Montogue

Review

Infectious Disease Modelling in Recent Epidemics – SARS, Ebola, COVID-19

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■ **Abstract**

This article presents a review of recent contributions to mathematical modelling of infectious diseases. Specifically, the review covers three of the most consequential outbreaks of the present century – namely, the 2002 – 2004 SARS epidemic, the 2014 – 2016 West African Ebola epidemic, and the ongoing COVID-19 epidemic. Over 90 model-driven studies are summarized, and each outbreak is associated with corresponding modelling techniques (e.g., deterministic compartmental models for SARS, spatiotemporal models for Ebola, agent-based models for COVID-19) and research topics (e.g., quarantine for SARS, travel restrictions for Ebola, lockdowns for COVID-19) that were commonly adopted by researchers in the wake of each event.

Keywords: SARS; Ebola; COVID-19; Deterministic compartmental models; Spatiotemporal models; Agent-based models.

1. Introduction

We are now approaching the 100th anniversary of *A Contribution to the Mathematical Theory of Epidemics*, a 1927 paper in which W.O. Kermack and A.G. McKendrick introduced deterministic compartmental models, a recurring infectious disease modelling technique, as we know them today. That paper is a seminal contribution to modern mathematical epidemiology, a discipline that employs quantitative tools to create representations and predictions of contagious disease outbreaks.

Since then, researchers have adapted the Kermack-McKendrick framework to increasingly complex formulations, while novel techniques such as spatial methods and individual-based methods have allowed modelers to circumvent the limitations of the deterministic compartmental approach. Although some of these

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theoretical developments were already in place at the time of, say, the 1980s AIDS crisis, it was not until the early 21st century that they were practically applied *en masse*. Specifically, we can attribute the recent renaissance in infectious disease modelling to two factors, namely (1) the birth of an interconnected medical research community that generates and processes data at unparalleled speed; and (2) the exponential growth in the processing power of commercial computers. Of course, factor (2) is one of the causes, though not the only one, of factor (1).

Thanks to this newly established mathematical epidemiology community, model-based forecasts of recent outbreaks have been produced within weeks of the first few cases, as in the case of SARS (Lipsitch *et al.*, 2003; Riley *et al.*, 2003), pandemic H1N1 influenza (Fraser *et al.*, 2009), MERS (Breban *et al.*, 2013), Ebola (Nishiura and Chowell, 2014), and, most recently, COVID-19 (Kucharski *et al.*, 2020).

In this article, I present a review of model studies inspired by three of the most consequential outbreaks of the past few years: the 2002 – 2004 Severe Acute Respiratory Syndrome (SARS) outbreak, the 2014 – 2016 West African Ebola outbreak, and the ongoing COVID-19 outbreak. Summarizing infectious disease modelling studies according to the outbreak that they tackle is warranted because it allows for a greater focus on the 'practical' side of this discipline, in that most of the papers I review are essentially case studies on the application of certain modelling techniques to one of three diseases. In this practical framework, we can appreciate the immense power of mathematical epidemic models without having to exhaustively discuss their theoretical underpinnings – something that most papers already do in an 'appendix' section at the end of their reports, not to mention the gallery of great textbooks (e.g., Keeling and Rohani, 2008) that cover such topics more comprehensively than any 20-page review could ever hope to. One additional advantage of maintaining a practical optics is that the ensuing material is made more accessible, in that a grasp of mathematical epidemiology, while helpful, is ultimately not imperative to our discussion.

Importantly, the papers I review were not selected with a particular systematic rationale; they were chosen subjectively, on the basis of which ones I found to be most interesting over the course of three and a half years as an active researcher. I've cited over 100 papers, only one of which was published before 2002. Two papers are not peer-reviewed, namely Kai *et al.* (2020) and Peng *et al.* (2020), but nonetheless come from authors in renowned universities and have their findings supported through charts, GitHub code, and other evidence of results. I've deliberately attempted *not* to quote findings summarized in the abstract of each paper, and instead tried to mention some of the more nuanced, 'obscure' conclusions offered by each model. Further, I've chosen not to report too

many reproduction numbers and other parameters because the literature is already ripe with reviews of epidemiological data.

Table 1 summarizes common the modelling techniques and important issues discussed in the review. Of course, mentioning a 'common modeling approach' does not imply that the technique mentioned was the only one used to analyze the outbreak; for example, while compartmental models were particularly common in SARS science, there are plenty of compartmental models for Ebola and COVID-19 as well. Likewise, the 'important issues' mentioned in the table were hotly debated in more than one outbreak.

Table 1. Common modelling approaches and important issues in recent epidemics.

Epidemic	Common modelling approach	Important issues
SARS	Deterministic compartmental models	→ Quarantine → Superspreading
Ebola	Spatiotemporal models	→ Travel restrictions
COVID-19	Agent-based models	→ Lockdowns → Also quarantine and superspreading

2. Modelling the 2002 – 2004 SARS Pandemic

2.1. Background

An atypical, unusually severe case of pneumonia was identified in Guangdong province, southern China, on November 16, 2002. Over 300 similar cases were identified in Guangdong from that date until February 9, 2003, one-third of them in healthcare workers. Between late February and early March, outbreaks of the novel disease were recognized in Hong Kong and Vietnam. On March 12, the WHO issued a Global Health Alert, the first such measure in over a decade, and instituted worldwide surveillance. In the same month, researchers at the Erasmus Medical Center in Rotterdam, the Netherlands, identified a coronavirus as the causative agent of the disease. Genetic sequencing of the virus soon followed. The new disease was named Severe Acute Respiratory Syndrome (SARS) and a preliminary case definition was provided.

SARS spread to more than two dozen countries in North America, South America, Europe and Asia before it was contained. On July 5, 2003, the WHO announced that the last known chain of human-to-human transmission had been broken. The virus re-emerged in China at the end of 2003, but Chinese authorities promptly isolated suspect cases and a combination of contact tracing and quarantine measures served to effectively contain the virus. By the end of February

2004, only three confirmed cases and one probable case had been confirmed, and no chains of onward transmission were verified. According to the WHO's final report, published in April 2004, the SARS outbreak involved 8096 known cases and 774 deaths (a mortality rate of 9.6%). Hong Kong was the most severely affected city when incidence figures are adjusted for population size or land area, having registered 1755 cases and 299 deaths (a mortality rate of 17%).

2.2. Model-Driven Studies of SARS

After several years of diminished activity, interest in deterministic compartmental models rekindled during the SARS epidemic (Brauer, 2005). The compartmental models that arose then differed from works motivated by, say, the AIDS crisis, which had focused on long-term outcomes and relied heavily on demographic effects (births and deaths).

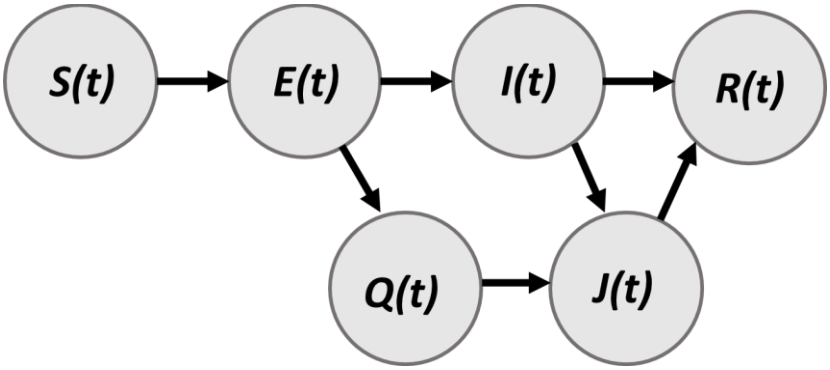
One of the first compartmental-model-based studies of the SARS outbreak is Chowell *et al.* (2003). Chowell's team adopted a 'SEIJR' framework to investigate the evolution of the epidemic in Ontario (Canada), Hong Kong, and Singapore. Since they had only preliminary data, both in terms of epidemic numbers and information about the virus, their ensuing model was somewhat crude. For one, it considered differences in susceptibility via two compartments S_1, for 'most susceptible' individuals, and S_2, for 'less so' individuals, and the differences in risk of infection between the two groups were related to an arbitrary parameter. Nevertheless, Chowell's model fit available data from the three regions well and showed that efficient isolation and a high diagnostic rate could bring the epidemics under control. In the following year, Chowell *et al.* (2004) conducted a sensitivity analysis of the parameters that most affected R_0 in the 2003 paper and found that the model was particularly sensitive to transmission rate and the rate of isolation of infectives.

Lipsitch *et al.* (2003) developed a simple 'SEIR' framework to model the early phase of the SARS outbreak. They stressed the importance of quarantine and isolation, while summarizing some factors that would limit the effectiveness of one or the other. Quarantine, they warned, could be compromised by factors such as an inability to trace all infected contacts or individual noncompliance; the latter turned out not to be an issue at least in Toronto, as only 27 out of 23,000 contacts were issued a legally enforceable quarantine order owing to initial noncompliance (Svoboda *et al.*, 2004). Isolation, Lipsitch's team argued, could be affected by the speed of the isolation process and failures of infection control for isolated patients; nosocomial infection would contribute overwhelmingly to the epidemic in the ensuing months.

