Vaccination and epidemics in networked populations—An introduction

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ABSTRACT

This is an introduction to the special issue titled "Vaccination and epidemics in networked populations" that is in the making at Chaos, Solitons & Fractals . While vaccination is undoubtedly one of the most important preventive measures of modern times, epidemics are feared as one of the most damaging phenomena in human societies. Recent research has explored the pivotal implications of individual behavior and heterogeneous contact patterns in networked populations, as well as the many feedback loops that exist between vaccinating behavior and disease propagation [1, 2]. Interdisciplinary explorations in the realm of statistical physics, network science, nonlinear dynamics, and data analysis have given rise to theoretical epidemiology, as well as to the theory of epidemic processes in complex networks. From classical models assuming well-mixed populations and ignoring human behavior, to recent models that account for behavioral feedback and population structure, we have come a long way in understanding disease transmission and disease dynamics, and in using this knowledge to devise effective prevention strategies. This special issue is aimed at helping the further development of these synergies. We hope that it contributes to enhance our understanding of vaccination and epidemics in networked populations, by featuring works related to vaccination and epidemics using techniques ranging from complex and temporal networks to network of networks and show-casing the possibilities of interdisciplinarity via complex systems science to tackle the challenges in our quest for a healthier future. Topics of interest include but are not limited to epidemiological modeling and vaccination, behavior-vaccination dynamics, reaction-diffusion processes and metapopulation models, evolutionary and game theoretical models in epidemiology, as well as to influence maximization and digital epidemiology.

1. Networks

During the past two decades network science has emerged as a central paradigm behind some of the most fascinating discoveries of the 21st century [3,4]. From the mathematical formulation of small-world properties and their omnipresence in seemingly diverse systems such as electric power grids, food chains, brain networks, protein networks, transcriptional networks and social networks [5], to universal scaling properties due to growth and preferential attachment that likewise pervade biological, social and technological networks [6], the field of research today known as network science has been going from strength to strength, as evidenced by the many reviews devoted to this field of research [7–14]. Network science has provided models, methods and algorithms that have revived not just statistical physics, arguably the nurturer to the field, but indeed many other fields of natural and social sciences, including of course research concerning vaccination and epidemics to which this special issue is devoted to.

In addition to static networks, network science allows us to study and take into account network evolution over time, for example due to changes in external factors, the onset of disease, targeted attack, or simply due to random failure. Such changes can be studied in the realm of temporal networks [11,15,16], where the theoretical framework accounts for the addition or removal of nodes, or similarly for the changes in the links between nodes, over time. A beautiful example of how changing links over time

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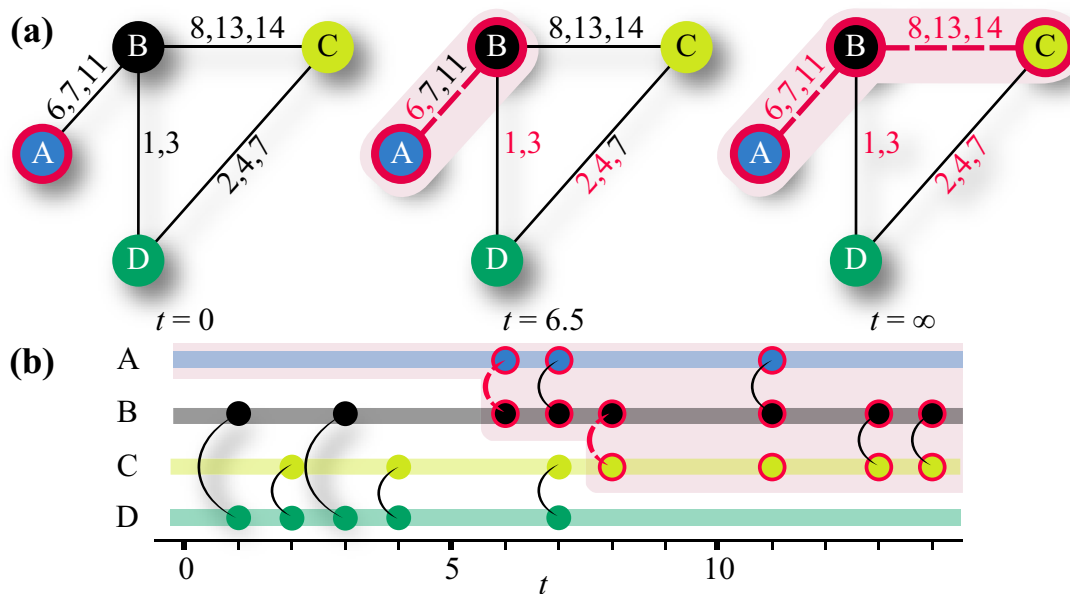*E-mail address:* matjaz.perc@uni-mb.si (M. Perc).

