Infectious Diseases in Structured Populations

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Editorial note. There are dozens of research projects carried out at CWI. It is the editors' policy to pay more attention to these projects. Therefore in the future short descriptions of such projects will be included in the CWI Quarterly. They are presented in a non-mathematical way. The following article belongs to this category.

1. Introduction

Epidemiology is the scientific description of the distribution in space and time of diseases and the search for factors responsible for the observed patterns of distribution. Originally most emphasis was put on the study of infectious diseases, but in the second half of this century and in the developed world the study of degenerative diseases such as cancer and cardiovascular diseases became predominant. The current AIDS epidemic, and the re-emergence of malaria, has led to an upsurge in interest for infectious diseases. In this short note we discuss what the main questions are concerning the spread of infectious diseases that are studied using mathematical models, some historical success stories of insight gained through mathematical modelling, and, in somewhat more detail, recent developments in the solution to the easiest of the main questions.

2. Mathematical questions in epidemiology

The understandable expectation that mathematical models are used for prediction of future trends in the spread of infectious diseases is unwarranted. Mathematical models are used for obtaining insight, in particular concerning the relative importance of factors influencing the spread of the infection and, more generally, concerning the relation between mechanisms on the individual level and phenomena at the population level.

There are some five main areas where mathematical models are used to answer epidemiologically relevant questions. We discuss them briefly in the order in which they occur 'naturally' after an infectious disease has entered a population where it was not present before. We assume that this disease confers permanent immunity to individuals that have recovered from the infection. For the time being we take all individuals in the population to be

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identical as far as their transmission behaviour is concerned.

To begin with we assume that the total number of individuals in our population is constant on the time scale on which the epidemic processes of infection and recovery occur. If all individuals are susceptible, the first question that arises is: if an infectious disease enters our population will it cause a spreading epidemic, or will it die out right away? This is referred to as the *invasion question*. A threshold-quantity called the *basic reproduction ratio* can be used to answer this question and its existence is a major insight that mathematical thinking has brought to epidemiology. The basic reproduction ratio is also important in studying the efficacy of different control measures and as a tool for discriminating between different vaccination strategies. Recently a framework has been developed to define and calculate this quantity for very general situations [2] (more about this in the next sections).

Suppose an epidemic does occur and we still ignore births of new susceptibles, then we can picture the epidemic as in Figure 1. Here the I symbolizes the infected part of the population and S the susceptible part. At first the infecteds will increase slowly in number, then more rapidly, and at some point in time they will decrease again in number because of (1) lack of sufficient susceptibles and, (2), by the fact that the infecteds are only infectious for a fixed amount of time after which they become immune or die. The relevant questions are: when does I reach its maximum value, how large will this value be, and what fraction of the susceptibles escapes from ever getting the disease? A second major insight furnished by mathematical modelling is that there will always be a positive (albeit possibly very small) fraction of individuals that never get the infection [5].

