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Mathematical models and vaccination strategies

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ABSTRACT

Infection transmission is a complex and dynamic process, and is therefore difficult to assess. Consequently, mathematical models are a useful tool to understand any leverage on this transmission, such as vaccination. Models can provide guidance to implement an optimal vaccination campaign whether it concerns the fraction of the population or the age-group to be vaccinated. Mathematical models can also provide insights on counter-intuitive collateral effects of vaccination campaign, given the possibility that the overall benefits for the general population may hide deleterious effects on some sub-groups.

As a large proportion of the population is now vaccinated, complex modelling taking into account individual and population heterogeneity and behaviour is necessary although challenging. But the most crucial aspect in the future of mathematical modelling still consists in obtaining precise and exhaustive data.

1. Introduction

The most important aspect driving the spread of an infection is the transmission of the pathogen from infectious to susceptible individuals. Infectious transmission is a dynamic process, influenced among other things by the number of susceptible individuals, the infectious period, the infectiousness and the duration of immunity resulting from the infection. The nonlinearity of infectious transmission renders it difficult and non-intuitive to gauge. Mathematical models are an efficient way, if not the only one, to assess complex processes such as infection dynamics. Besides, they provide useful and inexpensive tools to test hypotheses on the optimal way to control the spread of an infection, notably through vaccination. Although vaccines are not the only field of application for mathematical modelling, it is worth remembering that the first mathematical model of an infection was developed during the 18th century by the physician and mathematician Daniel Bernoulli to assess the potential impact of immunization with cowpox on the life expectancy of immunized individuals [1].

A common interrogation about mathematical models concerns their ability to be "right" or "true". "Essentially, all models are wrong, but some are useful" is the answer, stated by George P. Box [2], and it is now a motto among modellers. A good example of a "wrong but useful" model was developed to assess the impact of travel restriction on the H1N1 pandemic influenza strain. The model predicted that a <99% reduction in air travel would, at best, delay epidemic spread by only 2–3 weeks. Such reduction having never been implemented (the 9/11 terrorist attack resulted only in reduction of US air traffic of less than 50% for just a few days), the prediction is likely to be very approximate, and consequently "wrong". However, it is still extremely useful, as it shows that restricting travel would never result in the 6-month delay required to develop a new H1N1 vaccine [3].

With this warning in mind, we shall explain the basic tools used in mathematical modelling of vaccines and infections, and then the classic uses of these models. Finally, we shall comment on the future challenges for mathematical modelling in the domain of vaccines.

2. Tools and models

Daniel Bernoulli's 18th century model on smallpox, refined by Kermack and McKendrick in the 20th century, generated what is now the most widely used category of models [4]. By attributing conditions to members of a population, these models subdivide this population into compartments such as *Susceptible*, *Infected* or *Recovered* (for the simple SIR model), hence the expression: "Compartmental models" (Fig. 1).

The force of infection λ, namely the per capita rate at which susceptible individuals become infected, results from the degree of

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Fig. 1. The basic SIR model with compartments S (Susceptible), I (Infected) and R (Recovered). The force of infection λ represents the per capita rate at which individuals became infected and the removal rate ν represents the rate at which individuals recovered and became immune.

contact with infected individuals in the population and the transmission rate β (under the assumption of mass action principle [5]). As long as the transmission rate β is superior to the removal rate ν, infected individuals are generated at a higher rate than that at which they recover. This can be formally expressed as β/ν, also known as the basic reproduction number R_0, which can also be defined as the average number of secondarily infected individuals resulting from introducing one infected individual into an entirely susceptible population. Intuitively, if infected individuals recover faster than susceptible individuals get infected, the epidemic will die out; otherwise, it will grow. In other words, if $R_0 < 1$, namely if an infected individual "generates" less than one secondary case on average, the epidemic will die out. Conversely, a $R_0 > 1$ -an infected individual generating more than one secondary case- is required for an epidemic to grow. R_0 is then specific to a pathogen and does not depend on the environment. Conversely, the effective reproduction number R_e- namely the average number of secondarily infected individuals resulting from introducing one infected individual into a partly immune population- will vary according to the population and its level of immunization (Supplementary material). Fig. 2 shows how to build a basic compartmental model. The different ways of including vaccination in such a model are detailed in the supplementary material.

