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The estimation of the basic reproduction number for infectious diseases

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The basic reproduction number R_0 is the number of secondary cases which one case would produce in a completely susceptible population. It depends on the duration of the infectious period, the probability of infecting a susceptible individual during one contact, and the number of new susceptible individuals contacted per unit of time. Therefore R_0 may vary considerably for different infectious diseases but also for the same disease in different populations. The key threshold result of epidemic theory associates the outbreaks of epidemics and the persistence of endemic levels with basic reproduction numbers greater than one. Because the magnitude of R_0 allows one to determine the amount of effort which is necessary either to prevent an epidemic or to eliminate an infection from a population, it is crucial to estimate R_0 for a given disease in a particular population. The present paper gives a survey about the various estimation methods available.

1 What is R_0?

The concept goes back to demography where it is usually called the 'net reproduction rate'. The head of the Statistical Office of Berlin, Richard Böckh[1] calculated in 1886 what he called the 'total propagation of the population' ('die totale Fortpflanzung der Bevölkerung'). Using a life-table for females of the year 1879 he summed the products of the survival probabilities for all reproductive years between 14 and 53 and the rates of giving birth to a girl. He concluded that 2.172 female babies would be born to a representative women who throughout her life would be subject to current age-specific mortality and fertility rates. The formula for this quantity was given by Sharpe and Lotka[2] in 1911, but without symbol and name. At the time of writing this survey it is not clear to the author where exactly Lotka introduced the notation R_0 and the name 'net reproduction rate' for the first time. In 1939 he published a summary of his contributions to demography in French.[3] In a comparison of the advantages and disadvantages of various indices for natural increase he writes: 'La reproductivité nette, R_0, introduite par Boeckh, a plus de mérite, car elle donne une mesure essentiellement indépendante de la répartition de la population par âges.'

Let $p(a)$ denote the probability of a woman surviving age a and let $\beta(a)$ be the rate of giving birth to a girl for an individual of age a then

$$R_0 = \int_0^\infty p(a)\beta(a)\mathrm{d}a.$$

(The gross reproduction rate is given by

$$\int_0^\infty \beta(a)\mathrm{d}a,$$

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i.e. it is 'the number of female children that a female just born may expect to bear during her reproductive life, ignoring the possibility of mortality'.[4])

The index zero of R_0 is explained by the notation[5]

$$R_n = \int_0^\infty a^n p(a)\beta(a)\,da,$$

i.e. it is the moment of order zero of the net maternity function $\phi(a) = p(a)\beta(a)$.

The 'natural rate of increase' of the population is usually denoted by r. It satisfies the transcendental equation

$$1 = \int_0^\infty e^{-ra} p(a)\beta(a)\,da.$$

The sign of r equals the sign of $R_0 - 1$.

The demographic term 'basic reproduction rate' was introduced to epidemiology in 1952 by Macdonald[6] in the context of malaria: 'The number of infections distributed in a community as the direct result of the presence in it of a single primary non-immune case.' Macdonald's basic reproduction number was applied by Smith[7] to the transmission of arboviruses. He uses it to calculate the minimum proportion to be vaccinated and proposes to estimate it by the inverse of the proportion of susceptibles after an epidemic.

The concept of the basic reproduction number assumes that one infective case is introduced into a large susceptible population, such that the initial spread of the epidemic can be approximated by a branching process where one neglects the decline of the number of susceptibles in subsequent generations of the epidemic. The first model using a branching process approximation to epidemics is due to Bharucha-Reid.[8] This was followed up by Neyman and Scott[9] and Bartoszyński.[10] Becker[11] applied branching processes in order to evaluate vaccination strategies for the control of epidemics. In this framework it is clear that the key parameter is the number of secondary cases generated by the initial case. If this number is $\leqslant 1$, one will get only minor outbreaks with a probability 1 of extinction. If this number is >1, then there is a positive chance of a large outbreak affecting nearly the total population.

The concept of the basic reproduction rate for *directly transmitted infections* has independently been introduced by Dietz[12] and Hethcote.[13] (Hethcote used the phrase 'infectious contact number'.) Diekmann *et al.*[14] provide a mathematically rigorous framework for the definition of R_0 in the context of infectious disease models and propose to call this quantity either 'basic reproduction number' or 'basic reproduction ratio'. The term 'rate' should be avoided since R_0 is dimensionless and in epidemiology this expression should refer to quantities with dimension 'per unit of time', like 'hazard rate' or 'incidence rate'.[15]

For the evaluation of control programs it is not sufficient to find out that R_0 is greater than one. It is important to know whether R_0 is much or little above the threshold value of 1, because this will determine the necessary amount of control needed to reduce the corresponding parameters sufficiently to achieve a specified goal. Therefore Nåsell[16] calls R_0, or rather R_0^2, the 'eradication effort'.

