Opinion Paper

Luca Fiorillo*, Marco Cicciù, Rosa De Stefano*, Salvatore Bocchieri, Alan Scott Herford, Maria Fazio and Gabriele Cervino

Virtual reality and massive multiplayer online role-playing games as possible prophylaxis mathematical model: focus on COVID-19 spreading

https://doi.org/10.1515/em-2020-0003
Received March 25, 2020; accepted November 16, 2020; published online November 26, 2020

Abstract: The digital field certainly provides a lot of information in the medical field, it is possible, in a computerized way, also to simulate epidemics, and the spread of these. There have been events in the past, in some simulation games, which are currently being studied, as they could provide important clues for the resolution of epidemics such as the one from COVID-19. One of these events occurred due to a bug in 2005 in the role-playing online game World of Warcraft. Through these simulations it is possible to make prophylactic plans to intervene preventively or plan interventions throughout mathematical models.

Keywords: COVID-19; digital; epidemiology; games; health; mathematical model; MMORPG; simulation.

Introduction

Mathematics and medicine are allied against infectious diseases. Mathematical models are an important tool, used systematically as a guide to the control of endemic infections, and as a starting point to face new emergencies. The COVID-19 pandemic of 2019–2020, commonly referred to coronavirus epidemic, is a COVID-19 respiratory disease pandemic caused by the SARS-CoV-2 coronavirus, which probably started around the end of December 2019 in the city of Wuhan (Anzai et al. 2020; Deng and Peng 2020; Nishiura 2020; Nguyen, Duong Bang, and Wolff 2020), capital of the Chinese province of Hubei, and subsequently spread to various countries of the world. The first cases mainly involved workers from the Wuhan fish market, where live animals were on sale. In the first weeks of January 2020, scientists isolated a new coronavirus in these subjects, designated SARS-CoV-2 (New Coronavirus 2019), found to be similar to at least 70% of its gene sequence to that of SARS-CoV. Patients experience flu-like symptoms such as fever, dry cough, tiredness, difficulty breathing (Allam and Jones 2020; Ashour et al. 2020; Crimi et al. 2019; Fiorillo et al. 2020; Kobayashi et al. 2020; Linton et al. 2020; Veltkamp et al. 2020; Wang et al. 2020). In more severe cases, often found in subjects already
burdened by previous pathologies, pneumonia develops, acute renal failure, up to even death. Patients also have leukopenia and lymphocytopenia. The wider consequences of the outbreak include concerns about economic instability. Unfortunately, episodes of xenophobia and racism against people of Chinese and East Asian origin have been reported in several countries. Since mid-January 2020, the first cases have also been found outside of China, brought by international travelers, mainly to the nation’s major trading partners. In Europe, however, most were linked to Italy, where the authorities struggled to contain an outbreak that infected people, most of them in the north near Milan (Ahmed, Quadeer, and McKay 2020; Al-qaness et al. 2020; Amodio et al. 2020; Balzer et al. 2016; Bertke et al. 2013; Biondi-Zoccai et al. 2020; Di Pierro, Bertuccioli, and Cavecchia 2020; Grasselli, Pesenti, and Cecconi 2020; Huitfeldt, Goldstein, and Swanson 2018; Kuniya 2020; McAleer 2020; Porcheddu et al. 2020; Repici et al. 2020; Schwartz and Graham 2020; Spina et al. 2020; Sun et al. 2020).

Materials and methods

The word pandemic derives from the Greek “pandemos”, which means “the whole population”: demos means the population, pan means everyone. “Pandemos” is therefore a concept according to which it is believed that the entire world population will likely be exposed to an infection and potentially a part of them will fall ill. According to the World Health Organization, the conditions for a true pandemic to occur are three:

– the appearance of a new pathogen;
– the ability of this agent to target humans;
– the ability of this agent to spread rapidly by contagion.

The study of the timeline of disease cases within the community of individuals in which an epidemic develops provides a lot of information on the origin and the ways in which an infection tends to spread. As an example, should be considered a disease that develops spreading slowly and progressively over a period of months or years. Such a trend is rather indicative of an interhuman contagion by direct contact: this is the case of some venereal diseases. On the contrary, an extremely rapid and progressive spread with the rapid exhaustion of the epidemic in a few weeks or months lays down for a more effective transmission, for example by air, as happens in the case of many acute respiratory infections). The course of an epidemic could be studied and simulated with mathematical models. Among the simplest and best known are the SIR (susceptible-infected-removed, useful for immunizing diseases) and SIS (susceptible-infected-susceptible, typical of non-immunizing diseases such as the common cold) models (Boldog et al. 2020; Goh et al. 2020; Jung et al. 2020; Liu et al. 2020; Roosa et al. 2020; Wang et al. 2020b; Xu et al. 2020; Yu et al. 2020; Zhang et al. 2020).

In the formulation of a mathematical model three fundamental steps could be defined:

1. the approximate description of the phenomenon;
2. identification of status variables;
3. the setting of the law that regulates the phenomenon itself.

To describe the single epidemic episode, following this scheme, should be assumed that the population concerned is closed (a specific city, a region without immigration or emigration), homogeneous (individuals are all the same and do not count differences in age, sex, residence), demographically immobile (no births or deaths occur). This is a coarse description which can however be accepted within certain limits, in particular in a fairly short period of time. The second step is to establish the three categories of individuals relevant to our description. In epidemiology, as regards literature, different mathematical methods could be used: The main distinctions are between deterministic or stochastic models, closed or open, homogeneous or heterogeneous.

