A Rapid Literature Review on Novel Coronavirus Impact Modelling

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Introduction

On 31 December 2019, a cluster of atypical pneumonia cases of uncertain aetiology was reported in Wuhan, the capital of Hubei Province in China. On 9 January 2020, China CDC identified a zoonotic novel coronavirus (2019-nCoV) as the causative agent of this outbreak(1). On 20 January, health authorities in China confirmed human-to-human transmission outside of Hubei province. Cases were then reported in other Chinese cities, escalating concerns regarding the possibility of a global outbreak of 2019-nCoV (1).

The first three cases of 2019-nCoV imported into the EU/EEA were identified in France on 24 January 2020 and since that date further cases have been reported throughout the world (1). In response to the increasing threat posed by 2019-nCoV, the World Health Organization (WHO) then declared the virus outbreak a public health emergency of international concern (PHEIC) on 30 January 2020 (2). Although there is limited availability of data with respect to case severity and the effectiveness of control measures, data reported as of 10 February accounts for 40 553 confirmed cases worldwide, including 910 deaths (2.1%) (3). Therefore, health authorities in the EU/EEA Member States must remain vigilant and strengthen their capacity to respond to this rapidly evolving public health emergency.

Mathematical models aid in planning the public health response to pandemic potential diseases, by estimating and predicting: the likelihood that a disease will spread internationally, the expected number of cases within a set timeframe, and the predicted impact of any possible interventions (4). This rapid literature review provides a general background on mathematical modelling, discusses some of the contributions and limitations of mathematical modelling in the planning of pandemic preparedness and response, and highlights some of the models utilised in recent examples of pandemic/epidemic planning (H1N1, SARS and 2019-nCoV).

Methods

Given the rapid turnaround time necessary for this review, an electronic search of the literature was conducted to identify relevant peer reviewed publications using the Pubmed database. Publications pertaining to mathematical modelling techniques in general, and modelling of H1N1, SARS and 2019-CoV in particular, were also sourced via internet searches using Google and Google Scholar. In addition, a hand search of reference lists of suitable articles was conducted to identify additional material. Applicable grey literature pertaining to emerging modelling techniques for 2019-nCoV was also included.

Background to Mathematical Modelling

Mathematical models of infectious diseases facilitate quantitative description of epidemic processes based on the underlying biological mechanisms of the pathogen concerned (5). All

models are a trade-off between complexity and accuracy and it is therefore important to evaluate and carefully consider the modelling approach most suited to each individual circumstance (4,6). The model must be a satisfactory representation of reality in order to provide useful outputs (4). This concept has been referred to as the 'robustness thesis': if model assumptions approximately correspond to reality then it will make predictions that are approximately valid (7). Therefore, mathematical modelling activity demands transparency and accuracy regarding model assumptions, which permits testing of the understanding of disease epidemiology by comparing model results with observed epidemiological patterns (4,7).

In the early stages of a disease outbreak, information is often scanty. Paucity of data for model parameterisation, in conjunction with the inherent complexity of the mathematical approaches used in modelling emerging infections, presents a challenge (4). Confidence in model accuracy may be increased if multiple different independent research groups develop individual models that produce similar outputs (4,8). Model output confidence may also be increased through validation processes: conceptual validation, logical validation, experimental validation, operational validation and validation of the data used in the model (4,9).