This brings up the question how R_0 should be defined in the case of vector-borne infections like malaria or yellow fever. Traditionally R_0 is defined as the number of

human cases which one case could generate during the infectious period via the vector population. The paper of Diekmann *et al.*,[14] however, defines R_0 as the number of secondary cases *per generation*, i.e. for host-vector diseases one would take the square root of the classical basic reproduction number. In terms of the threshold condition $R_0 = 1$ this makes no difference. If one defines R_0 like Macdonald,[6] the minimum proportion to be vaccinated in the human population if one had a vaccine for the prevention of a vector-borne disease, would be given by the expression[7]

$$1 - R_0^{-1}.$$

If however one defines R_0 like Diekmann *et al.*[14] the corresponding minimum proportion to be vaccinated would be

$$1 - R_0^{-2}.$$

The same equations which describe the spread of malaria between humans and mosquitoes can also be used to describe the spread of a sexually transmitted disease (STD) in a heterosexual population. This analogy has already been noticed by Ross[17]: 'The venereal diseases may be looked upon as metaxenous diseases in which the two sexes take the part of the two hosts.'

Hethcote and Yorke[18] use the malaria equations of Ross for the description of the heterosexual transmission of gonorrhea. They speak of the 'second generation contact number' which 'is the average number of women (second generation) adequately contacted by men (first generation) who were adequately contacted by an average infectious woman during her infectious period.' If one retains the notion of R_0 as the average number of secondary cases *per generation*, then one has to determine the geometric mean of the number of secondary cases if the opposite sex generated by one newly infected case. Similarly one would also define the basic reproduction number in the case of vector-borne diseases as the geometric mean of the reproduction numbers per generation.

The definition of the basic reproduction number does not depend on the assumptions about the immunity after the infectious period. This means that R_0 is the same for the so-called SIS and SIR models, i.e. for models where an individual is either susceptible again after the infection or completely immune ('resistant').

Usually the transmission dynamics are described by a nonlinear system of differential equations which is then linearized. Let κ denote the number of persons contacted per unit of time by one infectious individual. The proportion of contacted persons who are infected given a contact is denoted by h. The rate of tranfer to a non-infectious state (either susceptible or immune) is denoted by γ. Let the initial size of the population be denoted by N_0 and let the initial number of infectious individuals be equal to one. Then the following differential equation describes the initial spread of the epidemic, where it is assumed that N_0 is large such that it is justified to apply differential equations. Let Y denote the number of infectives and X the number of susceptibles then

$$\frac{dY}{dt} = \kappa h \frac{X}{N_0 - 1} Y - \gamma Y.$$

Since X equals $N_0 - 1$ initially, we see immediately that Y will increase if and only if

$R_0 = \kappa h/\gamma$ is greater than one. The duration of the infectious period with mean D equals $1/\gamma$ and the total number of persons contacted during this period is κD. The fraction h of those individuals contacted will be infected. This deterministic model implictly assumes an exponentially distributed infectious period, and the rate of generating secondary cases $\beta = \kappa h$ defines a Poisson process as long as the individual is infectious. This means that the number of secondary cases per initial case has a geometric distribution:

$$q_k = \gamma \int_0^\infty e^{-(\gamma+\beta)t}[(\beta t)^k/k!]\,dt$$
$$= R_0^k/(1+R_0)^{k+1},$$

with mean value R_0 and variance $R_0(1+R_0)$.

2 Why would one need to know R_0?

2.1 Elimination or eradication

In the epidemiological literature the terms elimination and eradication are often used synonymously. Both refer to a state of zero prevalence of the infection. But a prevalence of zero may refer to a stable or an unstable equilibrium. Here stability refers to the result of an introduction of an infectious case into the population.

If the zero equilibrium is *stable* then the introduction of one case will at most lead to a small number of generations of secondary cases, and therefore to a return to the original prevalence of zero. This situation can either occur naturally, without special interventions because of low local contact rates and infection probabilities per contact, or because of permanent interventions like vaccination programmes which reduce the proportion of X/N susceptibles sufficiently such that $R_0\ X/N$ is less than one. Such a stable prevalence of zero is called *elimination*.

If however the zero equilibrium is *unstable* the introduction of an infectious case will lead to a major epidemic and potentially to a subsequent endemic state, depending on the size of the population and the rate of introduction of new susceptibles. A prevalence of zero would be the result of a time-limited intervention after which R_0 is allowed to go back to its original level. Such a programme is called *eradication*. A unique successful example is the global smallpox eradication programme. Presently it is planned to eradicate polio globally by the year 2000. Measles are targeted for elimination by the year 2000 in the USA and in Europe. Because of the ongoing risk of introduction of cases one would have to continue vaccination for the maintenance of a stable prevalence of zero until a global measles eradication programme was successful – which may mean forever.

