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REVIEW

Gaining insights into human viral diseases through mathematics

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Abstract. Mathematical models have been recognized as powerful tools for providing new insights into the understanding of viral dynamics of human diseases at both the population and cellular levels. This article briefly reviews the role of mathematical models and their historical precedents for creating new knowledge of the mechanisms of disease pathogenesis, transmission, and control of some human viral infections. Future research in the modelling of infectious diseases will need to rely upon incorporation of the fundamental principles that govern viral dynamics *in vivo* as well as in the population.

Key words: Mathematical models, Immunization, Viral pathogens, Control strategies

Introduction

Mathematical models of human diseases have a long history, dating back over two centuries to a justification for inoculation against smallpox by Daniel Bernoulli in 1760 [1]. Although his work predated by a century the identification of the agent responsible for the transmission of smallpox, he formulated and solved a differential equation describing the dynamics of the infection. The development of epidemiological models was stalled by a lack of understanding of the mechanism of infectious spread until the beginning of the last century [2]. Public health physicians including Sir Ross [3], Hamer [4], McKendrick and Kermack [5–7] laid the foundations of modern mathematical modelling of epidemiology between 1900 and 1935. McKendrick developed the first stochastic theory in 1926 [5], and in the 1930s Kermack and McKendrick [6, 7] established an extremely important principle, stating that the level of susceptibility must exceed a certain threshold in order for an epidemic to occur in a population. This principle was deduced from a simple model describing the dynamical behaviour of susceptible (S), infected (I), and recovered (R) individuals in a homogeneously mixed population, the so-called classical SIR epidemic model.

Over time, these models have been recognized as essential tools for addressing major public health concerns about the transmission and control of human diseases. Complexity has gradually been added to the newer generation of epidemic models by incorporating essential biological factors, including modes of transmission, age and social behaviour, incubation period, duration of infectiousness, socioeconomic demographics, and treatment and preventive strategies [8–12]. With advances in mathematical methods, particularly applied dynamical systems, the last two decades have also witnessed the emergence of new models that lead to a rich variety of dynamics, often not biologically justified or consistent with the characteristics of a real epidemic [13, 14]. This may be due to the lack of connection between the mechanisms of pathogenesis (at the individual level) and transmission (at the population level), which is central to the development of effective control strategies [15–17]. The bridging of these two different scales of disease pathogenesis and epidemiology is essential to the construction of a general framework that could elucidate fundamental principles for disease control, and will allow for the creation of new perspectives in immunoepidemiology [16].

The current spectacular interest in mathematical modelling of pathogenesis has gradually built up over the last twenty years, beginning with the advent of HIV in the 1980s [18]. The real explosion of interest in viral dynamics was triggered by the pioneering models of Perelson, Nowak, McLean, Kirschner, and Wodarz in the 1990s and later, which have proven to be powerful tools for understanding the biological processes central to HIV infection [18–29]. These models, in general, need a more comprehensive incorporation of immunological details of the interaction between viral pathogens and the immune system, which are still being analyzed model by model. Despite the rapid evolution of such models, the field of theoretical immunology lacks a unified framework [30].

Models of epidemics and control strategies

One of the major contributions of mathematical models of infectious diseases has been the evaluation

of public health measures to control the spread of human diseases [31]. In general, there are two classes of disease control methods. The first class includes traditional methods, such as reducing the number of contacts, therapeutic treatments (drugs), and quarantine/isolation; the second consists of modern methods including prevention, immunization (vaccination), and ecological interventions which have been the subject of much research in recent years [32]. In modern times, immunization has had perhaps the largest impact in reducing both the mortality and the morbidity of many infectious diseases, such as influenza and childhood infections [33–41].

Although mathematical models may not provide detailed descriptions of how to control diseases, they are elegant tools for assessing the potential impact of different strategies offered in public health intervention programs. The most important parameter in these models is a critical threshold, *the basic reproductive number* R_0 [8], defined as the number of new infections generated by a single infected individual introduced into a wholly susceptible population during the course of infection. Models provide a systematic way of formulating R_0 and characterizing important factors in disease transmission and control by examining their effect on R_0 [42]. The simplest epidemiological model [8] yields the expression $R_0 = \beta S_0/\alpha$, where β is the transmission rate of infection in an entirely susceptible population of size S_0, and α is the recovery rate of infected individuals. Naturally, the principal aim of public health measures would be to reduce R_0 below unity in order to make disease control feasible. This provides the criterion for improving control strategies, such as immunization that reduces S_0 (susceptibility of the population), or quarantine/isolation that lowers β (the incidence of infection).