In the same issue of *Science* as the study of Lipsitch *et al.* (2003), Riley *et al.* (2003) introduced a stochastic metapopulation compartmental model to assess the evolution of the epidemic in Hong Kong. A *metapopulation* approach was warranted because the incidence of SARS varied substantially by geographical district in Hong Kong; a *stochastic* model was chosen because, as one can glean from other models discussed in this review, stochastic methods are better in capturing the variability inherent to the initial stages of an epidemic, yielding a clearer picture of which changes are caused by chance and which ones in fact reflect the impact of interventions. Riley's team alternated model assumptions such as accounting for superspreading events and varying infectiousness of hospitalized patients, and ultimately found that the basic reproduction number for the local outbreak would be placed between 2.2 and 3.7. They went on to prepare scenarios and noted that while onset-to-hospitalization times comparable to those observed in the Hong Kong epidemic could achieve some reduction in transmission, they did not suffice to control SARS; additional measures were needed, such as improved infection control in hospitals and movement restrictions.

Gumel *et al.* (2004) is one of the most important modelling studies published in the period following the SARS epidemic. Gumel's team modelled the impact of control measures on four of the areas that had been most affected by the outbreak – Toronto, Hong Kong, Singapore, and Beijing. They worked with a deterministic model made up of six compartments, as shown in Figure 1: susceptible ($S(t)$), asymptomatic ($E(t)$), quarantined ($Q(t)$), symptomatic ($I(t)$), isolated ($J(t)$), and recovered ($R(t)$). Demographics were allowed for, suggesting that their model could be used for long-term control estimates. Gumel's team found that isolation and quarantine are effective control measures. Crucially, they posited that if limited resources are available for investment in these two strategies, then investing all resources in one of them would likely yield a better outcome than investing partly in both.

Figure 1. Compartments in the Gumel *et al.* (2004) model.



Trade-offs were also examined by Lloyd-Smith *et al.* (2003), who, unlike Gumel's team, worked with a stochastic model. Lloyd-Smith's team found that the potential for quarantining to aid in SARS containment increased with the basic reproduction number. Quarantine had little effect at low R_0, but in a setting with $R_0 = 5$, efficient quarantine implied that lower case isolation levels were needed to bring the outbreak into control. Quarantine also had to be timely, as its contribution to containment was markedly reduced when individuals were quarantined ~ 5 days after exposure.

Ng *et al.* (2003) adapted the compartmental framework to a *double epidemic* model in which individuals could be infected by two viruses, *A* and *B.* Importantly, recovering from disease *B* conferred immunity to disease *A*, but not vice versa. Ng's formulation was motivated in part by the fact that zoonotic coronaviruses can have their tissue tropism modified by simple mutations, leading to rapid development of pathogenic variants. Different strains of the original coronavirus never turned out to be a problem in the SARS epidemic, but would, years later, during the COVID-19 pandemic. Indeed, Ng's observation, 'The innocuous epidemic might still be there and generate, from time to time, variants that would have properties similar to those of SARS', could very well have been extracted from a paper written in 2020 or 2021.

Massad *et al.* (2005) fit the Hong Kong and Toronto epidemic data to a simple SIR model. Massad's team contended that omitting a compartment for 'latent' individuals, a characteristic of the SIR model, did not affect performance significantly because the incubation period of SARS is short, most incubating cases evolved to clinical cases, and cases were probably infectious before clinical recognition. They estimated that, in the absence of control measures, the final number of SARS cases would have been 320,000 in Hong Kong and 36,900 in Toronto; control measures reduced the contact rate to 25% of its value in the absence of intervention, decreasing the expected final number of cases to 1778 in Hong Kong and 226 in Toronto.

McLeod *et al.* (2006) recognized an important limitation of many compartmental models available at the time: the parameters they use can be subject to change as a result of modifications in intervention measures and other dynamic phenomena, but most workers adopted 'stiff' values with no time-wise dependence. This may be unimportant for retrospective analysis, but constitutes an important drawback when modelling an ongoing outbreak. Accordingly, McLeod's team adapted the model of Gumel *et al.* (2004) to include time-varying parameters as a means of accounting for the gradual refinement of quarantine, isolation, and hygienic precautions in response to a SARS outbreak. They went on

to perform a sensitivity analysis to establish which parameters governed the response to such a hypothetical epidemic.

Krumkamp *et al.* (2009) investigated intervention measure combinations to establish which ones most pronouncedly lowered the effective reproduction number of a SARS epidemic. Their model showed that merely isolating all cases 3 days after symptom onset and ensuring that hospital infection control prevented 90% of infections was enough to lower R_e to 0.88 – a viable control strategy. If, in addition to these two measures, 90% of exposed healthcare workers were contact-traced, R_e would be further reduced to 0.68. Tracing of close contacts of SARS cases was also considered; if SARS cases were isolated 3 days after symptom onset, 50% of close contacts of all SARS cases were traced and 70% of hospital-based infections could be avoided, a R_e of 0.96 would result. Krumkamp's team developed several other scenarios, but the main idea they wanted to get across is that, if 90 – 100% of hospital-based transmission were prevented, an effective reproduction number below unity could be attained with minimal supplementation by other intervention measures.

Years after the epidemic, Wong *et al.* (2013), a group that studies the interface between air pollution and respiratory illnesses, noted that hospitalizations due to such diseases in Hong Kong's healthcare system decreased in the aftermath of the SARS epidemic. They attributed this effect to a greater awareness of hygienic measures such as mask-wearing, as propagated by government campaigns and mass media. Unfortunately, respiratory-disease-related hospitalization levels increased rapidly afterwards and reverted back to pre-SARS levels in six months' time, illustrating the 'forgetfulness' of citizens as the epidemic faded from collective memory.

2.3. The Quarantine Debate

During the SARS outbreak, because development of a treatment, prophylaxis or vaccine was months into the future, governments had to rely heavily on isolation and quarantine. Some of the model studies cited in the previous section assessed the roles of isolation and quarantine; here, we mention a few more.

Of note, around 30,000 people in the Greater Toronto Area were quarantined, mostly in their homes; Beijing placed around the same number of its citizens in quarantine. These figures are dwarfed by the Taiwanese experience, as the Taipei government held about 131,000 people over the course of the outbreak (DiGiovanni *et al.*, 2004). Control measures included completely shuttering a hospital with 930 staff members, 240 patients, and 129 visitors for a period of 14 days; movement into or out of the facility was carefully regulated, and a 2-week

home quarantine was also mandated for discharged patients and the family members of the hospital staff (Barbisch *et al.*, 2015).

The Taiwanese government relied on two types of quarantine: Level A quarantine was aimed at people suspected of having close contact with a suspected SARS case, while Level B quarantine was aimed at travelers from affected areas. In a retrospective study of the response to SARS in Taiwan, Hsieh *et al.* (2007) noted that a modest Level A quarantine program, in which 4.7% of asymptomatic individuals who should be quarantined were in fact quarantined, sufficed to prevent more than 450 cases and more than 60 deaths. Table 2 indicates that even slightly greater quarantine rates would have led to significantly reduced cases and deaths.

Table 2. Theoretical impact of Level A quarantine on case number and fatality with various hypothetical quarantine rates q as compared with a quarantine rate of q = 0.047. A '+' denotes additional cases/deaths, and a '–' denotes less cases/deaths. From Hsieh *et al.* (2007).

	$q = 0.0$	$q = 0.025$	$q = 0.1$	$q = 0.6$	$q = 1.0$
Cases	+461(81%)	+167(29%)	−214(−38%)	−477(−84%)	−500(−88%)
Deaths	+62(63%)	+24(24%)	−33(−33%)	−80(−81%)	−85(−86%)

Extracting qualitative conclusions from compartmental models that include quarantine is made difficult by their odd mathematical behavior, which continues to be a topic of active research. For example, Hethcote *et al.* (2002) showed that even a simple SIQR model endowed with incidence terms adjusted for quarantine can exhibit periodic solutions that occur by Hopf bifurcation. Hethcote's team attempted to use such periodic solutions to reproduce the oscillatory patterns in the incidence of diseases such as measles, but were not successful.

In view of the complex dynamics of models with quarantine, it is no surprise that research has produced evidence both in favor and against this measure. Yan and Zou (2008) used control theory to show that timely implementation of an 'optimal' or a 'sub-optimal' quarantine/isolation strategy are both effective countermeasures. Interestingly, their 'sub-optimal' strategy, in addition to being cheaper and simpler than the 'optimal' strategy, was also nearly as effective.

On the other hand, Safi and Gumel (2010) conducted a rigorous analysis of a 'SEIQHRS' model that includes quarantine and isolation and found that, depending on the value of the reduction in infectiousness of hospitalized individuals, as represented by a parameter η, resorting to quarantine and isolation may actually raise the control reproduction number and *increase* the disease burden in a community. A similarly detailed analysis was conducted by Hsu and Hsieh (2006), whose own compartment model suggested that implementation of a quarantine

program that is not sufficiently comprehensive could have the adverse effect of causing a system that would have approached disease-free equilibrium without quarantine to converge to an endemic equilibrium instead.

