

# Deterministic Modeling Of Infectious Diseases: Applications To Measles And Other Similar Infections

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## Abstract

This paper is second in our series on deterministic modeling (DM) of infectious diseases. The first paper dealt with theories and methods of DM. The current paper provides sensitivity analyses. We used the SEIR model to show how changes in the transition rate from susceptibles to infectious (force of infection), variations in the latent and infectiousness period, and alteration to the vaccination proportion can alter the profile of common childhood epidemics. Various situations are explored so that the reader may grasp the effects of interventions, i.e., altering the main model parameters, upon the size and shape of epidemics, waiting times to epidemics, spreading out of infected cases in time, and switching from an epidemic to an endemic state and to cases eradication. The paper further shows that the introduction of infectious individuals into a community of susceptibles does not automatically give rise to an epidemic outbreak. This analysis thus provides the reader with an understanding of how epidemics evolve and how they can be controlled. Vaccination has been tackled as well as other public-health interventions that may have a bearing on the rate-limiting steps of epidemics. In spite of its limitations, the SEIR model helps gain insight into the dynamics of infectious diseases.

## INTRODUCTION

This paper is an application of the theory and methods of deterministic modeling (DM) to common childhood diseases. It is the second in a series of three. The first paper (1) dealt with the theory and the methods of DM. In this paper, we will show how changes in the transition rates from susceptibles to infectious, or simply varying the other parameters of the SEIR deterministic model, can alter the profile of an epidemic. More specifically, we will look into the variations of the reproduction number, the duration of the latent period, and that of the period of infectiousness. A few situations will be explored in order to allow the reader to grasp the effects of change in these crucial epidemic parameters on the population pattern of infections. Our main disease reference will be measles, but varying the main infection parameters will cover a slew of other childhood diseases such as chicken-pox, mumps or rubella. Mainly, this paper will provide an overview of the potential of DM for the study of common childhood infections. Our aim is to provide the reader with useful insights into the mechanic and control of epidemics.

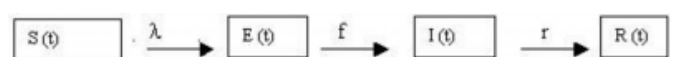
## A MODEL FOR MEASLES

The first step in DM consists in having a complete and realistic picture of the biology of the study disease (e.g.,

period of infectivity, latent period, immune status after infection), and to select a parsimonious model (in relation to data available). In the case of measles, susceptibles get the virus and then become exposed (infected but not infectious) cases. After a given latent period, exposeds become infectious (and can infect newly susceptibles) until they recover. Measles provides long-lasting immunity after infection so that immunizeds (recovereds) do not become susceptibles anew. An appropriate continuous-time interval model for measles would be the SEIR model (Figure 1):

**Figure 1**

Figure 1: The SEIR model



where:

$S(t)$  = number of susceptibles at time  $t$

$E(t)$  = number of exposeds (infecteds) but not yet infectious at time  $t$

$I(t)$  = number of infectious at time  $t$

$R(t)$  = number of recovereds at time  $t$

$\lambda$  = the rate (force) of infection per unit time (the time unit is an interval from  $t$  to  $t + \Delta$  where  $\Delta$  is a very small)

$f$  = the rate at which an infected individual becomes

infectious per unit time

$r$  = the rate at which an infectious individual recovers per unit time.

In this model the rate of change per unit time in the number of susceptibles, infecteds, infectious, and immunizeds is given by the following differential equations:

$$dS/dt = -\beta * S(t)$$

$$dE/dt = \beta * S(t) - f * E(t)$$

$$dI/dt = f * E(t) - r * I(t)$$

$$dR/dt = r * I(t)$$

This model posits the following assumptions: individuals mix at random within the population, age and sex are not crucial variables, and the population size is assumed to remain constant over time with no new entries from births (new susceptibles). Obviously, these assumptions are unrealistic; notwithstanding, the model is able to rescue the familiar cycle of population childhood infections.

The first step in infectious disease modeling is to estimate the transition rates,  $\beta$ ,  $f$ , and  $r$ . The rate of infection, can be expressed in terms of the probability of effective contact,  $\beta$  and the number of infectious at time  $t$ ,  $I(t)$  [see the first paper in this series]. Propagation of the infectious agent is effectively possible because infectious (and infectious only) can transmit the virus to susceptibles. Consequently, the number of newly infected (exposeds) at each time step depends on contacts between infectious and susceptibles. This is given by  $\beta = \beta * I(t)$ . To estimate the transition rate,  $\beta$ , an approximation related to the basic reproduction number ( $R_0$ ) is used that is defined as the average number of persons directly infected by an infectious case during his entire infectious period when he enters a totally susceptible population ( $N$ ). If each individual effectively contacts (infection is indeed transmitted)  $c$  individuals per unit time, then in a population of size  $N$ ,  $\beta$  is given by  $c/N$ . Assuming random mixing, the number of individuals effectively contacted by each person during the infectious period is given by  $R$  (in the following, we will use the symbol  $R$  for the actual reproduction number to distinguish it from  $R_0$  which is the basic reproduction number and a theoretical parameter by definition). The average number of individuals effectively contacted by each person per unit time is then  $c = R/\text{average duration of infectiousness (D)}$ . Substituting this expression into that for  $\beta$  above gives  $\beta = R/N * D$ . Accordingly,  $\beta$  equals  $(R/N * D) * I(t)$ .