The failure to achieve eradication of many infections, despite systematic intervention programs, remains a major public health concern. For example, measles is a serious disease of childhood and still contributes to over a million deaths annually, mostly in developing countries [38, 43]. This is notwithstanding immunization strategies, which have demonstrated substantial historical success in dramatically decreasing the number of new infections associated with the disease [43]. Measles is probably the most studied disease of childhood from the modelling dynamics standpoint. This is in part due to the high quality of available data, particularly from Great Britain. Grenfell and colleagues [33, 44–50] have conducted major studies on the transmission dynamics of childhood infections, with particular emphasis on measles and whooping cough, by developing simple models that could explain the complex dynamical transitions occurring during epidemics. One of the most important implications of their work is the possibility of designing vaccination programs that induce greater spatial synchrony, which would increase the probability of global eradication [33].

A simple, but profound, question is how mathematical models might help us understand the underlying principles of immunization, and develop effective vaccination strategies. Depending on the type of disease, these models include the necessary variables and parameters to describe the movement between different classes of individuals (variables) during disease progression and its control. They often take the form of difference or differential equations whose analysis leads to the determination of short- and long-term disease dynamics, whenever a vaccination program is put in place. The integration of important biological parameters that appear in the expression of the basic reproductive number (R_0) can substantially influence the outcome of the model analysis. A particular example is the recent modelling study of measles vaccination that questions the effectiveness of booster programs for controlling the disease [51]. Considering major parameters associated with a booster vaccination policy (such as primary vaccine coverage; vaccine efficacy; waning rate; and the rate of booster administration), an important epidemiological consequence is inferred that a booster program may fail if it is mostly targeted to primary vaccinated individuals, or if it functions, in effect, as a primary vaccine. The model predicts that the coverage of primary vaccine and the optimal timing of booster doses crucially impact the outcome of booster campaigns, and in fact impose stringent requirements for any practical public health policy.

Not only strategizing vaccination programs, but also recognizing the low efficacy of vaccines at the individual level and in the population as a whole has provided great opportunities for modelers to explore the causes of epidemic outbreaks of several infectious diseases [40, 52]. Influenza is a well-known candidate for such outbreaks, for which seasonal immunization has been a key strategy to reduce the risk of infection and prevent large epidemics with excessive mortality [53]. Annual influenza vaccination is needed due to continual mutations in the viral genome, in particular, the hemagglutinin (HA) and neuraminidase (NA) genes [54]. Vaccine-induced protection is, however, dependent on the immune status of the individual, ranging from 70–90% among immunocompetent to only 30–50% in elderly and immunocompromised subjects [54–56].

There has recently been a surge of interest in modelling of influenza infection with the aim of providing insights into the epidemiological aspects of the disease [57–62]. A recent study on transmissibility of influenza estimates that R_0 for the 1918 influenza pandemic was less than four [61]. The results of this study, based on fitting an SEIR (susceptible–exposed–infectious–recovered) model to pneumonia and influenza death epidemic curves from 45 cities in the United States, suggest that a similar novel influenza subtype could be controlled. Since influenza can be transmitted before symptoms appear, strategies for

transmission reduction (including vaccination) would need to be implemented more rapidly than other measures such as isolation. This may also support the idea that a pandemic influenza with a viral strain that has been circulating during the preceding few decades seems unlikely to occur due to some degree of protection of the population provided by annual vaccinations or previous exposure to the infection.

The possibility of preventing pandemic influenza raises the question of whether a strategic use of available vaccines could ever stop annual epidemics within a certain population. Despite annual vaccination policies, influenza still inflicts substantial morbidity, mortality and socio-economic costs, which call for revised vaccination programs [37, 53]. An effective vaccination strategy should consider the effect of vaccine failure among the geriatric and immunocompromised subpopulations [63]. Therefore, the development of mathematical models that allow for the interactions between different subpopulations, such as immunocompetent and those who remain susceptible despite vaccination, is highly desirable.