Fig. 1. The importance of temporal networks. Changes in the links between individuals A, B, C and D affect disease spreading. In the upper row, the contact times between the individuals are indicated on the edges. Let us assume that a disease starts spreading at individual A and spreads further as soon as contact occurs. This spreading process is illustrated for four different times from left to right. At $t = \infty$ the spreading stops as individual D cannot get infected. However, if the spreading starts at individual D, then all other depicted individuals would eventually be infected. Aggregating the edges into one static graph cannot capture this effect that arises from the time ordering of contacts. The lower row visualizes the same situation by showing the temporal dimension explicitly. This figure is reproduced with permission from [11].

between different individuals might affect disease spreading, reproduced from [11], is shown in Fig. 1.

Also of importance, networks exist between different layers of each studied system, and this is particularly apparent in social systems, where one person can be simultaneously member of many different networks that are to various degrees interdependent [17–21]. This can be accommodated in the theoretical framework of multilayer networks, or more generally networks of networks, which acknowledge that not only is the range of our interactions limited and thus inadequately described by well-mixed models, but also that the networks that should be an integral part of such models are often interconnected, thus making the processes that are unfolding on them interdependent [12,13,22–24]. From the world economy and transportation systems to the spread of epidemics, it is clear that processes taking place in one network can significantly affect what is happening in many other networks. From this point of view, the consideration of multilayer or interdependent networks is crucial for a comprehensive treatment of vaccination and epidemics in networked populations [25,26].

In addition to the theoretical coming of age of network science, technological breakthroughs in the acquisition and storage of vast amounts of digitized data have significantly aided the progress in our understanding of both vaccination and epidemic spreading. The data revolution has had a particularly deep impact on the social sciences, where social experiments in the past typically involved one-shot self-reported data on relationships and their outcomes in a small sample of people, while today the approach is to mine massive amounts of digitized data for both the structure and the content of relationships [27,28], which may in turn relevantly inform vaccination strategies [2] as well as the spread of epidemics [1].

In particular, the synergies between mathematical modeling and theoretical explorations and data-driven research, coupled with taking into account feedbacks between disease, behavior and vaccination, are likely the future of complex systems research aimed at a better understanding of vaccination and epidemics in modern human societies.

2. Vaccination

As already stated, vaccination is undoubtedly one of the most important preventive measures of modern times, unfolding on the planetary scale with the aim of preventing the spread of infectious diseases that have had a crippling impact on many human societies in the not so distant past. The 20th century, in particular, saw enormous progress in public health, especially in terms of preventing and treating infectious diseases. The use of vaccines was crucial to that effect. However, due to limited amounts of vaccines and knowledge, early studies simply assumed that vaccination should be done compulsively and/or randomly. Today we know that vaccination efforts on networks are more effective if random vaccination is combined with targeted vaccination and the vaccination of acquaintances [1,29–31]. While random vaccination of course does not require any information about the structure of the network, it needs in return a very broad coverage, and is thus very costly, in order to be effective [29,32]. More precisely, uniform vaccination is super inefficient for disease eradication in heterogeneous networks [29]. To offset this disadvantage, targeted vaccination according to the centrality indexes of individuals, like degree, betweenness and closeness [33–37] should be considered. For example, because large-degree nodes are known to be responsible for the spreading of disease, a degree-based targeted vaccination strategy was proposed to immunize the most highly connected individuals [34,38]. Compared with random vaccination, targeted vaccination thus greatly reduces costs, but since the identification of centrality-defined individuals usually takes a long(er) time, the practicability of targeted vaccination is doubtful in practice, especially in large populations [39]. There also exists inconsistencies in the definitions of some centrality indexes in more complex networks, especially in multilayer networks, which in turn restricts the universality of targeted vaccination [12]. Acquaintance vaccination is more suitable for practical applications in that a fraction of nodes is selected at random, and then random neighbors are vaccinated further [33,40]. This approach requires only partial knowledge of the network structure, and its variants have been studied

Fig. 2. Satirical cartoon by James Gillray capturing public fears of the smallpox vaccine in the 18th century, the first "vaccine scare". Edward Jenner stands in the middle, administering the smallpox vaccine. Vaccinated persons grow cow parts out of various parts of their bodies because the smallpox vaccine of the time was based on the virus that causes cowpox, hence producing the fear among some that the vaccine would turn humans into cow-like hybrids. A painting of the Worshippers of the Golden Calf hangs in the background. Source: Wikimedia Commons.

in substantial detail [41,42]. In addition to these different vaccination strategies, network structure also plays an important role in the transmission routes and infection levels [2,9–12]. For example, in community networks, bridge nodes, connecting different communities, provide pathways for disease propagation, so that how to identify and immunize these nodes thus decides the final success rate [43,44].