To estimate the transition rates  $f$  and  $r$  is a simple matter. Given a constant rate over a time period (duration), the rate at which the event occurs is determined by the inverse of the waiting time to the event (duration). Consequently, the transition rate by which exposeds become infectious,  $f$ , can be derived from the average latent period, and the recovery rate,  $r$ , can be obtained from the average duration of the infectivity period as follows: infectivity rate ( $f$ ) = 1/average latent period; recovery rate ( $r$ ) = 1/ average duration of infectiousness. It is crucial to grasp that the latent and infectivity periods are not the sole  $R$  components to bear upon the pattern of epidemics in populations. Therefore, any prediction of the number of new cases in an epidemic is not straightforward as the relationships among the various model compartments are nonlinear. The following graphs ought to be read as one would do for cohorts studies, i.e., time is the leading factor and, as time goes by, the susceptibles pass from one compartment to the following. The number of subjects within any given compartment over time hinges upon the transition rates, the differential of the various transition rates, and the value of  $R$ . We will now turn to the SEIR model and run it with software ModelMaker (Family Genetix) to assess the impact of different values of these transition rates on the epidemic.

**SIMULATIONS RESULTS**

**REPRODUCTIVE NUMBER  $R = 1$**

Let us suppose that we have a population of 100 000 individuals and that the reproductive number  $R$  is 15 (each infectious will infect 15 susceptibles on average during the infectious period). Let us further suppose that the latent period is about 8 days, and the duration of infectivity is 7 days. These data are in line with measles (3). The transition rates can then be derived as follows:

$$\text{Force of infection } (\beta) = \beta * I(t) = (R/N * D) * I(t) = (15/100000 * 7) * I(t) = 0.000214 I(t)$$

$$\text{Infectivity rate } (f) = 1/\text{average latent period} = 1/8 = 0.125$$

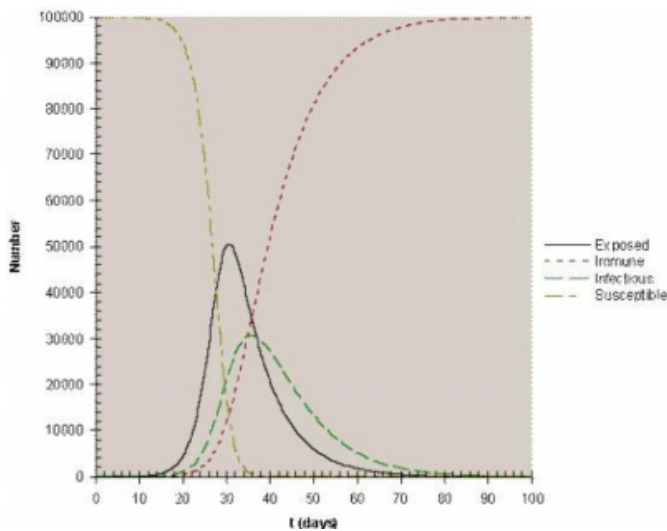
$$\text{Recovery rate } (r) = 1/\text{average duration of infectiousness} = 1/7 = 0.143$$

What is seen in Figure 2 (the distribution of the four SEIR compartments over time) is typical of what occurs after the introduction of one infectious case of measles in a population of susceptibles given its strong reproductive number  $R$ . The repetitive cycles of epidemics commonly observed in time series of measles are concealed because there are no new entries from births in that virtual

population, only depletion of susceptibles. Things therefore go as though only one epidemic were to be observed from only one wave of susceptibles that ultimately goes to extinction. As a matter of fact, the necessary condition for an epidemic is that  $R > 1$ . This means that every infectious person on average does infect more than one person. This is sufficient to disseminate the infectious agent. In this case, the number of exposeds and infectious increases rapidly until most susceptibles are infected. Of course, susceptibles decrease at the same rate as exposeds and infectious increase, and the velocity of these changes has an effect on the rate at which immunized appear. It is also worth noting that the curves of the infectious and exposed are not normal but slightly elongated towards the right in line with the asymmetry characterizing many epidemics. The slight positive asymmetry of these curves is also akin to the distribution of the incubation period described by Sartwell for common-exposure infections (4).