There are many varied approaches to mathematical modelling evident in the literature. In 1766, the first publication addressing the mathematical modelling of epidemics was published. In this seminal paper, *Essai d'une nouvelle analyze de la mortalité causée par la petite vérole,* Daniel Bernoulli developed a mathematical model to analyse the mortality associated with smallpox in England (10). Bernoulli's model demonstrated that inoculation against smallpox would increase life expectancy at birth at the time by approximately three years (10). Since then, many diverse modelling approaches have been utilised in three general categories (see Fig. 1): (i) statistical methods for surveillance of outbreaks and identification of spatial patterns in real epidemics, (ii) mathematical models within the context of dynamic systems (also termed state-space models) used to forecast the evolution of an ongoing epidemic, and (iii) machine learning/expert methods for the forecasting of the evolution of an ongoing epidemic (10). For all three of these categories many varying mathematical modelling approaches have been utilised and these approaches are discussed in detail elsewhere (10).
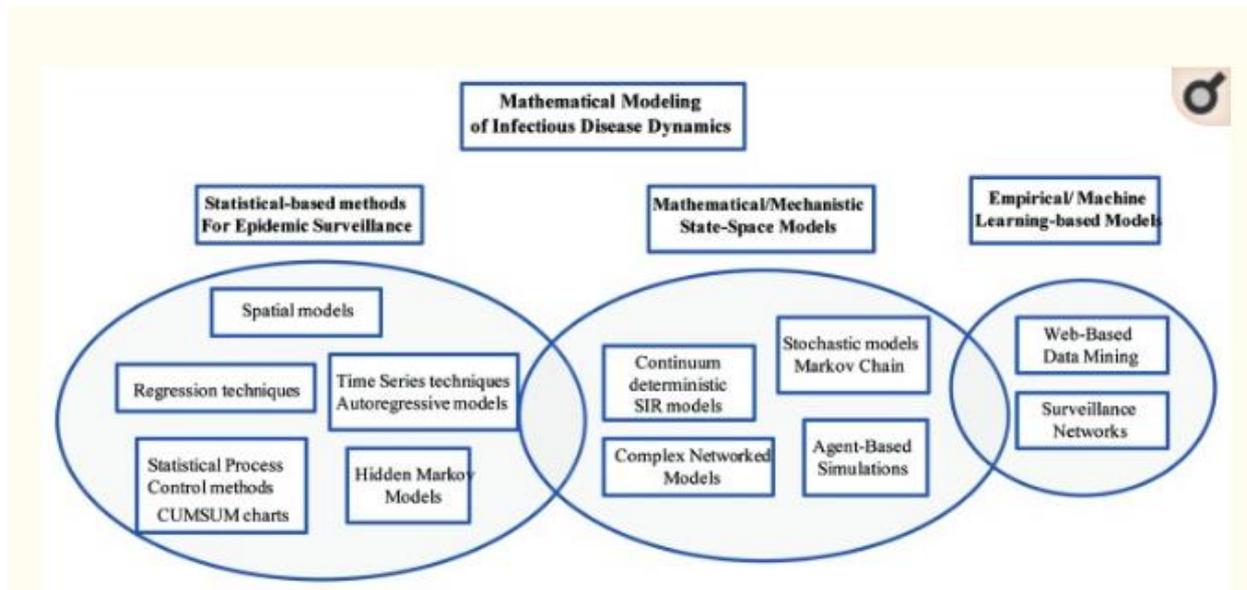
Figure 1. An overview of mathematical models for infectious diseases.

Reference: Siettos CI, Russo L. Mathematical modeling of infectious disease dynamics. Virulence. 2013 May 15;4(4):295-306.

Models utilised to inform influenza pandemic preparedness and response

In 2009, during the H1N1 pandemic, decision-makers had access to mathematical and computational models that were not available in the previous pandemics of 1918, 1957, and 1968 (11). This pandemic taught modellers and decision-makers many lessons as challenges were encountered: (i) expectations of modelling were not defined; (ii) appropriate contemporaneous data were not readily available; (iii) modelling results were not generated or disseminated in a timely manner; (iv) decision-makers could not always interpret the structure and assumptions of the models; (v) modelling studies varied in intervention representations and reported results; and (vi) modelling studies did not always produce the results or outcomes that are helpful to decision-makers (11). There were also some triumphs: (i) modelling characterised the role of social distancing measures such as school closure; (ii) modelling helped to direct data collection efforts; (iii) modelling aided in justifying the value of vaccination; (iv) modelling helped to target priority populations for vaccination; (v) modelling incorporated antiviral medication usage; (vi) modelling guided and informed health system preparedness planning; and (vii) modellers and decision-makers gained an educated insight into their combined collaborative capabilities (11,12).

The types of model utilised in the literature during the H1N1 pandemic ranged from decision-analytical to compartment to large-scale agent-based models and the complexity of the models varied widely (11,13).