Some authors have studied the costs of quarantine programs, which are inherently expensive. For instance, the Singaporean government allocated about USD 5.2 million to its quarantine operations during the SARS outbreak (Ooi, 2005). The Canadian government, in turn, set up *de novo* infrastructure such as a computer database to keep track of contacts, information and surveillance hotlines, and staff to monitor quarantined individuals' status. Still, a simple cost analysis by Gupta *et al.* (2005) indicated that the direct cost associated with the Canadian quarantine measures, which was placed at C$12 million (C$ = Canadian dollars), was greatly offset by the savings they entailed, which they estimated at over C$ 200 million. On a global scale, retrospective analysis revealed that the economic impact of the SARS pandemic turned out to be much less than initially feared (Keogh-Brown and Smith, 2008).

Using a statistical model, Day *et al.* (2006) argued that SARS is likely to be effectively contained in the absence of quarantine only if very stringent and effective isolation measures are in place. Fraser *et al.* (2004), in turn, argued that control policies involving isolation and contact tracing were effective for SARS because of its low reproduction number and the low proportion of transmission occurring prior to symptoms or asymptomatically; this may not be the case with future emerging pathogens.

There is some debate on possible alternatives to quarantine. Peak *et al.* (2017) argued for greater reliance on symptom monitoring, a management strategy in which health workers check on traced contacts one or two times a day and isolate them if symptoms occur. Symptom monitoring is of course less conservative, cheaper, and more palatable than quarantine, but, as Peak's team showed in a comparative assessment reminiscent of Fraser *et al.* (2004), does not constitute a perfect replacement for quarantine.

2.4. Super-Spreading

Super-spreading events (SSEs) are rare events where, in a particular setting, an individual may generate many more than the average number of secondary cases. SSEs were found to have fueled the SARS outbreaks in Hong Kong, Beijing, Toronto, and Singapore. Of note, SSEs have been reported for several other infectious diseases. Stein (2011) tells that in 1989, at a high school in Finland, a single student infected 22 others with measles, even though eight of the contacts were vaccinated. During the 1995 Ebola outbreak in the Democratic Republic of

the Congo, two individuals, both exhibiting gastrointestinal hemorrhage, are said to have been the source of infection for over 50 secondary cases.

SSEs were pivotal for the spread of SARS. A detailed study of a Beijing hospital revealed that one patient with 74 close contacts generated 33 secondary cases, and these secondary cases in turn generated a further 43 cases before the chain of transmission petered out (Shen *et al.*, 2003). Another extreme example stemmed from Hong Kong (Stein, 2011). In the Prince of Wales Hospital, a 26-year-old man was admitted on March 4, 2003 and was administered bronchodilators via a nebulizer. Overcrowding and an outdated ventilation system are thought to have facilitated the spread of SARS-CoV. Within the next two weeks, 156 individuals, among hospital staff, patients, and visitors, were admitted to the hospital, all of them traceable to this patient, and SARS was diagnosed in 138 of them.

Li *et al.* (2004) used a statistical model to study the SARS super-spreader issue. Li's team used the model to estimate the daily numbers of newly infected cases, and plotting the daily number of newly infected cases allowed them to identify peaks or aggregates of infections that could serve as indicators of SSEs. Their results reproduced the SSEs that were well-documented at the time and indicated the existence of a few more that had not yet been identified. Further, their analysis indicated the outsize contribution of SSEs to the two outbreaks, with 71.1% of cases in Singapore and 74.8% of cases in Hong Kong being attributable to super-spreading.

Lloyd-Smith *et al.* (2005) further expanded the theoretical understanding of super-spreading. They introduced the *individual reproductive number*, v, which is the expected number of secondary cases transmitted by a particular primary case, and went on to show that SSEs can be naturally accommodated in the right-hand tail of a distribution for this parameter. The representation of the individual reproductive number depends on the particular model's treatment of individual heterogeneity. In a generation-based model with no individual variation, $v = R_0$ (that is, the individual reproductive number equals the basic reproduction number) and the number Z of secondary infections caused by each case redounds to a Poisson distribution with rate R_0 (that is, $Z \sim \text{Poisson}(R_0)$). More generally, if v is gamma-distributed with mean R_0 and dispersion parameter k, then Z is represented by a negative binomial distribution (i.e., $Z \sim$ negative binomial (R_0,k)). The negative binomial model includes the conventional Poisson ($k \to \infty$) and geometric ($k = 1$) models as special cases. The variance is $R_0(1 + R_0/k)$, so smaller values of k indicate greater heterogeneity. After fitting possible models to the SARS outbreaks in Singapore and Beijing, Lloyd-Smith's team found that the negative binomial is indeed a viable choice for Z. The value of k for Singapore's

representative negative binomial model was estimated at 0.16, indicating a highly over-dispersed epidemic. Indeed, in Singapore a majority of SARS cases (73%) were barely infectious ($v < 1$), but a small proportion (6%) were highly infectious ($v > 8$) (Chun, 2016).

The earliest attempt to model super-spreading deterministically is Kemper (1980), who adapted compartmental SIR and SIS models to include two classes of infectives, I_1 and I_2, to which he assigned different transmission rates; superspreading was represented by a class of infectives with transmission rate several times greater than that of the other class. Kemper's approach was theoretical and did not include any practical applications.

In the same vein as Kemper (1980), Mkhatshwa and Mummert (2010) modified the SIR model to include two types of infectives, one for 'typical' infected individuals and another for super-spreaders. In contrast to Kemper's work, however, they associated both classes with the same transmission rate. Mkhatshwa and his colleague noted that, as per Li *et al.* (2004), in the SARS outbreaks 'the daily infection rate did not correlate with the daily total number of symptomatic cases but with the daily total number of symptomatic cases who were not admitted to a hospital within 4 days of onset of symptoms.' Accordingly, super-spreaders could be defined as individuals that were not timely isolated and hence had more time to spread the disease. In their model, this was represented by assigning different removal rates to the two classes of infectives. It was shown that, with the proper parameter-fitting procedure, their adapted compartmental model could apply to either a small-scale outbreak such as Hong Kong's Amoy Gardens SSE or a large-scale outbreak such as the entirety of Hong Kong itself.

Since SSEs are basically an individual-level phenomenon, they are not well-captured by deterministic compartmental models. Small and Tse (2004, 2005) successfully accounted for these phenomena by introducing a *small-world* model that replaces the homogeneous, fully-connected population of deterministic models with a computational arrangement of nodes (individuals) interconnected by a finite number of links. The probability of contact is greater for adjacent nodes than for distant ones, leading to patterns that realistically mimic infection clusters and SSEs. In Small's small-world framework, a super-spreader is not a highly infectious individual but rather a highly *connected* individual, which occurs naturally in the model and requires no special modifications.

3. Modelling the 2014 – 2016 West African Ebola Epidemic

3.1. Background

Ebola and its associated pathogen were first characterized in 1976, following two near-simultaneous outbreaks that occurred around Yambuku in Zaire (now Democratic Republic of the Congo) and Nzara in Sudan (now South Sudan). The Zaire outbreak involved 318 cases with a case-fatality ratio (CFR) of 88%, whereas the Sudan outbreak involved 284 cases with a CFR of 53%. These epidemics were shown to be caused by two distinct species of ebolavirus, a fact not recognized until years later.

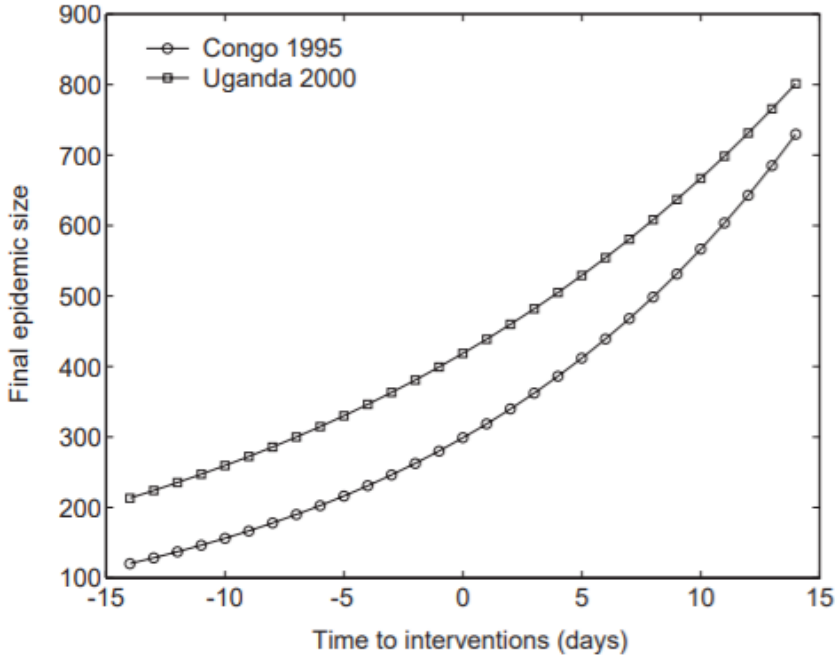
Although several more Ebola outbreaks would occur in Africa over the next few decades, the most devastating one, by far, took place in the western portion of the continent between 2014 and 2016. Starting with an index case in the village of Méliandou in Guinea, ebolavirus would eventually spread throughout the rest of the country and, in particular, the neighboring nations of Liberia and Sierra Leone. Following the report of the Méliandou case in December 2013, several further cases occurred in southeastern Guinea and on March 23, 2014, with 49 confirmed cases and 29 deaths, the WHO officially declared an outbreak of Ebola. Cases in neighboring Liberia and Sierra Leone were reported shortly afterwards, and on August 8, 2014 the WHO declared the outbreak a Public Health Emergency of International Concern (PHEIC).