2.2 Vaccination programmes

If one wishes to use R_0 in order to determine the minimum coverage required for elimination or eradication assuming a non-selective programme, one has to take into account the effect of a vaccine on an individual. In general the susceptibility of an individual is reduced by a certain factor. In addition a vaccine could also reduce the infectious period and the infectivity. In the following we concentrate however on the reduction in susceptibility. The paper by Svensson[19] assumes a general distribution function for the susceptibility among the vaccinated. Special cases have been discussed in the literature. For example Greenland and Frerichs[20] assume that a fraction r is

completely immunized, i.e. the susceptibility is reduced to zero. For the remaining fraction $1-r$, the susceptibility is reduced to the value $1-s$. If c denotes the coverage of the vaccination programme, i.e. the proportion of the population vaccinated, then the vaccination programme reduces the reproduction number to the value

$$R_0\{1-c[1-(1-r)(1-s)]\}.$$

From this it follows that the minimum coverage for elimination or eradication is given by

$$c>(1-R_0^{-1})/[1-(1-r)(1-s)].$$

For many vaccines it may be appropriate to set $s=0$, i.e. the vaccine has an all or nothing effect: either the vaccine completely protects the individual (which happens with probability r) or the individual is completely susceptible (which happens with probability $1-r$). In the terminology of Smith *et al.*[21] this corresponds to a 'Model 2' vaccine. The other extreme assumes $r=0$ such that all vaccinated individuals have the same reduced susceptibility $1-s$. Such a model may be appropriate for inactivated polio vaccines. The corresponding assumption is referred to as 'Model 1'. If r and s are smaller than 1 then the lower bound for the coverage may be greater than 1, which would mean that even for 100% coverage eradication or elimination is not possible. From the lower bound given above this conclusion depends very much on the value of the basic reproduction number.

2.3 Chemotherapy or reduction of the contact rate

If we consider a control programme which reduces either the duration of the infectious period by chemotherapy or the contact rate by changes in behaviour then the reproduction number $R^\star$ is given by the following formula

$$R^\star=\frac{h\kappa D}{r_\kappa r_D}=\frac{R_0}{r_\kappa r_D},$$

where r_κ and r_D denote the reductions for the corresponding parameters indicated in the index. For elimination or eradication $R^\star$ has to be less than one. Therefore the $r_\kappa r_D$ has to be greater than R_0. This inequality clearly shows that R_0 can be interpreted as the minimum absolute elimination or eradication effort, if we are dealing with a homogeneous population, and a control method which effects everybody in a non-selective way. This means that the minimum proportional reduction of the susceptible fraction is given by

$$1-R_0^{-1},$$

which is a highly non-linear function of R_0. For $R_0>10$, control programmes have to be nearly perfect requiring a reduction of the parameters by more than 90%; whereas for values of R_0 between 1 and 2 a reduction of the parameters by less than 50% will already be successful. This non-linear relationship between the minimum proportional reduction in the transmission factors κ and D, and the basic reproduction number R_0, is the key to understanding the puzzle that apparently the same control programme may be successful in one situation and not at all in other situations.

For the evaluation of control strategies it is not only important to estimate by how much R_0 exceeds 1 but also to determine how sensitive R_0 is with respect to changes of individual parameters entering into a formula of R_0. In the simple formula given above this is straightforward. But if individual parameters enter in a nonlinear way, then important conclusions may be drawn about the relative effect of different control strategies. We shall illustrate this point in the next section in comparing larvicides versus adulticides for malaria control, and use of condoms versus reduction of the number of partners in the prevention of STDs.

3 Estimation of R_0 using data about individual parameters

As we have seen above, R_0 depends on three parameters:

1 The contact rate
2 The duration of the infectious period and
3 The probability that a contact between an infective and a susceptible individual leads to an infection.

The last parameter is sometimes broken down into two factors describing infectivity and a factor describing the susceptibility.[22] Obviously if all individuals are alike then one cannot identify the individual components of this product. If however there is heterogeneity with respect to infectivity and susceptibility, then the ratios between the values in the corresponding subgroups may be estimated.

The estimation of R_0 on the basis of the individual parameters will be particularly relevant in populations where the infection is absent and there is a problem of assessing the risk of an epidemic. It is obvious that an attempt to estimate R_0 is only meaningful for diseases, where contacts are clearly defined such that they can be counted. This excludes whole classes of infectious diseases like measles and cholera, where the spread is either airborne or due to contamination of food and/or water. Because of this limitation, attemps to determine R_0 directly from individual parameters have been restricted: on the one hand to vector-borne infections based on estimates of the number of human bloodmeals which one vector takes per unit of time and the number of vectors contacting one human host per unit of time; and on the other side for STDs based on estimates of the number of new partners per person per unit of time and the number of contacts per partner.

3.1 Estimation of R_0 for malaria

The formula of R_0 for malaria involves the following parameters: let m be the number of female mosquitoes per human host and κ be the number of human bloodmeals which one female mosquito takes per day. This involves the rate of taking a bloodmeal and the probability of choosing man as a host. In the mosquito there is a latency period I_2, the so-called extrinsic cycle, which is necessary for the development of sporozoites after the mosquito was infected by gametocytes. Because of the high death rate μ_2, only a small fraction $\exp(-\mu_2 I_2)$ survives this latency period. Let D_1 be the duration of the infectious period in the human host and D_2 be the duration of the infectious period in the vector, and let h_1 and h_2 be the probabilities per bloodmeal of infecting a susceptible

human host by an infectious mosquito and *vice versa*, respectively. Putting all these parameters together one arrives at the following formula

$$R_0 = \sqrt{m\kappa D_1 h_2 e^{-\mu_2 I_2}(\kappa D_2 h_1)} = \sqrt{m\kappa^2 e^{-\mu_2 I_2} D_1 D_2 h_1 h_2}.$$