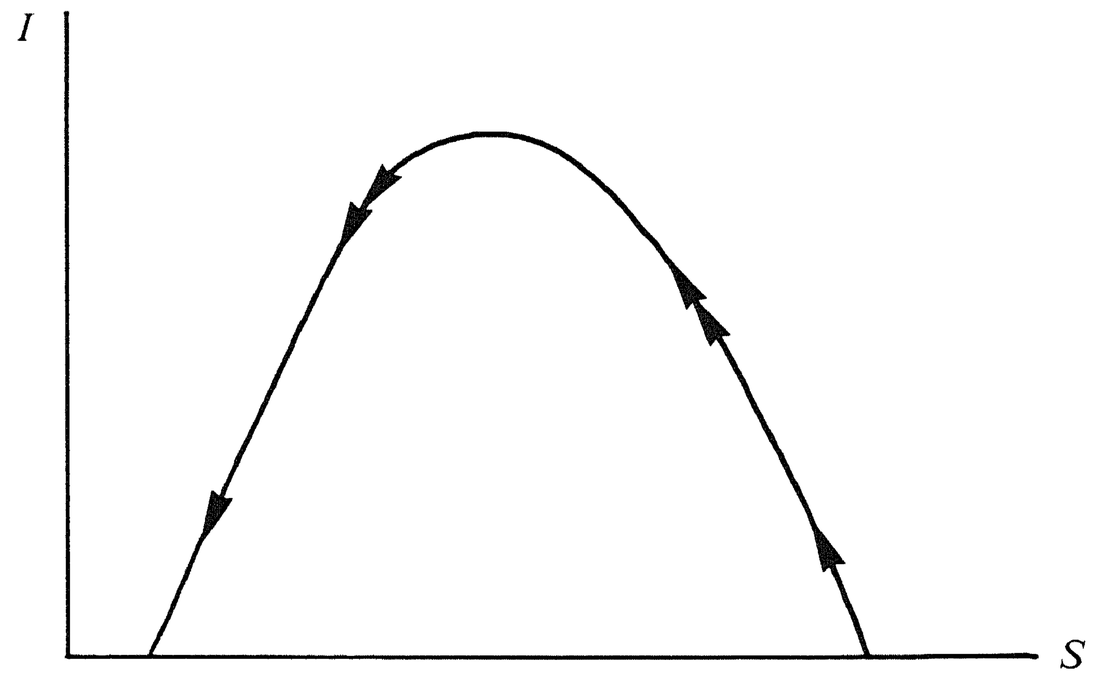

FIGURE 1. Epidemic outbreak

Now we go one step further and allow for an inflow of new susceptibles, for example by births. However we let these births occur on a much longer time scale than the time scale of the epidemic process. We then get a situation as

pictured in Figure 2, called 'recurrent behaviour'. After a rapid epidemic outbreak as described in the previous paragraph, the disease will go extinct. To describe this accurately we would have to take stochasticity into account. After the disease has gone extinct locally the population will gradually be replenished by the birth of new susceptibles. When the susceptible population is 'large enough' again, i.e. when the threshold-quantity is above threshold, a reintroduction of the disease from outside the population leads to a new epidemic. Measles in Iceland are the standard example of this behaviour, see [1]; there are not enough inhabitants to 'create' new susceptibles fast enough in order to maintain the disease in the population. It is an as yet unsolved theoretical problem to find a nice characterization of the 'borderline' between such behaviour and the behaviour we describe next.