In May 2015, Liberia became the first of the three most affected West African nations to be declared Ebola-free, but more cases were discovered less than six months later. The country was again declared Ebola-free in January 2016. Sierra Leone and Guinea themselves were also declared Ebola-free only to register new cases months later, but by June 2016 the epidemic had subsided in the whole of West Africa. The outbreak reportedly involved 28,646 reported cases and 11,323 deaths (for a case fatality ratio of 39.5%), but, because underreporting was a persistent issue, the real toll is probably far higher.

3.2. Before the 2014 – 2016 Crisis

Ebola had already motivated some mathematical epidemiology research before the 2014 crisis. In one example, Chowell *et al.* (2004) used data from two well-documented Ebola outbreaks, one in Congo in 1995 and the other in Uganda in 2000, to calculate the respective basic reproductive numbers in the absence of control interventions; the results were $R_0 = 1.83$ for the Congo event and $R_0 = 1.34$ for the Uganda event. Chowell's team used a simple SEIR model and evaluated the sensitivity of the final epidemic size to the time at which interventions begin. As shown in Figure 2, the final epidemic size increased exponentially with the time of

Figure 2. Sensitivity of the final epidemic size to the time of start of interventions in the 1995 Congo and 2000 Uganda outbreaks. Negative numbers represent the number of days before the actual reported intervention date and positive numbers represent a delay after the actual reported intervention date. From Chowell *et al.* (2004).



start of interventions, reaffirming the notion that timely identification of an outbreak remains the strongest determinant of final outbreak size.

Lekone and Finkenstädt (2006) used a stochastic SEIR model to perform a retrospective study of the 1995 Ebola outbreak in Congo. They estimated the basic reproduction number at 1.4, which is lower than the 1.83 result of Chowell *et al.* (2004). Importantly, Lekone and his colleague obtained a much greater standard deviation for R_0, which they interpreted as inherent to an approach of stochastic, discrete nature. By modelling the impact of intervention, they estimated that control measures reduced the duration of the epidemic from approximately 950 days to about 200 days and the final size from about 3.5 million cases to the observed size of just over 300 cases.

Legrand *et al.* (2007) noted that the retrospective estimate of R_0 in Chowell *et al.* (2004) for the Congo and Uganda outbreaks had not accounted for the contribution of different settings in transmission dynamics. Accordingly, Legrand's team developed a stochastic model that, in addition to the typical SEIR compartments, also included hospitalized individuals and deceased individuals who may have transmitted the disease in funerals. They estimated the basic

reproduction numbers of both the 1995 Congo outbreak and the 2000 Uganda outbreak at 2.7 (albeit with large confidence intervals), which is substantially greater than the estimates of Chowell *et al.* (2004) and Lekone and Finkenstädt (2006). Further, Legrand's team performed a sensitivity analysis and concluded that epidemic size in both the Congo and Uganda events are linked to time to deployment of intervention measures, hospitalization rate, and the mean time between onset of symptoms and hospitalization.

3.3. Spatiotemporal Modelling

One could argue that the Ebola crisis should have been easier to predict than, say, the SARS epidemic, because the latter involved an emerging pathogen whereas the former involved a virus that had been known since the late 1970s. However, the natural history of ebolavirus spread is convoluted, as it has caused over 20 outbreaks between 1976 and 2008, ranging from a few dozen to several hundred cases. Camacho *et al.* (2014) used a model built with data from the original 1976 Yambuku outbreak to demonstrate some of the difficulties associated with Ebola forecasting.

Although Ebola cases have occurred in many parts of Guinea, Liberia, and Sierra Leone, the geographical spread of the epidemic was not as sweeping as one might think; in the first 9 months of the epidemic, 24 of the more than 60 districts that constitute the three countries had no confirmed cases, and more than 90% of cases had been reported from just 14 districts (WHO Ebola Response Team, 2014). An exploratory data analysis by Suchar *et al.* (2018) also indicated that the outbreak was fairly localized for several weeks. The peculiar spatial distribution of infections has important implications for the modelling of intervention measures, as it has been suggested that intervention in Liberia had significant indirect protective effects on the epidemic dynamics of Guinea and Sierra Leone (D'Silva and Eisenberg, 2017). Simply put, the dissemination of the Ebola virus during the 2014 – 2016 crisis is a nuanced problem that calls for use of spatiotemporal tools that until recently were not commonly employed in mathematical epidemiology.

Rainisch *et al.* (2015) analyzed case counts, population data, and distances between affected and nonaffected districts in Guinea (where such spatial units are actually termed *prefectures*), Liberia (*counties*), and Sierra Leone (*districts*). Regression models were created to compute the weekly risk of a district being affected as a function of various variables. Rainisch's team found that the risk of becoming affected by Ebola was significantly higher for nonaffected districts that had a larger population and that were closer to affected districts with higher case counts. Dudas *et al.* (2017) also implicated greater population size and small distance to nearby urban settlements as important factors in Ebola proliferation,

and Fang *et al.* (2016) found that invasion of Ebola in chiefdoms in Sierra Leone was closely associated with the chiefdom's density of primary and secondary roads. Accordingly, Rainisch *et al.* (2015) argue that, in the appropriate situations, prediction of which regions would next become affected during the epidemic could be based on data on population size and distance to highly affected districts.

Kucharski *et al.* (2015) used variation in the number of treatment beds to investigate the epidemic dynamics in Sierra Leone. Kucharski's team used a stochastic model that allowed for time-varying transmission rate through a sigmoid function, so that reduction in infection achieved by extra beds could be disentangled from other effects. Although not inherently spatial in nature, their model was stratified by district and afforded some geographic insight; for example, it was observed that, as the outbreak waned, the drop in cases was greater in the northern and eastern portions of the country.

Drake *et al.* (2015) conceived one of the first major modelling studies of the 2014 outbreak that did not have the calculation of basic reproduction numbers as an overarching goal. Working with data from the Liberian outbreak, Drake's team used a discrete, stochastic multi-type branching process model that offered great flexibility to investigate a wide range of intervention scenarios for different combinations of individual behavior and hospitalization rate. They found that a hospitalization rate consistently maintained at 85% may have ensured near complete containment of the Liberian epidemic sometime between March and June 2015.

Merler *et al.* (2015) developed an agent-based spatial Markov chain Monte Carlo (MCMC) model that, they argued, would achieve more accurate predictions than models with homogeneous population and no spatial structure. Indeed, their approach accurately reproduced the decrease of incidence registered in Liberia in the second half of 2014, and captured some of the dynamics that may have accounted for this transition; for example, the high proportion of cases generated in hospitals early in the outbreak was followed by a consequent decrease of transmission in hospitals as more beds in Ebola treatment units became available, in consonance with data reported by the WHO.

Ivorra *et al.* (2015) introduced a novel spatiotemporal model, Be-CoDiS ('Between-Countries Disease Spread'), to assess the international spread of diseases such as Ebola. The model combines an individual-based framework (in which countries are the individuals) for between-country interactions with a deterministic compartmental approach for within-country disease spread. Be-CoDiS accounts for the movement of people between countries, models the effects of control measures, and allows for the temporal evolution of epidemics

through time-varying parameters. Ivorra's team validated the model with data from the Ebola crisis.

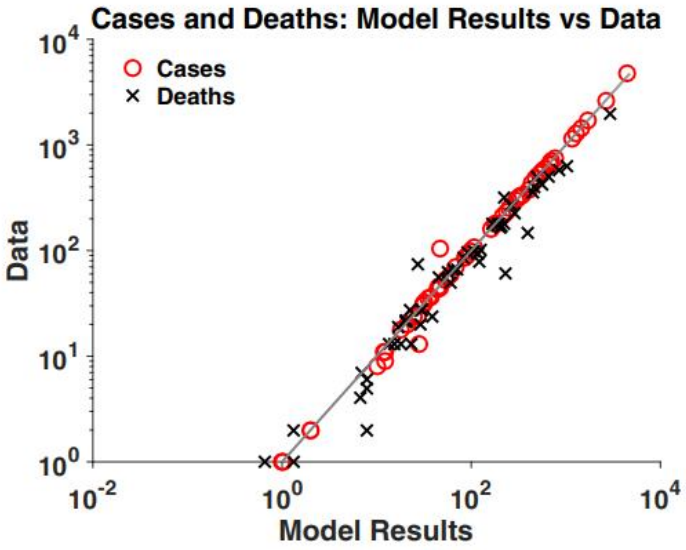
Backer and Wallinga (2016) developed a spatiotemporal model that affords a precise portrait of the evolution of incidence dynamics and effective reproductive numbers across the three affected countries. The model is mostly descriptive (as opposed to predictive or designed for forecasting), but nonetheless constitutes an important integration of an old concept (that is, effective reproduction numbers) to an approach that has only recently drawn considerable attention (namely, spatiotemporal methods).

Santermans *et al.* (2016) also combined old and new in their own study. Specifically, they introduced a spatiotemporal growth rate model to assess the district-specific epidemics in the affected West African countries, and, for some districts, complemented this approach with a classical SEIR compartmental model. While the heat maps afforded by the district-specific analysis gives decision-makers a detailed spatial framework with which to better allocate resources, the SEIR model yields valuable additional information such as effective reproduction numbers.

