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REVIEW ARTICLE

THE ROLE OF EPIDEMIC MODELLING IN POLICYMAKING AND THE CASES OF SARS AND COVID-19

Chiara Artico [1], Vanda Bostik [2]✉

[1] International Master's in Security, Intelligence and Strategic Studies (IMSISS), University of Glasgow (UK)
[2] Department of Epidemiology, Faculty of Military Health Sciences, University of Defence, Hradec Kralove, Czech Republic

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Summary

Over the past two decades, the world has witnessed the onset of three different coronaviruses: severe acute respiratory syndrome coronavirus (SARS-CoV), Middle East respiratory syndrome coronavirus (MERS-CoV) and the current severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). Each of these has resulted in features that have made it in some ways stronger than the previous one. Predictive epidemic models are widely recognised as one of the most reliable and valuable tools to help policymakers take decisions regarding the management of sanitary crises and have been helping governments by calculating potential consequences and benefits of related containment measures. A comparison of epidemic models that were elaborated on SARS-CoV, which caused severe acute respiratory syndrome (SARS), and on SARS-CoV-2, which is currently causing coronavirus disease 2019 (COVID-19) will lead to an overview of the potential reasons why the current one has led the world into an ongoing pandemic, while the other two remained relatively delimited.

Key words: coronaviruses; SARS-CoV-2; predictive epidemic modelling; pandemic; WHO; lockdowns; vaccination

Introduction

Only four years after the outbreaks of Ebola in West Africa (2013-2016) (1) and Zika in the Americas (2015-2016) (2) showed their potential of causing a pandemic and disrupting society as we know it, the world is now experiencing the first actual global pandemic since the Spanish Flu (1918-1919) (3). Increasing criticisms on how the early COVID-19 outbreaks were managed and whether the containment measures were timely and appropriate flooded the news. Similarly, the World Health Organization's (WHO) declaration of COVID-19 as a "public health emergency of international concern" (PHEIC) was deemed late (4). Nonetheless, it is also argued that the most significant problem in the management of the pandemic was that most of the countries around the globe ignored such a warning. The even later application of measures such as contact-tracing, massive testing and social distancing is considered the primary catalyst of an uncontrolled spread of the disease (4).

✉ University of Defence, Faculty of Military Health Sciences, Department of Epidemiology, Trebesska 1575, 500 01 Hradec Kralove, Czech Republic
vanda.bostikova@unob.cz

Predictive epidemic modelling can bring advantages to policymaking in case of disease outbreaks in order to curb the spread. An example of an epidemic model elaborated on SARS will be compared to a model elaborated on COVID-19, given the high similarity between the two viruses. These predictive models will show similar effectiveness of similar measures applied to similar diseases. Therefore, questioning why one became a worldwide pandemic, whereas the other one remained limited, seems legitimate. In order to explain such a divergent outcome, the structural characteristics of the two different viruses will be evaluated.

Methods

The present article is based on a compilatory method. Document analysis is the underlying method for each section. The first section introduces the analytical framework within which predictive epidemic modelling can be conceived and proceeds to describe its main elements and assets. The second section considers two existing studies on the situations caused by the two similar viruses. The two predictive models utilised in the present article were published in renowned peer-reviewed journals and are therefore considered a source of reliable and authoritative information. The last section also stems from a previously published article as the primary source for analysis.

Predictive epidemic modelling

The importance of the elaboration of mathematical epidemic models has met increasing recognition as a valid research method across the scientific community (5). In particular, mathematical models are employed when there is a need for evaluating the effectiveness of potential and relevant containment measures when disease outbreaks occur. Their primary purpose is to outline the transmission process of the infectious pathogen in order to foresee how it will spread (6). When an infectious disease spreads quickly to a high number of people, public health authorities need to evaluate the scope of the potential danger it poses, including information as to how many people will require medical treatment and hospitalisation, the duration of the outbreak and the chances of an extended spread, the need for quarantines and/or vaccines, and in general, doubts related to the measures to be taken in order to avoid catastrophic outcomes (7). Mathematical models can help find answers to these questions.