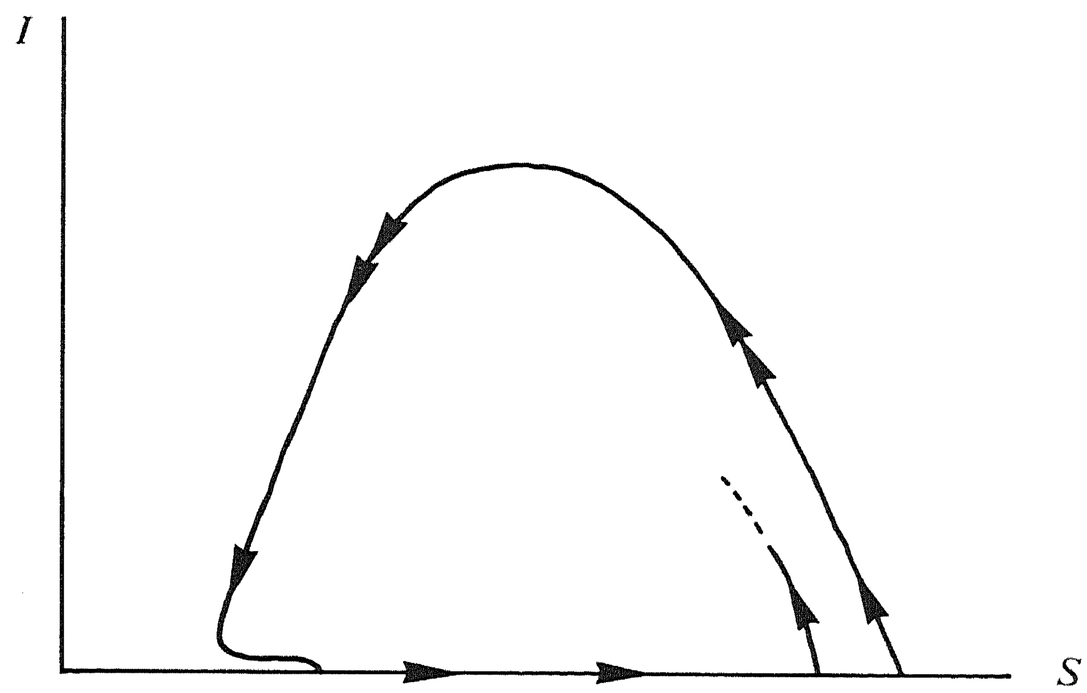

FIGURE 2. Recurrent behaviour

If the birth of new susceptibles occurs on the same time scale as the epidemic processes, the disease can be present within the population at all times, and it is called *endemic*, see Figure 3. Obvious questions are: Will there be a steady state? Is it stable? Are there perhaps oscillations? How does the period of oscillations depend on the relevant parameters? Finally in this setting there is the *regulation problem*. How does the disease affect the growth rate of the population? There is currently much interest in this problem for example with respect to AIDS in African countries.

The questions discussed above can all be answered, more or less easily, when we make no distinctions between the individuals in the population. However real life is more complicated, as individuals differ in their transmission behaviour. Examples of heterogeneity characteristics that could be relevant for the spread of an infection are: age, sex, sexual activity, spatial position. When we take arbitrary heterogeneity into account the above mentioned questions become much more difficult, and in fact only the invasion question can, at the present state of the art, be answered in great generality.

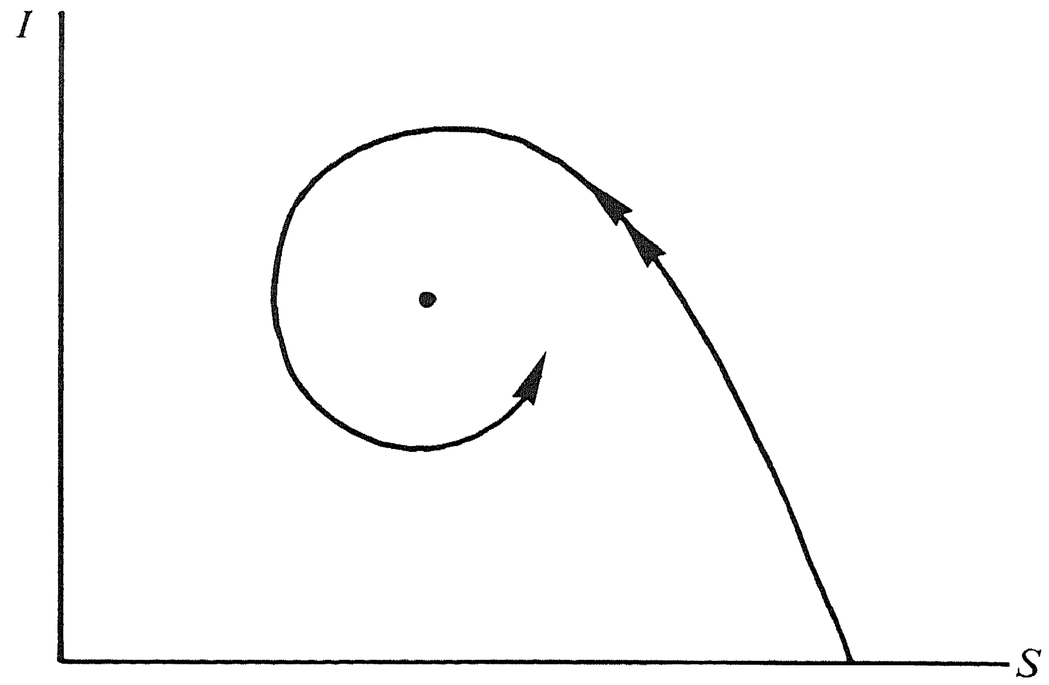

FIGURE 3. Endemic

3. TWO SUCCESSFUL EXAMPLES

In studying the above mentioned questions modelers have had an impact on public health decisions. Let us discuss two of these success stories of mathematical models in epidemiology.