**Figure 2**

Figure 2: Number of Susceptibles, Exposed, Infectious and Immunized



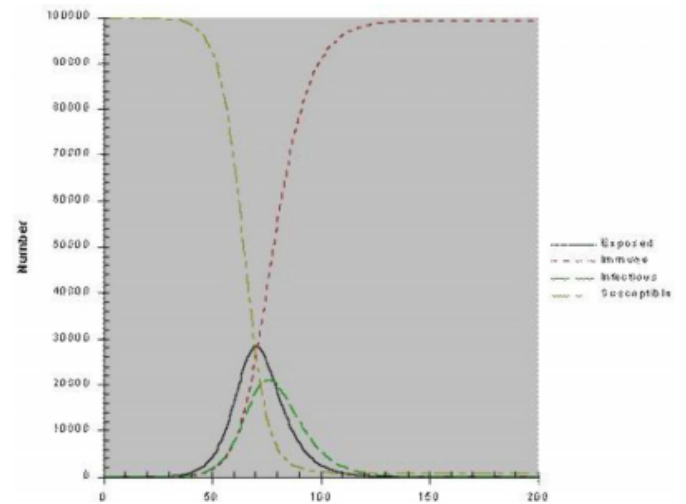
( $R=15$ , latent period=8days, period of infectivity =7days)

Although the pattern of such curves remains invariant for many values of the infection parameters, it will nevertheless evolve according to changing  $R$  values. Incidentally, let us now suppose that the reproductive number  $R$  falls off to 5 (because of vaccination, for instance) and that all other parameters remain constant. This means that the force of infection declines. Figure 3 shows what happens to the dynamics. Not only does it now take longer to bring about the expected epidemic cases, but the number of infected and infectious would also be reduced. Further, we would have to

wait until day 30 of the epidemic process before exposeds appear rather than day 14 as in Figure 2 (note that the x-axis scale is broader).

**Figure 3**

Figure 3: Number of Susceptibles, Exposeds, Infectious and Immunized

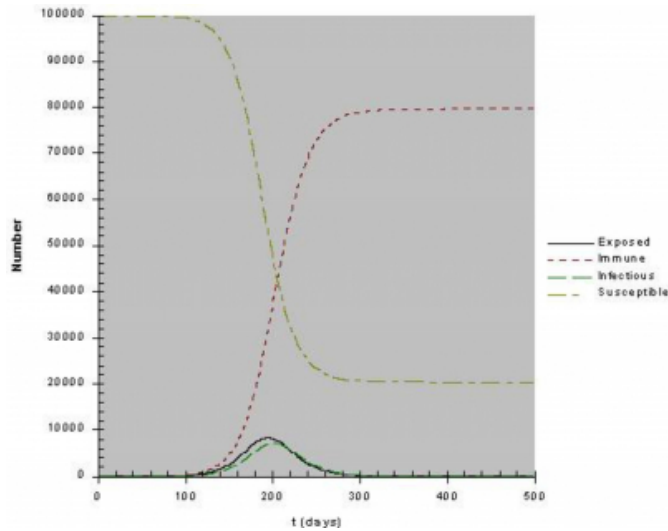


( $R=5$ , latent period=8days, period of infectivity =7days)

To now grasp what occurs when  $R$  is lowered even more, let us look at the graph when its value reaches 2. Figure 4 shows that the period of time for cases occurrence is longer. Furthermore, the number of susceptibles decreases more smoothly to reach 20 000 individuals. On the other hand, the number of immunized increases symmetrically up to 80 000. This means that 80 000 persons will get measles while 20 000 never will. The epidemic is thus less extensive; many new cases occur, but several individuals never get the disease because the force of infection (that depends upon the risk of transmission per contact) is low.

**Figure 4**

Figure 4: Number of Susceptibles, Exposeds, Infectious and Immunizeds



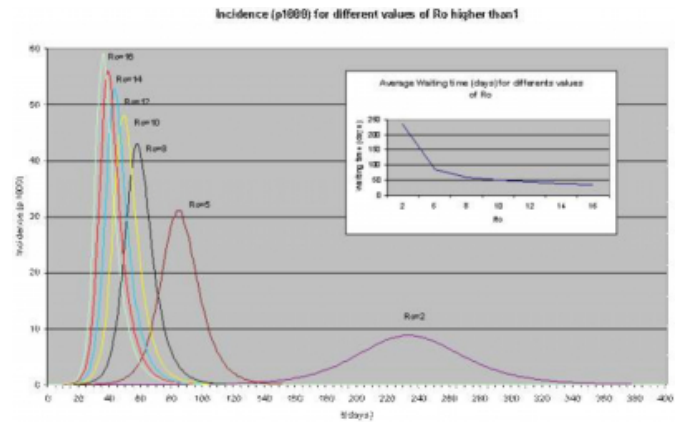
( $R=2$ , latent period=8days, period of infectivity=7days)