Stochasticity is implicitly taken into account in deterministic compartmental models, particularly with large populations, as these models describe or predict what happen *on average*. However, it may be useful to model it explicitly while taking into account individual heterogeneity, particularly for smaller populations. Stochastic models can be of two sorts, compartmental models –where all the susceptible individuals are considered in one single compartment- or agent-based models. Discrete-time compartmental models allow chance to determine the total number of individuals from the compartment *Susceptible* to being infected by infectious individuals from the previous generation. Continuous-time compartmental models allow chance to determine when the next event will occur, whether it is the infection of a susceptible individual or the recovery of an infected person. They are also known as time-to-next-event compartmental models. Agent-based models (ABM) – also known as individual-based models (IBM) – have become increasingly popular, thanks to the availability of powerful computers. In these models, every individual is tracked separately and chance decides what happens to each individual (infection, recovery...). Each individual is defined by an extensive set of characteristics relevant to the question for which the model is developed (age, gender, sexual behaviour, profession, household size, etc).

To choose the most useful among the many presently available models essentially requires definition of the purpose of the modelling: Is the model built to understand and to explain, to estimate or to predict? Indeed, the simplest models, such as the SIR model

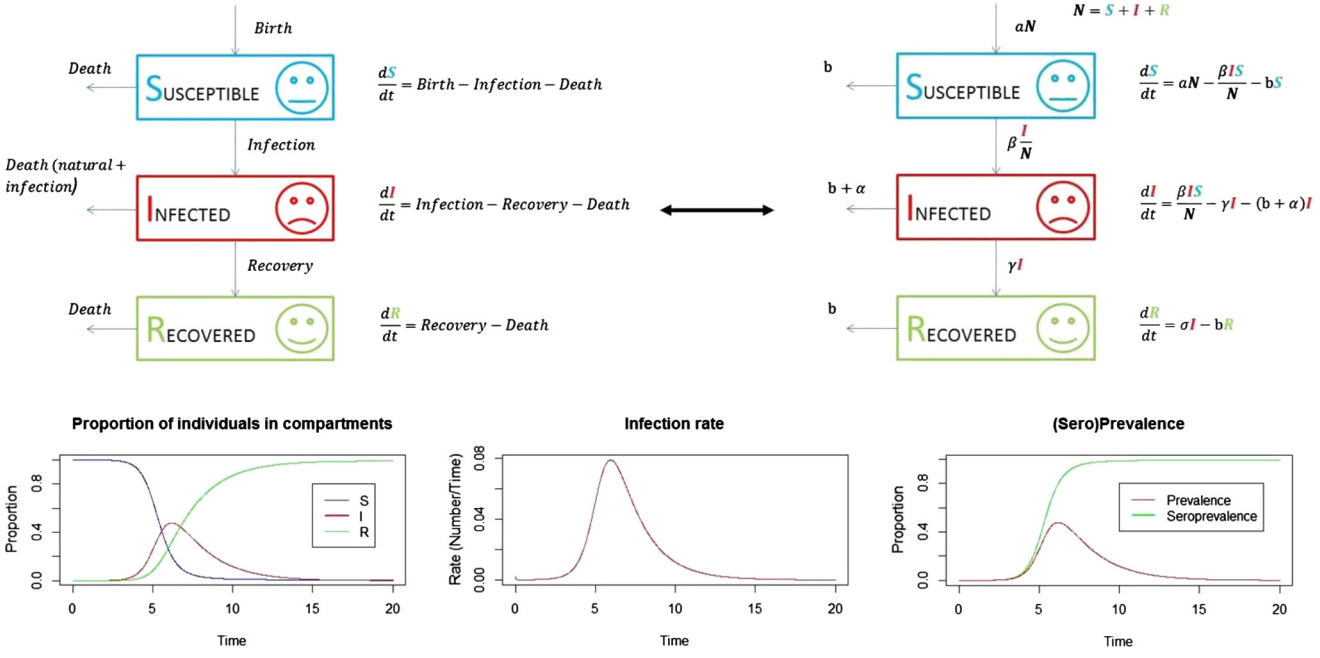

Fig. 2. How to build a mathematical model? The number of individuals from each compartment is estimated with a differential equation (one equation per compartment), and each arrow going to or leaving from a compartment is represented by a term of the equation. Arrows "leaving" a compartment (such as death, infected individuals leaving the Susceptible compartment...) are represented by a negative term, and arrows going to a compartment (birth, infected individuals going to the Infected compartment...) are represented by a positive term. When the infection of interest has a low mortality rate and is studied over a short period, a common assumption is to consider that population size will not change over time, therefore birth rate and mortality rate are considered equivalent and withdrawn from the model (they cancel each other out). This simplification is naturally not valid when a long period is considered and/or infection increases mortality in a sizable proportion.

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