect of the disease is not studied in our model.

The assumption that groups are homogeneous is clearly an oversimplification as there is evidence of
**MODELLING TUBERCULOSIS RISK**

**Figure 4** Deterioration in the French epidemiological situation but maintenance of tuberculosis programme efficiency

4.1: transfer from infected to case = 8% in 3 years.
- Detection rate = 75% in 1 year.
- Cure rate = 90% in 1 year.
- Relapse rate = 1% in 1 year.

A = basic situation.
B = tenfold increase of open cases.

4.2: transfer from infected to case = 8% in 3 years.
- Detection rate = 90% in 1 year.
- Cure rate = 90% in 1 year.
- Relapse rate = 1% in 1 year.

A = basic situation.
B = tenfold increase of open cases.

4.3: transfer from infected to case = 5% in 1 year.
- Detection rate = 75% in 1 year.
- Cure rate = 90% in 1 year.
- Relapse rate = 1% in 1 year.

A = basic situation.
B = tenfold increase of open cases.

4.4: transfer from infected to case = 5% in 1 year.
- Detection rate = 90% in 1 year.
- Cure rate = 90% in 1 year.
- Relapse rate = 1% in 1 year.

A = basic situation.
B = tenfold increase of open cases.
FIGURE 5 Deterioration of the French epidemiological situation with the tuberculosis programme unable to maintain its efficiency (one open case may infect 0.6 susceptibles, instead of 0.5)

5.1: transfer from infected to case = 8% in 3 years.
   detection rate = 75% in 1 year.
   cure rate = 90% in 1 year.
   relapse rate = 1% in 1 year.
   A = basic situation.
   B = tenfold increase of open cases.

5.2: transfer from infected to case = 8% in 3 years.
   detection rate = 90% in 1 year.
   cure rate = 90% in 1 year.
   relapse rate = 1% in 1 year.
   A = basic situation.
   B = tenfold increase of open cases.

5.3: transfer from infected to case = 5% in 1 year.
   detection rate = 75% in 1 year.
   cure rate = 90% in 1 year.
   relapse rate = 1% in 1 year.
   A = basic situation.
   B = tenfold increase of open cases.

5.4: transfer from infected to case = 5% in 1 year.
   detection rate = 90% in 1 year.
   cure rate = 90% in 1 year.
   relapse rate = 1% in 1 year.
   A = basic situation.
   B = tenfold increase of open cases.
MODELLING TUBERCULOSIS RISK

individual variability in relation to the disease.\textsuperscript{5,34,35} The simplest way to take this into account would be to stratify the population, each stratum having the same subgroups as in the present model but each with its own set of parameters. This generalization of the model is technically straightforward but requires assessment of many more parameters. For example, the assessment of the influence of some ‘high risk populations’, as refugees or homeless, on the overall TB situation in the population, depends on the knowledge of parameters measuring the access of these subjects to health services, and the degree of mixing between those individuals and the general population. This is beyond our current knowledge. Even if data for assessing the parameters of the relevant transmissions are missing at present, according to our results, the decline in ARI may nevertheless be preserved, if the TB programme is able to maintain its efficiency.

Another improvement of the model would be to introduce the effect of age, but at the cost of a more complicated system of partial differential equations. Here also, improved epidemiological surveys are needed to obtain sensible values for all the required parameters.

Several deterministic models, some based on differential equations, have been constructed to model TB.\textsuperscript{5,18,36–38} They all make the assumption that the open cases are homogeneously mixing. In countries where open cases are scarce compared to the number of susceptibles, this hypothesis is no longer tenable and we have used a specific functional form in the equation defining the flow of new infected to take this into account and limit the infectiousness of the disease. Other ways of modelling the variability of infection have been proposed.\textsuperscript{5}

Finally it should be pointed out that in a low prevalence situation, the number of newly infected is truly a stochastic quantity and it is the probability of becoming infected that should be modelled instead. For that reason, our simulations may become inaccurate after a few decades, since a deterministic model will be inappropriate to describe the eradication of the disease.