With the latest advances in science and technology, today, safe and effective vaccines exist for many of the most common infectious diseases, such as smallpox, measles, pertussis, influenza, hepatitis, chickenpox and diphtheria, and the use of vaccines has been estimated to save millions of children's lives per year [45]. However, due to high economic costs of vaccination, and often also personal beliefs and the fear of possible side effects, people usually regard vaccination as a voluntary rather than a compulsory measure. In this sense, behavioral vaccination, borrowing the framework of behavior dynamics in game theory and psychology, becomes a useful research framework to elucidate real-world disease spreading and prevention [2,46–48].

Despite of all the success, great challenges still remain, in part due to the difficulties in providing and administering vaccines in the world's poorest and war-torn regions [49,50], but also because in many wealthy countries, such as the United Kingdom, Switzerland and Germany, there is considerable parental vaccine refusal or vaccine hesitancy on account of unfounded concerns about significantly adverse side effects such as autism. Regarding the latter, it is important to acknowledge that vaccine refusal is not a new phenomenon, and even the first vaccine to be invented – the smallpox vaccine – was subject to considerable resistance, as nicely illustrated by James Gillray in his 18th century portrayal of the "vaccine scare" (see Fig. 2). The take-home message is that it is very impor-

tant to account for behavioral feedback effects, and to account for cognition and deliberation when devising mathematical models of vaccination. Namely, as logistic, financial, technological and administrative barriers to vaccination continue receding in the coming decades, enabling it to become easier to improve vaccine coverage everywhere in the world, it is not too far fetched to speculate that vaccine refusal and vaccine hesitancy will become an important barrier – and perhaps even the most important barrier – to global eradication of vaccine-preventable infections [2]. As a case in point, when we observe vaccinating behavior responding to changes in disease prevalence, as in the Disneyland, California measles outbreak of 2014 and other examples, it is impossible to overlook that vaccinating behavior and disease dynamics are strongly linked to one another, particularly near elimination thresholds.

Although human behavior is surely more difficult to mathematically model than the motion of a billiard ball or many of the somewhat more complex systems studied by physicists, it is nevertheless conceivable that at some levels of organization it is possible to develop simple models that have useful predictive power. For example, mathematical models incorporating behavior-disease interactions have been fitted to time series data of infectious disease prevalence, and model selection approaches have shown that models that include behavior can explain the data more effectively compared to models that neglect behavior [51,52].

Hence, there is a strong public health and scientific rationale for studying behavior-disease-vaccination interactions. Existing research shows that behavior, disease and vaccination choices are strongly coupled to one another, and further, that this coupling is particularly important near the elimination threshold [48]. Accordingly, vaccine refusal may become an increasingly important barrier to achieving elimination and eradication, as logistic barri-
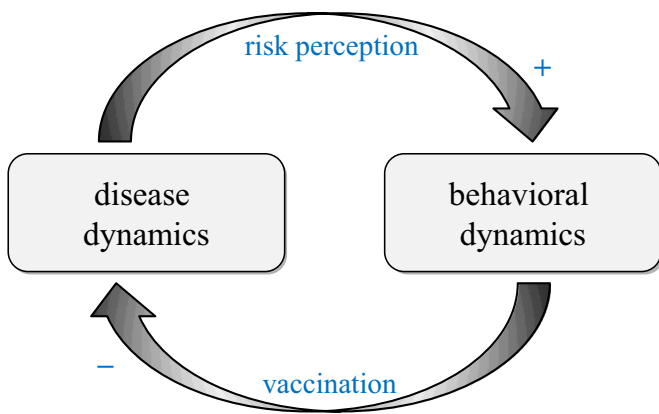
Fig. 3. Illustration of behavior-disease-vaccination interactions. The feedback loop, on the one hand, promotes vaccination as the disease spreads and risk perception rises, but on the other hand, people revert to abstaining when vaccination takes effect and the spreading of the disease is effectively mitigated. But this then of course restarts the loop sooner or later.

ers recede into the distance. Fig. 3 illustrates the behavior-disease-vaccination interactions, which form a feedback loop. The fast diffusion of a disease will increase the risk perception, based on which people feel an incentive to take protective measures, i.e., to vaccinate. In turn, the spreading of the disease is suppressed, to the point where risk perception drops again and people opt not to vaccinate.