In particular, mathematical modelling is deemed more effective than other tools, which are often considered less applicable (6). Firstly, scientific experiments are often not viable because a disease outbreak can affect a slice of the population too big to be fully tested and incorporated in such experiments. Secondly, precisely because of this, experiments conducted on a large scale might even be judged unethical. Thirdly, when considering statistical analysis, the problem becomes data coverage of the outbreak (7). This means that the available data sets would probably be inaccurate, in case of insufficient surveillance, to conduct a reliable statistical analysis, which relies on big numbers. Indeed, surveillance would most likely include values referring to one single outbreak (in this case, a sample), thus not allowing for a comprehensive statistical analysis since statistics is based on the analysis of large samples (7).

The added value of mathematical modelling is that it provides a comprehensive overview of all the data available (8). As experts proceed in their research and elaboration, they can discard models that they deem inadequate and proceed until they find the most appropriate. Moreover, mathematical models can incorporate biological mechanisms and social behaviours, which constitute the basis for disease spread (9). These models allow for an interpretation of how the disease can further spread based on how people behaved by transcribing the population's actions into numbers. Thus, they build viable hypotheses on how the situation could unfold by creating a spread scenario. Furthermore, in most cases of a disease with high infection rates, one single person is likely to infect others randomly, therefore not following a precise pattern (8). In these cases, mathematical models are considered the best option to outline the potential chain of infections (9).

Across the decades, many different models have been utilised by researchers to develop overviews of the unfolding of disease outbreaks. According to *Li* (7), the main approaches to mathematical modelling of infectious diseases are statistical models, deterministic models and stochastic models. Statistical models present some of the limitations of statistical analysis presented above, mainly related to the need for large amounts of data, but they are still relatively employed in epidemiology and public health research. Deterministic models rely

on the consideration of the size of both susceptible population and infectious population as continuous functions in time. They employ differential and difference equations in order to be less dependent on large amounts of data. Thus, they result in a clear description of dynamic interrelations between variables and in reliable predictions. However, they are discouraged when the population size is relatively small because "stochastic disturbances" are considered non-negligible (7). On the other hand, stochastic models focus specifically on the stochastic process of infections, intended as a "process describing the evolution in time of a random phenomenon" (10). While deterministic models rely on the law of large numbers, stochastic models embrace the randomness of disease transmission, the probability of being or not being infected (11). This model is effective when applied to small and delimited populations (e.g. hospitals), but because it relies on many numerical simulations, it is not the best option in more extensive contexts (7).

In general, however, mathematical models present some drawbacks and difficulties associated with them. Considering that what will be represented within the model will always be an approximation of reality, it is essential to remember that, due to the frequent lack of precise information about a specific disease, the assumptions inserted in the model may be mere hypotheses of the researchers. This limitation does not impede the elaboration of such a model, but it is crucial to be remembered when the model will be interpreted. Furthermore, the importance of validating these models through actual disease data is highlighted, even though this might not always be possible for the testing of the hypotheses. Then, it seems clear that surveillance over the population during the initial spread of the disease is crucial and that clearer and more comprehensive data will also allow for more precise and thus fit-for-purpose mathematical models. Lastly, it is argued that the analysis of the model might be slowed down or restricted by mathematical theory existing at the time of the elaboration (7).

Despite these possible limitations, the elaboration of mathematical models remains, in theory, one of the favourite tools in predicting infectious diseases because it saves significant time and resources compared to other tools (7, 8). The most important feature seems to be the possibility to build the model around the relevant data already in possession of the researchers and then to be able to introduce precise and desired elements into the model and see how this changes. This is the critical feature that makes predictions of the consequences of the various measures adopted by the authorities possible. The idea is to add variables that represent these containment measures, for example, vaccines, and see how the model reacts to the inclusion of new information (9). Sometimes, to understand the basic mechanisms of infectious diseases and better predict their outcomes, it can be helpful to compare several mathematical models of different diseases (9). In this case, models elaborated for SARS and COVID-19 will be assessed, given that SARS-coronavirus was confirmed to be the most akin to the novel one, as will be analysed later.