Macdonald[23] provides an example based partly on entomological observations and partly on assumed values: a mosquito density in relation to man $m = 10$, a daily feeding frequency on man $\kappa = 0.5$, a daily survival probability of the mosquito of 0.9, which corresponds to a life expectancy D_2 of 9.5 days, and a survival probability of 0.39 for a 9 day long extrinsic cycle. For the duration D_1 of the infectious period in man an interval of 80 days is assumed. Putting all these parameters together and assuming $h_1 = h_2 = 1$ Macdonald comes to a value for what we would now call R_0^2 of roughly $735 \approx 10 \cdot (0.5)^2 \cdot 0.39 \cdot 80 \cdot 9.5$ which gives a value of $R_0 = 27.1$. Since it is assumed that the infection probability per contact in each direction equals one, this means that the estimate represents an upper bound.

With the exception of the parameter D_1 all the other parameters are determined by entomological measurements. Garrett-Jones[24] introduced the expression 'vectorial capacity' for the product

$$m\kappa^2 e^{-\mu_2 I_2} D_2,$$

which he interpreted as 'the average number of inoculations with a specified parasite originating from one case of malaria in unit time that the population would distribute to men if all the vector females biting the case became infected'. Garrett-Jones clearly stressed that the vectorial capacity 'is a characteristic of a mosquito population related to the ecological conditions and may be assessed irrespective of whether any cases of malaria are present at the given place and time'. A comprehensive survey of methods to estimate the individual components of the vectorial capacity is given by Molineaux *et al.*[25] (See Dye[26,*] who raises the question of whether one must measure all the components.)

Najera[27] compared the methods of estimating R_0 on the basis of individual parameters with other methods based on equilibrium assumptions, and found great discrepancies which we shall explain later.

There have been some attempts to assess the effects of modifying certain assumptions on which the formula for R_0 given above is based. The present model assumes that there is an age-independent mortality in the mosquito. Clements and Paterson[28] however estimate the effect on the basic reproduction number if one takes into account that the vector's death-rate may increase with the vector's age. They assume an exponential increase according to a Gompertz function. It is shown that the neglect of increasing mortality may overestimate R_0 considerably.

It is very difficult to collect reliable data for the estimation of the individual entomological parameters. The product $m\kappa$ for instance, the so-called 'man-biting-rate' is estimated by exposing human baits during whole nights and catching all mosquitoes landing on their legs and trying to collect a bloodmeal. The daily survival probability is estimated from the interval between two ovipositions and the proportion of mosquitoes having laid eggs at least once, i.e. the proportion of parous mosquitoes. Particularly difficult is the estimation of the probability of choosing man as a host. One collects

*Dye C. The analysis of parasite transmission by bloodsucking insects. *Annu Rev Entomol* 1992; **37**: 1–19.

mosquitoes in their resting-places and determines the proportion of human bloodmeals which they are digesting. Since one is usually collecting mosquitoes near human dwellings the mosquito population sampled may give a highly biased estimate for the total mosquito population which is in contact with man. The greatest uncertainty is associated with the infection probabilities h_1 and h_2. In an endemic situation one can compare the so-called 'entomological inoculation rate' with the 'epidemiological inoculation rate'. The former would be the man-biting-rate by mosquitoes with sporozoites in their salivary glands. The latter is determined by fitting catalytic models to age-specific prevalance curves of infants in order to estimate the daily force of infection, i.e. the rate at which infections are acquired per unit of time (see Section 6.2 below). The ratio of the epidemiological and the entomological inoculation rate is an estimate of h_1. In certain places this may be as low as 0.01. But such an estimate may not be relevant for calculating R_0 because it may be affected by immunity in the human population.

In summary it is fair to say that it is impossible to give absolute estimates of R_0 based on individual parameters for malaria. However attempts to estimate the vectorial capacity, i.e. the contact rates between human hosts via the vector, are still valuable in order to provide relative estimates which explain differences of incidence and prevalence in different populations. Expressing R_0 in terms of the individual entomological parameters which may be affected by alternative control strategies helps to assess the different effect of larvicides and adulticides, i.e. the reduction of the mosquito density without effect on mosquito survival and the reudction of mosquito survival.

Let ν_2 denote the number of newly emerging female mosquitoes per human host per unit of time. Then the mosquito density m can be written as

$$m = \nu_2 D_3 .$$

Larvicides would reduce the emergence rate ν_2 and alduticides would reduce the life expectancy D_2 of the vector. The corresponding reductions are denoted by r_{ν_2} and r_{D_2}. We can express $R^\star$ on the one hand as a function of r_{ν_2} and alternatively as a function of r_{D_2}. Because the two expressions have to be equal, one can derive the following formula which expresses r_{ν_2} in terms of r_{D_2}:

$$r_{\nu_2} = r_{D_2}^2 \exp[\mu_2 I_2 (r_{D_2} - 1)].$$

All parameters which are not affected by the two control methods can be cancelled. It is clear that the situation without control ($r_{\nu_2} = r_{D_2} = 1$) must be a solution of this equation. But we also see that the reduction in mosquito emergence through larvicides r_{ν_2} which would bring about the same value of $R^\star$ as a given reduction in mosquito survival described by r_{D_2} is much greater. For $r_{D_2} = 2$ we obtain $r_{\nu_2} \approx 10$ and for $r_{D_2} = 4$ we have $r_{\nu_2} \approx 274$. This means that a reduction of the mosquito's life expectancy by 50% or by 75% brings about the same value of $R^\star$ as a reduction of mosquito density by 90% or by 99.6%, respectively. 'The single most important insight into public health from modelling has probably been in the consequences of different insecticidal methods for transmission of mosquito-borne disease agents with an extrinsic developmental cycle in the insect' (Bradley).[29]