Deterministic models are the simplest; in them, the input variables assume fixed, determined values. In a deterministic model, individuals in the population are assigned to different subgroups or compartments, each of which represents a specific stage of the epidemic. Transition rates from one class to another are expressed mathematically as derivatives, so the model is formulated using differential equations.
Stochastic models take into account variations in input variables, and provide results in terms of "probability". A stochastic model is a tool that allows you to estimate the probability distributions of potential outcomes by allowing random variations in one or more inputs over time. Stochastic models depend on changes in exposure risk, disease and other disease dynamics.

In the compartmental models, hypotheses are assumed to simplify the mathematical simulation of the dynamics of infectious diseases, synthetically these hypotheses assume that the population is divided into compartments and that each individual in the same compartment has the same characteristics. compartmental models can be used to predict the properties of the spread of a disease, for example the prevalence (total number of infected) or the duration of an epidemic (Figure 1).

The SI model is a particularly simple approach to describe the spread of infectious diseases where for a constant N, N = I + S. The rate of spread of the disease statistically depends on the number of infectious individuals and secondly on the number of individuals who can still be infected.

The SIS model (Figure 1), usable for short-lived diseases that do not give immunity such as colds, distinguishes only two groups of individuals: S, I. At the time t designated the number of susceptible S (t) and the number of infectious I (t) being constant N we have N = I (t) + S (t). The SIS model can therefore be used for diseases that have the following properties:
- After the disease has healed, each individual immediately returns to the healthy group and can be re-infected.
- The infected are immediately contagious.
- Healthy people get sick with a linear $\beta$ infection rate.
- Infected people recover with a linear cure rate $\alpha$.
- Each group interacts with the same probability. This justifies taking linear relationships.

One of the simplest compartmental mathematical models used in epidemiology representing immunity is the SIR model (Figures 2, 3). It is a three-variable equation, where each variable is indicated by an initial (precisely S, I and R). The number of people belonging to the three different groups changes over time as the contamination proceeds. While the number of susceptible (S) can only go down, the number of recovered/removed (R) can only increase: in mathematical terms, they are said to be in inversely proportional ratio. The number of infected (I) is the only one of the three that can increase and decrease over time. Depending on the number of daily infections, the number of infected people will modify increasing itself, while the number of healthy people will decrease proportionally. If the rhythm of the infection is high and instead the healing time is slow, the group R could drop below a certain threshold: it is then that the epidemic explodes. On the contrary, if the number of Recovered is sufficiently high when the outbreak occurs, the outbreak is self-extinguishing. The model consists of three compartments S, I, R. Where assuming constant N, we have N = I (t) + S (t) + R (t), N = I (t) + S (t) + R (t),

Figure 1: Curves over time of the number of susceptible (blue) and infected / infectious (green) in a SIS model with an infection rate higher than the cure rate. Public domain figure.
including in R (t) also i deaths due to illness. This model is reasonably predictive for infectious diseases that are transmitted from man to man and in which recovery confers lasting resistance, such as measles, mumps and rubella.

By observing the evolution of the infection, a first conclusion could already be drawn: if the trend is exponential, the number of infected could be destined to increase dramatically making the situation completely unmanageable (from a health and non-health point of view). With the current containment measures, it should hopefully arrive at an evolution curve called the logistics of the population in question, which would imply reaching zero value. In the case of COVID-19, the picture to be analyzed is far more complex than simple models such as SIR. We add in the population a possible exposed subject (E), that is an asymptomatic but still uninfected patient (I) who is however able to transmit the coronavirus. This leads to a new mathematical model otherwise defined with the acronym SEIR (Figure 4). For many important infections there is a significant incubation period during which individuals have been infected but are not yet infectious. During this period the individual is in compartment E which stands for “exposed”. In this case we are talking about the SEIR model. After observing that the model parameters depend on the dynamics of the virus and the interaction between human beings, the interactions between coronavirus and human beings in parameter R0: how many people, on average, infects a sick subject? If A is a sick patient and R0 is 2, then A will infect two people; these will infect four others which, in turn, will infect eight, and so on: the model is multiplicative and not additive. Keeping in mind that it is good to keep the number of sick people as low as possible at the same time, it is obvious to note that we should strive for an ever lower R0, at the lower limit of 1 (Chang, Piraveenan, and Prokopenko 2019; Li et al. 2019b; Shi, Zhang, and Zhu 2019).

Mathematical modeling experts used “corrupted blood” as a study. By applying mathematical models of epidemiology in fact to this curious virtual case. By applying models to predict the future spread of the disease and the adequacy of various interventions. The basic reproductive rate in virtual diseases could be quantified, the population infection could be assessed and the expected results could be compared with real events influenced by player-dependent behavior. Online multiplayer role-playing games can also be useful as a test for hypotheses on the spread of infectious diseases. Game programmers could allow characters to become infected with various infectious diseases, some of which may not be visible to the player, and keep track of disease spread patterns in specific subpopulations. Various interventions could be tested, including treatment, vaccination, isolation and quarantine. While the parallels to a real-world outbreak are striking, the artificial nature of the games limits them as real-world models and could even lead to misleading conclusions. The mixing patterns and interactions between the game figures can be significantly different. The most obvious example would be the risky behavior of the virtual characters, which depends heavily on the penalties for
death or illness and on the availability of a “save game” option. Experienced infectious disease modelers might consider collaborating with game administrators. Such collaborations could exploit the immense computational power invested in these economically driven large-scale virtual environments, allowing for larger simulations than any option currently available (Balicer 2007). Interventionary studies involving animals or humans, and other studies require ethical approval must list the authority that provided approval and the corresponding ethical approval code. There are different simulations, also for recreational purposes on the progress of the epidemics, one of which is Plague Inc. Plague Inc. is a strategy and simulation video game of 2012 developed by Ndemic Creations. But shrouded epidemics tend to develop among the avatar population of gamers even in an unwanted way. World of Warcraft, often referred to as the acronym WoW, is an action-packed MMORPG video game from 2004, developed by Blizzard Entertainment and published by Vivendi Universal for Microsoft Windows and macOS. The title is playable only with the use of the Internet through the payment of a monthly fee.