Modelling the SARS epidemic and the COVID-19 pandemic

In mid-May 2003, more than six months into the SARS outbreak, *Lipsitch et al.* (12) elaborated a model (shown in Figure 1) to predict the epidemic potential of the new disease. A pivotal factor in any epidemiological analysis is the basic reproductive number (R_0). It is defined as "the expected number of secondary infectious cases generated by an average infectious case in an entirely susceptible population" (12). "When R_0 is greater than 1, the epidemic is growing." (13). They calculated reproductive numbers considering both an uncontrolled situation and a situation in which containment measures were enforced. In the former scenario, which in their research was represented by the epidemic curve of Hong Kong by the end of March 2003 with a fully susceptible population and no measures enforced yet, the R_0 was around 3 (2.2 – 3.6). Moreover, once the epidemic had started, another factor was introduced, called effective reproductive number (R_e). It calculated the secondary cases generated by an infected person when within the population there are both susceptible and non-susceptible. The difference is that this new number considers that some susceptible become immune, either because of prior infection or because of the introduction of external controls, such as a vaccine. In order to end an epidemic, R_e below 1 needs to be achieved and maintained (14). Therefore, in order to reduce the original $R_0 = 3$ to an $R_e < 1$ (since the epidemic had already brought the basic reproductive rate to 3 but had also started introducing non-susceptible) and stop the epidemic, the enforced control measures needed to produce at least a two-thirds reduction in the total infectiousness through isolation of positive cases and quarantine of potential positive cases. It was demonstrated in the second scenario that these joint measures, including massive testing and contact tracing, would succeed, but it was also remarked that the more cases grow, the less effective these measures will be (12).

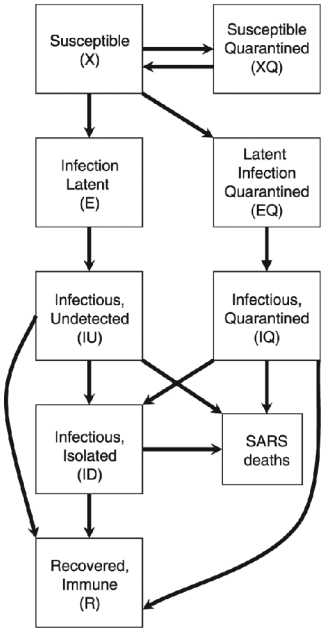

Figure 1. Mathematical model for SARS transmission (12).

Many models were also elaborated since the beginning of the current pandemic of COVID-19, but a perfect comparison between models of SARS and COVID-19 is unachievable for several reasons. These include differences in data availability, the size of the population of the different studies, and the underlying chances for infection that have significantly increased alongside a much more interconnected world in 2019-2020 than in 2002-2003. The analysed epidemic model of COVID-19 is the one proposed by *Giordano et al.*, shown in Figure 2 (15). In this case, the researchers evaluated the potential for the spread of the disease and the potential of the control interventions in Italy since the first outbreak on 20 February (day 1) until the beginning of April 2020 (day 46).