Molineaux[30] points out however two caveats with respect to this approach:

1 'The identification of the weakest point on which to concentrate control efforts does not follow *automatically* from the sensitivity analysis; it obiously depends also on the

cost and effectiveness of the intervention methods by which we can affect the various factors.'

2 'Models commonly assume more uniformity than there is in reality, and in terms of control this usually leads to exaggerated optimism.'

3.2 Estimation of R_0 for AIDS

The AIDS epidemic has tremendously stimulated the development of mathematical models of infectious diseases. Among the numerous problems addressed we restrict ourselves to the estimation of R_0 for the heterosexual population. In Europe the proportion of AIDS cases which are attributed to heterosexual transmission outside the group of IV drug users is (still) very low. Some authors[31–33] have raised the question whether R_0 for the heterosexual population is greater or smaller than 1. They use data on sexual behaviour for the heterosexual population to estimate a mean and variance of the number of new partners per year. They also use estimates for the average duration of the infectious period and for the infection probability per partner. On the assumption that individuals with different rates of acquiring new partners choose their partners randomly (proportional mixing), R_0 is proportional to the ratio of the second moment of the partner-acquisition rate and the mean.[34] Bonneaux and Howeling[31] and Blower *et al.*[32] obtain a value of R_0 which may be slightly below or slightly above the critical value of one. Stigum *et al.*,[33] using a much more complicated model, come to the conclusion that 'with present sexual behaviour the indigenous spread of HIV is not likely to sustain an epidemic in the Norwegian heterosexual population.' It must however be stressed that these estimates depend crucially not only on the underlying parameter values, which are sometimes based on rather small samples, but also on the model assumptions which determine the formula for R_0 which is used. One aspect for example which is neglected in the present models is the age preference in sexual choice. Knolle[35] shows in a simplified model how this factor may greatly influence the estimate of R_0.

The model of May and Anderson[34] assumes that the infection probability per partner does not depend on the number of contacts per partner. Later they justify this assumption by reference to data by Peterman *et al.*[36] where no relationship could be found between the risk of HIV transmission and the number of contacts at risk. Kaplan[37] presents a possible explanation by postulating that individuals with a high rate of partner change, and therefore a low number of contacts per partner, would tend to practise riskier sex acts. The model with a constant infection probability per contact is not consistent with the data of Peterman *et al.* One has to assume either variability *between* the individual couples or within a couple during the course of the infection.

Diekmann *et al.*[38] provide a framework for calculating R_0 for AIDS taking into account simultaneously variable infectivity and pair formation. The number of contacts per partner is modelled in a dynamic way. In models with pairing, i.e. multiple contacts with one partner, one has to take into account the time spent by the index case with the infecting partner. From the model equations it is clear that the relevant parameters which enter the formulae have to be estimated from data describing the behaviour of HIV infected individuals. What matters is the number of new partners which a newly infected individual acquires during the total infectious period, and the total number of contacts and how they are distributed among the various partners. The model takes into account that a partnership may have a higher risk of separation due to the disease-induced death of a partner. This raises the question to what extent data collected in the general population among susceptibles is representative for HIV infected individuals.

Also the number of contacts during the infectious period may undergo a disease-induced reduction. Therefore the present estimates for R_0 in the papers quoted above have to be considered very tentatively. New models have to be developed which would allow one to derive estimates of R_0 if one had the appropriate data. Also, further data are needed to improve estimates of the infection probability per contact and the duration of the infectious period. The models for R_0 also need extension in terms of behavioural variables such that alternative interventions can be compared with respect to their impact in reducing R_0.

Models which take partnership duration into account produce highly nonlinear formulae with respect to the parameters describing HIV transmission. For constant infection probability per contact h one gets the following formula:

$$R_0 = Nh_p,$$

where

$$N = \frac{\rho(\mu_1+\sigma)(\mu_0+\mu_1+\sigma+\beta h)}{\mu_1[(2\mu_1+\sigma)(\mu_0+\mu_1+\sigma+\rho+\beta h)+h\rho(\mu_0-\mu_1+\beta)]},$$

and

$$h_p = \frac{h(\mu_0+\mu_1+\sigma+\beta)}{\mu_0+\mu_1+\sigma+\beta h}.$$

Here N is the number of new partners during the infectious period and h_p is the infection probability per partner. The individual parameters have the following definitions (in the order of appearance in the formula for N):

ρ the rate of acquiring a new partner for a single individual;
μ_1 the death-rate of an infected individual;
σ the separation rate of a partnership;
μ_0 the death-rate of a susceptible individual;
β the rate of sexual contact during a partnership;
h the infection probability per contact.