Mathematical models hold the promise to help us better understand such coupled dynamics, and comparing models with data has often shown that behavior is important for understanding observed epidemic patterns. Also of notice, these models often exhibit interesting dynamics that is similar to those studied in physics, including phase transitions, oscillatory solutions, and spatiotemporal pattern formation, thus indicating that similar methodologies to those used in physics and complex systems research in general are likely to be helpful in their study [2,53].

For a more concrete perspective, we briefly review arguably the first phenomenological model to capture the impact of adaptive human behavior on disease transmission [54]. The model is given by the following ordinary differential equations

$$\frac{dS}{dt} = -g(I)S,$$
$$\frac{dI}{dt} = g(I)S, -\gamma I \quad (1)$$
$$\frac{dR}{dt} = \gamma I,$$

where S is the number of susceptible individuals, I is the number of infectious individuals, R is the number of recovered individuals, γ is the per capita recovery rate, and $g(I)$ is the force of infection. The form of $g(I)$ is chosen to reflect the phenomenological impact of unspecified psychological effects. One of the functional forms explored in [54] included

$$g(I) = \frac{\beta I}{1 + \beta \delta I}, \quad (2)$$

which saturates at a high prevalence of infection I. Such saturation of the transmission rate at high levels of prevalence could occur if individuals reacted to high prevalence by reducing their contact rate through hand-washing or other means, which is a plausible assumption for a sufficiently dangerous infectious disease. The model is phenomenological because, although it is motivated by psychological factors, the equations only describe the impact of such psychological factors on the transmission rate without actu-

ally modeling specific psychological processes such as individual cognition or social learning.

An apt theoretical framework to account for behavior-disease-vaccination interactions is also evolutionary game theory [55–59], which has already been used to study the clash between what is optimal for the individual and what is optimal for the group in a variety of contexts [16,23,60–65], including vaccination [66,67]. At the heart of the choice whether or not to vaccinate is of course a social dilemma, which invokes the puzzle of human cooperation [68]. To vaccinate is clearly the socially responsible choice, but it comes at a cost that has to do with offsetting the fear and potential side effects. But if individuals choose not to vaccinate, they may become infected, which will inflict larger costs for recovery. Those that do not vaccinate but still benefit from herd immunity, which is generated by a large fraction of those who do vaccinate, is individually the better choice, i.e., like free-riding in evolutionary games. Obviously, if everybody chooses not to vaccinate the herd immunity is lost and the public good, which in this case is the precious absence of an infectious disease, is lost with it. Accordingly, uninfected non-vaccinators are the defectors who benefit from herd immunity generated by vaccinators without paying any real or perceived cost of vaccination, while vaccinators are the cooperators.

In terms of the integration of cognitive abilities, a new model for looking at the evolution of intuition versus deliberation as well as at the evolution of cooperation versus defection has recently been introduced [69], which lends itself to research in networked populations, and which could also be a viable starting ground for more realistic evolutionary game theoretical modes of vaccination.

To conclude this section, we note that traditional epidemiological models that do not take into account behavioral dynamics have been very successful over the past century, both in terms of yielding rich theoretical opportunities for research as well as in terms of providing insights into epidemiological mechanisms and how to improve infection control. Nevertheless, the impact of human behavior on disease dynamics and vaccination is ubiquitous, and vaccinating behavior itself is certainly no exception in this important feedback loop.

3. Epidemic processes

Research on epidemic outbreaks in complex heterogeneous networks has roots that go back to the beginning of the 21st century [70], when it was shown that large fluctuations in the degrees of individuals in social networks considerably strengthen the incidence of epidemic outbreaks. Scale-free networks, for example, were shown to altogether lack an epidemic threshold and thus always contain a finite fraction of infected individuals. This particular weakness of networked populations in comparison to well-mixed populations, which was observed also in models without immunity, at the time defined a new epidemiological framework characterized by a highly heterogeneous response of the system to the introduction of infected individuals with different connectivity. Fast forward 15 years into the future, and today we have a comprehensive theory of epidemic processes in complex networks [1], but with many challenges and open problems still remaining.