By the way, lower  $R$  values set in progressively in the course of an epidemic because the increasing number of immunizeds in the population finally impinges on the probability of contacts between infectious and susceptibles; this is known as the gradual setting of herd immunity. Acknowledgement of this phenomenon may help understand why vaccination does control epidemics. Aiming at increasing herd immunity, vaccination actually reduces the number of susceptibles (converting them directly into immunizeds) and decreases the probability of effective contacts between susceptibles and infectious. Further, decreasing  $R$  towards 1 introduces stochastic elements into the system, thereby loosening the relationships between the various system compartments; this could contribute to the eventual drifting of the infection out of the population. If the disease ever disappears from the population during an epidemic trough, it can be brought back only if one infectious enters the population anew later on. This can elicit long periods of extinction of the disease as observed in small islands like the Faroe that have unexpectedly dispersed epidemics of measles (among others) separated by large troughs with no cases (5). Admittedly, about 250 000 susceptibles (critical community size) are required to maintain measles at the endemic state in populations (6).

In order to provide a more thorough picture of the effect of  $R > 1$  on the epidemic pattern, Figure 5 depicts the impact of different  $R$  values on the incidence of cases and the mean waiting time to cases.

**Figure 5**

Figure 5: Incidence (per 1000) and average waiting time to epidemic according to various values of  $R$  (latent period= 8 days, period of infectivity = 7 days)

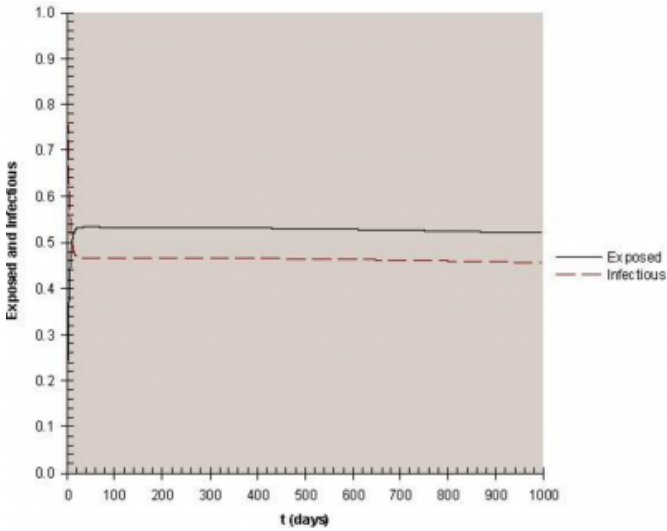


Clearly, when  $R$  decreases, not only the frequency of infected cases decreases, but the epidemic curve spreads out and shifts to the right. The decrease from high to low  $R$  values, while linear in the high-value domain, becomes increasingly more nonlinear when low values of  $R$  are reached. Further, the inset shows that the smaller  $R$ , the longer the mean waiting time to cases and the longer the period over which cases occur. Again, the relation of the waiting time to  $R$  is nonlinear. It is also worth pointing out that, following the introduction of an infectious in a population, even small positive  $R$  values induce infected cases, the number of which is however expected to remain low; this is because the probability of contact between susceptibles and infectious approaches zero. However, changes in waiting times and epidemic sizes become substantial for  $R$  values higher than 5.

Finally, a reproductive number  $R$  exactly equal to 1 creates a particular situation as this threshold will set in the conditions for the turnover of an epidemic into an endemic state. Let us posit that  $R=1$  (latent period = 8 days and period of infectivity = 7 days). Figure 6 shows that the number of infected cases (exposeds and infectious) is constant over time. The total number of infected cases is 0.53 exposed and 0.47 infectious per day. On the other hand, susceptibles and immunizeds decrease and increase respectively (not shown here). The major point is that disease remains endemic.

Figure 6

Figure 6: Number of Exposeds and Infectious



( $R=1$ , latent period = 8 days and period of infectivity = 7 days)

**REPRODUCTIVE NUMBER  $R < 1$**

Another situation signals a bifurcation in the dynamic, it is when  $R < 1$ . In this case, the disease eventually disappears from the population because the exploding potential of the epidemic reverses. The exploding potential of an epidemic is based on a large number of contacts between infectious and susceptibles, thereby generating many secondary cases. In the reversed situation, the frequency of these contacts is rare because herd immunity level in high; consequently, susceptibles can hardly turn over to exposeds and, later, to infectious because most contacts occur among non-infectious. In other words, when  $R < 1$  one infected cannot make sure that, on average, the microorganism he/she carries will successfully be transmitted to one susceptible. In this situation, an epidemic cannot thrive. On the contrary, it dampens out quickly. Figure 7a shows that the number of susceptibles remains constant and at very high levels and the immunizeds frequency (Figure 7b) is low and virtually unchanged with time while the number of exposeds and infectious (Figure 7c) decreases down to zero quickly after the appearance of a few sporadic cases. The case when  $R < 1$  then points out that the introduction of infectious individuals into a community of susceptibles does not automatically induce an epidemic outbreak.