CONCLUSION
The aim of the modelling approach that we have developed is not to reproduce exactly the value of an epidemiological parameter (i.e. the ARI), but rather to reproduce the variations of this fundamental quantity with regard to the modifications of the controlled parameters of the model (i.e. detection rate, cure rate, relapse ...). For a long time the TB situation has been improving in developed countries.\textsuperscript{39} In low prevalence countries where the disease has ceased to be a major hazard for the general population, decisions concerning the objectives and the ways of implementing TB programmes have to be taken. One of these decisions may be interruption of the BCG vaccination programme but a re-inforcement of open case detection procedures; an alternative which is being currently discussed in France. Some of our results indicate that the latter alternative might be a good choice. In developed countries there is, at present, a new phenomenon: an increase in AIDS-related cases of tuberculosis. Simulations from our model have shown that if a tenfold increase in open cases is controlled by the TB services, the epidemiological situation will not be impaired. Such an increase is far above the most pessimistic forecast of AIDS-related new cases.

Our model, despite the simplifications made, gave some qualitative clues about plausible evolutions. This model may be considered as a first step towards building valid tools to assess the major effects of TB programme modifications. The efficiency of such tools is strongly dependent on the quality and availability of data, and thus it now seems very important to build up again surveys and control programmes in all countries, as proposed by Sudre et al.\textsuperscript{40}

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(Revised version received June 1996)
APPENDIX 1

Differential Equations of the Model

Notation used in the equations and Figure 1.

Populations
- SUSCEPTIBLES: S
- PROTECTED: P
- INFECTED: I
- OPEN CASES: O
- NON OPEN CASES: NO
- CHRONICS: C
- HEALED: H

Demographic and epidemiological flows
- BIRTH (numbers): b
- DEATH RATE (non TB related): d1
- BCG IMMUNITY LOSS RATE: k1
- NUMBER OF CONTAMINATIONS: Nc
- RATE OF TRANSFER FROM INFECTED TO CASE: k2
- DETECTION AND STERILISATION RATE: k3
- RATE OF TRANSFER TO CHRONICITY: k4
- CURE RATE: k5
- RELAPSE RATE: k6
- TB INDUCED EXCESS MORTALITY RATE: d2

Differential equations
\[
\frac{dS(t)}{dt} = 0.4b - d1S(t) + Nc \cdot \phi[S(t)] \cdot O(t) + k1 \cdot P(t)
\]
\[
\phi[S] = \inf (S, \text{maximum number of contacts of an open case})
\]
\[
\frac{dP(t)}{dt} = 0.6b - (d1 + k1) P(t)
\]
\[
\frac{dI(t)}{dt} = Nc \cdot \phi[S(t)] \cdot O(t) - (d1 + k2) I(t)
\]
\[
\frac{dO(t)}{dt} = (0.5 \cdot k2) I(t) + (0.5 \cdot k6) C(t) - (k3 + d1) O(t)
\]
\[
\frac{dNO(t)}{dt} = (0.5 \cdot k2) I(t) + (0.5 \cdot k6) C(t) + k3 O(t) - (k5 + k4 + d1) NO(t)
\]
\[
\frac{dC(t)}{dt} = k4 NO(t) - (k6 + d1 + d2) C(t)
\]
\[
\frac{dH(t)}{dt} = k5 NO(t) - d1 \cdot H(t)
\]

APPENDIX 2

Number of Infections Caused by One Open Case in the General Population of Developed Countries

Without treatment one open case infects 10 susceptibles in one year, i.e. 0.8 each month on average.

With a detection rate of 100% and an average duration of the disease of around 4 months, one open case can thus infect \((0.8) \times 4 = 3.2\) susceptibles.

In fact, once detected, the infectiousness is usually less than one week, and then the number of infections caused by one open case under these conditions is less than \(0.8/4\); let it be \(0.1\).

In France where detection rate is nearer to 80%, the number of infections caused by one open case is probably greater and can be loosely assessed as follows, by applying the efficiency of tuberculosis programme from 100 open cases: 80% are detected, 90% (72) are sterilized in a few days, causing \((72/0.1 = 7\) infections. This leaves 10% (8) incorrectly treated, but at least partially sterilized, causing one infection each on average.

Of the 100 open cases: 20% (20) are neither detected nor treated, each of them being responsible for, theoretically, 10 infections (200). Then, in such situations 100 open cases cause \(200 + 8 + 7\) infections leading to an average number of 2.15 infections by case.

However, in such countries, infectious cases occurred preferentially in sub-groups which are not very crowded with susceptibles in the general population (old persons, homeless, refugees ...), and then, it seems not unrealistic to suppose that, on average, one open case infects less than one susceptible in the general population.