World of Warcraft is the most played MMORPG in the world, with approximately 5.2 million active registrations in October 2017 (the maximum peak was 12 million in October 2010). The game servers, originally available only in English, French and German, were subsequently made active also in Spanish, Chinese, Korean, Russian, Portuguese and Italian. The Corrupted Blood incident was a glitch of the MMORPG World of Warcraft video game which from 13 September 2005 it triggered a virtual epidemic, which lasted for a week. The cause of the accident is linked to the introduction of the raid Zul’Gurub and his boss Hakkar, which applies to the players who attack him a negative effect, a debuff, which decreases the character’s life points and is transmitted to other healthy players by proximity (Graham and Gosling 2013; Guitart, Chen, and Periáñez 2018; Kohana, Sakamoto, and Okamoto 2019; Lavorgna et al. 2019; Lis et al. 2016; Marzouki et al. 2017; Sapienza, Bessi, and Ferrara 2018; Sims Bainbridge 2010).

**Results**

It is not the first and it will not be the last time that humanity will face an epidemic: viruses have always existed and history teaches us that these dynamics can be avoided, prevented or moderate, but that in some way something Always “passes”. Not even the world of video games is exempt from this claim: World of Warcraft, Blizzard’s MMORPG, confirms this, and back in 2005 suffered what went down in history as the “Corrupted Blood” accident.

The Corrupted Blood, gave “symptoms” (to the avatars of the players) a continuous loss of life until death and could infect all the characters close to the infected one in a fairly restricted area (Figure 5). The disease, or rather the debuff, was foreseen only for the boss fight: in fact, the various players, once they left the raid, found themselves healed from this continuous damage. The problem arose through the companions of the players, demons or animals that could be used as support in combat: once summoned out of the Raid, those who had

---

**Figure 4:** SEIR model process.

**Figure 5:** World of warcraft in-game advice. For gentle concession of blizzard CC BY-SA 4.0.
been discharged with the virus still on them found themselves passing it on to the characters, thus making “escape Corrupted Blood” from the boss fight. Even non-playing characters became reservoirs of infection: merchants, mission NPCs and everything else, once infected, were able to transmit the virus to every nearby healthy character (Alontaga 2018; Choi, Hums, and Bum 2018; McClay 2018; Northrup et al. 2015; Paik et al. 2017).

Only a reset of the servers and a patch fixed the problem at the root, but without first leaving room for really interesting reactions (Blasi et al. 2019; Buiza-Aguado et al. 2018; Chen et al. 2020; Lee and Leeson 2015).

At that time, game servers were populated by two million players. In the beginning it was not immediately clear if all this had been deliberately programmed or instead a system error: the thing was taken lightly initially, to then make the title truly unplayable. The interesting thing developed shortly after the release of the Corrupted Blood: if in fact the death in World of Warcraft is not definitive, it still involves a loss of money (the character’s equipment is damaged and must therefore be repaired) and takes some time before to be able to return to the game. The various players then began to have proactive or destructive attitudes related to what was defined as an epidemic. Some players did not enter the game until the end of the pandemic, forcing themselves to a real “isolation” from the game. Others, with healing skills, made themselves available to the sick to remove this debuff and save them. The streets were populated with skeletons of the fallen due to the virus, and many players avoided these spaces in favor of remote, less populated and safer areas of the map. The approach to the game simulated attitudes that were very close to reality. Many players without healing skills spent their time indicating safe areas in common chats, while others aimed to spread the disease as much as possible. There have been other cases in the world of similar videogames, linked to bugs that caused real epidemics, even if WoW is one of the most aesthetic in terms of number of players (Hui et al. 2019; Li et al. 2019a; Sinatra and Szell 2014; Wang et al. 2020a). The most complex model developed to deal with a potential COVID-19 pandemic should therefore be SEIR. There are different models, provided by the statistical institutes of the individual countries. For example, in Italy, the model had provided three different scenarios based on the hypotheses of estimated R0 (R0 is the rate of reproduction of disease cases from a single contagious case) (R0 = 1.4; R0 = 1.7 and R0 = 2).

– For the highest value considered, equal to 2, the scenario envisaged an introduction of the infection in Italy after 37 days from the first world case, through the main international airports.

– For R0 = 2 the model estimated that the diffusion peak, in the absence of containment measures, would arrive after 90 days.