The first is probably the earliest example of insightful application of mathematics to epidemiology. It dates back to 1909 when Ross [7] introduced the notion of a threshold-quantity already referred to above. He observed that eradication of malaria should be possible by decreasing the density of mosquitos present in a certain area below a critical value. Prior to that it was generally believed that malaria would always survive as long as some mosquitos were still present and that total eradication of mosquitos was impossible. Using a simple model, Ross showed that there was a quantity which, when suppressed below unity, would guarantee the disappearance of malaria from the area, and that this quantity was proportional to the ratio of mosquito density to human density. Thus he found a critical mosquito density. Empirical corroboration was later obtained in India with the discovery of neighbouring areas with and without malaria and mosquito densities respectively above and below the critical level.

A second example is the evaluation of different vaccination strategies. For example for rubella (German measles), which is a mild illness in most individuals but is a serious threat to the unborn offspring of pregnant women, there are three strategies. One is to vaccinate all young children, a second is to vaccinate only prepubertal girls, and a third is a combination: vaccination of all children at young age (about 1 year old) and again at about 11 years old (because one can never reach a 100% successful coverage). The second strategy was used in The Netherlands up to 1984, after which a switch was made to the third. Mathematical analysis shows that certain strategies can in fact increase the fraction of serious cases [4]. This is because complications of rubella

infection are more likely to occur at a higher age, and the average age at which the infection is contracted can rise when the probability per unit of time to get the disease decreases. Important questions which can be answered by mathematical analysis, e.g. by studying the effect of vaccination on the threshold-quantity, are:

- which immunization coverage is required to eliminate rubella? (For The Netherlands the answer is: around 95% of young children, a percentage attainable only in highly developed countries [4].)
- how many serious cases occur on the way to elimination and how does this depend on the way in which the change of strategy is effectuated?
- if elimination cannot be attained what consequences does this have for the fraction of unvaccinated individuals?

It is thought that with The Netherlands' current combined vaccination strategy against measles, mumps and rubella it should be possible to eliminate these three diseases in the first half of the nineties [4].

4. The basic reproduction ratio

A paper by W.O. Kermack and A.G. McKendrick which appeared in 1927 [5] has had a major influence on mathematical modelling of epidemics. Nowadays most people refer to a certain simple system of ordinary differential equations as *the* Kermack-McKendrick model, whereas in fact they treated a much more sophisticated model. Their key idea was to describe the *average infectivity of an individual τ units of time after it became infected* by a non-negative function $A(\tau)$. The assumption is that infection triggers an autonomous process which develops within the host without any further influence of the environment and that, consequently, we can use an 'age' representation to describe the average infectivity. All relevant aspects of the detailed stochastic time evolution of the internal population of viral particles or bacteria and the concomitant reaction occurring in the immune system are incorporated in the function A. The diseases where such a representation is possible are usually referred to as 'micro-parasitic' diseases; one should think of diseases like measles, cholera, influenza, AIDS. There is also a large class of diseases where repeated infections from outside influence the course of the disease; these include malaria and the diseases caused by worms such as schistosomiasis and riverblindness. We shall not concern ourselves with this class in this note, but refer to [6] and the references given there. However, for most considerations we need not even specify A in any detail. Examples of possible shapes of the function A are given in Figures 4 and 5.

Assuming that the number of contacts between susceptibles and infectives is proportional to the density of susceptibles times the density of infectives (the 'law' of mass action), Kermack and McKendrick were led to introduce $R_0 = S\int_0^\infty A(\tau)d\tau$ as the expected number of secondary cases (new infected individuals) produced by one infectious individual during its entire infective