Figure 7

Figure 7a: Number of Susceptibles ( $R=0.75$ , latent period=8 days, infectivity period=7days)

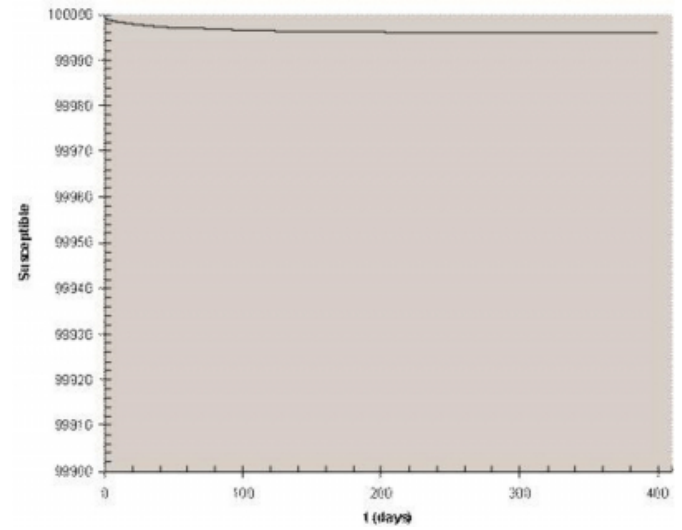
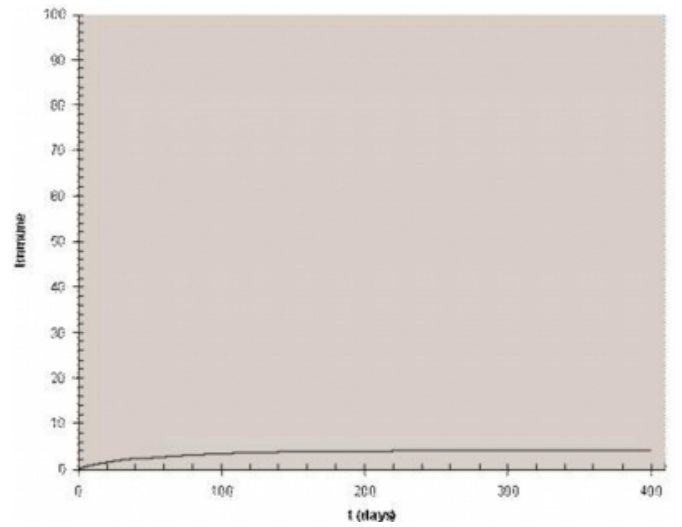


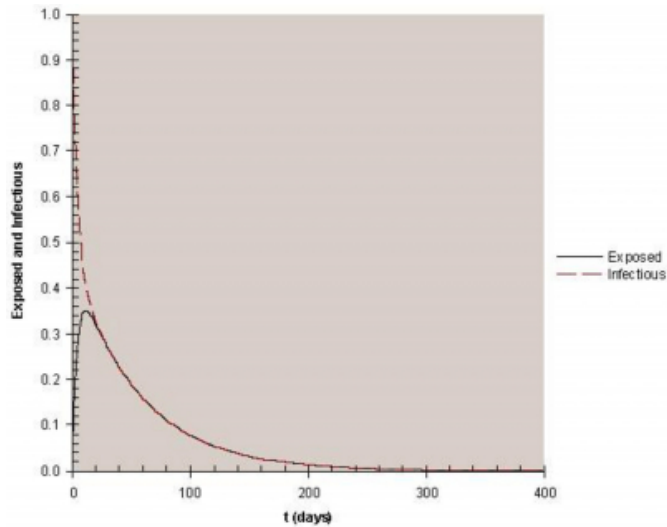
Figure 8

Figure 7b: Number of Immunizeds ( $R=0.75$ , latent period=8 days, infectivity period=7days)



**Figure 9**

Figure 7c: Number of Exposeds and Infectious



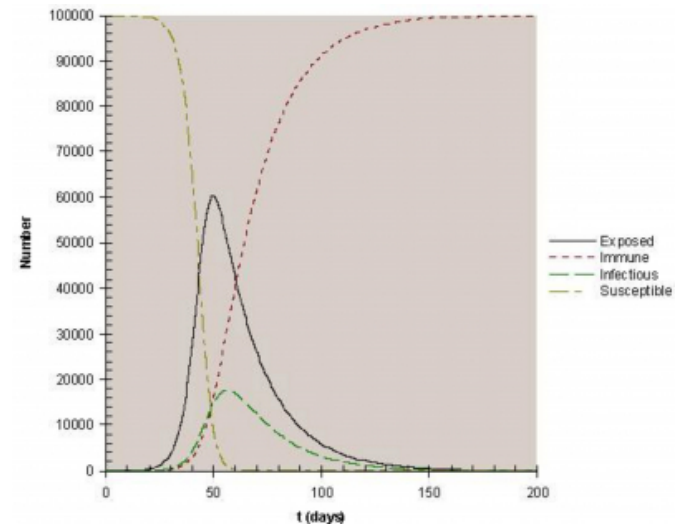
( $R=0.75$ , latent period=8 days, infectivity period=7days)