Kramer *et al.* (2016) adopted a network model and exhaustively tested 16 types of weighting of network links that incorporated data such as distance between locations and population density. The model that led to the best fit of observed Ebola spread was a gravity model in which population density contributed heavily to link weighting. The second and third models that fared best were also gravity models, underscoring the value of this technique in spatiotemporal epidemic modelling. Interestingly, a model that relied on mobility data from cell phone records yielded some of the worst results, which goes counter to the growing predilection towards models that make use of such data (see below).

D'Silva and Eisenberg (2017) created a gravity compartmental model to revisit the impact of intervention measures during the crisis. Following the approach of Legrand *et al.* (2007), their compartment division included groups for 'funeral' individuals and two stages of infection. The model was used to evaluate the effectiveness of both country-level and district-level interventions in the three Ebola-stricken West African countries. Their deterministic model was found to accurately replicate the general patterns of outbreak data for cases and deaths in each district, as shown in Figure 3. Although the model was primarily deterministic, a stochastic variant based on Tau-leaping was used to assess district-level interventions. The deterministic and stochastic district-level gravity models led to a reasonably accurate approximation of the dynamics of the outbreak.

Figure 3. Final size of the outbreak in West Africa, as predicted by D'Silva and Eisenberg (2017); comparison of deterministic model values (*x*-axis) and data (*y*-axis).

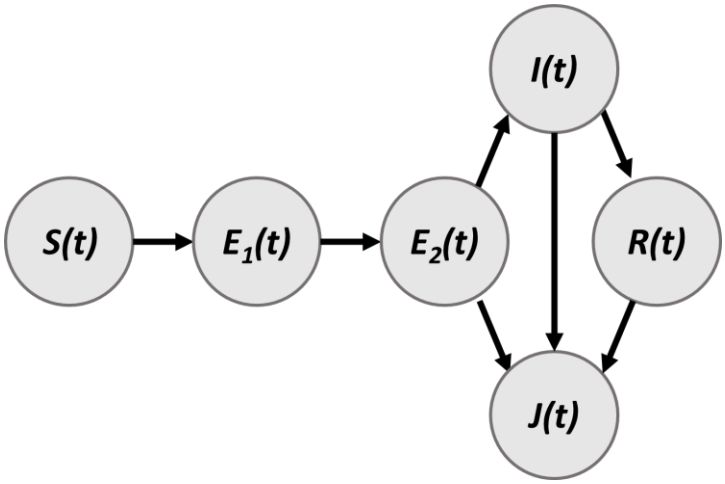


In the wake of the Ebola crisis, authors have called for a greater emphasis on models that incorporate population mobility patterns (e.g., Halloran *et al.* (2014)). Cellphone activity is a powerful candidate source for mobility data, because the global mobile phone penetration rate (that is, the ratio of active subscriptions to the population) nowadays exceeds 90% even in nations with substandard telecommunications infrastructure (Wesolowski, 2014). Peak *et al.* (2018) used phone call detail records (CDRs) to develop a detailed picture of human mobility dynamics in Sierra Leone between March and July 2015 – a period that included imposition of a lockdown by the local government in an effort to eradicate Ebola. Peak's team noted that the impact of travel restrictions on mobility was expressive, reducing trips longer than 30 km by 76%. Peak's team concluded that CDRs constitute an inexpensive, reliable tool for monitoring and evaluating travel restriction policies within national boundaries. With the possibility of measuring the impact of travel restrictions on human mobility now well-established, it remains to better integrate these models with the issues of disease spread, effect on commerce, human rights, and so forth.

3.4. Deterministic Compartmental Models

Deterministic compartmental models such as the ones employed in the SARS epidemic were not as enthusiastically pursued after the Ebola crisis, because they are somewhat limited in capturing spatial variation (Keeling and Rohani,

Figure 4. Compartments in the model by Chowell *et al.* (2016).



2008); but there are important exceptions. Chowell *et al.* (2016) assessed the impact of early diagnosis of pre-symptomatic individuals on the transmission dynamics of Ebola virus disease. Their deterministic model consisted of six compartments (Figure 4): susceptible ($S(t)$), non-detectable latent ($E_1(t)$), detectable latent ($E_2(t)$), infectious ($I(t)$), isolated ($J(t)$), and recovered ($R(t)$). Chowell's team performed a sensitivity analysis of the control reproduction number, R_c, for several parameters. It was found that R_c declined appreciably in response to an increased fraction of pre-symptomatic individuals diagnosed and isolated, f_T, provided that isolation is highly effective. Further, Chowell's team provided a threshold formula for a fraction f_T^* of diagnosed/isolated pre-symptomatic individuals, above which the effective control of Ebola can be achieved.

Another noteworthy compartmental model for Ebola was introduced by Diaz *et al.* (2017). In contrast to similar endeavors, Diaz's team emphasized how their model could inform the allocation of resources in the epidemic-stricken West African countries. Through sensitivity analysis, they found that the basic reproduction number R_0 was most pronouncedly affected by a greater hospitalization of infected individuals. Analyzing the outbreak data in Sierra Leone and Liberia, their local metrics indicated that Liberia would benefit the most from a greater hospitalization rate. However, additional analysis using an *active subspace* method indicated that it was Sierra Leone that would experience a greater decrease in R_0 through greater hospitalization rate.

In Ebola, not all symptomatic hosts are equally symptomatic; an infected individual may progress through different stages: firstly, there is a stage with non-

specific symptoms (fever, headache and myalgia); secondly, there is a gastrointestinal stage (diarrhea, vomiting, abdominal symptoms and dehydration); thirdly, the patient progresses to a deterioration stage (collapse, neurological manifestations and bleeding) or recovery. Some of the peculiarities of Ebola in epidemic dynamics were captured in the age-of-infection deterministic model of Webb and Browne (2016). The most successful such endeavor, however, is probably Hart *et al.* (2019), who worked with a deterministic model that included individual compartments for infectives in the three aforementioned symptomatic stages; they went on to compare the performance of this model, which they called the *variable symptoms model*, relatively to a model with a single compartment for infectives irrespective of disease stage, which they called the *constant symptoms model*. Crucially, they found that both models fit Ebola epidemic data efficiently, but, when used to forecast the impact of certain interventions, the two models gave rise to very different results. For instance, when predicting the effect of intensified surveillance in the 2018 – 2019 Democratic Republic of Congo (specifically, the city of Beni) Ebola epidemic, the constant symptoms model underestimated the number of cases by 24% relatively to the more medically realistic variable symptoms model. Thus, in order to achieve greater forecasting accuracy, deterministic models of Ebola may benefit from a framework that allows for variations in symptoms during infection.

One aspect in which the Ebola crisis diverged from, say, the SARS epidemic was the outsize role that traditional/cultural beliefs played in shaping individuals' response to control measures, leading to resistance and, at times, outright hostility towards healthcare workers (e.g., BBC, 2014). It has been suggested that community behaviors such as avoidance and denial may hinder the capacity of an epidemic control strategy to achieve the outcomes predicted by mathematical modelling (Drake *et al.*, 2015). Agusto *et al.* (2015) provided a quantitative assessment of the role that traditional beliefs may have played in the Ebola crisis. Using data from Guinea, Agusto's team developed a compartmental model that included the dynamics of healthcare workers and, most importantly, accounted for the strength of traditional belief systems and customs. Their sensitivity analysis showed that the disease burden when traditional beliefs and customs are taken into account is at least 50% greater than that for the case when these systems and customs do not induce any detrimental effect.

3.5. Travel Restrictions

An influenza pandemic scenario by Cooper *et al.* (2006) suggested that even a 99% restriction of air travel in affected cities yields a low probability of delaying a widespread outbreak. Further, experience gained during the SARS epidemic indicates that travel restrictions have negative economic effects, especially in the

tourism and transportation sectors. Thus, there are important epidemiologic and economic issues in travel restriction measures, which were hotly debated as countries across the world assessed how to shield themselves from the spread of Ebola in Guinea, Liberia and Sierra Leone circa August 2014. Restrictions ranged from partial cancellation of international flights coming from these countries to outright closure of international borders to passengers from the affected countries; most nations that adopted the latter approach were in the African continent. At the apex of the crisis, Royal Air Maroc and Brussels Airline were the only two large commercial airlines still operating flights to the epidemic-stricken West African countries (Ferrell and Agarwal, 2018).

There is important infectious disease modelling research to inform the travel restrictions debate. Bogoch *et al.* (2014) suggested that exit screening at international points of departure would offer greater efficiency than entry screening all flights arriving directly from affected countries; a November 2014 document by the WHO provided guidance on exit screening procedures for airports (WHO, 2014). In a simulation study, Poletto *et al.* (2014) assessed the impact that travel restrictions imposed during the crisis had on the global spread of Ebola, and found that a total estimated reduction of 60% of airline passenger traffic connecting the rest of the world to the West African countries most affected by the disease provided relatively small delays, mostly no greater than one month, in the risk of case importation. Using a hazard-based statistical model, Otsuki and Nishiura (2016) also pointed to a low effectiveness of travel restrictions in reducing risk of importation of Ebola cases, especially among European countries. A recent review of the relationship between travel restrictions and infectious disease outbreaks can be found in Vaidya *et al.* (2020).