For COVID-19, the first cases registered in Italy are on February 21, 2020, so it is easy to go back to mid-January as the date of the first introduction of the virus. If R0 is greater than two (as it seems to be for COVID-19) in the model the times are proportionally shortened, placing a likely introduction date towards the end of January. Since the introduction, in the absence of effective containment measures, the pandemic model foresaw the continuous growth of the number of cases with a maximum diffusion estimated between 54 and 125 days. Also for this estimate, if R0 is greater than the value two considered, the peak is reached first. If the virus was introduced in late January, and if the model is likely to be the current situation, the apex of the epidemic curve can be expected in mid-April. Certainly, the scenario is approximate. We know that COVID-19 does not behave like the flu, above all there is no clear data on its spread in children who, on the other hand, have a key role in supporting the transmission of flu, even seasonal. In addition, the R0 of the 2009 pandemic was estimated at 1.4 and also during the seasonal flu it is lower than two. Regarding the role of children, they too are at risk of SARS-CoV-2 infection in a similar way to adults with very mild symptoms, but we do not know enough about their ability to transmit the infection. The model described a probable scenario, both in the absence and in the presence of containment measures (such as restrictions on international travel, use of antivirals, close contact quarantine, closing of schools, and vaccination). However, the model took into account a specific risk of contagion in the family, in the workplace and randomly not well defined linked to the sociability of people based on specific parameters for influence that are now difficult to consider due to the absence of adequate data.
Quarantine maneuvers that can bring satisfactory and mathematically predictable results are all those that create an ideal system for mathematical models. The closure of schools is a drastic measure of social distancing that had also been taken into consideration for the 2009 flu pandemic. In that case, the transmission of the infection was strongly supported by the youngest in the population, who, up to 15 years of age ages showed an attack rate of clinical forms of about 25%. At the resumption of the school year in September, the measure was reconsidered in light of the availability of the pandemic vaccine and the decrease in the intensity of the infections. The available scenarios estimated that the closure of the schools would have delayed the epidemic peak of two weeks and on that occasion the measure was not deemed necessary. At this time, no alternatives have been shown to the only measure of containment of social distancing, considering that there are no specific antivirals, nor vaccines available in the short term. If containment will take effect, the epidemic curve a will be lower, but over a longer period of time, obtaining the desired result of diluting the intensity of the request for treatment over time. The recommended measures to contain and prevent infection vary depending on the likelihood that people will come into contact with sick people. A number of countries have advised against traveling to mainland China, Hubei province or just Wuhan. There is no evidence that pets, such as dogs and cats, can be infected. In any case, the Hong Kong government has warned everyone traveling outside the city not to touch animals, eat game meat and avoid going to live poultry markets and farms. Many governments advise against all non-essential travel to the countries and areas affected by the epidemic. In order to limit the spread of the infection, the World Health Organization recommended “washing hands regularly for more than 20 s, covering the mouth and nose when coughing and sneezing and avoiding close contact with anyone showing symptoms of respiratory disease (such as coughing and sneezing), also considering the duration of the active virus on the surfaces”. Furthermore, the strategy of quarantine and self-isolation in case of suspected infections are among the most used maneuvers worldwide (Fiorillo et al. 2020). The critical aspect would be the maintenance of containment measures for a long time, due to the risk of re-introduction of cases in areas with staggered trends. The awareness of a probable scenario and the times to be addressed is important for everyone’s contribution, without considering all the psychosocial and economic repercussions of the quarantine (Figure 6) (Brehm 2013; Longman, O’Connor, and Obst 2009; Obst et al. 2018; Reer and Krämer 2017).

Figure 6: COVID-19 spreading at 15th May 2020. From white: no confirmed case/no data to intense red: 1,000,000+ confirmed cases.
Discussion

A pandemic is an epidemic caused by a new virus, against which there are no immune individuals, which therefore invades an entirely susceptible population. The case of a possible flu pandemic, caused by a virus generated by mutation from the avian influenza virus, is only a current example of a general problem that is being brought to the attention of health institutions. Preparing to face a pandemic in fact means facing a problem a priori with a lot of missing data and with tools that often cannot be prepared in advance. In particular, until the virus appears on the scene triggering the epidemic, it is not possible to prepare a specific vaccine that creates a consistent band of immune systems that prevent the disease from exploding. Generic antivirals could be used or vaccines based on viral strains close to the feared one, organizational tools to decrease the chances of contagion but the coordination of all these possible measures should be developed without direct verification. It is here that the mathematical model could exercise its role of support for political-administrative choices, verifying virtually the effect of each intervention. It is not easy to build a mathematical model for an infection that depends on various factors: biology, social interactions, economic and political aspects. The sense is that these variables that influence the course of the infections are not always the same (in particular the last two) and provide for restrictions and changes that also lead to re-evaluate the mathematical formulation of the problem. It is the individual-based mathematical models that provide the most realistic estimates of the spread of infectious diseases. The use of this particular mathematical model is possible having a lot of data available “individual by individual”, with accuracy and fine detail. In fact, information is needed on where people live, on how they move (workers and commuting students), on school attendance and on the employment rate by age. There are two categories of countermeasures that should be taken in the event of a pandemic: pharmacological ones (use of vaccines and administration of antivirals) and those aimed at limiting contacts between people (limiting international flights, closing schools, offices and places of aggregation in general). Vaccination serves to increase the number of people recovered/removed, preventing the continuation of the infection. On the contrary, the terrorist expert Stuart Gottlieb highlighted how a video game could not be taken seriously for real calculations: since the death of the real game character is not (in World of Warcraft you can return to the game) pushes the player to have less brakes, and therefore be distant from the behavior it would hold in real life. In Baltimore, during the Games for Health conference, the differences between the Corrupted Blood pandemic and the real pandemic were distinguished: among all the one related to the evidence of the disease stood out, which unlike symptoms to look for and study was reduced to a report in evidence about the player (Balicer 2007). On the other hand, there was also talk of the fact that this incident also allowed us to understand the curiosity effect, which in a real epidemic could push people (such as journalists or just curious) to visit the infected places. The most recent news related to this Corrupted Blood affects us personally: today, in 2020, several research teams are studying COVID-19, a virus of the Coronavirus family that is giving many headaches to cities and people. Dr. Eric Lofgren is part of one of the teams working in the USA and was one of the authors of the article related to the World of Warcraft epidemic. He says: “It was a great way for me to understand how important human behaviors are and how much they define the next steps of a possible epidemic. We often see epidemics as something that happens to people. There is a virus and it does things, the truth is that the virus spreads among people based on how they interact and how they react to the authorities. They are very important, and above all very chaotic. You cannot predict that all people will accept quarantine” (Thier 2008).