**THE LATENT PERIOD**

The R values studied above could pertain to different diseases or be the result of public health measures (e.g., vaccination) to control the epidemic. The latent period as well as the infectivity period refer to R components, i.e., they are the key parameters that determine the value of R. Variations in the duration of the latent period due to public-health interventions would thus have an effect on infectious disease dynamic. The general pattern of the epidemic, however, would remain much the same for most R values. To observe changes in the epidemic dynamic, let us suppose that the latent period is 20 days rather than 8 days, R is fixed at 15, the population of susceptibles is 100 000, and the infectious period is 7 days. Figure 8a, though similar to that of Figure 2 (latent period = 8 days), shows that the exposed and infectious occurrences would be postponed. The majority of cases would occur between day 20 and day 170 rather than between day 10 and 100 (Figure 2). Not only cases would occur later, but their occurrence would also be more spread out.

**Figure 10**

Figure 8a: Number of Susceptibles, Exposed, Infectious and Immunized

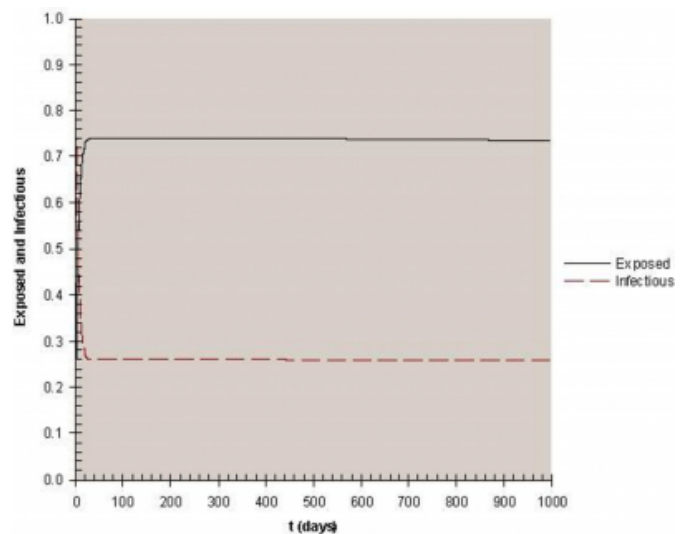


( $R=15$ , latent period = 20 days, infectivity period=7 days)

Now, let us hypothesize the same scenario but with  $R=1$ . The infection dynamic then becomes endemic, and the pattern of occurrence of exposeds and infectious looks different. In Figure 8b the number of exposeds is larger than in Figure 6. In the latter, the number of infectious were about 0.48 per day and exposeds 0.52 per day. In Figure 8b, which is based on a longer latent period, the two curves moved away from each other, down to 0.27/day for infectious and up to 0.73/day for exposeds. The number of infectious is relatively decreased because individuals spend more time in the exposed state.

**Figure 11**

Figure 8b: Number of Exposed and Infectious

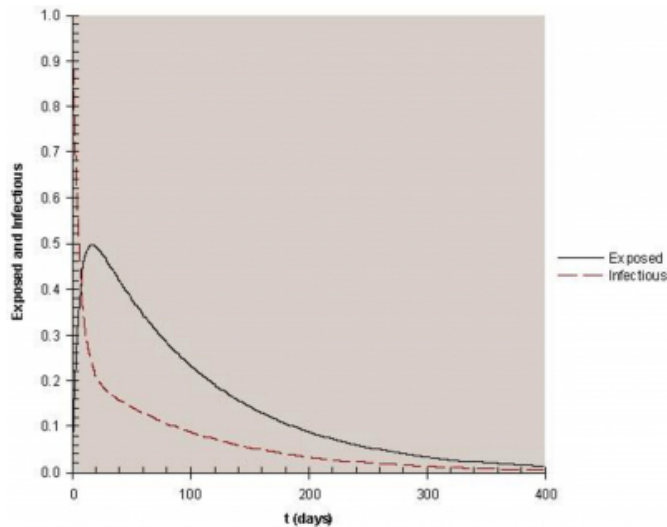


( $R=1$ , latent period=20 days, infectious period=7days.

Increasing the duration of the latent period with  $R < 1$  (figure 8c) entails disease dying out as has been seen in Figure 7c, but the difference between the occurrence of exposeds and infectious is wider with a longer latent period. This is due to the fact that exposeds spend more time, and therefore accumulate, in this state before becoming infectious, and this reflects on the disease which takes more time to disappear.