In the absence of proven vaccines, the emergence of novel infectious diseases is a great scourge to human populations. This becomes even more critical with destitution of preexisting immunity, or a lack of required technology and knowledge of a diagnostic test or therapy. Such a critical situation was recognized in 2003 with the appearance of the global epidemic of severe acute respiratory syndrome (SARS) as the first major infectious disease threat of the 21st century [64]. Soon after the SARS outbreaks, different groups of researchers were assembled to investigate the most beneficial strategies for controlling such a highly contagious disease [65–68]. One of the most significant studies concerning modelling strategies for controlling SARS outbreaks showed that a timely implementation of an optimal isolation program under stringent hygienic precautions is critically important to halt SARS epidemics with or without quarantine [68]. However, the model's ability to predict disease control depends greatly on the assumptions made in the modelling process, as well as the transmissibility and incubation period of the disease. The possibility of recurrence of SARS with a more infectious virus warrants further study on feasible control strategies, perhaps through a modelling approach that integrates more elaborate mechanisms of disease pathogenesis and epidemiology.

With daily growth in epidemics of some infectious diseases, the role of mathematical models in creating new knowledge for controlling them appears ever more crucial. Whether such diseases can be controlled by means of available public health tools remains a fundamental question, especially in the context of HIV infection. Since its discovery in 1983, HIV has been responsible for over 20 million deaths, and its epidemic is spreading at approximately 6000 new infections daily [69]. The true mechanism by which HIV defeats the immune system is still unknown, and this is perhaps a reason for many fruitless research efforts in vaccine development or treatment. HIV, although not old, is the first disease for which mathematical models of both pathogenesis and epidemiology were developed at an early stage of its discovery [18]. The success of these models in exploring the dynamical course of HIV infection *in vivo* has been proven by many studies, most notably those of Perelson and Ho, Nowak, McLean, Kirschner, and Wodarz [18–29]. On the other hand, models of HIV epidemiology [70, 71] have had relatively less impact in advancing the knowledge of HIV infection and its control.

Ambitious efforts have been made with the hope that HIV could one day be completely eradicated. The evolution of antiretroviral therapy has been promising in retarding the progression of HIV and extending the length, though not the quality, of life [70–73]. This, however, has somewhat diverted attention away from preventive measures in industrialized countries, which has led to the further spread of infection [72, 73]. With no cure in sight, and the failure of conventional vaccines, prevention remains the most effective strategy against HIV/AIDS epidemics. This conclusion was evinced by a modelling study on condom use in HIV prevention [74], based on the critical evaluation of clinical investigations in a recent NIH report [75], which relies upon the meta-analysis of Davis and Weller [76]. The results suggest that the HIV/AIDS epidemic could be stopped if the *preventability*, the product of condom efficacy and condom compliance, exceeds a certain threshold. This will require the development and application of techniques that are effective in setting and monitoring quantitative measures for compliance and efficacy.

With such strong evidence appearing in the literature, the role of mathematical models for gaining new insights into human diseases cannot be denied. Whether the maximum potential for their contribution has been reached is a well-posed question that future models will allow us to address.

Future models of viral diseases

Integration of epidemic models with further immunological details of infectious mechanisms may be a key approach for future research in modelling of human viral diseases. In order to design effective control strategies, the micro-dynamics of viral pathogens *in vivo* must be linked to the macro-dynamics of disease spread in the population. This may increase the complexity of the models, and preclude a detailed mathematical analysis using standard techniques. Computational aspects of these models will therefore play a major role in understanding their dynamics and creating new knowledge.

To rationalize the criteria for effective control of viral diseases, it is important to engage the underlying mechanisms of pathogenesis, in addition to the epidemiological components, in developing mathematical models. These could then be integrated with aspects of the evolutionary biology of viral pathogens, which is essential for linking the interactions of within-host dynamics with population-level phenomena, such as diseases transmission and control [77–79]. Empirical data are then indispensable to quantitatively draw out the interplay between pathogen dynamics and genetic diversity at both individual and population levels [15].

There is a greater need than ever for uniting the wide range of expertise in mathematics, computer science, statistics, virology, immunology, epidemiology and evolutionary biology. This is extremely important for modelling studies whose aim is to approach global strategies for defense against infectious diseases, particularly concerning an imminent influenza pandemic or the emergence of new viral infections. These strategies may not be effective or even feasible, given the available resources of public health, unless they are founded upon basic principles that govern viral dynamics *in vivo* as well as in the population. Many of these principles are within our grasp, but are not yet exploited in existing models, and must guide future research in the modelling of infectious diseases.

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