In August 2007, Nina Fefferman – assistant to Tufts University – mentioned the similarities with biological epidemics in one of her articles. Some scientists are interested in studying the human reaction to pathogens, using the virtual world as a reference (“PLAYING WITH EPIDEMICS” 2007). As a result, Fefferman co-published an article in the Lancet Infectious Disease that discussed the implications of the virtual epidemic on epidemiological modeling (Lofgren and Fefferman 2007). Were also exposed the incident and utility considerations of studying populations of online multiplayer environments at the 2008 Games for Health conferences and the 2011 Game Developers Conference (Bonnaire and Baptista 2019; Na et al. 2017; Stavropoulos et al. 2017). Fefferman also expressed interest in the design of new, possibly non-lethal, diseases to be introduced in
the game to allow the study of risk perception, the spread of rumors and the management of the information flow concerning health, claiming that they would not ruined the gameplay, but they would have made it more realistic, as infectious diseases were a not indifferent aspect in the medieval life in which the game is set. Blizzard initially showed some interest in the proposal, which however was not materialized. In fact, he believed that this could be the only way to carry out such a study, as traditional computer models can only approximate human behavior through mathematical formulas. Neil Ferguson, director of the Center for Outbreak Analysis and Modeling at Imperial College London, instead expressed skepticism about the idea, arguing that such studies would not provide a model that adhered to real life behaviors. For example, considering the zombie outbreak of World of Warcraft: Wrath of the Lich King, many players would get infected on purpose, to acquire zombie powers. Additionally, virtual characters can regenerate or be reborn after death, so infection poses a less serious danger than real life (Anderson et al. 2004; Blasi et al. 2019; Brehm 2013; Longman, O’Connor, and Obst 2009; Obst et al. 2018; Reer and Krämer 2017).

Conclusion

Mathematical modeling is important in the study of infectious diseases and in the development of public health policies (Gubar, Taynitskiy, and Zhu 2018). Nonetheless, agent-based modeling and similar simulations have limited potential to account for changes in human behavior during epidemics. This has led researchers to new methods for assessing epidemics. Despite limitations, there may be advantages for studying in the virtual worlds. The mixing patterns and behavior observed in the game can be precisely measured and explained. Applying mathematical models, within virtual simulations, where individuals behave as in real life, can represent an excellent method both for developing further mathematical models and for predicting the course of certain epidemics. Virtual model could be useful for these simulations. Much has been read in the literature about cases of reinfection with COVID-19 unfortunately; therefore, it is still not clear which model can be applied. however, it is likely to think that the reinfections were caused by modified strains of the first virus, therefore it is not a question of reinfections but of new infections to another pathology. The SEIR model could offer an excellent example for predicting the end of the pandemic, in compartments. Furthermore, the rules and the virtual environment could be adapted to allow a better prediction of real-life scenarios. Experienced infectious disease modelers might consider collaborating with game administrators. Such collaborations could exploit the immense computational power invested in these economically driven large-scale virtual environments, allowing for larger simulations than any option currently available.

Research funding: None declared.

Author contributions: validation, G.C. and M.F.; methodology, R.D.S.; investigation, S.B.; data curation, writing—original draft preparation and writing—review and editing, conceptualization, project administration L.F.; supervision, A.S.H. and M.C. All authors have read and agreed to the published version of the manuscript.

Competing interests: Authors state no conflict of interest.

References

Ahmed, S. F., A. A. Quadeer, and M. R. McKay. 2020. “Preliminary Identification of Potential Vaccine Targets for the COVID-19 Coronavirus (SARS-CoV-2) Based on SARS-CoV Immunological Studies.” Viruses 12 (3): 254.

Al-qaness, M. A. A., A. A. Ewees, H. Fan, and M. Abd El Aziz. 2020. “Optimization Method for Forecasting Confirmed Cases of COVID-19 in China.” Journal of Clinical Medicine 9 (3): 674.

Allam, Z., and D. S. Jones. 2020. “On the Coronavirus (COVID-19) Outbreak and the Smart City Network: Universal Data Sharing Standards Coupled with Artificial Intelligence (AI) to Benefit Urban Health Monitoring and Management.” Healthcare 8 (3): 46.

Alontaga, J. V. Q. 2018. “Internet Shop Users: Computer Practices and its Relationship to E-Learning Readiness.” Education Sciences 8 (2): 46.
Amodio, E., F. Vitale, L. Cimino, A. Casuccio, and F. Tramuto. 2020. “Outbreak of Novel Coronavirus (SARS-Cov-2): First Evidences from International Scientific Literature and Pending Questions.” *Healthcare* 8 (3): 51.

Anderson, R. M., C. Fraser, A. C. Ghani, C. A. Donnelly, S. Riley, N. M. Ferguson, G. M. Leung, T. H. Lam, and A. J. Hedley. 2004. “Epidemiology, Transmission Dynamics and Control of SARS: The 2002-2003 Epidemic.” *Philosophical Transactions of the Royal Society of London B Biological Sciences* 359 (1447): 1091–105.

Anzai, A., T. Kobayashi, N. M. Linton, R. Kinoshita, K. Hayashi, A. Suzuki, Y. Yang, S.-M. Jung, T. Miyama, A. R. Akhmetzhanov, and H. Nishiura. 2020. “Assessing the Impact of Reduced Travel on Exportation Dynamics of Novel Coronavirus Infection (COVID-19).” *Journal of Clinical Medicine* 9 (2): 601.

Ashour, H. M., W. F. Elkhatabi, Md. M. Rahman, and H. A. Elshabrawy. 2020. “Insights into the Recent 2019 Novel Coronavirus (SARS-CoV-2) in Light of Past Human Coronavirus Outbreaks.” *Pathogens* 9 (3): 186.

Balicer, R. D. 2007. “Modeling Infectious Diseases Dissemination through Online Role-Playing Games.” *Epidemiology* 18 (2): 260–1.

Balzer, L., J. Ahern, S. Galea, and M. van der Laan. 2016. “Estimating Effects with Rare Outcomes and High Dimensional Covariates: Knowledge Is Power.” *Epidemiologic Methods* 5 (1): 1–18.