"A review of the methods sections of many publications revealed descriptions such as 'spatially structured meta-population approach' (14), 'geographical backcalculation model' (15), 'stochastic, spatially structured, individual-based discrete time simulation' (16), 'age

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and risk group structured deterministic transmission dynamic model' (17)*, 'agent-based, social contact network model'* (18)*, 'network-based statistical approach'* (19)*, 'transmission model for which parameters are estimated from the data via Markov chain Monte Carlo sampling and data augmentation techniques'* (20)……"*(11).

In Ireland, an interim report for the national Pandemic Influenza Expert Group on the modelling impact of pandemic influenza produced in 2008 (21), detailed the pandemic predictions of three different mathematical models: the Health Protection Agency (HPA) Model (22), the Meltzer Model (23), and the Gani model (24).

The **HPA Model** adopted in the United Kingdom was derived using data from three previous UK influenza pandemics. The main assumption of the HPA empirical model is that an influenza pandemic will occur over a single wave of 15 weeks and will have a profile resembling that of previous pandemics (21). In the 2008 interim report for the Pandemic Influenza Expert Group, the HPA model was applied to an Irish influenza pandemic context and used to predict the clinical attack rate, hospitalisation rate of clinical cases, and the associated death rate. The report noted that the model was limited by the fact that it did not quantify the impact of antivirals on the pandemic and it assumed that the next pandemic would mimic previous pandemic profiles. However, a noted strength of the HPA model was that it made no assumptions with respect to the inherent infective nature of the influenza virus itself (21). For planning purposes in Ireland, the Pandemic Influenza Expert Group recommended the use of the HPA model in their 2008 guidance (25).

The **Meltzer Model** is an economic model of pandemic influenza derived by Meltzer et al in the USA. This model has been used to predict the total number of hospitalisations and deaths that will occur in the absence of interventions (21,23). An advantage of this model is that it makes no assumptions regarding the duration of the pandemic, however this limits model applicability for planning. Meltzer et al originally devised the model to explore the cost effectiveness of vaccination against influenza, rather than to act as a pandemic prediction model (23). FluAid 2.0 and FluSurge 2.0 are two software packages developed by Meltzer and colleagues that are available for download from the Centers for Disease Control and Prevention website (26). FluAid 2.0 provides a range of estimates of impact in terms of deaths, hospitalisations, and outpatients visits due to pandemic influenza. The software is not an epidemiological model and can't be employed to predict how a pandemic may spread over time (26) .

The **Gani Model** is an epidemiological model devised in the United Kingdom by Gani et al and can be used to predict the weekly number of clinical cases and hospitalisations that may occur. The model also assesses the benefits of antiviral interventions (21,24). The Gani model presupposes that members of the public exist in one of four states during a single wave of the influenza epidemic: Susceptible, Exposed and infected, Infectious and Removed (the S-E-I-R sequence). The rate of initial infection and transitions between states is dependent upon variables such as: the proportion of the population who are infectious (I), the reproductive number of the influenza virus (R_o), the length of time exposed and the length of time spent in the infectious state (21). The Gani model is useful for planning purposes, however the validity of the model predictions are heavily dependent upon the accuracy of the multiple model parameters and assumptions (21).

In England, advice (last updated in November 2018) from the Scientific Pandemic Influenza

Group on Modelling summarises the results of multiple epidemiological model approaches on pandemic influenza and their implications for policy makers on dealing with any future pandemic influenza outbreak (27).

Models utilised in the Severe Acute Respiratory Syndrome (SARS) epidemic

Severe acute respiratory syndrome (SARS), emerged as a highly transmissible and contagious new viral infection in China in 2002. SARS rapidly spread to 32 countries and caused more than 774 deaths and 8098 infections worldwide (28). The published literature reveals the use of many different dynamic transmission modelling approaches to assess the epidemic potential and control of SARS throughout the world (29), including: deterministic (28,30), SEIR, stochastic/deterministic (31,32), and, deterministic with Monte Carlo simulation and heterogenous stochastic effects (33).