4. Modelling the 2019 – (Ongoing) COVID-19 Pandemic

4.1. Background

On December 31, 2019, the government of Wuhan, Hubei province, China, confirmed that health authorities were treating dozens of cases of an unknown respiratory disease. About a week later, a Chinese state broadcaster confirmed that a coronavirus had been detected in 15 of the people who fell ill. On January 11, 2020 the first known death from the disease was reported: a 61-year-old man who had been a regular customer of Wuhan's Huanan Seafood Wholesale Market, a local marketplace that concentrated several of the initial cases. Japan, South Korea, and Thailand soon confirmed their own cases of the novel disease.

On January 30, the WHO declared the newly established disease a Public Health Emergency of International Concern, and on February 11 it proposed 'COVID-19', short for 'coronavirus disease 2019', as a name for the emerging

disease. Over the course of February, COVID-19 infections would be reported in France, Italy, Iran, and Brazil. In March, following advice from infectious disease experts, several western governments implemented a spectrum of intervention measures to slow the spread of the virus, including restrictions on mass gatherings and school closures. By April 2, the outbreak, now a full-blown pandemic, had sickened more than one million people in 171 countries and killed over 50,000.

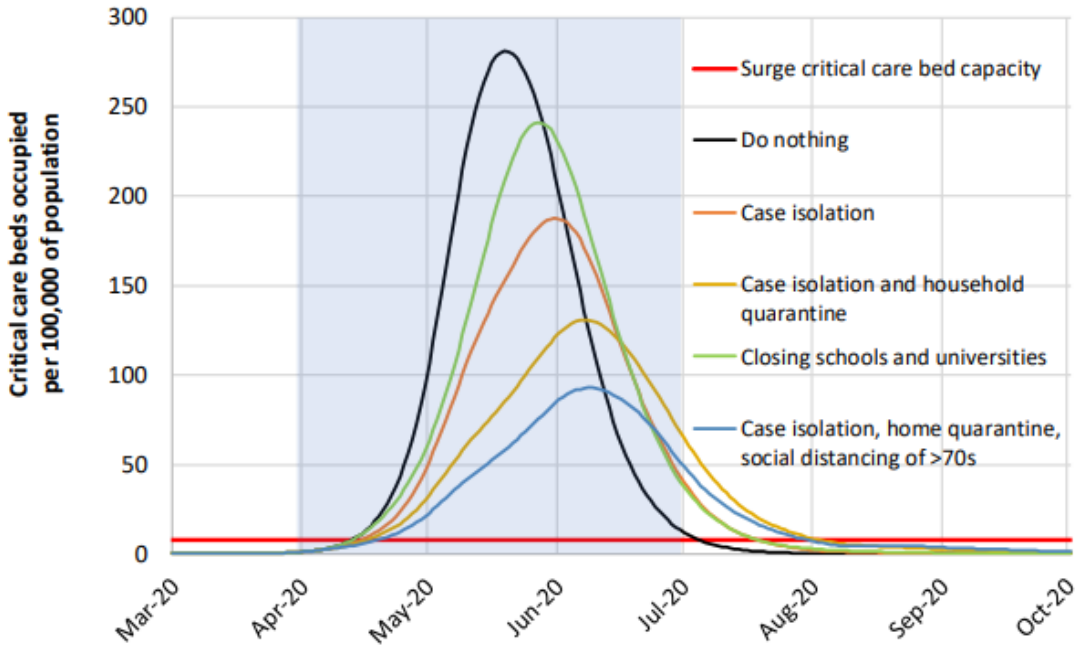
Restrictions and other intervention measures would be periodically loosened and reinstated for many months, as the world tried to reconcile issues such as economic damage, individual freedom, coronavirus variant strains, vaccination rollouts, and more. As of March 14, 2022, the global toll of COVID-19 stands at over 458 million cases and over 6.04 million deaths, though a recent study has indicated that up to three times as many deaths, as measured by excess mortality, could be attributed to the pandemic (COVID-19 Excess Mortality Collaborators, 2022).

4.2. The Early Pandemic Literature

Ferguson *et al.* (2020) is one of the first model-driven studies of the COVID-19 pandemic. Informed by data for deaths in Great Britain through March 14, 2020, coupled with estimates for basic reproduction number and other parameters derived from the Chinese experience, Ferguson's team recommended population-wide social distancing, home isolation of cases, and school/university closure as parts of a package to quickly achieve the reproduction number = 1 threshold and reduce case incidence (Figure 5). They added that such measures needn't necessarily be sustained until the introduction of a vaccine, but may be alternatively eased and reinstated in case of a rebound in infection numbers. The model from which they derived such recommendations was an individual-based stochastic framework akin to the one that Halloran *et al.* (2008) had used to simulate an influenza pandemic in a population of size similar to that of Chicago. Individual-based models such as the one adopted by Halloran's team would turn out to be a mainstay of COVID-19 modelling (see below).

Ferguson and colleagues at Imperial College London, Johns Hopkins University and elsewhere had been studying pandemic scenarios for years. In Ferguson *et al.* (2005), the reaction to an emerging influenza pandemic in Southeast Asia was assessed. A high probability of successful containment was shown to be associated with rapid identification of the original case cluster; population cooperation with the containment strategy; and international cooperation in policy development, epidemic surveillance and control strategy

Figure 5. COVID-19 mitigation strategy scenarios for Great Britain as predicted by Ferguson *et al.* (2020). The black line refers to the evolution of the epidemic with no interventions at all. Colored lines indicate epidemic scenarios for various intervention combinations. The shaded region is the period during which the measures remain in place.



implementation. A year later, Ferguson *et al.* (2006) discussed ways to proceed in the containment of an influenza pandemic in Great Britain and the United States. Since, however, the two papers dealt with influenza pandemics, most of the scenarios outlined were not immediately applicable to the COVID-19 crisis; for instance, the mitigation patterns described in Ferguson *et al.* (2006) ascribe an important role to antiviral drugs – of which there were none in early 2020 – and assume an inherently greater danger of development of clinical cases in children as opposed to the elderly – which would be expected in a flu outbreak, but happened to be the opposite with SARS-CoV-2.

Some stakeholders, both inside and outside of the scientific community, have taken aim at the Ferguson *et al.* (2020) paper and other model-driven papers published early in the pandemic. Critics argue that, because some of the predictions in these studies never materialized, the models they employ are inherently flawed and thus should not be relied upon in policymaking. This is wrong; these earlier models were flawed because they were informed by very limited data, both in the level of case reporting and in the more fundamental level of epidemic characteristics, as parameters such as incubation period were not well-established at the time. Holmdahl and Buckee (2020) name three important

parameters that hindered accurate COVID-19 predictions, especially in the first few months of the outbreak. First, until recently there was limited information on the extent of *protective immunity* after a SARS-CoV-2 infection, a limitation that is especially important for long-term or periodic epidemic forecasting. Second, the *extent of transmission and immunity among people with no or minimal symptoms*, including children, was poorly understood. Third, measuring and modelling *contact rates* between susceptible and contagious persons was particularly problematic early in the pandemic due to the scant information on individual behavior under physical distancing policies, especially in locations that had no recent experience with such policies.

Kucharski *et al.* (2020) authored one of the most cited data-driven models of COVID-19. Kucharski's team developed a stochastic transmission dynamic model to assess the spread of SARS-CoV-2 in Wuhan during the first few weeks of the outbreak. The model was shown to accurately reproduce the temporal trend of cases in the city, but it predicted ten times more symptomatic cases in late January 2020 than were reported as confirmed cases, and it did not output the slowdown in cases that was observed in February. They went on to investigate the possibility that an exported case from Wuhan could initiate an outbreak elsewhere, and noted that the introduction of four or more infections in a location sufficed to place the risk of an outbreak at over 50%.

Contemporarily to Kucharski's study, a mobility-data-based model by Lai *et al.* (2020) also painted a worrying picture of the risk that outgoing travelers from Wuhan had for spreading SARS-CoV-2 both inside and outside of China. They estimated that up to 834 airline travelers may have been infected with the novel coronavirus from Wuhan two weeks prior to the city's lockdown. Further, they forecast that, in order to mitigate the risk of case importation, the number of airline travelers who should have been screened for COVID-19 in the three months from February to April 2020 exceeded 6 million.

4.3. Deterministic Compartmental Models

Several pieces of model-oriented research on COVID-19 have resorted to the ages-old deterministic compartmental approach. A number of these studies worked with the situation in China, which was the origin of the outbreak and quickly contained its first wave through stringent intervention measures; as a result, the Chinese experience is particularly amenable to modelling. Anastassopoulou *et al.* (2020) fit preliminary data to a SIDR model (the *D* stands for the 'dead' compartment) to forecast the Chinese outbreak through the end of February 2020. Peng *et al.* (2020) expanded the classical SEIR model to include quarantine and a population of susceptibles that gradually decreased as a result of compliance

with control measures such as use of face masks. This time-wise decrease is one simple example of how researchers, devoid of relevant data, tweaked compartmental models to account for early intervention measures.