Bertke, S., M. Hein, M. Schubauer-Berigan, and J. Deddens. 2013. “A Simulation Study of Relative Efficiency and Bias in the Nested Case-Control Study Design.” *Epidemiologic Methods* 2 (1): 85–93.

Biondi-Zoccai, G., G. Landoni, R. Carnevale, E. Cavarretta, S. Sciarretta, and G. Frati. 2020. “SARS-CoV-2 and COVID-19: Facing the Pandemic Together as Citizens and Cardiovascular Practitioners.” *Minerva Cardioangioligica*, https://doi.org/10.23736/s1026-4725.20.05250-0.

Blassi, M. D., A. Giardina, C. Giordano, G. L. Coco, C. Tosto, J. Billieux, and A. Schimmenti. 2019. “Problematic Video Game Use as an Emotional Coping Strategy: Evidence from a Sample of MMORPG Gamers.” *Journal of Behavioral Addiction* 8 (1): 25–34.

Bolgog, P., T. Tekeli, Z. Vizi, A. Dénès, F. A. Bartha, and G. Röst. 2020. “Risk Assessment of Novel Coronavirus COVID-19 Outbreaks outside China.” *Journal of Clinical Medicine* 9 (2): 571.

Bonnaire, C., and D. Baptista. 2019. “Internet Gaming Disorder in Male and Female Young Adults: The Role of Alexithymia, Depression, Anxiety and Gaming Type.” *Psychiatry Research* 272: 521–30.

Brehm, A. L. 2013. “Navigating the Feminine in Massively Multiplayer Online Games: Gender in World of Warcraft.” *Frontiers of Psychology* 4: 903.

Buiza-Aguado, C., A. Alonso-Canovas, C. Conde-Mateos, J. J. Buiza-Navarrete, and D. Gentile. 2018. “Problematic Video Gaming in a Young Spanish Population: Association with Psychosocial Health.” *Cyberpsychology, Behavior, and Social Networking* 21 (6): 388–94.

Chang, S. L., M. Piraveenan, and M. Prokopenko. 2019. “The Effects of Imitation Dynamics on Vaccination Behaviours in SI-R- Network Model.” *International Journal of Environmental Research and Public Health* 16 (14): 2477.

Chen, A., S. Mari, S. Grech, and J. Levitt. 2020. “What We Know about Massively Multiplayer Online Role-Playing Games.” *Harvard Review of Psychiatry* 28 (2): 107–12.

Choi, C., M. A. Hums, and C.-H. Bum. 2018. “Impact of the Family Environment on Juvenile Mental Health: eSports Online Game Addiction and Delinquency.” *International Journal of Environmental Research and Public Health* 15 (12): 2850.

Crimi, S., L. Fiorillo, A. Bianchi, C. D’Amico, G. Morosso, F. Gorassini, R. Mastroieni, S. Marino, C. Scoglio, F. Catalano, and P. Campagna. 2019. “Herpes Virus, Oral Clinical Signs and QoL: Systematic Review of Recent Data.” *Viruses* 11 (5): 463.

Deng, S.-Q., and H.-J. Peng. 2020. “Characteristics of and Public Health Responses to the Coronavirus Disease 2019 Outbreak in China.” *Journal of Clinical Medicine* 9 (2): 575.

Di Pierro, F., A. Bertucciolli, and I. Cavecchia. 2020. “Possible Therapeutic Role of a Highly Standardized Mixture of Active Compounds Derived from Cultured Lentinula Edodes Mycelia (AHCC) in Patients Infected with 2019 Novel Coronavirus.” *Minerva Gastroenterologica e Dietologica*, https://doi.org/10.23736/s1121-421x.20.02697-5.

Fiorillo, L., G. Cervino, M. Matarese, C. D’Amico, G. Surace, V. Paduano, M. Teresa Fiorillo, A. Moschella, A. La Bruna, G. L. Romano, and R. Laudicella. 2020. “COVID-19 Surface Persistence: A Recent Data Summary and Its Importance for Medical and Dental Settings.” *International Journal of Environmental Research and Public Health* 17 (9): 3132.

Goh, G. K.-M., A. K. Dunker, J. A. Foster, and V. N. Uversky. 2020. “Rigidity of the Outer Shell Predicted by a Protein Intrinsic Disorder Model Sheds Light on the COVID-19 (Wuhan-2019-nCoV) Infectivity.” *Biomolecules* 10 (2): 331.

Graham, L. T., and S. D. Gosling. 2013. “Personality Profiles Associated with Different Motivations for Playing World of Warcraft.” *Cyberpsychology, Behavior, and Social Networking* 16 (3): 189–93.

Grasselli, G., A. Pesenti, and M. Cecconi. 2020. “Critical Care Utilization for the COVID-19 Outbreak in Lombardy, Italy: Early Experience and Forecast during an Emergency Response.” *JAMA*, https://doi.org/10.1001/jama.2020.4031.

Gubar, E., V. Taynitskiy, and Q. Zhu. 2018. “Optimal Control of Heterogeneous Mutating Viruses.” *Games* 9 (4): 103.

Guitart, A., P. P. Chen, and A. Periáñez. 2018. “The Winning Solution to the IEEE CIG 2017 Game Data Mining Competition.” *Machine Learning and Knowledge Extraction* 1 (1): 252–64.

Hui, B. P. H., M. Anise, S. Wu, Y. Nicolson, F. Siu, M.-L. Chung, and P. Ngai. 2019. “The Effects of Need Satisfaction and Dissatisfaction on Flourishing Among Young Chinese Gamers: The Mediating Role of Internet Gaming Disorder.” *International Journal of Environmental Research and Public Health* 16 (22): 4367.
Huitfeldt, A., A. Goldstein, and S. A. Swanson. 2018. “The Choice of Effect Measure for Binary Outcomes: Introducing Counterfactual Outcome State Transition Parameters.” Epidemiologic Methods 7 (1), https://doi.org/10.1515/em-2016-0014.