Many lessons in modelling were learned during the SARS epidemic. Most modelling studies assumed a relatively homogeneous population, however SARS demonstrated extensive heterogeneity in space, transmissibility, and susceptibility. This heterogeneity has the capacity to considerably alter parameter estimates and model predictions (30,31,34,35). Prior to the emergence of SARS, discussions surrounding control have traditionally focused on reducing R_o (35). This is a satisfactory approach for the control and elimination of endemic diseases when disease prevalence is considerable. However, epidemic emerging infectious diseases are critically affected by chance events in the initial stages of their development, and control efforts are centred around isolation (35). Following SARS, the importance of other parameters that are complementary to R_o in assessing the efficacy of control measures have been re-identified and accentuated (35). These parameters include the proportion of transmission occurring before onset of symptoms (36), variance in the number of secondary cases produced per infected individual, and heterogeneity in the number of case contacts (37).

Models used for 2019-nCoV

Since the advent of the 2019-nCoV outbreak in China, there have been many worldwide efforts to model the possible spread of the virus and predict the impact on public health resources (38–41).

An early model detailed in a report produced by researchers in Imperial College London on 17 January 2020, used a negative binomial likelihood function to obtain maximum likelihood estimates. The model used internationally reported cases of 2019-nCoV to infer the likely magnitude of comparable cases that may have occurred up to that point in Wuhan City (38). This model estimated that a total of 1,723 cases of 2019-nCoV in Wuhan City (95% CI: 427 – 4,471) had onset of symptoms by 12th January 2020 (41 cases had been reported in Wuhan at that time). The report concluded that it is likely that the Wuhan outbreak of a novel coronavirus had caused considerably more cases of moderate or severe respiratory illness than had been reported, thus suggesting surveillance measures should be broadened to include all hospitalised cases of pneumonia or severe respiratory disease in the Wuhan area and other cities in China (38).

A further modelling study from researchers in the University of Hong Kong was published online by The Lancet on 31 January 2020. This study utilised available data on the number of cases exported from Wuhan internationally to infer the number of infections in Wuhan from 1 December 2019 to 25 January 2020. Researchers used a SEIR-metapopulation model to simulate the spread of 2019-nCoV across mainland China and estimated R_o using Markov Chain Monte Carlo methods. The model estimated that Wuhan alone had 75,815 cases by 25 January (39).

Another global risk assessment model was created by researchers from the Humboldt University of Berlin and the Robert Koch Institute (40). The core structure of this stochastic network dynamic model is the worldwide air transportation network (WAN) which connects over 4000 airports with more than 50 000 flight routes. This model is based on the concept of effective distance and is an extension of a model previously introduced in a 2013 paper (42). This approach to modelling is practical given that Wuhan (a city of 11 million residents), functioned as a major domestic air transportation hub with many onward connecting international flights before Wuhan airport closed on 23 January 2020. The model estimates the relative import risk, most probable spreading routes, effective distance and expected arrival time (40).

A team from the London School of Hygiene and Tropical Medicine have also produced a model, the details of which were published online on 11 February 2020 (paper not yet peer reviewed)(43). The model was developed with the aim of understanding how human-to-human transmission varied in Wuhan during the early stages of the 2019-nCoV outbreak and project forward based on current trends. The team employed a stochastic SEIR model implemented using the Euler-Maruyama algorithm with a 6hr timestep, with transmission rate following geometric brownian motion. The model assumes that no travel occurs out of Wuhan after 23 January, when restrictions were put in place. Cases that travel were distributed among other countries based on risk inferred from connectivity to those particular countries (43). The model estimated that (i) the median effective basic reproduction number, Rt, had likely been fluctuating between 1.5-4.5 prior to the introduction of travel restrictions on 23 January 2020, (ii) if Rt continues to vary as it has in Wuhan, the outbreak would peak in mid-to-late-February, (iii) a single introduction of 2019-nCoV with SARS-like or MERS-like individual-level variation in transmission would have a 20–30% probability of causing a large outbreak. Full detailed information on these model methods are available elsewhere (43).

Conclusion

Thus, the advantages of mathematical modelling techniques and simulations in aiding public health planning in the context of new emerging infectious diseases is clear. While each modelling technique has limitations, the information provided is crucial to decision-makers when prioritising resource allocation and determining control measures in the initial stages of an outbreak of disease.

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