**Figure 12**

Figure 8c: Number of Exposed and Infected



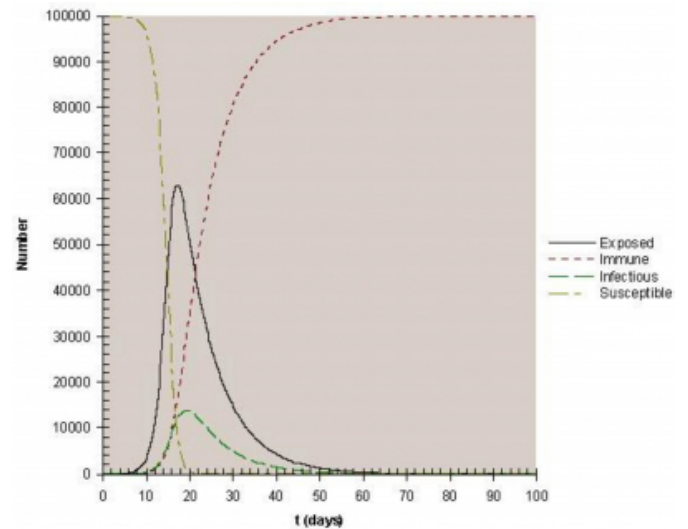
( $R=0.75$ , latent period=20 days and infectivity period=7days)

**THE INFECTIVITY PERIOD**

Now, let us hypothesize an infectivity period of 2 days rather than 7 days, and all other parameters remaining fixed at  $R=15$ , latent period = 8 days, population of 100 000. Figure 9a shows that it takes less time for the exposeds and infectious to occur. Accordingly, the number of susceptibles decreases more rapidly and immunizeds increase in the same way. The number of infectious is reduced with respect to the number of exposeds because they turn over to immunizeds more rapidly.

**Figure 13**

Figure 9a: Number of Susceptibles, Exposeds, Infectious and Immunizeds

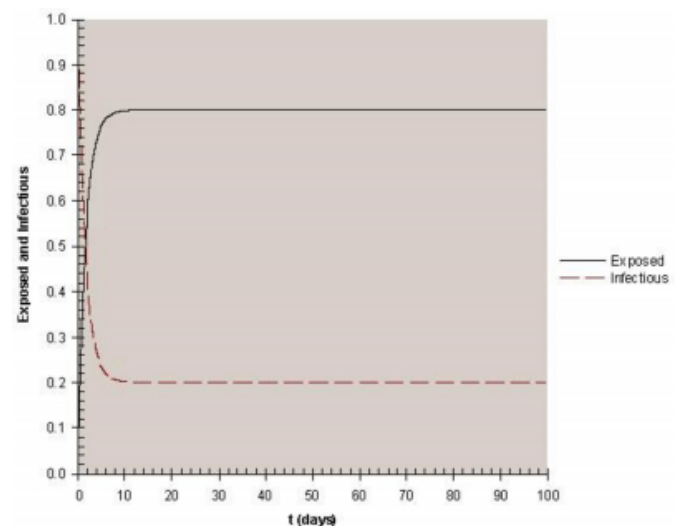


( $R=15$ , latent period=8days, infectivity period=2days)

When  $R=1$  (Figure 9b), the disease becomes endemic, but there is much more difference between the number of exposeds and infectious. The difference is wider between the curve of the exposeds (0.80/day) and the infectious (0.20/day). There is lesser infectious because the period of infectiousness is shorter.

**Figure 14**

Figure 9b: Number of Exposed and Infectious



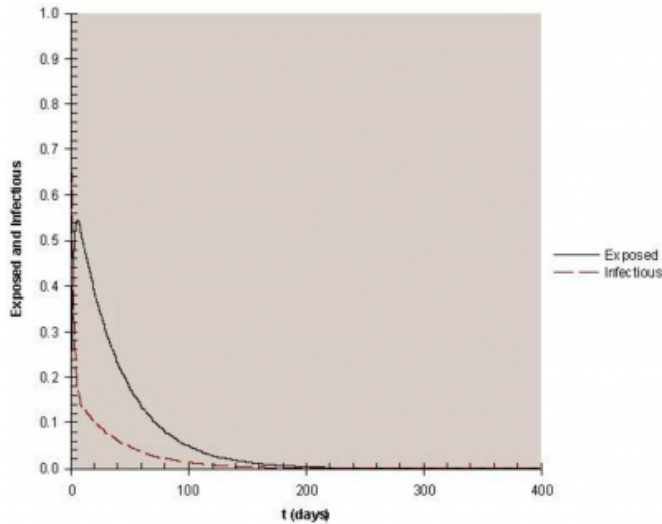
( $R=1$ , latent period=8days, infectivity period=2days)

When  $R$  happens to get less than 1 (Figure 9c), the disease disappears more rapidly from the population with a shorter infectivity period. When considering an infectious period of 8 days (Figure 7c), measles disappeared after 300 days.