The formula for the infection probability per partner can be considerably simplified if one introduces the probability generating function $f(x)$ for the number of contacts per partner:

$$f(x) = \sum_{k=1}^{\infty} p_k x^k.$$

The summation starts with $k = 1$ since by definition of a partner at least one contact takes place. If the number of contacts during a partnership equals k, then

$$h_p = 1-(1-h)^k,$$

and in general one gets[39]

$$h_p = 1-f(1-\mathrm{h}).$$

In the simple case of partnerships with an exponentially distributed duration and a Poisson process of contacts with rate β, one obtains a zero-truncated geometric distribution:

$$f(x) = x/[1 + (c-1)(1-x)],$$

where c is the average number of contacts per partner. The expected number of contacts of an infected partner with a susceptible partner is given by

$$c = 1 + \beta/(\mu_0 + \mu_1 + \sigma),$$

because the average duration of such a partnership is $(\mu_0 + \mu_1 + \sigma)^{-1}$. Let C denote the total number of expected contacts with susceptible partners during the infectious period:

$$C = Nc.$$

Then the formula for R_0 may be simplified as follows:

$$R_0 = hCN/[hC + (1-h)N].$$

This simple formula clearly shows how R_0 depends jointly on the number of partners and the number of contacts during the infectious period. If $C = N$, i.e. if only one contact takes place per partner, then

$$R_0 = hN = hC.$$

For a given number of total contacts C, this formula provides a lower bound for the number of partners for $R_0 > 1$:

$$N > 1 + (1-h)/[h(C+1) - 1].$$

This inequality is only meaningful for

$$h > (C+1)^{-1}.$$

This shows that for a per-contact-infection probability h of 0.2% and $C = 1000$ (100 contacts per year for 10 years) only 2 partner in 10 years are required to bring R_0 above 1.

Let r_h and r_N denote the reductions for the per-contact-infection probability h and the number of partners N, respectively. It is assumed that the total number of contacts C is kept fixed. In order to compare the relative efficiency of reducing h and N we can first express the reduced $R^\star$ as a function of r_h and r_N, respectively, and subsequently express r_N as a function of r_h:

$$r_N = 1 - q + qr_h,$$

where

$$q = N/(hC).$$

Obviously we have $r_N = 1$ for $r_h = 1$. Whether a given proportional reduction of N is more effective in reducing $R^\star$ than the same reduction of h depends on q. For $q > 1$; i.e. for $N > hC$, the best advice would be to reduce h, i.e. to use condoms. For $q < 1$; i.e. for $N < hC$, a given proportional reduction of the number of partners N would reduce R_0 more than a similar reduction in h. In applying this conclusion the two caveats of Molineaux[30] given in Section 3.1 should be kept in mind.

4 Estimating R_0 from the initial rate of growth of the epidemic

When the AIDS epidemic started to attract the attention of the press, the increase of the cumulative number of cases seemed to be exponential with doubling times in the order of less than one year. This caused some authors to derive relationships between the initial growth and R_0. For a very simple model, Jacquez and Simon[40] use the following formula of Anderson *et al.*[41] which yields a value of R_0 of 19.7 for the San Francisco gay community:

$$R_0 = 1 + \frac{D \ln 2}{t_d}.$$

Here D is the duration of the infectious period and t_d is the initial doubling time. Cairns[42] applies a more detailed model to establish a relationship between the initial rate of growth and R_0 which is now no longer explicitly determined because it has to be calculated as the eigenvalue of a certain matrix, taking into account the heterogeneity in the contact rates and variable infectivity.

5 Estimates of R_0 based on the final size of an epidemic

Smith[7] proposed to estimate R_0 by the inverse of the proportion of susceptibles after the termination of an epidemic. As an example he refers to urban yellow fever epidemics which stopped when 48–65% of the population had become immune. Accordingly the estimate of R_0 would be between about 2 and 3. According to the theory of the deterministic general epidemic one gets the following simple formula[12] between the proportion u_∞ of susceptibles after the termination of an epidemic and R_0:

$$R_0 = (1 - u_\infty)^{-1} \ln u_\infty^{-1}.$$

This means for the values reported by Smith the estimates of R_0 would be between 1.4 and 1.6, with the consequence that immunizing about 38% of the population would have been sufficient to prevent the epidemic. (If one takes the inverse of the proportion of susceptibles one would require immunizing about $\frac{2}{3}$ of the population.) It should be stressed however that the formula given above assumes that the total population was susceptible at the beginning of the epidemic. In general one has the following formula[43]:

$$R_0 = (u_0 - u_\infty)^{-1} [\ln u_0 - \ln u_\infty],$$

where u_0 denotes the initial proportion of susceptibles. If for example due to previous

epidemics already 25% of the population would be immune, i.e. $u_0 = 0.75$, then R_0 would be 1.9. The differences of the various estimates do not appear to be large, but one has to keep in mind that small differences of R_0 between 1 and 2 imply important differences of the resulting prevalence.

