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Modelling in infectious diseases: between haphazard and hazard

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Abstract

Modelling of infectious diseases is difficult, if not impossible. No epidemic has ever been truly predicted, rather than being merely noticed when it was already ongoing. Modelling the future course of an epidemic is similarly tenuous, as exemplified by ominous predictions during the last influenza pandemic leading to exaggerated national responses. The continuous evolution of microorganisms, the introduction of new pathogens into the human population and the interactions of a specific pathogen with the environment, vectors, intermediate hosts, reservoir animals and other microorganisms are far too complex to be predictable. Our environment is changing at an unprecedented rate, and human-related factors, which are essential components of any epidemic prediction model, are difficult to foresee in our increasingly dynamic societies. Any epidemiological model is, by definition, an abstraction of the real world, and fundamental assumptions and simplifications are therefore required. Indicator-based surveillance methods and, more recently, Internet biosurveillance systems can detect and monitor outbreaks of infections more rapidly and accurately than ever before. As the interactions between microorganisms, humans and the environment are too numerous and unexpected to be accurately represented in a mathematical model, we argue that prediction and model-based management of epidemics in their early phase are quite unlikely to become the norm.

Keywords: Epidemics, epidemiology, models, pandemic, prediction

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Introduction

> Prophecy is a good line of business, but it is full of risks.
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> Mark Twain in *Following the Equator*

Epidemics have played a role in human history since ancient times, and will continue to do so in the foreseeable future, despite overoptimistic assurances to the contrary. When the Black Death pandemic was ravaging Europe during the Middle Ages, the only sound advice given to the citizens was "flee early, flee far, return late". As reflected in the Introduction of Boccaccio's *Decameron*, the citizens of Florence "decided that the only remedy for the pestilence was to avoid it … [that] none ought to stay in a place thus doomed to destruction". Modern medicine does not have to resort to such extreme measures of public health, and nor does it ascribe the occurrence of epidemics to a certain alignment of the stars, the will of God, harmful vapours, or the poisoning of wells by non-believers. Surveillance systems make the early detection of disease outbreaks possible through data supplied by sentinel clinics, or by the use of syndromic surveillance (e.g. Web queries, other forms of Internet biosurveillance, over-the-counter drug sales, or school absence records) [1]. We would

argue, however, that timely prediction of epidemics before they occur, and accurate forecasts of their course in their early phase, remain, by and large, unreliable.

Pathogen–pathogen Interactions and other Unknowns

The Division of Tuberculosis Control shares the belief of the symposium participants that tuberculosis will virtually disappear in the United States in the next 50 years. The control and eradication of tuberculosis, *New England Journal of Medicine*, 1980.

Since the early 1950s, tuberculosis (TB) rates in high--income countries have decreased rapidly. In 1980, treatment was available and effective, and it seemed reasonable to include TB in the list of "disappearing and declining diseases" in Britain [2]. The authors were naturally unaware of the fact that the AIDS pandemic was already making hundreds of thousands of people worldwide susceptible to a disease previously considered to be a remnant of the 19th century [3]. The surge in the incidence of TB and the appearance of multidrug-resistant and extensively drug-resistant TB in eastern Europe in recent decades is causally linked to a wide variety of actors: the AIDS pandemic, the collapse of the Soviet Union, and the increase in intravenous drug abuse there. Predicting the occurrence of these epidemiological and political phenomena was not possible in 1980. Beijing genotype strains of *Mycobacterium tuberculosis* now account for approximately 50% of TB cases in China, and are spreading worldwide [4]. This genotype has been observed to spread more successfully in the population than other *M. tuberculosis* strains. The reasons for this are incompletely understood [4]. Will this genotype change the epidemiology of TB? Will vaccination and treatment trigger the appearance of other successful genotypes? Nearly 20 years after the first description of the *M. tuberculosis* Beijing genotype, and more than 30 years after the recurrence of the TB pandemic, we still lack elementary biological and epidemiological data to help with TB control.

The association between influenza virus infection and subsequent susceptibility to *Streptococcus pneumoniae* infections was already well known nearly 100 years ago during the Spanish influenza pandemic. However, the virus itself has the capacity to mutate, and human society changes continuously, so that predictions cannot be based on such historical associations. If predictions were to rely on past observations, one would expect adults aged ≥65 years, who are known to be susceptible to both severe influenza and pneumococcal infections, to have extremely high mortality rates during influenza pandemics. Hygienic conditions today, however, are different from those of 1919, pneumococcal sepsis being the exception among patients with influenza. During the 2009 A/H1N1 influenza virus pandemic, patients aged ≥65 years were found to have death rates 81% lower than expected in a regular influenza season [5]. In fact, obesity, not ageing, was found to be a significant risk factor for severe disease [5,6]. Not only was the influenza virus itself different, but it also interacted with other viruses in important ways. In France, for instance, a rhinovirus epidemic was found to delay the onset of the influenza pandemic, which in itself delayed the onset of the respiratory syncytial virus bronchiolitis season [6–8]. To complicate things further, increasing evidence suggests that some bacterial infections can also increase the susceptibility of patients to viral infections [9].

Pathogen–environment Interactions

Not only the pathogens themselves, but also the complex ecosystems, which include vectors and/or reservoir animals, are crucial to understanding the dynamics of many infectious diseases with an epidemic potential. The interaction between the *Anopheles* mosquito vector, the *Plasmodium falciparum* parasite and humans is a good example of such complexity. In recent years, long-lasting insecticide-treated bed-nets have been distributed in many sub-Saharan African countries, following evidence from randomized controlled trials that these reduce *P. falciparum* malaria prevalence, morbidity, and mortality [10]. Although it was reasonable to assume that the continuation of such efforts would lead to a gradual and predictable decrease in malaria morbidity, the results of a recent longitudinal study performed in Senegal highlight the problematic nature of such simplistic forecasts. In this study, the average incidence density of malaria attacks, which was 5.45 per 100 person-months before the distribution of treated bed-nets, decreased to 0.41 immediately afterwards, only to increase again to 4.57 per 100 person-months 27–20 months after the initial intervention, despite continued use of the bed-nets. The prevalence of knockdown resistance mutation, which confers reduced sensitivity of the *Anopheles* vector to pyrethroid insecticides, increased from 8% in 2007 to 48% in 2010. The mosquitoes were shown to become somewhat more aggressive during the early evening, thereby avoiding the need to 'confront' bed-nets [11]. Unpredictable events such as these undermine the various attempts to model and predict trends in malaria control and eradication [12,13].

There has been no cholera epidemic in the Caribbean island of Hispaniola for more than a century, although cholera has been present in Latin America since 1991. The *Vibrio cholerae* strain that spread to all Haitian provinces after the 2010