However, when the infectivity period is of 2 days, this figure drops down to 200 days.

**Figure 15**

Figure 9c: Number of Exposed and Infectious



( $R=0.75$ , latent period=8 days and infectivity period=2days)

**DISCUSSION**

As it stands, the SEIR model of common childhood infections bear some unrealistic assumptions. The major problem is that the contact pattern in the population is rarely well determined. Contact patterns are often derived from familial settings (2) which, obviously, are not representative of the population at large. Further,  $R$ , which is an average, is not the same for all individuals over all conditions. We have considered that each individual has a constant probability to meet every other individual. Indeed, the probability of effective contacts depends on many different factors that were ruled out of the models in order to keep them simple and easily interpretable. If, for example, subgroups of the population have different contact modes, the variance of the frequency of contacts increases, and the outcome of the epidemic may depart from the situations studied in this paper. Therefore, the potential for an epidemic lies not only with the mean biological parameters of a disease, such as transmission risk or the duration of the infectivity period, but just as much with the way society is organized (variance): how often we travel, the size of our family, division of the school year, density of the population, etc. (2). In the case of measles, for example, it is well known that the transmission potential is higher in autumn with school entry, but this factor was set aside in this paper. In more involved models, variation in contact rates are taken into account with a sinusoidal function or more realistic assumptions. In

addition, the SEIR model does not stratify individuals according to age and sex, and the birth and mortality rate is assumed to remain unchanged over time and space.

Be that as it may, the SEIR model is sophisticated enough to understand the tenets of epidemics. It is remarkable that the SEIR differential equations have captured the main scheme of any epidemic, be it large or small. This regularity has been depicted by the aid of mathematical analyses, and matched with what is indeed observed in populations or expected from real epidemics. We indeed have shown how changes in the transition rates or simply varying the parameters of the SEIR model, can alter the profile of an epidemic. This step of data analysis provided us with a powerful mean to understand how epidemics set up and how they can be controlled.

The rate limiting step of epidemics is the reproductive number  $R$ . By reducing the actual reproductive number, it is possible to reduce epidemic spread in the population. The higher  $R$  is, the more explosive is the disease. If  $R$  reduces to 1, the disease turn from an epidemic to an endemic state. On the other hand, if  $R$  gets less than 1, the disease eventually disappears from the population. Further, the simulations have shown that controlling the infectivity period or the length of the latent period can have a bearing on  $R$ , thus altering the size of the epidemic. Notwithstanding, changes in these parameters do not change the general pattern of the epidemic. More specifically, changing the latent or the infectivity period modifies the waiting time to either the exposeds or infectious while also varying their ratios.

The crucial public-health intervention to limit epidemics is vaccination. Vaccination reduces  $R$  directly, and has a nontrivial effect on the dynamic. Models such as the SEIR can help determine the herd immunity level a population needs to reach to get protection from epidemics. In fact, DM has important implications for the issue of vaccination coverage. What proportion of the population must be vaccinated to prevent an epidemic? Let us suppose that  $R=2$  in a population. In the unvaccinated state, a primary case will infect 2 people. However, if slightly more than 50% of the population are vaccinated against the disease, then  $R<1$ , and the probability of an epidemic evolving from first cases is, on the average, reduced below the threshold, even though any one individual cannot insure that he/she will escape infection.  $R$  is around 15 for measles in North-American populations. To attain an endemic state ( $R=1$ ), 14 persons out of the 15 (93.3% ) need be vaccinated. For the disease to die out, more than 93.3% of the population has to be



vaccinated. Therefore, to prevent epidemics, the proportion,  $p$ , of the population that must be vaccinated is:

$$p > (R-1)/R = 1 - (1/R)$$

With this vaccination proportion, some diseased cases nevertheless occur, but there cannot be any real epidemic. This kind of reasoning was used by WHO to eradicate smallpox. The remaining susceptibles can be protected by the large number of immunized because they reduce the probability of transmission. Therefore, not all individuals from a population need be vaccinated; this is of practical interest as some vaccines bear complications or are costly. Among other interventions that have a bearing upon epidemics, antibiotics can act to reduce the infectivity period of some diseases, and isolating infected cases from susceptibles during the infectivity period can lower  $R$ . Further, given that only some of the contact types are infectious, simple public-health measures can be taken to prevent dissemination of the microorganisms from these contact types; among them are condoms, masks, etc.

This paper has shown how a cohort of new cases accrue from a group of susceptibles, and why epidemics finally die out. Further, detailing the mechanic of epidemic set-up has allowed us to show how targeted interventions, either directly on  $R$  or its components, can alter an epidemic building blocks in predicted ways. DM shows that public-health interventions can be efficient if the detailed mechanic of epidemics is available. An approach that grasps the main

system outcomes is, however, required as well as the nonlinearities naturally involved in complex systems.

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