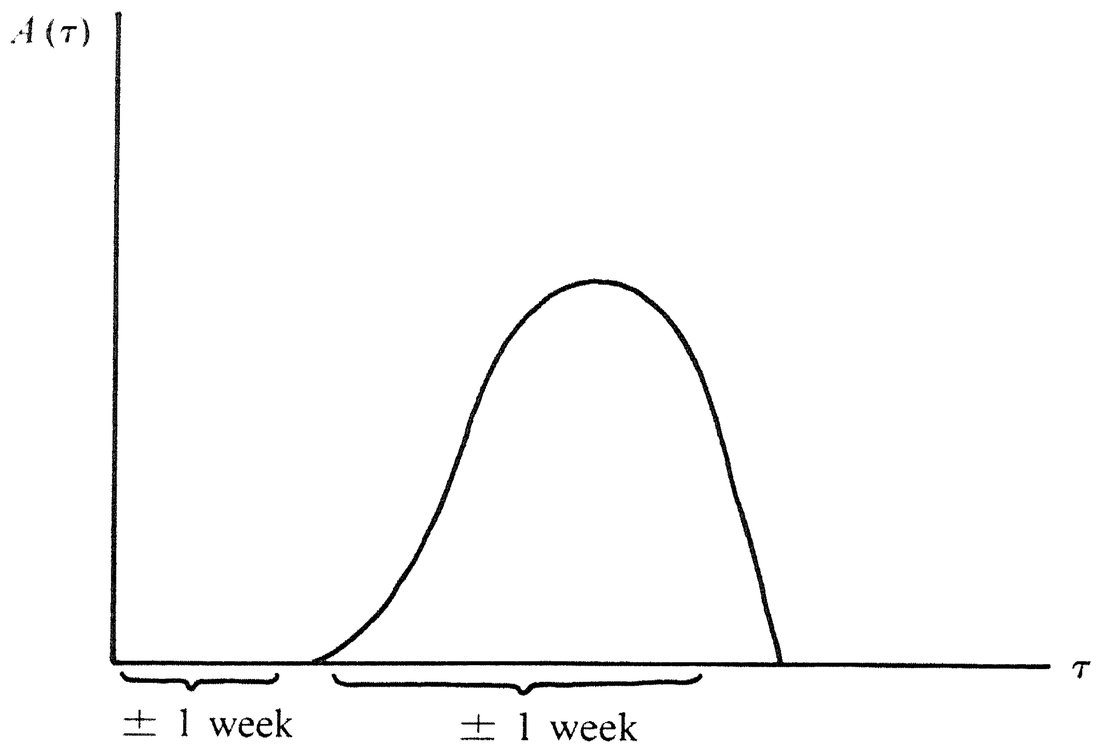

FIGURE 4. Measles infectivity as a function of time

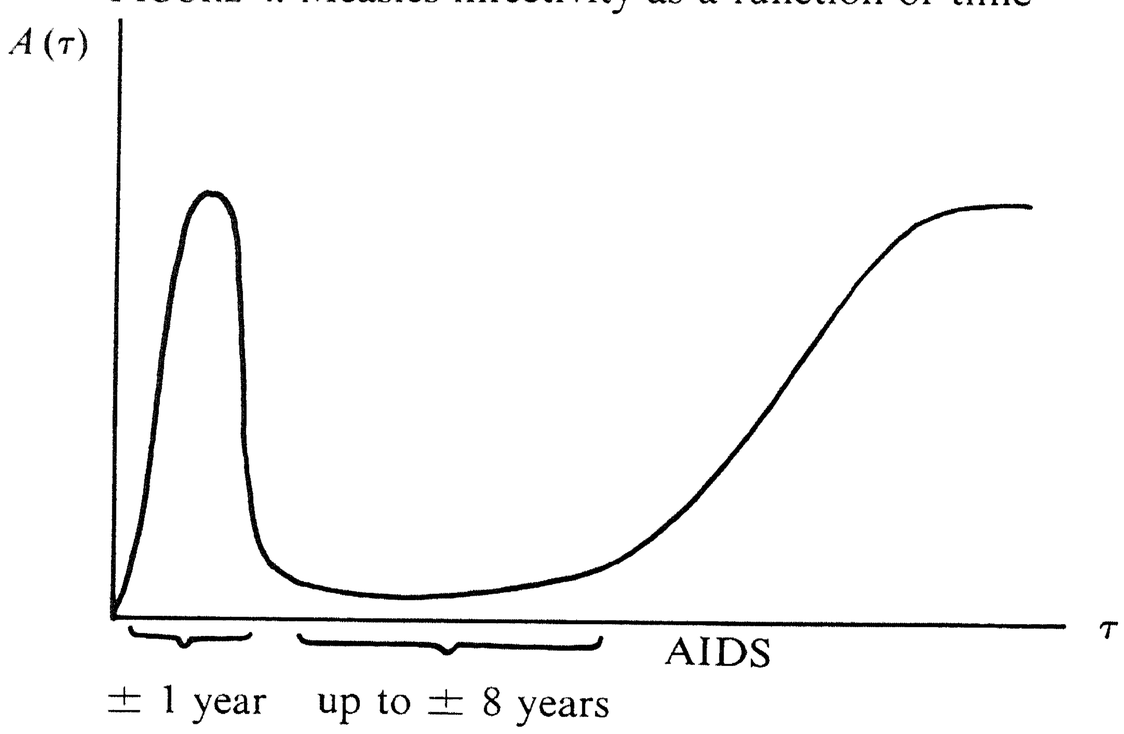

FIGURE 5. HIV-infectivity as a function of time

life in a susceptible population of density S. Clearly R_0 has *threshold-value* one, i.e. when $R_0<1$ no epidemic develops upon introduction of the infection into the population, whereas when $R_0>1$ an epidemic gets started. R_0 is called the *basic reproduction ratio.*

Things become more complicated when not all individuals are equally susceptible. Disease transmission will reflect differences in susceptibility and we have to carry out the right averaging procedure to arrive at R_0. The bookkeeping should take into account the different 'structures' present in the population and the distribution of the population with respect to these. In recent years considerable attention has been paid to the modelling of such more complex—and realistic—systems. The project presently described reflects this interest.

Suppose we have a population of humans, other animals or plants. We distinguish the individuals by attaching to each a variable ξ which we call the *h*-state (*h* for heterogeneity) of that individual. ξ can be static or dynamic, discrete or continuous. The *h*-state space, i.e. the range of all relevant ξ, we call Ω. Let $A(\tau,\xi,\eta)$ be the expected infectivity of an individual which was infected τ units of time ago while having *h*-state η, with respect to a susceptible with *h*-state ξ. So all medical, behavioural, physiological and social aspects which are relevant for disease transmission are summarized by A and we shall need sub-models later on to specify A on the basis of certain assumptions. Because in the parametrization only the *h*-state at the infection time enters, it is not necessary—for the time being—to specify the dynamics of the *h*-state. Let $S(\xi)$ be the susceptible population density as distributed over Ω. The *next generation operator*

$$(K(S)\phi)(\xi) = S(\xi)\int_{\Omega}\int_{0}^{\infty} A(\tau,\xi,\eta)d\tau\phi(\eta)d\eta$$