While epidemic models based on reaction-diffusion processes have arguably been the workhorse of the field since its inception [71–74], one of the more exciting recent developments that we here mention as example concerns agent based models, and network epidemiology in particular [75–81]. This approach draws on synergies between large-scale simulations and data-based network construction, the outcome of which is typically an agent-based model that evolves in a spatially structured population. A schematic illustration of the construction of a synthetic population

Fig. 4. Network epidemiology. At the macroscopic level (left), a synthetic population and the movements of its members can be constructed from census and demographic data. A bipartite network associating individuals to locations can be derived based on data from the synthetic population (middle). Lastly, the unipartite projection of the bipartite network provides a contact network (right), upon which an agent-based model can unfold. This figure is reproduced with permission from [1].

is presented in Fig. 4, where based on census and demographic data as input the network of contacts is constructed from an intermediate bipartite network associating individuals to locations. The GLobal Epidemic and Mobility (GLEAM) model [82] is a particular example that integrates census and mobility data in a fully stochastic metapopulation network model that allows for the detailed simulation of the spread of influenza-like illnesses around the globe.

Importantly, while the spread of infectious diseases is most commonly the focal point of research on epidemic spreading, in particular because this is one of the most damaging phenomena in human societies in the past and present day, the resulting mathematical models can of course be generalized and adapted to describe diffusion of information [83], the spreading of rumors and scientific memes [84], the emergence of online virality [85], and indeed many other phenomena that are inherent to our modern existence, both off and online. Recently, a null model for social spreading phenomena has been proposed [86], which can reproduce several characteristics of empirical micro-blogging data, such as for example the heavy-tailed distribution of meme popularity. The model clearly distinguishes the roles of two distinct factors affecting popularity, namely the memory time of users and the connectivity structure of the social network.

Along these lines, research on epidemics in the broadest possible sense continues to draw together different fields for us to arrive at a better understanding of processes that are behind one of the greatest challenges that lie ahead for human societies, namely the maintenance of public health and the mitigation of large-scale epidemics and the spread of infectious disease. As an added benefit, one finds that the same spreading phenomena that drive epidemics drive also social contagion processes, which surely adds to the arguments to actively engage in this research.

4. Future research

As we hope we have succeeded to outline in this introduction, vaccination and epidemics in networked populations merit outstanding attention from the research community, not only for their obvious importance to the wellbeing of our societies, but also from the purely scientific point of view due to the many open problems and fascinating challenges that remain to be addressed. The triptych *The Garden of Earthly Delights* shown in Fig. 5, painted by Hieronymus Bosch around the turn of the 16th century, is a lucid portrayal of events that may transpire if we fail to keep the public health in the best possible order, and if we fail to cooperate in vaccinating our children and working together to minimize the risk of epidemics.

Particularly promising areas of research that warrant attention include the consideration of mathematical and statistical laws that govern the coevolution of the network and the evolution of vaccination or of the epidemic process that unfolds. Here the formalism of temporal networks is a necessary prerequisite [11], while further ideas how to proceed can be sought in [15,16], where research in closely related fields has already been reviewed.

Further in terms of the interaction network, recent research has revealed that social networks are almost inherently interdependent and layered, in the sense that a particular network of contacts seldom exists in isolation [12,13]. Consequently, processes unfolding in one network can have significant and also to a large degree unexpected consequences in another network [17–21,25,26]. It remains subject to future research to reveal to what degree this influences our ability to predict and control the epidemics, and what are the consequences of vaccination abstinence in one social group for others that are codependent.

Regarding mathematical modeling, it remains of interest to further integrate the many feedbacks between disease and behavior, in particular vaccinations behavior, and to introduce cognition and deliberation as processes that are inseparable to humans. Here research in psychology and anthropology can provide vital guidance and relevantly inform the next generation of models for them to realistically represent these processes that thus far remain under explored.

Lastly, one has to mention the ever-increasing availability of digital data and the many exciting prospects this creates, not just for testing theoretical predictions, but also in terms of using the data during the modeling process itself, as has already been demonstrated, for example in [82].

Fig. 5. *The Garden of Earthly Delights* serves as a didactic warning on the perils of life's temptations, which applies as much to shirking on vaccination, as it does to abandoning vigilance in times of epidemics. From left to right, we first have the meeting of Adam and Eve, followed by a socially balanced state of wellbeing in the center, and ending with a hellscape that portrays the torments of damnation that may result due to excesses in modern human societies. The picture was taken by Alonso de Mendoza, and reproduced here from the public domain. Source: Wikimedia Commons.

To conclude, we note that this special issue is also to feature future research. In order to avoid delays that are sometimes associated with waiting for a special issue to become complete before it is published, we have adopted an alternative approach at Chaos, Solitons & Fractals. The special issue will be a virtual one, updated continuously from the publication of this introduction onwards, meaning that new papers will be published immediately after acceptance. The down side of this approach is that we cannot feature the traditional brief summaries of each individual work that will be published, but we hope that this is more than made up for by the immediate availability of the latest research. Please stay tuned, and consider contributing to "Vaccination and epidemics in networked populations".

Acknowledgments

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