Spain and Italy were some of the first countries outside Asia to face a sweeping COVID-19 outbreak, and their researchers were also some of the first to publish model-oriented studies on the pandemic. López and Rodó (2021) adapted the modified SEIR model of Peng *et al.* (2020) to study the spread of SARS-CoV-2 in Spain, reporting that, in the absence of stricter control measures, up to 100,000 deaths would occur nationwide in the first few months of the epidemic. López and Rodó further analyzed all the 17 Spanish administrative regions and found that regions closest to the initial foci of the national outbreak were expected to witness earlier peaks, whereas more distant ones were expected to lag a few days behind. Identifying regions in which the epidemic was still incipient was important, as timely deployment of social isolation measures in these regions reportedly would have a greater effect than elsewhere in the country.

Working with the situation in Italy, Giordano *et al.* (2020) proposed a sophisticated deterministic model with eight compartments akin to the one that Gumel *et al.* (2004) had developed for SARS. Giordano's team predicted that, over a 350-day horizon, with no further policy changes, 0.06% of the Italian population would die from COVID-19. This fraction would rise to 0.12% if the lockdown that the Italian government had imposed were suddenly weakened, or decrease to 0.04% if stricter measures were implemented instead. Giordano's team argued for a more restrictive lockdown and adoption of widespread testing and contact tracing.

Of course, Western Europe concentrates high-income countries whose demographic structure is very different from the developing world. For example, it has been reported that the household is a key setting for the transmission of SARS-CoV-2 (see below), and the average size of households that have a resident over 65 years – a particularly vulnerable group – is substantially higher in low-income countries than in middle- and high-income nations (Walker *et al.*, 2020). Walker *et al.* (2020) used an age-structured SEIR framework to investigate epidemic dynamics under different mitigation/suppression scenarios and health system capacity constraints. Walker's team noted that larger household sizes, a feature of developing nations, may enhance household-based transmission and limit the impact of self-isolation. Further, while they predicted lower demand for critical care in lower-income settings because of developing countries' younger populations, this supposed advantage was greatly offset by their limited medical resource supply.

Oliveira *et al.* (2021) is an outstanding example of model-driven COVID-19 research in the developing world. Oliveira's team assessed the spread of SARS-CoV-2 in the Brazilian state of Bahia, a region characterized by large population and unequal distribution of medical resources. Theirs was an eight-compartment 'SEIIHURD' model that includes asymptomatic and hospitalized individuals. Oliveira's model showed that in the absence of the intervention measures imposed by Bahia's government, ICU bed occupancy numbers would rise over six-fold and exceed 1100, greatly outstripping the statewide capacity of 422 beds. They further warned that a reduction in transmission rate of 25%, enforced 7 days before the predicted collapse of the system, would produce a delay in ICU bed overload no greater than 8 days. A 50% reduction in transmission sustained for 30 days or a 75% reduction for 14 days would be more effective, delaying exhaustion of both clinical and ICU beds by about 40 days.

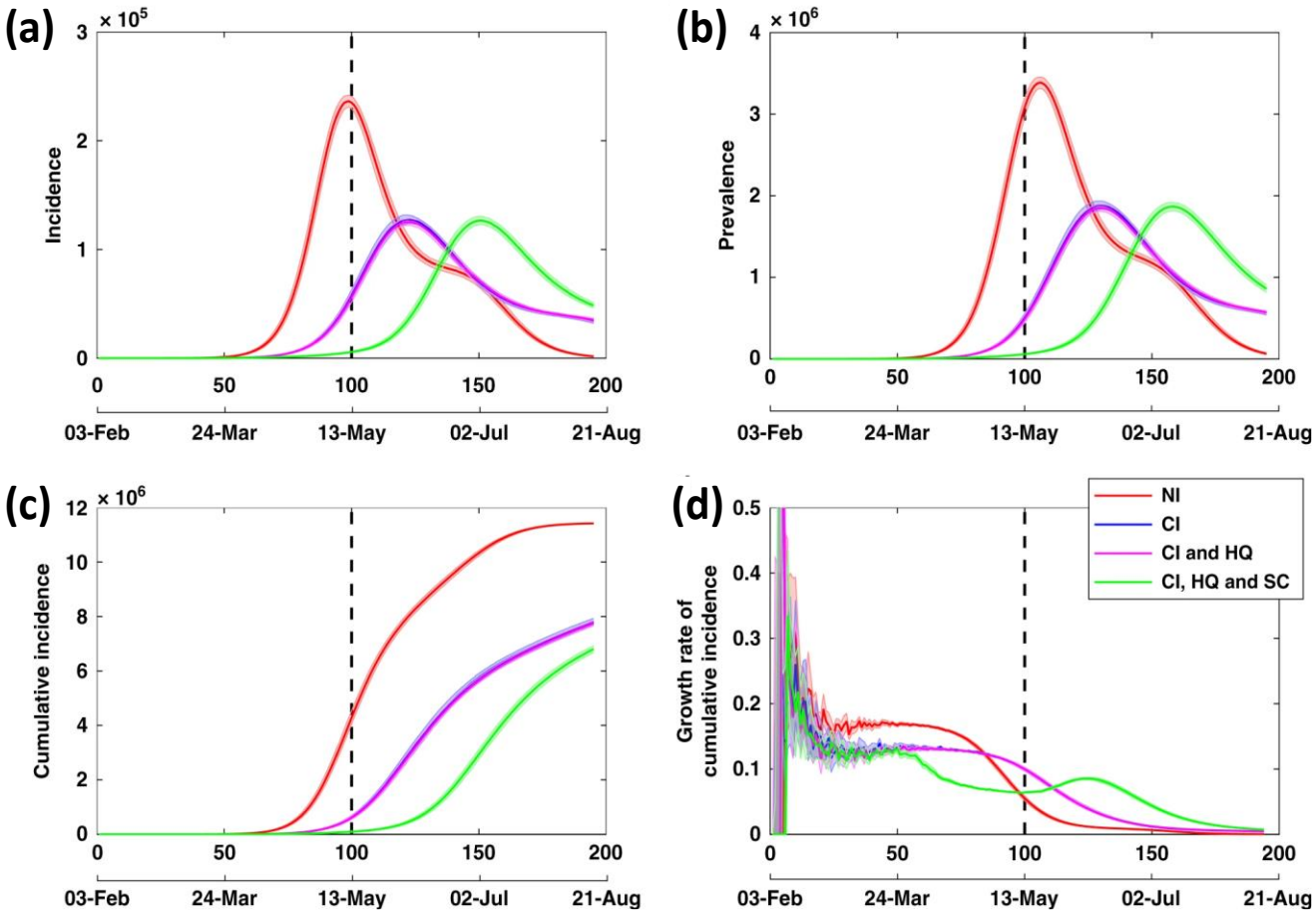
Workers around the world have innovated in deterministic compartmental models. Kim *et al.* (2020) used a SEIR model with compartments for quarantined individuals and 'behavior-changed susceptibles', that is, individuals that are complying with preventative measures such as social distancing. Tomochi and Kono (2020) adapted a SIR model to include two types of infectives and noted that such a modification increases the herd-immunity threshold. Dehning *et al.* (2020) used the spreading rate of a SIR model to quantify the impacts of interventions in Germany. Moein *et al.* (2020) put some pandemic SIR models to the test and showed that while they fitted first-wave case numbers across the world reliably, they generally failed to predict subsequent surges.

Several authors have warned against overreliance on deterministic compartmental models, but few have gone on to illustrate their limitations in practical terms. One exception is a paper by Raimúndez *et al.* (2021), who emphasized the problem of parameter estimation. Using a SEIRD model informed by early COVID-19 data, Raimúndez's team showed that uncertainty in parameter estimates can lead to very flawed predictions and results that fail to cover reported data. For example, Bayesian analysis using MCMC sampling of one of their SEIRD models led to a 99%-credibility interval for incubation period ranging from 23.4 to 257.6 days, when WHO data available at the time indicated a mean incubation time of 5 – 6 days. Still, Raimúndez's team noted that refined models and improved data were bound to improve results, as studies such as Giordano *et al.* (2020, discussed above) showed in the ensuing months.

4.4. Individual-Level and Household-Stratified Models

Deterministic compartmental models are well-established, but fail to capture social heterogeneity and other individual-level features that may contribute appreciably

Figure 6. Evolution of COVID-19 cases in Australia as predicted by Chang *et al.* (2020). The charts refer to (a) incidence; (b) prevalence; (c) cumulative incidence; and (d) daily growth rate of cumulative incidence. A combination of case isolation (CI) and home quarantine (HQ) measures delays epidemic peaks and reduce their magnitude, whereas school closures (SCs) have short-term effect. The strategy with school closures combined with case isolation lasts 49 days, beginning at the vertical dashed line.



to an ongoing epidemic. As an alternative, one may instead resort to purely data-driven (or 'big data') approaches, which have gained traction with the exponential growth of computing power witnessed in recent years. However, these models require a steady stream of reliable data, and pervasive underreporting in the Ebola crisis showed that this is a luxury that the mathematical epidemiologist often cannot count on. Agent-based models (ABMs), on the other hand, strike the right balance between modelling and real data and are thus increasingly preferred to their compartmental and statistical counterparts (Venkatramanan, 2018).

In one of the pandemic's best examples of intervention-measure analysis through ABMs, Chang *et al.* (2020) used a large-scale ABM to evaluate the

effectiveness of non-pharmaceutical interventions in Australia. Chang's team posited that case isolation and home quarantine could appreciably delay the epidemic spread and reduce its peak, but adding school closures yielded only marginal benefits (Figure 6). On the other hand, an 80 to 90% compliance with social-distancing, in conjunction with case isolation, home quarantine, and restrictions on international arrivals, would suffice to suppress incidence to negligible values within less than 20 weeks.