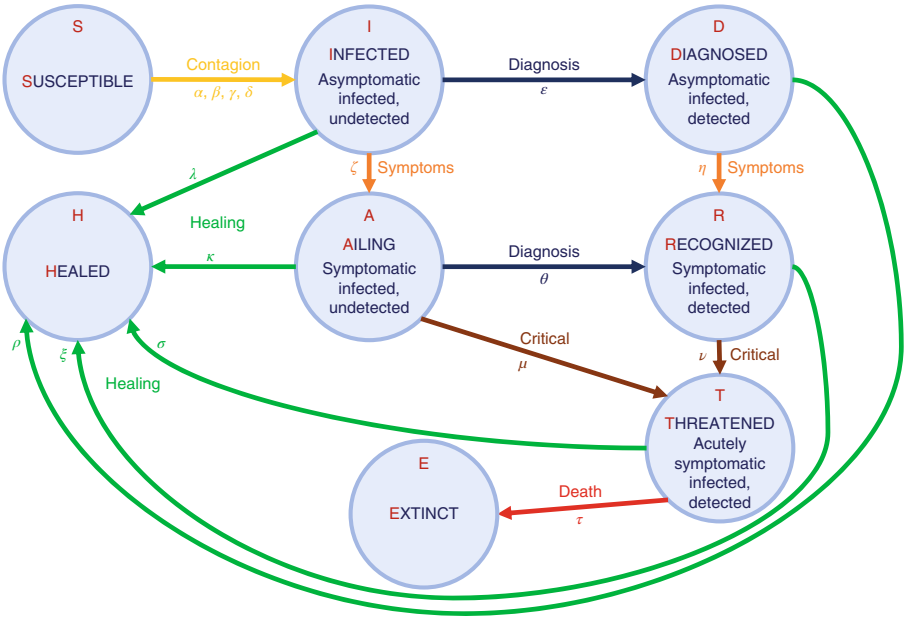

Figure 2. Mathematical model for COVID-19 transmission (15).

Considering the national lockdown in place since 9 March (day 18), the model predicted that, should confinement measures have been relaxed, the R_0 would have increased to 0.98 on day 50, as shown in Figure 3 (15).

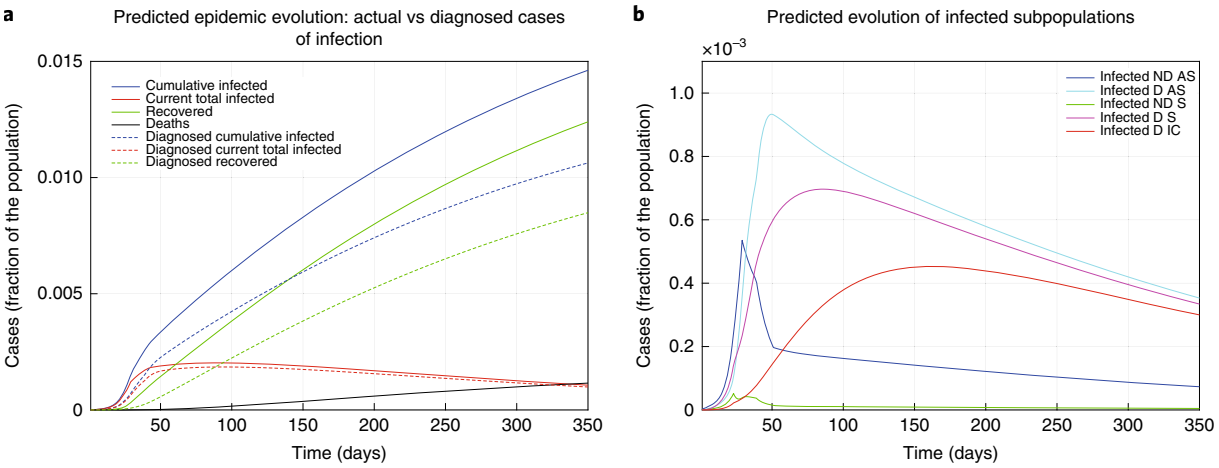

Figure 3. Epidemic evolution when, after day 50, the social distancing countermeasures are loosened (15, p. 858). (ND AS) non-diagnosed asymptomatic; (D AS) diagnosed asymptomatic; (ND S) non-diagnosed symptomatic; (D S) diagnosed symptomatic and (D IC) diagnosed with life-threatening symptoms (15).

Instead, should they have been strengthened, it would have decreased to 0.50, as shown in Figure 4 (15). Similarly, they argued that when parallel massive testing and effective contact tracing are enforced, the R_0 could have reached 0.59 after day 50. As opposed to this, in case social-distancing measures were loosened, the R_0 would have increased again to 0.77 (15). This is to prove further that, even in the case of COVID-19, mathematical models have shown significant improvements in the predicted spread of the virus when containment measures were effectively adopted.