tells us both how many secondary cases arise, and how they are distributed over Ω, when we start with a 'distributed' individual ϕ. We consider $K(S)$ as an operator on $L_1(\Omega)$. Note that $K(S)$ is a positive operator (since S and A are non-negative, $K(S)$ preserves non-negativity). So, as a rule, there is a dominant eigenvalue λ_d and

$$K(S)^n\phi \sim c(\phi)\lambda_d{}^n\phi_d \quad \text{as} \quad n\to\infty$$

for any non-negative ϕ, where ϕ_d is the eigenfunction corresponding to λ_d, and $c(\phi)$ is a constant depending on ϕ. In other words after transients, which reflect how exactly the epidemic got started, have died away (i.e. for sufficiently large n) the next generation will be a factor λ_d larger than the current one and the distribution of new cases with respect to *h*-state will be invariant. Clearly the biological quantity we are after is mathematically described by λ_d or, in symbols, $R_0=\lambda_d$. Under various special assumptions it is now possible to calculate the basic reproduction ratio when arbitrary heterogeneity characteristics which influence the spread of an infection are taken into account. For mathematical details and examples we refer to [2,3]. Reference [3] also contains a more detailed discussion of the use of mathematical models in epidemiology.

The current project on mathematical epidemiology focusses on gaining some insight in the problems discussed in the introduction in the case where heterogeneity among the characteristics of the individuals can strongly influence the spread of the infection. The aim of the project is to provide an overall picture of the common mathematical structure of epidemic models or, more generally, to provide a survey of the various structures inherent in such models, and their bearing on the dynamics. This was started during a colloquium organized in 1989 and is to culminate in the writing of a book by M. Kretzschmar and the present authors, during 1990 and 1991.

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