Jung, S.-M., A. R. Akhmetzhanov, K. Hayashi, N. M. Linton, Y. Yang, B. Yuan, T. Kobayashi, R. Kinoshita, and H. Nishiura. 2020. “Real-Time Estimation of the Risk of Death from Novel Coronavirus (COVID-19) Infection: Inference Using Exported Cases.” Journal of Clinical Medicine 9 (2): 523.

Kobayashi, T., S.-M. Jung, N. M. Linton, R. Kinoshita, K. Hayashi, T. Miyama, A. Anzai, Y. Yang, B. Yuan, A. R. Akhmetzhanov, and A. Suzuki. 2020. “Communicating the Risk of Death from Novel Coronavirus Disease (COVID-19).” Journal of Clinical Medicine 9 (2): 580.

Kohana, M., S. Sakamoto, and S. Okamoto. 2019. “Web Browser Network Based on a BA Model for a Web-Based Virtual World.” Future Internet 11 (7): 147.

Kuniya, T. 2020. “Prediction of the Epidemic Peak of Coronavirus Disease in Japan, 2020.” Journal of Clinical Medicine 9 (3): 789.

Lavorgna, L., G. Cervino, L. Fiorillo, G. Di Leo, G. Troiano, M. Ortensi, L. Galantucci, and M. Cicciù. 2019. “Reliability of a Virtual Prosthodontic Project Realized through a 2d and 3d Photographic Acquisition: An Experimental Study on the Accuracy of Different Digital Systems.” International Journal of Environmental Research and Public Health.

Lee, B. W., and P. R. Leeson. 2015. “Online Gaming in the Context of Social Anxiety.” Psychology of Addictive Behaviors 29 (2): 472–82.

Li, Q., Q. Liu, X. Guo, S. Xu, J. Liu, and H. Lu. 2019a. “Evolution and Transformation of the Central Place Theory in E-Business: China’s C2C Online Game Marketing.” Sustainability 11 (8): 2274.

Li, X., Y. Liu, C. Zhao, X. Zhang, and D. Yi. 2019b. “Locating Multiple Sources of Contagion in Complex Networks under the SIr Model.” Applied Sciences 9 (20): 4472.

Linton, N. M., T. Kobayashi, Y. Yang, K. Hayashi, R. Andrei, A. Sung-Mok Jung, B. Yuan, R. Kinoshita, and H. Nishiura. 2020. “Incubation Period and Other Epidemiological Characteristics of 2019 Novel Coronavirus Infections with Right Truncation: A Statistical Analysis of Publicly Available Case Data.” Journal of Clinical Medicine 9 (2): 538.

Lis, E., C. Chiniara, M. A. Wood, R. Biskin, and R. Montoro. 2016. “Psychiatrists’ Perceptions of World of Warcraft and Other MMORPGs.” Psychiatric Quarterly 87 (2): 323–7.

Liu, Z., P. Magal, O. Seydi, and G. Webb. 2020. “Understanding Unreported Cases in the COVID-19 Epidemic Outbreak in Wuhan, China, and the Importance of Major Public Health Interventions.” Biology 9 (3): 50.

Lofgren, E. T., and N. H. Fefferman. 2007. “The Untapped Potential of Virtual Game Worlds to Shed Light on Real World Epidemics.” The Lancet Infectious Diseases 7 (9): 625–9.

Longman, H., E. O’Connor, and P. Obst. 2009. “The Effect of Social Support Derived from World of Warcraft on Negative Psychological Symptoms.” CyberPsychology and Behavior 12 (5): 563–6.

Marzouki, Y., V. Dusaucy, M. Chanceaux, and S. Mathôt. 2017. “The World (Of Warcraft) through the Eyes of an Expert.” PeerJ 5: e3783.

McAleer, M. 2020. “Prevention Is Better Than the Cure: Risk Management of COVID-19.” Journal of Risk and Financial Management 13 (3): 46.

McClay, W. 2018. “A Magnetoencephalographic/Encephalographic (MEG/EEG) Brain-Computer Interface Driver for Interactive iOS Mobile Videogame Applications Utilizing the Hadoop Ecosystem, MongoDB, and Cassandra NoSQL Databases.” Diseases 6 (4): 89.

Na, E., I. Choi, T. H. Lee, H. Lee, M. J. Rho, H. Cho, D. J. Jung, and D. J. Kim. 2017. “The Influence of Game Genre on Internet Gaming Disorder.” Journal of Behavior Addiction 1–8, https://doi.org/10.1556/2006.2016.6.2017.033.

Nguyen, T., D. Duong Bang, and A. Wolff. 2020. “2019 Novel Coronavirus Disease (COVID-19): Paving the Road for Rapid Detection and Point-of-Care Diagnostics.” Micromachines 11 (3): 306.

Nishiura, H. 2020. “Backcalculating the Incidence of Infection with COVID-19 on the Diamond Princess.” Journal of Clinical Medicine 9 (3): 657.

Northrup, J. C., C. Lapierre, J. Kirk, and C. Rae. 2015. “The Internet Process Addiction Test: Screening for Addictions to Processes Facilitated by the Internet.” Behavioral Sciences 5 (3): 341–52.

Obst, P. L., X. Zhao, K. M. White, E. L. O’Connor, and H. Longman. 2018. “Game Identity-Based Motivations of Playing World of Warcraft and Their Psychological Outcomes.” Cyberpsychology, Behavior, and Social Networking 21 (10): 655–60.