Hoertel *et al.* (2020) used a stochastic ABM to examine the COVID-19 situation in France as it exited from its national lockdown. They warned that a lockdown, on its own, would not prevent a rebound of infections. Moreover, adhesion to mask-wearing and physical distancing would not suffice to prevent an overwhelming second wave, but, when coupled with shielding of vulnerable people, may lower cumulative incidence, mortality, and number of ICU beds required, with the result that a second lockdown ultimately may not be needed.

Mask-wearing is difficult to model through classical deterministic models because it is fundamentally an individual effort, and, as already mentioned, individual nuance is not well represented in SEIR models and their variants. Agent-based models can easily circumvent this limitation. Kai *et al.* (2020) used an ABM to demonstrate that universal mask wearing instituted at the onset of an outbreak could lead to a rapid, near-total suppression of infection spread. Kai's team acknowledged that most countries outside of East Asia had already missed that time window, but ABM simulations showed that introduction of universal mask wearing at day 50 of an outbreak still led to expressive reductions in infection rate.

Although ABMs can be hard to code and computationally intensive, some workers have made strides in converting them into more accessible tools. For example, Kerr *et al.* (2021) developed Covasim, a Python-based ABM that can be used to simulate COVID-19 spread scenarios and guide policymaking. The program can be used to model intervention measures such as physical distancing, contact tracing, and contact quarantine. Covasim has remarkable computational efficiency: Kerr's team note that a scenario involving tens of thousands of infections among a susceptible population of hundreds of thousands of people, for a duration of 12 months, can be processed with a personal laptop within less than a minute. Kerr's team close their introduction to the program by noting that future iterations should support variant SARS-CoV-2 strains and vaccine rollout.

Silva *et al.* (2020) developed an agent-based model, COVID-ABS, that integrates intervention scenarios with simple assessments of economic impact. Their simulations showed that a total or conditional lockdown was the best approach to save the most lives, albeit with significant economic impact. Further,

they showed that a policy based on 50%-social isolation with mask-wearing and physical distancing – a package more palatable than full-fledged lockdowns – could save numerous lives and minimize economic harm.

With the purpose of adding heterogeneity to an infectious disease model, the epidemiologist does not necessarily have to focus on the individual scale; COVID-19 lockdowns have led citizens to spend more time in their homes, and research has shown that infection risk of household contacts is several-fold higher than other contacts (Lei, 2020). Accordingly, a viable alternative, which may complement but not necessarily substitute individual-scale modelling, is to assess disease spread at the household level.

One crucial variable to calibrate household-level models is the household secondary attack rate (SAR). An early review by Madewell *et al.* (2020) placed this parameter at 16.6%, which is considerably higher than the values reported for the original SARS coronavirus (7.5%) and MERS coronavirus (4.7%), but within mid-range when compared to the 1 – 38% reported for influenza (values quoted in Madewell *et al.*, 2020). The same authors revisited the same parameter in mid-2021 and updated the household SAR to 18.9% (Madewell *et al.*, 2021).

Fung *et al.* (2021) proposed an estimate of 17.1% for household SAR and noted that studies that tested contacts more frequently tended to generate larger SARs. Reuters *et al.* (2022), in turn, noted that many secondary attack rate studies published until then used a rather poor individual assessment strategy, as they only tested household contacts with COVID-19-related symptoms, relied only on reverse-transcription polymerase chain reaction (RT-PCR) in nasopharyrngeal swabs, and did not perform any follow-up. In contrast, Reuters's team used a more clear-cut approach, wherein all household contacts were tested as soon as possible after a laboratory-confirmed infection in the household was established and subsequently followed up for 4 – 6 weeks. Of note for the present review, they also analyzed their data through a stochastic SEIR model. The estimated household infection SAR was 43%, which is substantially higher than most other estimates and exemplifies the observation of Fung *et al.* (2021) that more frequent testing and follow-up may lead to greater SAR values.

Liu *et al.* (2021) used a discrete-time stochastic model to investigate the effect of different household size distributions on COVID-19 transmission dynamics. Specifically, Liu's team employed the same model to two regional health authorities of the Greater Vancouver area in Canada. The two regions, Fraser Health and Vancouver Coastal Health, had different COVID-19 case count numbers and, most importantly, different average household sizes: 2.68 for the former and 2.31 for the latter. Through scenario-making, they found that keeping 55% of

individuals isolating at home could bring cases into a decline under the household size distribution of the Vancouver Coastal Health region while the number of cases continued to increase at a moderate rate under the household size distribution of the Fraser Health region. Simply put, home isolation is more effective in regions with smaller household sizes than in regions with large household sizes.

Such a finding is also evidenced in Nande *et al.* (2021), who used a network model to obtain more granular details on the transmission dynamics of COVID-19. Nande's model indicated that risk of infection is significantly greater for individuals in large households than for individuals living alone. Further, Nande's team also assessed the increased risk faced by households with 'essential workers', that is, workers that maintained contacts in their 'work' networks in spite of widespread social distancing; individuals living in households with such workers had much greater risk of infection than those living in households where everyone was social distancing.

4.5. After the First Wave

After the first few months of the pandemic were brought to a close, researchers began to assess the effect of nonpharmacological measures retrospectively. Lai *et al.* (2020) used a stochastic SEIR model based on travel networks to simulate before-and-after scenarios in hundreds of Chinese cities subjected to three NPIs, namely (1) restriction of intercity population movement; (2) identification and isolation of cases; and (3) contact restrictions and social distancing measures. Lai's team found that in the absence of NPIs, the number of infections by 29 February, 2020 would have increased 51-fold in Wuhan and 125-fold in cities outside of Hubei province. There were also differential impacts for the three types of NPI, with early detection and isolation of cases preventing more infections than the introduction of contact reduction and social distancing. However, combinations of NPIs worked better to avert infections and spread than any individual approach on its own. Earlier, a paper by Chinazzi *et al.* (2020) had contended that the travel restrictions imposed in Wuhan had delayed the growth of the Chinese epidemic by no more than 3 – 5 days.

Pei *et al.* (2020) used a dynamic metapopulation model informed by human mobility data to investigate the experience with NPIs in the United States. Pei's team ran counterfactual simulations and found that, had the control measures adopted across the country been implemented a week earlier, the US would have avoided over 600,000 cases and 32,000 deaths nationwide by May 2020; the numbers were even greater for a scenario in which the intervention measures were adopted two weeks earlier. Pei's team also found that over 95% of the US

population remained susceptible as of May 2020, revealing an absence of herd immunity and indicating the possibility of additional COVID-19 waves.

Friedman *et al.* (2021) took up the issue of differences in mortality figures of seven COVID-19 forecasting models, which, they noted, could differ by more than one order of magnitude, even within a 6-week forecasting window. Nonetheless, they found that the mortality predictions for the United States converged in their predictions for the June 2020 – August 2020 period; disparities were greater in the November 2020 – February 2021 period because many models did not consider seasonality. Further, Friedman's team noted that models that relied on an exponential growth in transmission had a greater tendency to overestimate mortality numbers.

In a paper that was widely quoted in mass media, Niu *et al.* (2021) used a SEIAR model to evaluate the response of 160 countries to the first few months of the pandemic. The countries that had the strongest national control capability were mostly in Europe, as 76.4% of European nations were able to control COVID-19 within 60 days from their first discovered case. In terms of continuous control, the Western Pacific region fared better, with 73.76% of its countries registering a steady low level of cases through August 22, 2020.

More recently, COVID-19 National Preparedness Collaborators (2022) conducted an exploratory data analysis in an attempt to link 177 countries' differential outcomes in registered cases and deaths to variables such as population density, gross domestic product (GDP) per capita, and body mass index (BMI). Their study was motivated by findings such as those of Haider *et al.* (2020), who had noted a weak correlation between COVID-19 mortality outcomes and countries' Global Health Security Index (GHSI) and WHO Joint External Evaluation (JEE) scores, two well-established metrics for health security. The COVID-19 Collaborators' research corroborated the fact that neither GHSI nor JEE are associated with standardized infection rates or infection-fatality ratios (IFRs). Their most striking findings, however, are that high levels of trust in government, high interpersonal trust, and low government corruption all have significant associations with fewer infections. Nations with high indicators in these areas, such as Denmark, have weathered the pandemic with greater success than others.

5. Conclusion

Each of the outbreaks reviewed have offered novel challenges to mathematical epidemiologists, who in turn have responded with ever more sophisticated representations of reality. SARS tested modelers' ability to show whether quarantine can help drop effective reproduction numbers below unity and thereby bring an epidemic under control. Ebola tested modelers' ability to show how an

infectious disease can diffuse through porous borders or, internally, through complex arrangements of rural areas and dense population centers. Finally, COVID-19 tested modelers' ability to personalize their mathematical formulations, describing an epidemic that has affected hundreds of millions at the level of a single individual. Complexity issues aside, the models produced in the wake of these events have informed policymakers and are sure to have reduced the burden of disease in countries across the world. Certainly, the next pandemic may pose an even greater threat than SARS, Ebola or even COVID, but the proper combination of good models and mathematical ingenuity is bound to keep humankind one step ahead of any emerging pathogen.

– L.M.N.

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