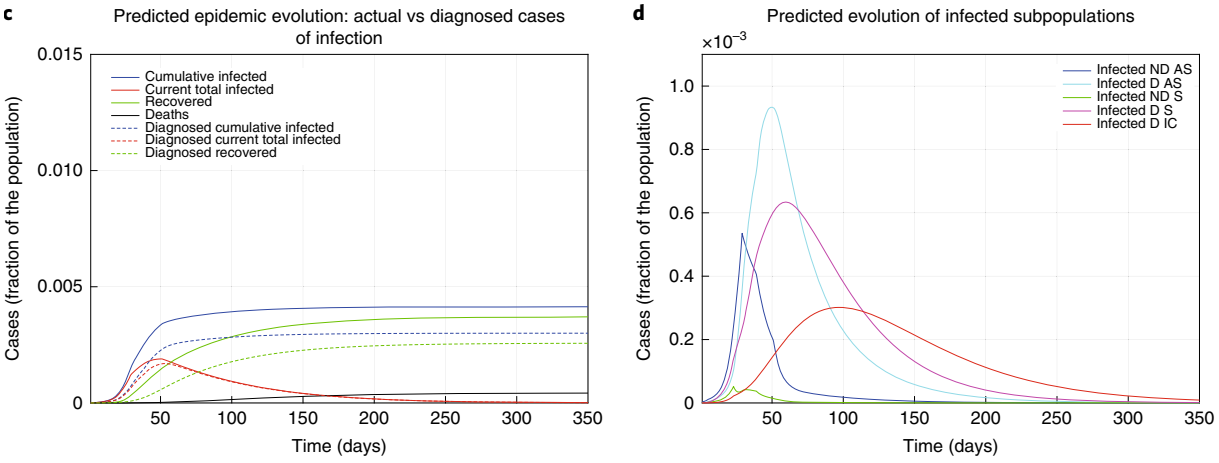

Figure 4. Epidemic evolution when the social distancing countermeasures are strengthened (15, p. 858). (ND AS) non-diagnosed asymptomatic; (D AS) diagnosed asymptomatic; (ND S) non-diagnosed symptomatic; (D S) diagnosed symptomatic and (D IC) diagnosed with life-threatening symptoms (15).

Nevertheless, despite the similarities encountered between the models in the predicted efficacy of the same set of measures for both SARS and COVID-19, it might seem curious, then, that the former caused a relatively limited epidemic with a total of 774 deaths (13), while the latter resulted in a global (and ongoing) pandemic that counts

nearly 2 million deaths in 13 months (16). Moreover, not even the third recent coronavirus (MERS-CoV) caused that many fatalities, stopping at 858 globally (13). The reasons can be researched in the analysis of the coronaviruses themselves. *Asrani et al.* argue that "susceptibility of humans to coronavirus outbreaks in the 21st century calls for comparisons of the transmission history, hosts, reservoirs, and fatality rates of these viruses so that evidence-based and effective planetary health interventions can be devised to prevent future zoonotic outbreaks." (17).

Structural comparison of the three recent coronaviruses

The two predecessors of the current SARS-CoV-2 are the widely known SARS-CoV and MERS-CoV. Coronaviruses were believed to only transmit among animals until SARS-CoV managed to spill over to humans. Allegedly originated in China, SARS-CoV is thought to be related to a specific species of bats as the primary host of this virus (18). Despite the first SARS outbreak occurring in 2003, a series of serological tests among the population of former patients in Hong Kong revealed that the virus was present since 2001 (19). The outbreak of MERS-CoV originated in Qatar in 2012 and was soon related to dromedary camels (20). More than half of the infected patients were found to have had contacts with these animals and had no previous respiratory issues (21). Nonetheless, it was later suggested that the original hosts of both viruses were bats (22). The novel coronavirus (SARS-CoV-2) is also thought to have originated from bats in China, even though certainty on whether there was an intermediate host is still to be confirmed (23). China is currently hampering further research on this. It has, in fact, recently denied visas to a group of World Health Organisation (WHO) experts that were supposed to travel to China in order to investigate the origins of the virus, thus increasing suspects of a cover-up (24).