Paik, S.-H., H. Cho, J.-W. Chun, J.-E. Jeong, and D.-J. Kim. 2017. “Gaming Device Usage Patterns Predict Internet Gaming Disorder: Comparison across Different Gaming Device Usage Patterns.” International Journal of Environmental Research and Public Health 14 (12): 1512.

PLAYING WITH EPIDEMICS. 2007. Science 316 (5827): 961.

Porcheddu, R., C. Serra, D. Kelvin, N. Kelvin, and S. Rubino. 2020. “Similarity in Case Fatality Rates (CFR) of COVID-19/SARS-COV-2 in Italy and China.” Journal of Infection in Developing Countries 14 (2): 125–8.

Reer, F., and N. C. Krämer. 2017. “The Connection between Introversion/Extraversion and Social Capital Outcomes of Playing World of Warcraft.” Cyberpsychology, Behavior, and Social Networking 20 (2): 97–103.

Repici, A., R. Maselli, M. Colombo, R. Gabbiadini, M. Spadaccini, A. Anderloni, S. Carrara, A. Fugazza, M. Di Leo, P. A. Gallieri, and G. Pellegratta. 2020. “Coronavirus (COVID-19) Outbreak: what the Department of Endoscopy Should Know.” Gastrointestinal Endoscopy, https://doi.org/10.1016/j.gie.2020.03.019.
Roosa, K., Y. Lee, R. Luo, K. Alexander, R. Rothenberg, J. M. Hyman, P. Yan, and G. Chowell. 2020. “Short-term Forecasts of the COVID-19 Epidemic in Guangdong and Zhejiang, China: February 13–23, 2020.” *Journal of Clinical Medicine* 9 (2): 596.

Sapienza, A., A. Bessi, and E. Ferrara. 2018. “Non-Negative Tensor Factorization for Human Behavioral Pattern Mining in Online Games.” *Information* 9 (3): 66.

Schwartz, D. A., and A. L. Graham. 2020. “Potential Maternal and Infant Outcomes from Coronavirus 2019-nCoV (SARS-CoV-2) Infecting Pregnant Women: Lessons from SARS, MERS, and Other Human Coronavirus Infections.” *Viruses* 12 (2): 194.

Shi, Z., N. Zhang, and L. Zhu. 2019. “Understanding the Propagation and Control Strategies of Congestion in Urban Rail Transit Based on Epidemiological Dynamics Model.” *Information* 10 (8): 258.

Sims Bainbridge, W. 2010. “Virtual Sustainability.” *Sustainability* 2 (10): 3195–210.

Sinatra, R., and M. Szell. 2014. “Entropy and the Predictability of Online Life.” *Entropy* 16 (1): 543–56.

Spina, S., F. Marrazzo, M. Migliari, R. Stucchi, A. Sforza, and R. Fumagalli. 2020. “The Response of Milan’s Emergency Medical System to the COVID-19 Outbreak in Italy.” *Lancet* 395 (10227): e49–50.

Stavropoulos, V., D. J. Kuss, M. D. Griffiths, P. Wilson, and F. Motti-Stefanidi. 2017. “MMORPG Gaming and Hostility Predict Internet Addiction Symptoms in Adolescents: An Empirical Multilevel Longitudinal Study.” *Addictive Behaviors* 64: 294–300.

Sun, Z., K. Thilakavathy, S. S. Kumar, G. He, and S. V. Liu. 2020. “Potential Factors Influencing Repeated SARS Outbreaks in China.” *International Journal of Environmental Research and Public Health* 17 (5): 1633.

Thier, D. 2018. “World of Warcraft Shines Light on Terror Tactics.” *Wired*. Also available at https://www.wired.com/2008/03/wow-terror/ (accessed March 17, 2020).

Veltkamp, H.-W., F. A. Monteiro, R. Sanders, R. Wiegerink, and J. Lötters. 2020. “Disposable DNA Amplification Chips with Integrated Low-Cost Heaters†.” *Micromachines* 11 (3): 238.

Wang, X., B. Asad Hassan, Q. Zhang, M. N. Shafique, H. Ahmad, and Z. Nawaz. 2020a. “Gaming Avatar Can Influence Sustainable Healthy Lifestyle: Be like an Avatar.” *Sustainability* 12 (5): 1998.

Wang, C., Z. Cheng, X.-G. Yue, and M. McAleer. 2020b. “Risk Management of COVID-19 by Universities in China.” *Journal of Risk and Financial Management* 13 (2): 36.

Wang, C., R. Pan, X. Wan, Y. Tan, L. Xu, C. S. Ho, and R. C. Ho. 2020c. “Immediate Psychological Responses and Associated Factors during the Initial Stage of the 2019 Coronavirus Disease (COVID-19) Epidemic Among the General Population in China.” *International Journal of Environmental Research and Public Health* 17 (5): 1729.

Xu, J., S. Zhao, T. Teng, A. Elgaili Abdalla, W. Zhu, L. Xie, Y. Wang, and X. Guo. 2020. “Systematic Comparison of Two Animal-To-Human Transmitted Human Coronavirus: SARS-CoV-2 and SARS-CoV.” *Viruses* 12 (2): 244.

Yu, H., X. Sun, W. Deng Solvang, and X. Zhao. 2020. “Reverse Logistics Network Design for Effective Management of Medical Waste in Epidemic Outbreaks: Insights from the Coronavirus Disease 2019 (COVID-19) Outbreak in Wuhan (China).” *International Journal of Environmental Research and Public Health* 17 (5): 1770.

Zhang, W., Y. Wang, L. Yang, and C. Wang. 2020. “Suspending Classes without Stopping Learning: China’s Education Emergency Management Policy in the COVID-19 Outbreak.” *Journal of Risk and Financial Management* 13 (3): 55.