In 1967 an outbreak of smallpox occurred in a socially isolated community in Abakaliki in south-eastern Nigeria. It was investigated by Thompson and Foege.[44] It would be interesting to find out more details about this epidemic because starting with Bailey and Thomas[45] many statistical analyses of this data set have been published (see Becker[46] for references). Bailey and Thomas[45] list the number of days between 30 cases. Part of the population consisted of 120 members of a religious group who in principle refused to be vaccinated. If one assumes that initially all individuals except the introductory case were susceptible then the formula given above yields an estimate of 1.15 for R_0. Bailey and Thomas[45] mention however that 'about a quarter of them appeared from scars in fact to have been vaccinated at some time or other'. This suggests that the initial proportion of suceptibles was 75%, which would bring the final proportion of susceptibles to 50% which corresponds to R_0 of 1.62. This religious group lived together with other individuals who did not belong to this group and who were vaccinated. A re-analysis of this epidemic, based on the original report, is in preparation. The survey paper by Becker[47] in the present issue contains a description of his estimation approach for R_0 using martingale theory.

6 Estimating R_0 using data from equilibrium situations

6.1 Estimation of R_0 based on age-independent prevalence data

As indicated above the definition of R_0 does not depend on the assumptions about immunity subsequent to the infectious period. The concept is based on a hypothetical situation where one infective is introduced into a large susceptible population. In practice such situations hardly ever occur, such that one has to base estimates of R_0 on data available in endemic situations where the infection is present for a long time. However, this requires detailed knowledge about the density-dependent regulation of the transmission process which determines the equilibrium endemic level. It also assumes knowledge about the heterogeneities in transmission patterns, as it is obvious that estimates of R_0 based on equilibrium data are highly dependent on the availability of this required information or on the degree to which the assumed mechanisms reflect reality. Macdonald[48] was the first to derive an estimate of R_0, or rather R_0^2 as discussed above, from data on equilibrium prevalence. In Macdonald's model the only regulating factor was the prevention of superinfections in the mosquito, i.e. only susceptible mosquitoes could be infected. He allowed superinfections in man, and the infection risk of the mosquito was not proportional to the prevalence of human infections but to the mean number of infections per human host. (It has been pointed out earlier by Fine[49] that Macdonald's mathematical equations did not correspond to his biological assumptions.) In the notation of the present paper, Macdonald's formula for R_0^2 reads as follows:

$$R_0^2 = [1 - y_2 \exp(\mu_2 I_2)]^{-1},$$

where μ_2 and I_2 have the same meaning as above and y_2 is the equilibrium prevalence of mosquitoes with sporozoites in their salivary glands, i.e. the proportion of infectious

mosquitoes. Based on data from Tanganyika he found a value of R_0^2 of 1.15 which is based on a probability of surviving the extrinsic cycle of 0.39 and a proportion of sporozoite positive mosquitoes of 5%. Macdonald[48] attributed the discrepancy of the present estimate and the previous estimate to the factors h_1 and h_2, i.e. the infection probabilities. In a further paper Macdonald *et al.*[50] derived the following formula for R_0^2 which is based on the force of infection λ_1 (see next section) and on the prevalence y_1 of infectious individuals in the human host:

$$R_0^2 = \lambda_1 D_1(\kappa D_2 + y_1^{-1}).$$

Dietz[51,52] provides a system of formulae which relate the equilibrium variables of the prevalence of infection in the human and the vector host and the force of infection with the square of the basic reproduction number. The five models differ with respect to their assumptions about density dependent regulation:

Model I: No superinfections in man and mosquito.
Model II: Superinfections in man but infectivity to vector proportional to prevalence of infection; no superinfection in the vector.
Model III: Superinfection in man; infectivity to vector proportional to number of infections; no superinfection in vector.
Model IV: No superinfection in man; superinfections in the vector and infectivity to man proportional to number of infections.
Model V: Superinfections in man; infectivity to vector proportional to prevalence of infection; superinfections in vector and infectivity proportional to number of infections.

From the formula for R_0 based on the force on infection one can see that it corresponds to Model II in the list given above. Najera[27] used these formulae with data collected in a field project in Nigeria, which was carried out to test whether malaria could be eradicated in Africa with a combination of spraying DDT and mass drug administration. For example, in the treated zone for the period mid-July to mid-September 1967 he gets the following three estimates for R_0^2:

1.02 (based on the proportion of infectious mosquitoes);
2.88 (based on the force of infection and the proportion infectious in the human population);
135.77 (based on the vectorial capacity).

It is no surprise that the first two estimates differ because they are based on different assumptions about the density-dependent regulation. The first one is based on Model III and the second one on Model II.