Overall, the SARS-CoV-2 genome seems to be more similar to SARS-CoV than MERS-CoV, with 82% similarity versus nearly 70%, respectively (25). Compared to SARS-CoV, despite the common origins, the main differences of the current coronavirus are represented by the absence of one accessory gene and the modification of two in its genomic structure. However, it is hypothesised that the most remarkable difference in SARS-CoV-2 is a modification in its spike (S) protein (constituting the famous "crown" on the outside), which seems to have a significantly enhanced affinity with the angiotensin-converting enzyme 2 (ACE2) receptors (17). These are the receptors to which the virus particles bind, which were also the ones exploited by SARS-CoV and are predominantly located in the lungs and renal tissues (26). This might be related to the fact that coronaviruses cause acute respiratory syndrome and that renal failure is the leading cause of mortality for SARS infections (17).

These variations in the genome of the novel coronavirus are believed to be the underlying conditions that make it much more easily transmissible than its predecessors. Similarly, MERS-CoV and SARS-CoV presented different traits, and MERS disease had a much higher fatality rate than SARS. On the other hand, COVID-19 has a much lower fatality rate, but it transmits surprisingly quickly compared to the other strains (17). This is shown by the basic reproductive rate or R_0. On the one hand, the R_0 of SARS was eventually estimated to be 1.1 (27), while the R_0 of MERS was significantly lower, estimated to be 0.69 without relevant containment measures, thus explaining why it never caused any epidemic (28). On the other hand, COVID-19 is still ongoing. Therefore the estimates have been varying significantly. According to the WHO, as of June 2020, it was calculated to be between 2 and 4 globally (29). According to a more recent study (November 2020), *Billah et al*. (30) estimated it to be 2.87, while another study even set it to 4.5 in many countries (31). Moreover, *Katul'*s model suggests that "if intervention measures still result in $R_0 > 2.7$ within 44 days after the first infection, intervention is unlikely to be effective in general for COVID-19" (31).

The last element deemed crucial in the swift spread of COVID-19 compared to the previous strains of coronavirus, and that also poses a significant challenge to predictive models is viral shedding. It occurs when the virus starts to replicate in the host who, thus, becomes contagious (32). This value is crucial in understanding since when and for how long the infected patient will be able to transmit the virus. Moreover, this is a vital element to be included in mathematical modelling because it can heavily influence the promptness necessary to enforce a quarantine in order to keep the spread under control (33). According to a recent systematic review of existing studies on SARS-CoV-2 shedding, the mean duration of viral shedding in COVID-19 patients is calculated to be 17 days, with its peak around 5-6 days since symptoms onset, but likely to start even before the first symptoms (13, 33). In comparison, despite the absence of data on its mean duration, SARS-CoV shedding peaked around 12-14 days since symptoms onset (34). The direct and crucial consequence is that, in the SARS case, there was a whole extra week available

to trace contacts and impose quarantine before the infection spread extensively (13). Therefore, this could explain why the containment measures adopted for COVID-19 were often ineffective.

Conclusion

Despite the valuable contribution that mathematical models were shown to provide to policymaking in scientifically determining whether specific measures were more or less effective and the acknowledgement of their increasing recognition, their employment is still seemingly limited. The main reason for this is that it still takes a significant amount of time, although less than other tools, to collect the data when comprehensive data sets are not available, elaborate the model and validate or discard the implementation of certain measures. Moreover, it is believed that when the proposed models are deemed too complex, policymakers are unlikely to rely on them (35). Nonetheless, the application of predictive epidemic models remains the most advantageous way to evaluate the cost-effectiveness relation of the employed measures since national lockdowns and vaccination campaigns are likely to be expensive both in the short and the long term. Indeed, these models can systematically absorb data and translate them into compelling interpretations of the outer system in which policymakers must act. Furthermore, they apply a transparent framework to an analysis that logistics, funds or ethics could otherwise impede, and that can also be open to questioning. This strengthens its transparency and acceptance, which remains preferred over expert opinions that are often considered not systematic or transparent (35). Therefore, predictive epidemic models remain complex but necessary and are likely to be employed as more epidemics are expected to happen soon.

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Conflict of Interest

The authors state that there are no conflicts of interest regarding the publication of this article.

Adherence to Ethical Standards

This article does not contain any studies involving animals performed by any of the authors. This article does not contain any studies involving human participants performed by any of the authors.

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