The observation that estimates of R_0 based on prevalences in equilibrium situations in the human and the vector host tend to be smaller than expected from direct observations of the transmission intensity has also been discussed by Barbour.[53] He considers a model for schistosomiasis which mathematically speaking is equivalent to Model III given above. According to this model the basic reproduction number is only determined by the proportion of susceptible snails. Since these proportions are usually in the order of 1 to 10% the corresponding values for R_0^2 are only slightly above 1. Because this is considered

to be unrealistic, Barbour takes into account immunity in the human host and derives equations which would allow one to estimate R_0^2 by the inverse of the product of the proportion of susceptible human hosts and susceptible vectors, suitably modified to adjust for temporary immunity. By using data from the field he obtains an estimate of $R_0^2 = 6.5$. Similar attempts to estimate R_0^2 for other vector transmitted diseases have been carried out by Rogers[54] for the African trypanosomiases and by Hasibeder *et al.*[55] for canine leishmaniasis. The particular emphasis of the second paper is the development of methods for assessing the influence of heterogeneous biting rates of sandflies on dogs. Formulae are derived which allows one to estimate R_0^2 if the proportion of susceptibles in the various subgroups and the ratios of the contact rates between the subgroups are known. Effects of heterogeneity on the relationship between the equilibrium prevalence and the heterogeneity in contact rates has also been investigated by Dietz.[51] Assuming that there is a gamma distribution of contact rates in the human population and that vectors choose hosts randomly proportional to their contact rates (which is called 'proportional mixing' in the epidemiological literature) then the prevalence in equilibrium always decreases as the variance increases. If σ^2 denotes the variance of the contact rate it is shown that the slope of the variance with respect to the square of the basic reproduction number equals $(1+2\sigma^2)^{-1}$, i.e. it decreases for increasing variance. This means that values for R_0 which are based on the assumption of homogeneous mixing, and which use the equilibrium proportion of susceptibles, invariably underestimate R_0.

6.2 Estimation of R_0 based on age-specific prevalence data

In the epidemiology of infectious diseases the data available are often cross-sectional surveys of populations with the aim of determining the age specific prevalence of antibodies with respect to a particular infection indicating past infection. This means that one has only censored data in the statistical sense, i.e. one only knows that for a certain age of an individual the age of infection is less than the current age if antibodies are present, and that the age of infection is greater than the current age if antibodies are absent. Such age specific prevalence data show a typical increase which can be described by so-called catalytic models according to Muench.[56] Muench introduced the term 'force of infection' for the hazard function of a susceptible to be infected in an endemic situation. Dietz[12] showed that this hazard rate can be related to the basic reproduction number in the following way:

$$\lambda = \mu(R_0 - 1),$$

where μ denotes the death rate of the population and λ is the force of infection. In this model it is assumed that there is a constant death rate and an age independent force of infection. If one calculates the average age A at infection one gets the following expression:

$$A = \frac{\lambda \int_0^\infty a e^{-(\mu+\lambda)a} da}{\lambda \int_0^\infty e^{-(\mu+\lambda)a} da} = (\lambda+\mu)^{-1}.$$

If one denotes the life expectancy of a human host by $e_0 = \mu^{-1}$ then the formula for the force of infection yields the following simple expression for R_0:

$$R_0 = e_0/A.$$

This means that the basic reproduction number R_0 can simply be estimated by the ratio of the life expectancy and the average age at infection. In the original paper Dietz[12] denoted the average age at infection by λ^{-1} which yields the formula $R_0 = 1 + e_0/A$. Usually μ is negligible compared to λ such that the difference can be neglected. Anderson and May[57] provide numerous estimates of R_0 based on this formula for common childhood diseases in industrialized and developing countries.

In general, for age-dependent mortality and age-specific force of infection, one gets the following formula for the average age A at infection:

$$A = \frac{\int_0^\infty a\lambda(a)e^{-(M(a)+L(a))}da}{\int_0^\infty \lambda(a)e^{-(M(a)+L(a))}da},$$

where

$$M(a) = \int_0^a \mu(s)ds,$$

and

$$L(a) = \int_0^a \lambda(s)ds.$$

If the force of infection is age-dependent in an equilibrium situation then this reflects heterogeneous contact rates between different age groups. In principle one cannot measure the age-specific contact rates directly in order to calculate R_0. One would need to know the elements of the contact matrix if one would discretize the population into a finite number of age strata. Anderson and May[58] and Schenzle[59] study various assumptions about the structure of the contact matrix. Dietz and Schenzle[60] consider the case of proportional mixing. Under the assumption that the length of the infectious period can be neglected compared to the life expectancy of the individual they derive the following formula for R_0 based on the age-dependent hazard rate $\lambda(a)$:

$$R_0 = \frac{\int_0^\infty \lambda^2(a)e^{-M(a)}da}{\int_0^\infty \lambda^2(a)e^{-(M(a)+L(a))}da}.$$

This shows that R_0 can no longer be simply estimated by the inverse of the proportion of susceptibles in the population. This formula leads to the statistical problem of estimating the force of infection on the basis of a data set where all observations are censored. Grenfell and Anderson[61] use the maximum-likelihood method for some polynomial function describing the age-specific force of infection.

Recently, Keiding[62] presented a nonparametric method to estimate the age-specific

prevalence and the corresponding smoothed force of infection. He applies this method to a data set for hepatitis A in Bulgaria and obtains $R_0 = 3.8$.

7 Concluding remarks

The present review tries to give a summary of attempts to define R_0 in a meaningful way, to derive estimates of R_0 based on epidemic and endemic situations and to interpret R_0 for the evaluation of control strategies. During the last twenty years R_0 has emerged as a basic concept in infectious disease epidemiology, but it has also become apparent how difficult it is to apply in actual field situations. It is hoped that this survey will stimulate further research in this direction.

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